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CLINICAL FEATURES AND NEW DIAGNOSTIC AND THERAPEUTIC APPROACHES IN GIANT CELL ARTERITIS AND RHEUMATOID ARTHRITIS RELATED INTERSTITIAL LUNG DISEASE

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A chi ho lasciato e a chi ho trovato.
A chi, comunque, mi riempie il cuore.

ABBREVIATION INDEX

18-FDG: 18F-fluorodeoxyglucose
ABA: Abatacept
ACR: American College of Rheumatology
AE: Acute exacerbation
AZA: Azathioprine
bDMARDs: Biologic disease modifying anti-rheumatic drugs
cDMARDs: Conventional disease modifying anti-rheumatic drugs
CDS: color-Doppler sonography
CRP: C-Reactive Protein
CT: Computer Tomography
CTA: CT-Angiography
CTD: Connective tissue diseases
CYC: Cyclophosphamide
DLCO: Diffusing capacity of the lungs for carbon monoxide
ERS: Erythrocyte sedimentation rate
FVC: Forced vital capacity
GCA: Giant cell arteritis
GCs: glucocorticoids
HRCT: High-resolution computer tomography
IL-6: interleuchin 6
ILD: Interstitial lung disease
IPF: Idiopathic pulmonary fibrosis
LEF: Leflunomide
LV-GCA: Large vessel-GCA
LVV: large vessel vasculitis
MMF: Mycophenolate mofetil
MR: Magnetic Resonance
MRA: MR-Angiography
MRI: Magnetic Resonance Imaging
MTX: Methotrexate
NSIP: Nonspecific interstitial pneumonia
OP: Organizing pneumonia

PET/CT: positron emission tomography/computed tomography
PFTs: Pulmonary function tests
PMR: polymyalgia rheumatica
RA: Rheumatoid arthritis
RA-ILD: Rheumatoid arthritis related ILD
RCTs: randomized controlled trials
RDs: rheumatic diseases
RTX: Rituximab
TCZ: Tocilizumab
TNF: tumor necrosis factor
TNFi: Tumour necrosis factor alpha inhibitor
tsDMARDs: Targeted synthetic disease modifying anti-rheumatic drugs
UIP: Usual interstitial pneumonia

ABSTRACT

English version

Autoimmune rheumatic diseases are chronic diseases with a major health impact worldwide.
Their economic and social burden results from a decreased quality of life, lost productivity, and increased costs of health care. Without appropriate approaches to patient management and control of these diseases, this impact can be expected to increase as the population ages. Challenges in studying rheumatic diseases lie in achieving accurate epidemiological data and making efforts to obtain significant progress in terms of early diagnosis, treatment, and management of patients.
Section A:
Giant-cell arteritis (GCA) is the most common form of vasculitis in patients over 50 years old. Extra-cranic large vessel involvement (LVI) has emerged in recent decades, especially with the development of new imaging tools such as PET-TC, MR-Angiography (MRA) and CT-Angiography (CTA). It is unknown, however, how effective these methods are for assessing disease activity while patients are under treatment. GCA treatment is mainly based on long term use of corticosteroids (GCs). Tocilizumab has recently been approved for the treatment of GCA. However, it is often use in combination with GCs, with subsequent high risk of side effects.
Starting from these considerations, we underwent a monocentric observational study to evaluate clinical and functional/morphological imaging variations in a series of patients with GCA treated with ultra-short corticosteroids (GCs) and tocilizumab (TCZ) s.c. We also evaluated effectiveness and safety of TCZ monotherapy as a maintenance treatment in GCA.
In our preliminary results, radiologic tools seem to be useful methods for assessing disease activity in GCA patients during treatment. TCZ demonstrated a good safety profile in patients with GCA, however its potential effect in stabilize or resolve large vessels inflammation without the concomitant use of GCs has yet to be demonstrated in large randomized clinical trials.
Section B:
Rheumatoid arthritis (RA) is the most common chronic inflammatory disease, affecting 0.5%-1% of the population worldwide. Interstitial lung disease (ILD) is the most common and serious complication of lung involvement in RA.
All the available studies about the prevalence of ILD in AR are retrospective, with small series of patients and numerous biases, and therefore not reliable. Moreover, this complication is often underrated, particularly in its earliest stages. An early diagnosis is challenging, and the increase of the opportunities to diagnose ILD could improve the quality of life of patients and decrease the mortality and the high utilization of healthcare resources. Although lung involvement represents the second cause of death in RA patients, there are no randomized screening approaches or management guidelines.
Several therapeutic agents have been suggested for the treatment of RA-ILD, but nowadays there are no randomized controlled clinical trials to support therapeutic guidelines and treatment of RA-ILD is still based on empirical approaches.
In this background, aims of this study project were:
-to review the current literature on the treatment of ILD in RA patients and discuss the unsolved problems regarding this challenging patient cohort, even suggesting a framework for their management and analyzing the evolution of RA-ILD in patients treated with tocilizumab and abatacept;

-to investigate the usefulness of detecting velcro crackle in lung sounds by analyze them using a suitably developed algorithm, as an early screening of RA-ILD;
-to perform an international prospective multicenter observational study to evaluate incidence and prevalence of ILD in patients with RA.

Italian version

Le patologie reumatiche autoimmuni sono malattie croniche con un importante impatto sanitario in tutto il mondo. Il loro impatto economico e sociale deriva da una diminuzione della qualità della vita, dalla perdita di produttività e dall'aumento dei costi dell'assistenza sanitaria. Senza approcci adeguati alla gestione dei pazienti e al controllo di queste malattie, ci si può aspettare che questo impatto aumenti con il progressivo invecchiamento della popolazione. Attualmente, per alcune patologie reumatiche, mancano ancora accurati dati epidemiologici e rimane la necessità di progressi significativi in termini di diagnosi precoce, trattamento e gestione dei pazienti.
Sezione A:
L'arterite a cellule giganti (GCA) è la forma più comune di vasculite nei pazienti di età superiore ai 50 anni. Negli ultimi decenni molta attenzione è stata data al coinvolgimento extracranico dei grandi vasi (LVI), in particolare dopo lo sviluppo di nuovi strumenti di imaging come PET-TC, angio-RM (MRA) e angio-TC (CTA). Non è noto, tuttavia, quanto queste metodiche siano efficaci per valutare l'attività della malattia durante la terapia. Il trattamento della GCA si basa principalmente sull'uso a lungo termine di glucocorticosteroidi (GC). Tocilizumab è stato recentemente approvato per il trattamento della GCA, tuttavia viene spesso utilizzato in combinazione con GC, con conseguente alto rischio di effetti collaterali.
Partendo da queste considerazioni, abbiamo realizzato uno studio osservazionale monocentrico per valutare le variazioni cliniche e di imaging in una serie di pazienti con GCA trattati con glucocorticosteroidi (GCs) per breve periodo e tocilizumab (TCZ) s.c. Abbiamo inoltre valutato l'efficacia e la sicurezza della monoterapia con TCZ come trattamento di mantenimento nella GCA.
I nostri risultati preliminari hanno dimostrato che le tecniche di imaging sembrano essere utili nel valutare l'attività della malattia nei pazienti con GCA durante il trattamento. TCZ in monoterapia ha dimostrato un buon profilo di sicurezza nei pazienti con GCA, tuttavia il suo potenziale effetto nello stabilizzare o risolvere l'infiammazione dei grandi vasi senza l'uso concomitante di GC deve ancora essere dimostrato in ampi studi clinici randomizzati.
Sezione B:
L'artrite reumatoide (AR) è una malattia infiammatoria cronica che colpisce lo 0,5%-1% della popolazione mondiale. L'interstiziopatia polmonare (ILD) è la forma di coinvolgimento polmonare più comune e grave dell'AR.
Tutti gli studi disponibili sulla prevalenza di ILD in AR sono retrospettivi, con piccole serie di pazienti e numerosi bias, e quindi non affidabili. Inoltre, questa complicanza è spesso sottovalutata, soprattutto nelle sue prime fasi. La diagnosi precoce rimane un essenziale ma difficile obiettivo clinico, in quanto l'aumento delle opportunità di diagnosticare l'ILD potrebbe migliorare la qualità della vita dei pazienti e diminuire la mortalità e l'elevato utilizzo delle risorse sanitarie. Sebbene il coinvolgimento polmonare rappresenti la seconda causa di morte nei pazienti con AR, non esistono approcci di screening randomizzati o linee guida di gestione di tale complicanza.

Diversi agenti terapeutici sono stati suggeriti per il trattamento della RA-ILD, attualmente però non esistono studi clinici controllati randomizzati che supportino solide linee guida terapeutiche, pertanto il trattamento della RA-ILD è ancora basato su approcci empirici.
In questo contesto, gli obiettivi di questo progetto di studio sono:
-effettuare una revisione della letteratura e dello stato dell'arte sul trattamento dell'ILD nei pazienti con AR e discuterne i problemi irrisolti, anche suggerendo una proposta per la loro gestione clinica e analizzando l'evoluzione dell'RA-ILD nei pazienti trattati con tocilizumab e abatacept;
-indagare l'utilità di uno strumento di screening tramite la rilevazione dei crepitii polonari a velcro e la loro analisi mediante un algoritmo opportunamente sviluppato;
- eseguire uno studio osservazionale multicentrico prospettico internazionale per valutare l'incidenza e la prevalenza di ILD in pazienti con AR.

GENERAL INTRODUCTION

Autoimmune rheumatic diseases are chronic inflammatory diseases with a major health impact worldwide. Rheumatic diseases (RDs) are among the oldest diseases recognized, but their classification is sometimes difficult due to unknown aetiology and heterogeneity in their clinical presentation. Rheumatoid arthritis (RA) and Giant Cell Arteritis (GCA) are two chronic RDs, accounting for a large percentage of disability.
Rheumatic disorders had the largest and rather stable impact across ages on the population level and affect a significant proportion of the population. The economic and social burden of these diseases worldwide is great, with various degrees of impact on quality of life, resulting in a significant number of physician visits, work disability, medication use, as well as lost productivity and increased costs of healthcare. However, their heterogeneity and the lack of any clear clinical correlation with pathology make inexact estimate of incidence and prevalence difficult. Hence, one of the challenges in studying RDs is deriving epidemiological data that can be used to better understand the underlying disease process and the risk factors that contribute to the initiation and progression of these diseases. Only with such understanding can significant progress be made in the diagnosis, treatment and management of patients. Moreover, although RDs affect people of all ages, the demographic structure of the population indicates an increasing tendency toward an older population along with an increasing prevalence of these diseases. Therefore, the need for a better understanding of RDs becomes critical for appropriate diagnosis, treatment and patient management, as their economic and social impact can be expected to increase as the population ages.

The prevalence of RDs in the general population ranges from 9.8% to 33.2%[1,2], and it has been estimated that 15-45% of primary care physician consultations are for musculoskeletal problems[3].
The prevalence of locomotor disability rises from 3.1%, in those aged less than 60 years, to almost 50% in those aged more than 75 years and, in older patients, almost one third has a significant rheumatologic problem[4]. A survey carried out in Italy showed a prevalence of 27% of chronic pain caused by a rheumatic disorder in the general adult population[5].
In Europe, chronic RDs affect around one-quarter of the population (more than 120 million of people). Many of them have developed some disability or impairment, which reduces their mobility, limits their independence and, sometimes, prevents them from continuing normal working and social lives. 72.9% of workers report exposure to risk factors of RDs during their working life. Being the most common cause of severe long-term pain and physical disability, RDs represent the main cause of early retirement and long-term sick leave in Europe, which significantly affects the productivity and costs of companies across Europe[1,6,7].
The burden of some of these conditions is increasing with ageing as well as with changes in lifestyle risk factors, such as obesity and reduced physical activity.
In Europe, rheumatic and musculoskeletal conditions represent an economic burden of estimated 240 billion Euros per year, with growing tendency due to demographic development and behavioural changes. The direct cost of RDs within the EU is estimated to be 2% of its gross domestic product. RDs elicit the highest costs to European health care and socioeconomic systems, by virtue of direct expenses for medicines, surgery, physiotherapy, hospitalisation and rehabilitative measures but also indirectly by production losses, sick leave and disability pensions.

Rheumatic and musculoskeletal diseases represent the most disabling group of diseases affecting the working population, explaining most of the early retirement from the labour market. This not only

imposes and enormous burden on the overall economy and on the health and social systems. It also affects the quality of life of dozens of millions of people throughout Europe, not only in terms of their mobility but also in terms of their economic well being. No other disease affects such a number of people, compels such a number of workers and employees to leave the labour market either temporarily or permanently, and represents a comparable cost for the overall economy as well as for the health and social systems. Moreover, their burden is going to increase dramatically in conjunction with the ageing of the population.

In this sense, rheumatic and musculoskeletal diseases represent a major challenge. Being the second cause of short-term sick leave (after respiratory diseases), one of the main causes of long-term sick leave, work disability and early retirement, rheumatic and musculoskeletal diseases represent a serious threat to the health of our economies and social systems.

Improving the knowledge of the causes, clinical behaviour and mechanisms of these diseases is crucial for developing innovative treatment and therapies in order to improve the physical conditions of millions of people, and therefore their employability. Although diagnosis and treatment of RDs have improved in recent years, much more investigation is needed on the causes and mechanisms affecting the development of these disorders, while more studies are needed to discover innovative treatments.

Early diagnosis of RMDs is pivotal to allow for the institution of effective therapies aiming at prevention of disability. Consequently, means to diagnose RDs at the earliest time points or even allowing to diagnose evolving disease should be a major focus point for future research activities.

Moreover, integrated research efforts should focus on: evaluating the incidence/prevalence and outcome of rheumatic diseases; the development of early diagnosis, prognostic diagnosis and prevention strategies; the development of curative therapies and different therapeutic strategies for dfferent clinical subtypes of the diseases. There is a strong necessity for more instruments in the area of epidemiologic research and innovative biometric approaches focusing on early determination of efficacy or inefficacy of therapies in patient groups and individual patients, pharmacovigilance, safety, costs and socio-economic impact of new cost intensive therapies. Pan-European networks are also required for joint clinical trials of novel therapies.

In conclusion, challenges in studying rheumatic diseases lie in achieving accurate epidemiological data and making efforts to obtain significant progress in terms of early diagnosis, treatment, and management of patients.

In this paper we will discuss the emerging problems and unmeet needs in some selected sectors of rheumatic diseases.

In the first section we will discuss new therapeutic approaches to GCA by analyzing the evidence based data available in litterature and adding the data of our phase 2 open-label clinical trial.

In the second section we will deal with the emerging problem of rheumatoid arthritis related-interstitial lung disease (RA-ILD). In particular, we will deepen the therapeutic dilemma. As some bDMARDs seem to be more safety in patients with RA-ILD, we decided to performe two ad hoc studies for tocilizumab and abatacept. We will also describe our real-life experience with antifibrotic drugs and tsDMARDs in RA-ILD patients through anedoctical case reports. Moreover, we will talk about the problem of early diagnosis of RA-ILD and we will present our proposal of a new software developed with this goal. Finally, we will introduce the epidemiological problem of RA-ILD and present the first data of our prospective study.

Section A

Treatment Of giant cell arteritis Patients with ultra-short glucocorticosteroids And tociliZumab, role of Imaging: the TOPAZIO study

INTRODUCTION

Giant-cell arteritis (GCA) is a granulomatous vasculitis affecting large-sized and medium-sized arteries, in particular temporal artery and the aorta with its large extracranial branches. It is the most common form of vasculitis in patients over 50-year-old in high-income countries and it is historically identified through cranic symptoms, according to the 1990 American College of Rheumatology (ACR) criteria [8].

GCA has a decreasing incidence with a north – south gradient. The reported rates for GCA are highest in northern European countries and in Minnesota (USA), which has a population of similar ethnic background, and are 20 or more per 100 000 people older than 50 years [9–11]. Rates of this disease are lower in Mediterranean countries [12,13] and lowest in Arabian and Asian countries [14,15]. The lowest prevalence was reported in Japan (1 • 47 per 100 000 population older than 50 years) [15]. The lifetime risk for GCA had been estimated as 1% for females and 0.5% for males in a North American predominantly white population, which is similar to the North and Middle European population [16]. Autopsy studies suggest that GCA might be more common than is clinically apparent [11]. The incidence of GCA has increased over the past 20 – 40 years, possibly because of raised awareness.

Common GCA symptoms include cranial symptoms such as jaw and tongue claudication, scalp tenderness and new onset headaches, visual symptoms like vision loss, amaurosis fugax and double vision, and systemic symptoms such as anorexia, fever, and weight loss [11,17]. Approximately half of individuals with GCA also have symptoms of polymyalgia rheumatica (PMR), namely morning stiffness lasting at least 45 minutes, hip pain or limited range of motion, and bilateral shoulder pain [11]. Large-vessel GCA can cause upper extremity claudication and asymmetric blood pressures [18]. GCA may lead to vision loss and blindness, stroke, arterial dissection, aortic aneurysm, and aortic rupture [13,19].

Suspicion of a diagnosis of GCA is based on careful history and clinical evaluation, in association with elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [20]. Although, computed tomography – positron emission tomography (CT-PET), magnetic resonance (MR) imaging (MRI), computed tomography (CT), angiography, and ultrasound may aid in GCA diagnosis [21]; however, a positive temporal artery biopsy is still the gold standard diagnostic test. It shows an inflammatory infiltrate with the presence of multinucleated giant cells between the media and intima layers in 50% of the cases and disruption of the internal elastic lamina, ultimately leading to partial or complete obstruction of local arterial blood flow. The 1990 American College of Rheumatology criteria for GCA classification (Table 1), which were originally created to help dfferentiate GCA from other vasculitides, may guide the diagnosis with sensitivity of 95.3% and specificity of 90.7% [8]. Studies are under way with the goal of developing and validating criteria for GCA diagnosis [22].

In recent decades, evidence of extracranic large-vessel involvement in GCA has emerged, especially after the development of new imaging tools, making it possible to distinguish extracranial forms affecting aorta and its large branches from typical cranial forms [11,23–25]. The concept of GCA as a clinical syndrome comprising cranial GCA, large-vessel-GCA (LV-GCA) and PMR has emerged and extracranial GCA is now included into the GCA-concept [17,19]. Clinical subtypes have been proposed according to preferential affection of specific vascular regions (Table 2), such as (1) cranial GCA, also associating cranial ischemic complications (visual loss and cerebrovascular events); (2) large-vessel GCA with occlusions in the subclavian or axillary vessels; (3) aortic GCA; and (4) GCA presenting as an intense systemic inflammatory syndrome with only systemic manifestations without typical cranial signs and symptoms and with non-stenosing vasculitis [11,17,26,27].

Ultrasound, PET, MRI and/or CT may be used for detection of mural inflammation and/or luminal changes in extracranial arteries to support the diagnosis of LV-GCA, even if ultrasound is of limited value for assessment of aortitis [19,21,28]. Experts in the field consider that in some cases imaging techniques may also be used to monitor response to treatment [29].

Patients with GCA have a 2- to 17-fold higher risk of aortic complications (dilation or dissection), occurring in 8% to 22% of patients during the first years of the disease, especially in the thoracic segment [19,30]. Previously Blockmans et al. showed that patients with aortitis revealed by FDG-PET at diagnosis were more likely to develop a late increase in the volume of the thoracic aorta. It has also been suggested that aortic inflammation may be associated with a higher risk of cardiovascular death and a higher relapse rate. Moreover, pathological evidence of active giant-cell aortitis has been reported in patients with long-term GCA undergoing aortic surgical procedures. Overall, there is probably a subset of patients who are more predisposed to large-vessel inflammation and subsequent aortic complications, and early identification of these patients remains a clinical challenge [31].

The precise etiology and pathogenesis of GCA are not well known. It has been proposed that GCA is the results of unknown environmental factors in individuals genetically predisposed.

Interleukin-6 (IL-6) has been shown to be involved in the pathophysiology of GCA [32], and it is elevated in both the serum and in inflamed vascular tissue [26,33]. IL-6 is expressed in the monocytes and produced in the inflamed arteries of patients with GCA [34,35].

Several reports have suggested that increased serum levels of IL-6 can be detected in patients with PMR and GCA [32]. The majority of these studies have found a significant increased of circulating IL-6 in patients with active disease, and a significant decrease of circulating IL-6 levels that correlate with remission of clinical symptoms after glucocorticosteroids (GCs) therapy [32]. Persistence of high serum IL-6 levels suggests the presence of disease activity in glucocorticoid-treated patients with GCA [36]. Moreover, another common finding is that the increase in IL-6 circulating levels in patients with active GCA was especially seen in patients with a strong inflammatory response, indicating that IL-6 may participate in the development of the acute-phase response in GCA [37].

Since the decrease of IL-6 in serum was associated with a reduction in disease activity, the blockade of IL-6 was considered to be a good therapeutic option in GCA [38,39].

Nowadays, tocilizumab (TCZ), a humanized monoclonal antibody against the interleukin-6 receptor [40], is the first drug approved in Europe for the treatment of GCA-patients, in combination with corticosteroids.

Table 1: 1990 criteria for the classification of giant-cell (temporal) arteritis

For purposes of classification, a patient with vasculitis is said to have giant-cell (cranial) arteritis if at least three of these five criteria are present.

Criteria		Score
Age at disease onset ⩾50 years	Development of symptoms or findings beginning at 50 years or older	1
New headache	New onset of or new type of localised pain in the head	1
Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries	1
Increased ESR	ESR ≥50 mm/h	1
Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis with a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells	1

Adapted from: Hunder GG 1990[8]; Salvarani 2008[11]; Betrains 2021[28]

Table 2: Different Subtypes of the Giant-Cell Arteritis Syndrome

Cranial GCA	***Cranial Arteritis***	Also associating cranial ischemic complications (visual loss and cerebrovascular events)
Extra-cranial GCA	***Large-Vessel Arteritis***	Large-vessel GCA with occlusions in the subclavian or axillary vessels
	Aortitis	Isolated aortic GCA
	Systemic Inflammatory Syndrome with Arteritis	GCA presenting as an intense systemic inflammatory syndrome with only systemic manifestations without typical cranial signs and symptoms and with non stenosing vasculitis
Polymyalgia Rheumatica	***Isolated PMR***	

References: Weyand 2003[26], Dejaco 2017[17,23]

Imaging and risk of complications in GCA

In the last years, imaging methods such as MR-Angiography (MRA), PET-CT and Color-Doppler sonography (CDS) have been used to diagnose large vessel vasculitis, and recruitment of patients for recent randomized controlled trials (RCTs) was based either on positive histological findings in biopsies of temporal arteries or on unambiguous signs of vessel wall inflammation [21,41]. Imaging has recently been acknowledged as at least equivalent to histology for confirming large-vessel vasculitis in the recommendations of scientific societies [21,41]. CDS is particularly useful in the evaluation of

temporal artery, axillary artery, subclavian artery, and carotid artery, but has limited access for the aorta and abdominal vessels. In these conditions, MRI/MRA and CT provide a higher diagnostic accuracy, as they provide an excellent overview particularly on extracranial arteries.

Positron emission tomography combined with computed tomography (PET/CT) with 18F-fluorodeoxyglucose (FDG) can be used to assess large-vessel inflammation and has demonstrated high sensitivity in detecting extracranial forms, even in patients without clinical symptoms or only with systemic manifestations [24].

Moreover, a study demostrating the role of PET to predict vascular complications was published by De Boysson et al. In this study a positive FDG-PET/CT was significantly associated with a higher risk of aortic complications [42]. Another study clearly demonstrated that patients with GCA and large vessel vasculitis are at increased risk of aortic dilatation compared with age and sex-matched controls. Significant predictors of aortic dilatation were male sex, hypertension and aortic FDG uptake grade 3 at first PET/CT [43]. These findings corroborate the concept that arterial FGD-uptake is a risk factor for subsequent anatomical complications in the same vessel segment, suggesting a prognostic role for PET.

On the contrary, it should be kept in mind that PET per se cannot adequately visualize the vessel wall; hence, morphological imaging techniques are always required to adequately monitor patients for vascular damage (stenosis, occlusion, dilatation, and aneurysm) over time.

A recent study compared MRA and PET for disease extent and disease activity in large-vessel vasculitis. This study demonstrated that these two imaging techniques are complementary. MRA better captures disease extent, while PET scan is better suited to assess vascular activity [44,45]. Taken together, PET and MRA could provide complementary information in the assessment of LVV.

The 2018 EULAR recommendation stated that in patients with LVV, MRA, CTA and/or CDS may be used for long-term monitoring of structural damage, particularly to detect stenosis, occlusion, dilatation and/or aneurysms. The frequency of screening as well as the imaging method applied should be decided on an individual basis. But It is still unknown how effective these methods are for assessing disease activity while patients are under treatment. The role of 18F-FDG PET/CT for monitoring disease activity and guide treatment strategies is yet to be determined. Even though arterial FDG uptake rapidly diminishes with the institution of glucocorticoid treatment, 18F-FDG PET/CT performed during the disease course shows persistent pathological arterial FDG uptake in the majority of patients, even in patients considered otherwise in clinical remission [46–48]. Remodelling or smouldering inflammation are thought to be possible explanations for this arterial metabolic activity. Serial PET scans during the disease course have reported a higher incidence of subsequent relapse among patients with high composite arterial PET scores (PETVAS) [49]. Also, PETVAS scores are inversely associated with preceding treatment changes [50]. These findings support the hypothesis that persistent FDG uptake may reflect smouldering inflammatory activity, but data are still too scarce to establish specific criteria to guide treatment decisions.

A fair agreement between MRI and PET findings in large arteries has been reported. However, the association between clinical assessed disease activity and imaging findings on body MRI seems to be inferior to PET [45,51]. Luminal abnormalities, such as stenosis, occlusion and aneurysm can also be evaluated by MRI and provide information regarding disease extent and damage [45]. The advantages of MRI are the potential assessment of both disease activity, damage and to some extent disease involvement.

Recent published data have shown persistent signs of inflammation on imaging techniques even in cases of full clinical and laboratoristic remission.

In the study by Grayson et al., FDG-PET can differentiate patients with clinically active LVV and other disease comparators such as atherosclerosis with a sensitivity=85% and specificity=83%. Of interest, FDG-PET scans were interpreted as active vasculitis in most patients with LVV in clinical remission (58%). In these patients, future clinical relapse was more common [52].
Moreover, Reichenbach et al have shown for the first time in the setting of a RCT on GCA that MRA signals do not disappear in a group of patients apparently in complete remission, defined by the complete absence of symptoms and normalization of ESR and CRP [53].

Treatment of GCA (particularly regarding tocilizumab)

Treatment of GCA is mainly based on long term use of GCs, although never formally tested in RCTs [54]. High-dose GCs have served as first-line treatment for GCA, but relapses may occur once steroids are tapered. The necessary duration of GC therapy is variable, and a sizeable proportion of patients with GCA may require long-term GC treatment, sometimes indefinitely [55]. Studies showed highly variable initial GC doses and wide differences in terms of duration of GC therapy, rate of GC discontinuation, and recurrences. At 2 years evaluation, 16% to 76% of patients could discontinue GC therapy, while 25-45% needed GC for longer than 3 years [56,57]. One study reported that as many as 25% of patients remained on GC therapy after 9 years of follow-up [57]. In patients who were able to discontinue GC, mean duration of therapy ranged from 16 months to 5.8 years [55]. Recurrences have been reported in 23% to 57% of patients, usually during the first 12-24 months after GC discontinuation [55].
Therefore, patients usually need long-term GC therapy, leading to numerous adverse effects, in particular diabetes, osteoporosis, hypertension, and infection [56]. In a population-based study, 86% of patients with GCA had adverse events including bone fractures (38%), avascular necrosis of the hip (2.5%), diabetes mellitus (9%), infections (31%), gastrointestinal bleeding (4%), cataract (41%), and hypertension (22%). Adverse events were related to the age and the cumulative dose of GC [56]. Recently, a nested case-control analysis was performed to examine the risk of GC-related serious adverse events in a UK population of patients with GCA. Patients in the highest daily prednisolone dose category (30mg/day) had an increased risk of diabetes, osteoporosis, fractures, glaucoma, serious infection, and death compared to those with lower average daily prednisolone doses (5mg/day) [58]. Treatment with alternate-day GCs administration has been proposed to reduce the risk of adverse reactions related to GCs, but is associated with a higher rate of treatment failure than is daily administration and is therefore not recommended [59].
Hence, several studies have been conducted to look at possible steroid-sparing agents (Table 3). However, the results of treatment trials with conventional immunosuppressive agents have overall been disappointing in that no reduction in GC-related side effects could be demonstrated [60,61]. Moreover, in 2014 a meta-analysis showed that the use of adjunct agents to GCs was not associated with improved outcome in GCA patients [61].
The advantage of the treatment effect of MTX is modest and belated, and biological agents like anti-TNF-α agents did not show any positive effect so far. Only abatacept has shown to slightly reduce the risk of relapse in patients with remission.
On the other side, TCZ recently showed an important glucocorticoid-sparing effect in two RCTs [62,63].

Table 3: Main drugs used in the management of giant cell arteritis

Gold standard therapy	
Glucocorticoids	
Tocilizumab	First drug approved to treat giant cell arteritis In newly diagnosed patients with severe comorbidities, as a first line treatment in association with GC
2nd Line	
Methotrexate	Glucocorticoid-sparing agent (moderate efficacy)
Tocilizumab	In relapsing patients
Leflunomide?	
3rd Line	
Tocilizumab	
Abatacept?	
Under research	
Abatacept	
Ustekinumab	
Sarilumab and other anti-IL6	
Jak-inhibitors	
IFNgamma-inhibitors	

References: Schirmer 2018[54], Gonzalez-Gay 2019[64]

METHOTREXATE (MTX)

MTX is the conventional immunosuppressive drug most commonly used for the management of refractory GCA [41].

Three RCTs have assessed the efficacy of methotrexate (MTX) in recent-onset GCA, with conflicting results [61,65 - 67]. The first included 21 patients with GCA treated with high-dose glucocorticoids along with MTX (n = 12) or placebo (n = 9) [65]. No significant differences was found between the MTX and the placebo groups regarding the cumulative GC dose, number of weeks to achieve GC discontinuation, weeks required to taper prednisone to less than 10 mg/day and bone mineral density in lumbar spine or hip at one year [65].

A second trial conducted in a single center included 50 patients with GCA receiving a single dose of 10 mg/ week of oral MTX or placebo. The initial dose of prednisone was 60 mg/day, which was gradually tapered [68]. MTX use was associated with a significant decrease in the frequency of relapses of GCA [68]. This was the first trial showing that treatment with MTX and GC is safer and more effective than GC therapy alone to reduce the frequency of relapses of GCA.

On the contrary, in the third multicenter randomized clinical trial the use of MTX along with glucocorticoids did not yield benefits in GCA patients [69]. The study enrolled 98 patients treated wih prednisone 1 mg/kg/day (maximum 60 mg/day) along with 0.15 mg/kg/week MTX (increased to 0.25 mg/ kg/week, for a maximum weekly dose of 15 mg) or placebo. The median dose of MTX was 15 mg/week. The frequency of treatment failure after 12 months was similar in both group. No differences between MTX and placebo groups in the cumulative glucocorticoid dose were observed [69].

A meta-analysis of data from the three above RCTs reported that adjunctive MTX treatment in doses of 7.5 – 15 mg per week had a modest role to reduced the frequency of relapses and the cumulative exposure to GC. However, the advantage of the treatment effect as adjunctive therapy to glucocorticoids of MTX compared with placebo fully appeared only after 24 – 36 weeks, and there was no difference between groups in the occurrence of adverse events [70].
Higher doses of MTX (20 – 25 mg per week) have not been adequately studied.
In clinical practice, MTX can be considered in relapsing disease or in patients who are regarded at high risk for developing adverse events related to long-term GC exposure [41].

LEFLUNOMIDE (LEF)
Some studies indicate the steroid-sparing effect of leflunomide in GCA [71,72]. However, the experience with leflunomide in GCA is limited.
A retrospective study recently compared LEF and MTX in the treatment of GCA. Patients with GCA treated with LEF achieved remission earlier than those treated with MTX, with a significant difference in patients with a higher baseline disease activity (prednisolone dose > 7.5 mg at the start of treatment with LEF and MTX): LEF 49.4 weeks and MTX 104.9 weeks. No difference in the steroidsparing effect was found [73].

TNF-alpha BLOCKERS
Three RCTs investigated the efficacy of anti-tumor necrosis factor (TNF)-α agents in GCA. Infliximab and adalimumab were ineffective in new-onset GCA [74,75], while the pilot RCT evaluating etanercept in patients with longstanding GCA was underpowered to draw any accurate conclusion [32]. In another study, adalimumab did not show efficacy to reach remission and patients had more infections [75]. Taken together, these results strongly suggest that TNF-α blockers are ineffective or at best have only a marginal beneficial effect in new-onset GCA, and their use in new-onset GCA is therefore not recommended [76,77].
The role of TNF-α inhibitors in refractory GCA needs further investigations, in particular in patients with relapsing disease.

ABATACEPT (ABA)
The recombinantIg-CTLA-4 molecule abatacept is a selective T cells costimulation modulator able to bind with high-affinity CD80/CD86 molecules blocking its interaction with CD28, leading to a decrease of T cell activation [78].
A recent RCT evaluated the safety and efficacy of abatacept to maintain remission in patients with newly-diagnosed or relapsing GCA [79]. All patients were treated with prednisone and abatacept. At week 12, 41 patients who had achieved remission were blindly randomized to receive either monthly placebo intravenous infusions (n=21) or monthly intravenous abatacept (n=20), along with a standardized tapering prednisone dose until discontinuation at week 28. The median duration of remission was significantly longer in abatacept-treated patients (9.9 months versus 3.9 months in those who received intravenous placebo). The primary outcome of the study, relapse-free survival at 12 months, was also significantly more common in patients treated with intravenous abatacept (48%) than in those treated with placebo (31%). There were no differences in side effects between abatacept and placebo-treated groups [79].

Further trials encompassing larger number of patients are needed to to assess the efficacy of abatacept for induction of remission in GCA ant to confirm whether abatacept is useful as adjunctive treatment to reduce relapses or as a glucocorticoid‐sparing agent in patients with GCA.

USTEKINUMAB

Ustekinumab is a monoclonal antibody that acts targeting both IL12 and IL-23 pathways.

The safety and efficacy of ustekinumab in patients with refractory GCA have been evaluated in an open-label proof-of-concept study with promising results [80]. Ustekinumab use allowed to reduce the glucocorticoid dose. Also, glucocorticoids were successfully discontinued in 3 patients and in 8 patients ustekinumab allowed the discontinuation of the baseline immunosuppressive agents. Although there were not relapses while the patients were undergoing ustekinumab therapy, relapses were common following ustekinumab discontinuation [80].

On the contrary, another open label study did not confirmed the safety and efficacy of ustekinumab in patients with active new-onset or relapsing GCA [81]. In fact, patients' enrollment was closed prematurely becouse of high rate of treatment failure. Only 3/10 (23%) patients achieved the primary endpoint, while 7 relapsed after a mean period of 23 weeks. One serious adverse event occurred [81].

JAK KINASE INHIBITORS

Baricitinib is an inhibitor of JAK1 and JAK2 that inhibits Th17 (IL-6, IL23) and Th1 (IL-12, IFN-γ) pathways. A phase-II single-institution, open-label pilot study recently evaluated the safety and effectiveness of baricitinib with a tiered glucocorticoid (GC) entry and accelerated taper in patients with relapsing GCA [82]. Of 14 patients who completed the 52 weeks of follow-up, only 1 (7%) patient relapsed. The remaining 13 patients achieved steroid discontinuation and remained in disease remission during the 52-week study duration. In this proof-of-concept study, baricitinib at 4 mg/day was well tolerated and discontinuation of GC was allowed in most patients with relapsing GCA [82].

IL1 BLOCKERS

Anakinra, a recombinant and slightly modified version of the human IL-1 receptor antagonist, was used at a dose of 100 mg/day in three patients with refractory GCA [83], with favorable results. A phase-3 study is intended to be performed to assess its efficacy in GCA (NCT02902731); the estimated study completion date is on March 2022. Gevokizumab, a recombinant humanized anti-IL-1β antibody, is also under investigation for the management of GCA (European Clinical Trials Database Identifier 2013‐002778‐38).

TOCILIZUMAB (TCZ)

Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor [40]. TCZ binds to both soluble and membrane-bound IL-6R and inhibits IL-6R-mediated signaling, and is currently the only approved biological agent for the treatment of GCA patients in addition to rapid tapering of GCs. TCZ was initially approved in Japan in 2005 as an orphan drug for the treatment of Castleman's disease [84]. TCZ is now recommended as monotherapy or in combination with disease-modifying antirheumatic drugs (DMARDs) in adults with moderate to severe active rheumatoid arthritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, or cytokine release syndrome (EMA 2008).

Tocilizumab was approved in Europe in September 2017 and in the US by the Food and Drug Administration in May 2017 for GCA, mainly as a steroid-sparing agent. It is reccomended as an

adjunctive therapy in combination with ongoing reduction of corticosteroids in selected patients with GCA: refractory or relapsing disease, presence or an increased risk of GC related adverse effects or complications [41]. TCZ is not recommended as monotherapy without GCs for treatment of acute relapses.

The safety profile of TCZ in GCA appears similar to placebo with comparable numbers of adverse events per 100 patient years. Immunogenicity of TCZ is low, and efficacy of TCZ in RA patients was independent from the existence of antidrug antibodies.

Single cases, small series and small retrospective studies showed that TCZ was effective in both newly diagnosed and relapsing patients with GCA [85–87].

Two randomized placebo-controlled trials (RCTs) confirmed the efficacy and safety of TCZ both for induction and maintenance of remission in patients with new-onset and relapsing GCA (Table 4, p. 23) [62,63]. In these studies, both arms received a predetermined corticosteroid taper and were followed up for 52 weeks. The addition of TCZ to prednisone also led to a reduction in the cumulative prednisone doses required to control GCA, with a glucocorticoid-sparing effect of TCZ of at least 50%. Moreover, additional data showed that a 52-week treatment with TCZ induces a lasting remission that persists in half of the patients after treatment stop [88].

Nevertheless, the glucocorticoid exposure times were still long, raising the question whether glucocorticoid exposure could be reduced further. In addition, neither of these studies could determine whether TCZ had a potential contributory role in inducing remission.

Recently, a systematic review indicates that TCZ therapy may be beneficial in terms of proportion of participants with sustained remission, relapse free survival, and the need for escape therapy [89]. While the evidence was of moderate certainty, only these two studies were included in the review, suggesting that further research is required to corroborate these findings [89]. Authors indicate that compared to glucocorticoids, TCZ therapy in people with GCA may be beneficial in terms of proportion of participants with sustained remission, relapsefree survival, lower cumulative median dose of glucocorticoids, as well as the need for no escape therapy. However, these studies found no clear benefit of TCZ therapy compared with glucocorticoids in quality of life. Although the most frequently occurring adverse event of TCZ was infection, and the frequency of adverse events was similar among participants in both the TCZ and placebo groups, the paucity of data rendered it impossible to rule out significant adverse events of TCZ [89].

Last year, efficacy and safety of TCZ monoterapy for the treatment of GCA was evaluated in two open-lable trial, with promising results (Table 5, p. 24) [90].

Finally, noteworthy, a recent real-life observational multicenter study reported that the addition of immunosuppressive drugs to TCZ in refractory GCA seems to allow a higher rate of prolonged remission, even in patients with a longer GCA duration, more extra-cranial LVV involvement, and higher acute-phase reactants [91].

Phase II study (Villiger 2016 [62])

The first single center, phase II, randomized, double-blind, placebo-controlled trial was performed in Switzerland in 2016. It evaluated the intravenous effects of TCZ in GCA patients with new-onset or relapsing disease [62]. The study included 23 newly diagnosed and 7 with relapsing patients with GCA who were randomized to receive intravenous TCZ at a dose of 8 mg/kg every 4 weeks plus prednisolone (n = 20 patients) or placebo infusion every 4 weeks plus prednisolone (n = 10), over 1 year, together with oral prednisolone tapered down from 1 mg/kg per day to 0 mg. As primary outcome, 17 (85%) of 20 patients in the TCZ group versus 4 (40%) of 10 patients in the placebo group

achieved complete remission at a prednisolone dose of 0 • 1 mg/kg per day at week 12 (risk difference 45%, 95% CI 11 – 79; p=0 • 0301).
Rapid glucocorticoid tapering followed by discontinuation after 36 weeks from the onset of therapy was achieved in TCZ -treated patients. The cumulative prednisolone dose at 52 weeks was also significantly lower in the TCZ group (43 mg/kg) than in the placebo group (110 mg/kg).
Besides, relapse-free survival was achieved in 85% of patients in the TCZ group and 20 % in the placebo group by week 52 (risk difference 65 %, 95 % CI 36 – 94; p=0 • 0010), and the mean survival-time difference to stop GCs was 12 weeks in favor of TCZ (95 % CI 7 – 17; p<0 • 0001).
Seven (35%) patients from the TCZ -treated group and 5 (50%) from the placebo group had serious adverse events.
This trial was the first to show the efficacy of TCZ in the induction of complete remission, with favorable effects on reduced cumulative doses of GCs.
As a limitation, the use of CRP along with the clinical response as a combined final endpoint could have overestimated the actual number of remissions, because TCZ is very effective to decrease the levels of CRP. Moreover, treatment in the control group was not consistent with international standards of GCA care, which has also overestimated the efficacy of TCZ in this trial.

Phase III study (Stone 2017 [63])
The GiACTA-trial is an international randomized, double-blind, placebocontrolled, phase 3 trial designed to assess if TCZ led to higher rates of sustained glucocorticoid-free remission of GCA than placebo through a period of 52 weeks [63]. The GiACTA trial included 251 patients from 14 countries and 76 centers from Europe and North America. Newly diagnosed (n = 119) and relapsing (n = 132) GCA patients were randomly assigned to four treatment arms: a weekly dose of 162 mg of subcutaneous TCZ plus a 26-week prednisone taper (n = 100), a dose of 162 mg of subcutaneous TCZ given every other week along with a 26-week prednisone taper (n = 50), a third group of weekly placebo-treated patients along with a 26-week prednisone taper (n = 50), and a fourth group of weekly placebotreated plus a 52-week prednisone taper (n = 51) [92].
As primary and key secondary outcomes of this trial, 56% of the patients receiving subcutaneous TCZ every week and 53% of those treated with subcutaneous TCZ every other week achieved remission, only 14% and 18% of the patients treated with placebo plus 26-week prednisone taper or 52-week prednisone taper reached sustained GC-free remission at week 52 (P<0.001). Also, TCZ -treated patients had lower frequency of relapses of the disease (23% and 26% in those treated with TCZ every week or every other week) than those included in the 26 and 52- week placebo arms (68% and 49%, respectively). Patients undergoing TCZ therapy had longer duration of remission free of relapses than those treated with placebo.
Moreover, TCZ use was associated with a powerful glucocorticoid-sparing effect. The cumulative median prednisone dose over the 52-week period was 1862 mg in each TCZ group, 3296 mg in the placebo group with the 26-week taper (P<0.001 for both comparisons) and 3818 mg in the placebo group with the 52-week taper (P<0.001 for both comparisons). This effect was stronger in the patients who had suffered relapses before randomization.
Finally, TCZ-treated patients had less serious adverse events than those treated with placebo.
Nevertheless, the GiACTA trial has several limitations [64]. For example, half of the patients had short disease duration, remission was defined considering the normalization of the CRP, and the scarce information on the effect of TCZ on visual loss.

This large international trial showed a sustained GC-free remission in patients undergoing TCZ with less need for GCs both in relapsing GCA as well as new-onset patients.
In 2021 the GiACTA Part 2 trial was conducted to analyze TCZ long-term benefits in new-onset vs relapsing disease and the value of weekly vs every-other-week dosing [93]. 215 patients entered in part 2 (open-label). They were treated at investigator discretion for 104 weeks and evaluated according to their original treatment assignments and outcomes beyond 52 weeks were assessed. At baseline, 48% had new-onset disease and 52% had relapsing disease. In patients with new-onset and relapsing disease, median time to first flare in the TCZ QW group was 577 and 575 days, respectively, vs 479 and 428 days with TCZ Q2W and 179 and 224 days with placebo; median cumulative glucocorticoid dose was 3068 mg and 2191 mg with TCZ QW, 4080 mg and 2353 mg with TCZ Q2W, and 4639 mg and 6178 mg with placebo.
This analysis confirmed that TCZ QW delays the time to flare and reduces cumulative glucocorticoid dose in patients with relapsing GCA and new-onset GCA. These data support initiating TCZ QW as part of first-line therapy in all patients with active GCA [93].

Tocilizumab monotherapy in GCA: The GUSTO Trial ([90])
To date, few cases have been published documenting patients with GCA effectively treated with TCZ monotherapy [85,94].
In 2020 an open-label japanese study tested TCZ monotherapy in 8 patients with newly diagnosed GCA [95]. Four of the patients had normal cranial arteries, as assessed by ultrasound, and none exhibited eye involvement at baseline. TCZ monotherapy showed a high response rate for newly diagnosed LVV patients, and the majority of patients did not relapse for 1 year after TCZ cessation.
More recently, the GUSTO trial aimed to evaluate the efficacy and safety of TCZ monotherapy after ultra-short-term glucocorticoid treatment in patients with new-onset giant cell arteritis.
This single-arm, single-centre, open-label, trial enrolled 18 patients aged older than 50 years newly diagnosed with giant cell arteritis (within 4 weeks before the screening visit) satisfying the ACR criteria or with large vessel vasculitis-associated polymyalgia rheumatica. The participants received 500 mg methylprednisolone intravenously for 3 consecutive days. Thereafter, glucocorticoid treatment was discontinued and a single infusion of TCZ (8 mg/kg bodyweight) was administered intravenously, followed by weekly subcutaneous TCZ injections (162 mg) until week 52. The primary endpoint was the proportion of patients who had remission within 31 days and showed no relapse at week 24. The secondary endpoints were the proportion of patients with complete relapse-free remission of disease at weeks 24 and 52, and time to first remission, first relapse (after induction of remission), and first partial remission.
The GUSTO trial showed that a 3-day glucocorticoid-treatment followed by TCZ monotherapy is effective in inducing remission in 14 of 18 patients (78%) with new-onset giant cell arteritis. Overall, three of 18 patients did not respond to treatment and two of 18 discontinued the study due to an adverse event.
The primary endpoint was not met, remission was achieved after a mean of 11 • 1 weeks, which is longer than expected for standard glucocorticoid treatment. This delayed response strongly argues for a true remission-inducing effect of TCZ. The secondary endpoint of sustained remission at week 24 was achieved by 13 (72%) of 18 patients. Remarkably, no patient relapsed between weeks 24 and 52 of TCZ monotherapy.
The study design provides a glimpse of the respective roles of glucocorticoid and TCZ during the initial phase of treatment. The time to remission was longer than anticipated in the protocol (ie, 11

weeks instead of 4 weeks). Tocilizumab was effective in maintaining remission in all responding patients up to week 52. Collectively, the data support a remission-inducing effect of TCZ after a 3-day glucocorticoid pulse therapy and suggest that a shorter glucocorticoid exposure can be used to reduce glucocorticoid-related side-effects.

The main weaknesses of this study are the small sample size and the inclusion of patients from a single study site. The study strengths include detailed monitoring including repeated ophthalmological assessments, the high-risk profiles of patients with ischaemic symptoms, and the homogeneous cohort of patients with a first diagnosis of giant cell arteritis and with very short-term glucocorticoid intake before randomisation.

Notably, one patient underwent vision loss 15 days after the last glucocorticoid pulse therapy. In this patient, it appears probable that the ultra-short duration of glucocorticoid treatment contributed to the vision loss. This clinical event may suggest that the glucocorticoid regimen used in this study was too short. However, it is likely that pre-existing advanced structural changes in the vasculature were at least partly causative of AION of the patient.

Table 4: RCTs for tocilizumab (in association with GCs) in GCA

	Study design	N. pt	Duration	Therapeutic regimen	Results
Villiger 2016[62]	Phase II single center (Switzerland)	Tot 30 New onset=23 Relapsing=7	52 wk	**TCZ + GCs:** 1) i.v. TCZ (8 mg/kg every 4 weeks) + oral GCs (n=20) 2) placebo + oral GCs (n=10)	85% of patients given TCZ and 40% of patients given placebo reached complete remission by week 12 (p=0·0301). Relapse-free survival was achieved in 85% patients in the TCZ group and 20% in the placebo group by week 52 (p=0·0010). Cumulative prednisolone dose of 43 mg/kg in the TCZ group versus 110 mg/kg in the placebo group (p=0·0005) after 52 weeks.
Stone 2017[63] ***GiACTA Trial***	Phase III multicenter (76 sites across the USA, Canada, and Europe)	Tot 251 New onset=119 Relapsing=132	52 wk	**TCZ + GCs**: 1) s.c. TCZ 162 mg weekly + 26-wk pred taper (n = 100) 2) s.c. TCZ 162 mg Q2W + 26-	Sustained remission at week 52 occurred in 56% of the patients treated with TCZ weekly and in 53% of those treated with TCZ every other week, as compared with 14% of those in the placebo group that underwent

				wk pred taper (n = 50) 3) s.c. Pla + 26-wk pred taper (n = 50) 4) s.c. Pla + 52-wk pred taper (n = 51)	the 26-week prednisone taper and 18% of those in the placebo group that underwent the 52-week prednisone taper (P<0.001 for the comparisons of either active treatment with placebo). The cumulative median prednisone dose over the 52-week period was 1862 mg in each TCZ group, as compared with 3296 mg in the placebo group that underwent the 26-week taper (P<0.001 for both comparisons) and 3818 mg in the placebo group that underwent the 52-week taper (P<0.001 for both comparisons).

Table 5: Trial for tocilizumab monotherapy in GCA

	Type	N. pt	Duration	Therapeutic regimen	Results
Saito 2020[95]	Prospective, single center (Japan), open-label study	Tot 8	52 wk	i.v. TCZ (8 mg/kg) monotherapy every 2 weeks for 2 months and then every 4 weeks for 10 months	Complete and partial responses rates were 75% and 25% at week 24 and week 52. Five GCA patients remained disease-free for 1 year after therapy.
Christ 2021[90] ***GUSTO Trial***	Phase II, single-arm, single center (Switzerland), open-label, proof-of-concept trial	18 new onset GCA	52 wk	500 mg i.v. methylprednisolone for 3 consecutive days. Then, a single infusion of i.v. TCZ (8 mg/kg),	78% of patients had remission within 24 weeks (mean time to first remission 11·1 weeks, 95% CI 8·3–13·9) and 13 of 18 showed no relapses up to 52 weeks (72%, 47–90). Mean time to

	followed by weekly subcutaneous TCZ injections (162 mg) until week 52.	first partial remission was 6·2 [3·7–8·7] weeks.

OTHER IL6-BLOCKERS

Other anti-IL-6 monoclonal antibodies, different from TCZ, are currently under investigation for the treatment of GCA. Sarilumab is actually under study for its potential use and safety in GCA (ClinicalTrials.gov Identifier: NCT03600805), while a phase-3 randomized, controlled, double-blind study using sirukumab (ClinicalTrials.gov Identifier: NCT02531633) was initiated but it was cancelled.

In this background, an adequate follow-up and treatment to achieve and maintain remission in GCA are a challenge. The management of GCA should aim to decrease disease's complications and therapeutic side effects, in order to improve quality of life and decrease mortality and high utilization of healthcare resources.

Moreover, the full glucocorticoid-sparing potential of TCZ is currently unknown, as it remains unclear to what extent remission was induced and maintained by TCZ (vs glucocorticoids) in the published trials.

Additionally, it is still unknown how effective are imaging techniques for assessing disease activity while patients are under treatment.

Therefore, we designed the Treatment Of giant cell arteritis Patients with ultra-short glucocorticosteroids And tociliZumab role of Imaging (TOPAZIO) study.

Aim of the study

The aim of this phase 2 clinical trial is to evaluate effectiveness and safety of TCZ monotherapy and the clinical and functional/morphological imaging variations in a series of patients with GCA treated with ultra-short glucocorticosteroids and TCZ.

PATIENTS AND METHODS

Study design and participants

This phase 2, investigator-initiated, single-arm, single center, open-label clinical trial enrolled patients aged older than 50 years with active large vessel giant cell arteritis (LV-GCA) at the Department of Rheumatology, Azienda USL-IRCCS di Reggio Emilia, Italy. The study was approved by the Reggio Emilia Provincial Ethics Committee and registered in ClinicalTrials.gov (NCT05394909). All

patients provided written informed consent prior to enrolment. The study was done in accordance with the Declaration of Helsinki.
The diagnosis of LV-GCA was based on evidence of large vessel vasculitis (LVV) on computed tomographic (CT) or magnetic resonance (MR) angiography, or positron-emission tomography/computed tomography (PET/CT) in patients older than 50 years.
We included patients with active newly diagnosed or relapsing LV-GCA according to the following inclusion criteria:
PET/CT showing vascular FDG uptake ≥2 in at least one vascular district and at least one among
ESR >40 mm/h or CRP >10 mg/l
Cranial or systemic symptoms of GCA or symptoms of polymyalgia rheumatica (PMR)
Patients taking more than 10 mg/day of prednisone (or equivalent) for more than 10 consecutive days in the previous three months were excluded. Other exclusion criteria included previous treatment with tocilizumab, other rheumatic diseases (except for chondrocalcinosis and gout), active infection, previous complicated diverticulitis, and substantial cardiac, pulmonary, or hepatic disease.

Procedures

Patients received 500 mg per day methylprednisolone intravenously for 3 consecutive days. Thereafter, glucocorticoid treatment was discontinued. Weekly subcutaneous TCZ injections (162 mg) from day 3 until week 52. Visits took place on days 0, 3, and 31 and every 12 weeks thereafter. In case of relapse, persistent, or worsening of GCA or PMR symptoms, glucocorticoid treatment was started on investigator discretion on the basis of severity of manifestations.
PET/CT was performed in all patients at baseline and at week 24 and 52. Scans will be performed using a hybrid PET/CT device (Discovery MI,GE) and acquiring images with a standardized protocol (2 minutes of emission scan/bed; from the apex of the skull to knees). Free breathing, low dose, and non-contrast enhanced helical CT will be carried out for PET coregistration and CT attenuation correction. All subjects will be in fasting state at least 6h before ^{18}F-FDG injection (37 MBq of 18F-FDG per 10 kg of patient weight). Blood glucose levels before tracer injection and mean time from injection to acquisition will be < 200 mg/dl and 60 minutes, respectively. Transverse, coronal, and sagittal images will be obtained using standard company reconstruction algorithms.

All FDG-PET/CT examinations will be performed to assess of 18F-FDG uptake in 4 segments of the aorta (ascending, arch, descending thoracic, and abdominal) and in 11 branch arteries (innominate, carotids, subclavians, axillaries, iliacs, and femorals). Scans were evaluated by one nuclear medicine specialist using the visual 0 to 3 vascular to liver FDG uptake grading scale: 0 = no uptake (≤ mediastinum); 1 = low-grade uptake (< liver); 2 = intermediate-grade uptake (= liver), 3 = high-grade uptake (> liver). Scans showing grade 2 and 3 FDG uptake were classified as active. Additionally, the 0 to 3 visual scale of four segments of the aorta (ascending, arch, descending thoracic and abdominal) and five branch arteries (carotids, brachiocephalic trunk, subclavian/axillary arteries) was used to calculate a score of 0 to 27 points (positron emission tomography vascular activity score, PETVAS[49]). PETVAS was calculated by one nuclear medicine specialist.
All PET/CT scans were also independently evaluated by a radiologist (non-contrast enhanced CT-attenuation correction study), who measured the diameter of the aorta in a transverse plane at four different levels (ascending aorta, descending thoracic aorta, suprarenal and infrarenal abdominal aorta). Aortic dilatation was defined by a diameter >40 mm in the ascending aorta, ≥40 mm in the

thoracic descending aorta and ≥30 mm in the abdominal aorta. Any change of ≥5mm on serial CT was considered significant progression of vascular damage.
MR was performed in all patients at baseline and at week 24 and 52. All MRA examinations was performed with a 1.5 system of very similar technical standards (Ingenia Omega HP - R5).
To quantify the inflammation of the vessel wall, a cerebral vasculitis score from 0 to 3 will be used to identify:
0 = no mural thickening (maximal vessel wall thickness <2.3 mm), no enhancement
1 = no thickening, slight mural enhancement
2 = mural thickening (>2.3 mm), significant mural enhancement
3 = strong thickening (>3 mm), strong mural and perivascular enhancement
Scores 2 and 3 were indicative of active mural inflammation

Outcomes

Primary outcome
The primary endpoints were the variation of PETVAS at week 24 and 52 compared with baseline and the proportion of patients with relapse-free remission at week 24 and 52.
The primary endpoints were the proportion of patients with relapse-free remission at week 24 and 52; and the variation of PETVAS at week 24 and 52 compared with baseline (ie, 8% less than the mean PETVAS reduction in the glucocorticoid arm of the RIGA study[96]).
Secondary outcome
Secondary endpoint was the proportion of patients with new aortic dilatation at week 24 and 52.
Definitions
Remission was defined as the absence of any clinical symptoms directly attributable to GCA, including normalization of CRP and ESR, and absence of new/worsened vascular damage at CT.
Relapse was determined by the investigator and defined as one or more of the following: the recurrence of signs or symptoms of GCA or PMR; CRP values greater than 10 mg/L, or ESR values greater than 40 mm/h if these were considered by the investigator to be due to GCA; evidence of worsening vascular FDG uptake at PET/CT. The definition of relapse included the necessity for introduction of prednisone.
Relapse-free remission was defined as the presence of remission without any relapse.
Responders will be classified the patients who will not develop relapse, as previously defined, during therapy or follow up period and complete the assigned therapeutic protocol.
Non-Responders will be classified the patients who will develop relapses during therapy or follow-up phase and patients with imaging interpretation of 'active' vasculitis by MRA and/or PET/CT.

Statistical analysis

Simon's minimax two-stage design was used. The null hypothesis that the true response rate would be 40% (ie, the placebo response proportion in the phase 2 study) was tested against a one-sided alternative. In the first stage, we planned to recruit 12 patients and stop the study for futility if there were six or fewer responders. Otherwise, the study was planned to recruit a total of 18 patients (with more than ten responders needed to reject the null hypothesis). This design yields a type I error rate of 5% and power of 90% when the true response rate is 75% (ie, 10% less than the TCZ arm in the

phase 2 study). The primary outcome was tested using a one-sided exact binomial p value with 40% as reference. The primary and binary secondary outcomes are presented as percentage with 95% binomial exact CIs. Patients who discontinued the study before or at week 20 were imputed as non-responders to treatment. Time to first relapse was analysed using the restricted mean survival time truncated at 52 weeks with 95% CIs. Drop-outs were censored at the timepoint of drop-out.
PETVAS at week 24 and 52 was compared with baseline value using the Wilcoxon test for paired sample. The binary primary (proportion of patients with relapse-free remission at week 24 and 52) and secondary outcome are presented as percentage with 95% binomial exact confidence intervals (Cis). Patients who discontinued the study before or at week 20 were imputed as non-responders to treatment.

RESULTS

From March 2019 to November 2020, 20 patients were screened for eligibility, and 18 patients were included. Nine patients (50%) had newly diagnosed LV-GCA, and the remaining 9 (50%) had relapsing disease. All 18 patients received the three glucocorticoid infusions, and 14 of 18 completed the follow-up until week 52. A total of 4 patients dropped out before week 52 due to non-responsiveness (two out of four), relapse (one of four), and withdrew informed consent (one of four). One patient discontinued TCZ at week 44 because of adverse event and was followed-up until week 52 without therapy.
Thirteen (72%) of 18 patients were female and the mean (SD) age was 68.5 (SD 10.6) years. Overall, 15 (83%) had symptoms of active vasculitis, namely: 11 (61%) had systemic symptoms, 7 (39%) had polymyalgia rheumatica symptoms, 4 (22%) had signs or symptoms of vascular insufficiency, 1 (6%) had cranial symptoms and none had visual symptoms. The mean (SD) ESR was 56 (41) mm/1h, and the mean CRP was 35 (36) mg/L at baseline (day 0).
Baseline characteristics of the study cohort are summarized in table 6, while imaging and laboratory parameter changes comparing weeks 0, 24 and 52 are shown in table 7a and 7b.

PET/CT and aortic CT data

All 18 baseline PET/CT scans were classified as active by nuclear medicine physician; mean (SD) PETVAS was 17.3 (5.1). At baseline CT, mean (DS) diameter of the aorta were 39.1 (4.4), 31.1 (5.1), 26.6 (4.5) and 21.7 (3.5) mm respectively for the ascending, descending thoracic, suprarenal and infrarenal abdominal aorta. Eight patients had evidence of aortic dilatation (4 of the ascending aorta, 2 of the abdominal aorta, 1 of the ascending and abdominal aorta, and 1 involving the ascending, descending thoracic and abdominal aorta).

Primary and secondary endpoints

Compared to baseline value, a significant reduction of PETVAS was observed at week 24 and 52. Thirteen of 18 patients (72%, 95% CI 47-90) achieved relapse-free remission at week 24, and 10 (56%, 95% CI 31-78) maintained relapse-free remission until week 52. At week 24 and 52 no patient showed new aortic dilatation. However, 3 dilated patients showed significant increase of aortic diameter (≥5 mm) at week 24, and one further dilated patient showed significant increase of aortic diameter at week 52.

Two (11%) of 18 patients did not respond to treatment, and rescue glucocorticoid treatment was necessary. Of these two patients, one showed persistent systemic symptoms (glucocorticoid treatment was started on week 8) and one showed persistent polymyalgia rheumatica (glucocorticoid treatment was started on week 15). Two patients (11%) relapsed (1 on week 24 and 1 on week 52), and glucocorticoid treatment was started. Mean time to relapse was 38 (95% CI 11-65) weeks. One patient who achieved relapse-free remission at week 24, withdrew informed consent on week 29. Finally, one patient discontinued TCZ at week 44 because of adverse events (cutaneous rash) and maintained relapse-free remission without therapy until week 52.

Adverse events

Up to week 52, adverse events occurred in 9 patients. Neutropenia of less than 1.5 × 109/L occurred in 1 of 18 patients and of less than 1.0×109/L in 1 patient (TCZ was withheld in this patient until neutrophil count increased to 1.0×109/L or more). Tocilizumab was administered every other week in one patient due to recurring neutropenia. Hypercholesterolemia occurred in 2 of 18 patients and required specific therapy. Three patients had coutaneous rash. Two of 18 patients had infectious events, namely COVID19 in 2 patients and a dental abscess in the other one.

Of note, 1 patient underwent aortic aneurysm surgical repair at week 44.

No patients had diverticulitis or a rise in transaminases more than five times the upper limit of normal. Methylprednisolone pulse therapy was well tolerated, and no psychosis, gastrointestinal bleeding, or neuropsychiatric problems occurred.

Table 6: Baseline characteristics of the study cohort

Study population (n=18)	
Age, years	68.5 (10.6)
Sex	
Female	13 (72%)
Male	5 (28%)
Ethnic origin	
White	18 (100%)
Newly-diagnosed LV-GCA	9 (50%)
Relapsing LV-GCA	9 (50%)
Glucocorticoid pretreatment	13 (72%)
CRP, mg/L	35 (36)
ESR, mm/h	56 (41)
Symptoms of active vasculitis	15 (83%)
Systemic symptoms	11 (61%)
Polymyalgia rheumatica symptoms	7 (39%)
Signs or symptoms of vascular insufficiency	4 (22%)
Cranial symptoms	1 (6%)
Visual symptoms	0 (0%)
Active vasculitis on PET/CT	18 (100%)
PETVAS	17.3 (5.1)
Aortic dilation	8 (44%)
Aortic diameters	
Ascending, mm	39.1 (4.4)
Descending, mm	31.1 (5.1)
Suprarenal, mm	26.6 (4.5)

Infrarenal, mm	21.7 (3.5)

Data are median (IQR) or n (%)

Table 7a: Imaging and laboratory parameter changes comparing weeks 0 and 24 for 16 patients on TCZ treatment at week 24

	Baseline	Week24	Difference Weeks 24-0 (95% CI)	P value
PETVAS	18.3 (4.7)	9.6 (4.9)	-8.6 (-11.5 to -5.7)	0.001
ESR	56 (41)	4 (4)	-52 (-72 to -31)	<0.0001
CRP	35 (34)	1 (1)	-34 (-54 to -15)	0.001
Ascending	38.88 (3.26)	39.69 (4.42)	0.81 (-0.31 to 1.93)	0.141
Descending	31.50 (5.12)	32.31 (7.18)	0.81 (-0.39 to 2.02)	0.066
Suprarenal	26.88 (4.71)	27.56 (5.83)	0.69 (-0.18 to 1.55)	0.066
Infrarenal	21.19 (2.97)	21.50 (3.68)	0.31 (-0.23 to 0.85)	0.180

Table 7b: Imaging and laboratory parameter changes comparing weeks 0 and 52 for 13 patients on TCZ treatment at week 52

	Baseline	Week52	Difference Weeks 52-0 (95% CI)	P value	P value (NP)
PETVAS	18.2 (4.3)	7.9 (4.6)	-10.4 (-13.6 to -7.2)	<0.0001	0.002
ESR	53 (45)	4 (3)	-49 (-79 to -19)	0.004	0.005
CRP	28 (30)	0.5 (0.3)	-28 (-47 to -1)	0.008	0.002
Ascending	38.69 (3.57)	39.85 (5.06)	1.15 (-0.34 to 2.65)	0.119	0.066
Descending	29.92 (2.18)	30.38 (2.50)	0.46 (0.06 to 0.86)	0.027	0.034
Suprarenal	25.46 (3.02)	25.85 (3.08)	0.39 (-0.14 to 0.91)	0.137	0.102
Infrarenal	20.31 (1.97)	20.46 (1.85)	0.15 (-0.07 to 0.38)	0.165	0.157

DISCUSSION, CONCLUSION and RESEARCH AGENDA

In this study protocol, TCZ monotherapy after ultra-short-term glucocorticoids induced a significant reduction of PETVAS at week 24 and 52 in all patients (100%). Moreover, the primary endpoint of relapse-free remission was achived in 13 of 18 patients (72%, 95% CI 47-90) at week 24, and 10 (56%, 95% CI 31-78) patients maintained relapse-free remission until week 52. All patients (100%) achived the secondary endpoint, as no patient showed new aortic dilatation during the follow-up.

Tocilizumab, a humanized monoclonal antibody inhibiting both soluble and membrane-bound forms of IL-6 receptor, nowadays is the only bDMARD approved for the treatment of GCA. A growing body of evidence supporte its use in GCA. In particular, a phase II study by Villiger et al.[62] followed by the phase III GIACTA study[63] found a significantly high relapse-free survival and sustained remission rate in patients treated with TCZ. Both protocols led to a glucocorticoid-sparing effect of around 50%.

However, in these RCTs the glucocorticoid exposure was still long, raising the question whether glucocorticoid exposure could be reduced further. In addition, neither of these studies could determine whether TCZ alone had a potential contributory role in inducing and/or maintain remission.

To date, only two studies attempted to answer this question[90,95].

In the first one, eight japanese patients with newly diagnosed GCA were treated with open-label TCZ alone with a complete responses rates of 75%. However, the number of patients was too small to have adequate statistical significance and the study population seemed to have low GCA disease activity[95].
In 2021 data from the GUSTO trial was pubblished[90]. The study enrolled 18 patients with newly diagnosed GCA that received 500 mg methylprednisolone intravenously for 3 consecutive days, followed by weekly subcutaneous TCZ injections (162 mg) until week 52. Overall, three of 18 patients did not respond to treatment and two of 18 discontinued the study due to an adverse event. The primary endpoint - proportion of patients who had remission within 31 days and showed no relapse at week 24- was not met. However, remission was achived by 78% of patients within 24 weeks and 72% of patients had no relapses up to 52 weeks. On the other hand, one patient of the GUSTO trial experienced anterior ischaemic optic neuropathy (AION) 15 days after the last glucocorticoid pulse therapy, raising doubt about the glucocorticoid regimen used in this study.
Taken toghether, the results of these trials suggeste that a large proportion of GCA patients treated according to the GiACTA protocol could be overtreated. Moreover, these two studies enrolled only newly-diagnosed GCA, thus without providing any information about disease flare and their response to therapy.
Our study is the first study that evaluates efficacy and safety of TCZ monotherapy even in relapsing GCA patients.
We enrolled 18 patients with active LV-GCA who received the same treatment protocol as the GUSTO trial. All patients underwent PET and/or CTA and/or MRI at baseline and at follow-up evaluation within 24 and 52 weeks from the start of the treatment.
According to previous data from the GiACTA and GUSTO trial, to reduce the risk of AION, we maintained a 3-day pulse of glucocorticoids in our protocol. We chose ultra-short use of GCs becouse most of the deleterious glucocorticoid side-effects develop after long-term use, and the potential side-effects of a glucocorticoid pulse therapy are uncommon, short lasting and easy to control. As expected, methylprednisolone pulse therapy was well tolerated, and no adverse events occurred. No AION occurred in our population. Two (11%) of 18 patients did not respond to treatment, and other two patients (11%) relapsed. At the end of follow-up, most patients were in clinical, serological, and radiological remission. Primary and secondary goals were rapidly obtained after TCZ starting, with no serious or unexpected adverse events.
Therefore, our results confirmed the efficacy and safety of TCZ monotherapy in patients with newly-diagnosed GCA and further they demonstrate for the first time its effectiveness even in patients with relapsing GCA.

In our preliminary results, PET/CT and MRI or CTA seems to be usefull methods for assessing disease activity in GCA patients during treatment. In light of these findings, we advise to repeat major diagnostic imaging procedures during follow-up since inflammatory markers may be unreliable in revealing LVV, expecially during TCZ therapy.
Moreover, long-term complications of LVV, such as aneurysms and stenosis, cannot be diagnosed without CTA and MRI, potentially leading to dreadful outcomes in therapy. In particular, FDG-PET and MRA, alone and combined, could represent the best choice for monitoring LVV [21,44,45]. FDG-PET provides the highest sensitivity for the assessment of mural inflammation, and their relatively low dose of radiation makes it suitable for repetitive scans. On the other hand, MRA, although time-consuming and expensive, is essential for the assessment of intracranial arteries and vessel wall, as well as in the monitoring of the common, and unpredictable, onset of long-term vascular complications (e.g. aneurysms and stenosis), as mentioned in EULAR recommendations[21].

Nevertheless, we must remind that the role itself of PET during follow-up should be further evaluated and is still a matter of debate[97]. It is well-known that FDG decreases after an effective treatment[98], but a persistent FGD uptake may be variously interpreted as a persistent disease activity as well as a sign of reparatory processes arising within vessel walls[99].
For example, even in refractory LV-GCA patients treated with TCZ, although most patients achieve clinical remission, less than one-third show normalisation of 18F-FDG vascular uptake[100].
Uncertainty remains also in the interpretation of MRA findings during follow-up: in the only randomized control trial of GCA treated with TCZ and monitored with repeated MRA, signals normalized in only one-third of patients, despite being all considered in remission[53].
In our cohort, even if no new vascular abnormalities occurred, 22% of patients showed significant worsening of pre-existent aortic dilatation on serial CT.
Therefore, TCZ potential effect in stabilize or resolve large vassels inflammation without the concomitant use of GCs has yet to be demonstrated in large randomized clinical trials.

Our study has some important potential limitations to consider. This was a single-center study with a small number of partecipants. However, LVV are rare diseases and the study was conducted by the same expert physicians. Moreover, inter-rater agreement for independent and blinded PET scan interpretation was excellent. Finally, the short term of our observational data cannot be considered sufficient to demonstrate a lower progression of aneurysms and stenosis in patients treated with TCZ.
This study has several important strengths. The study was prospective and patients could be enrolled at any time in the disease course, also including patients with relapsing GCA. For these reasons, this study provides novel, prospective evidence about the potential value of TCZ therapy for the treatment of GCA.

Tocilizumab targets interleukin-6 (IL-6) receptors which affects the usual inflammatory acute phase reactants usually used to monitor the disease activity. Given the interest in this agent for GCA, future studies looking at TCZ for GCA should look at other possible cost-effective laboratory (biomarkers) and neuroimaging parameters to monitor disease activity. Future research should also look into the duration of treatment with TCZ and evaluate its effect on outcomes that are meaningful to care providers, patients, and regulators.
We did not performed an analysis of the health-related quality of life, and economic outcomes were not an objective of our study. Future studies should consider addressing these outcomes, to better inform decision making in terms of provider and patient choice as well as policy changes.
To date, TCZ is the only DMARDs approved for treatment of GCA. Despite it demonstrated its efficacy and safety in RCTs, it remains an expensive drug that is not always accessible, especially in developing countries. Moreover, to date there are no alternative drugs in intollerant patients or in GCA patients with contraindications to TCZ.
Other studies are looking at other biologics targeting other areas in the immune cascade (T cells, interleukin-1, interleukin-23, B-cells, tumor necrosis factor-alpha, interleukin-1 beta, etc.) in GCA patients with relapsing disease. The identification of other drugs usefull for the treatment of active GCA would lead to a better management of each individual patient. Like TCZ, these drugs will be especially usefull in patients with comorbidities like osteoporosis or to prevent side effects of GCs.
Furthermore, looking at real-world data of those patients treated with TCZ and their course of GCA-related visual loss and stroke is recommended, given that GCA patients with ischemic complications had lower tissue expression and circulating levels of IL-6 compared to those without ischemic events[101].

In the open-label extension of the GiACTA trial (part 2) by Adler 2019[88], 197 participants completed 3 years follow up. It was shown that half of patients relapsed after TCZ was discontinued after remission had been achieved. Participants receiving TCZ were also treatment-free (no TCZ or glucocorticoid treatment), which was higher than those in the placebo group who maintained clinical remission. Median time to first flare without TCZ was also longer for participants in the original TCZ groups compared to the placebo groups. This open-lable study concluded that TCZ retreatment, with or without glucocorticoid, was effective for restoring clinical remission. Cumulative steroid dose over the 3-year study was lowest in the weekly TCZ group.
However, longer follow-up is also needed to provide better data for the use of TCZ in GCA.

In conclusion, our results demonstrated the efficacy of ultra-short glucocorticoids and TCZ in controlling clinical symptoms of GCA, lowering acute phase responses and leding to a significant reduction of vascular inflammation in many patients with active LV-GCA.
Imaging tools are usefull in assessing disease activity and monitoring therapeutic response at different time points of follow-up. A close disease monitoring also with imaging techniques is therefore warranted to optimize patient’s management.
Further multicentric prospective studies are needed to clarify the role of functional and morphological imaging for assessing disease activity in GCA. Moreover, larger studies are urgently needed to clarify a shared protocol of monitoring of these patients and to assess the longterm efficacy of bDMARDs in providing a persistent remission and preventing further complications.

Section B

Rheumatoid arthritis related-interstitial lung disease: an epidemiological, diagnostic, and therapeutic dilemma

INTRODUCTION

Original article 1[102]**:**

Review: Rheumatoid arthritis related interstitial lung disease

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting 0.5–1% of the population worldwide, characterised by joint swelling and tenderness with destruction of synovial joints[103]. Rheumatoid factor (RF) and anti-cyclic citrullinated protein antibodies (ACPA) are frequently detected also many years before the occurrence of joint involvement, defining RA as an autoimmune systemic disease with frequent extra-articular manifestations[103]. Lung involvement is common in RA, and it includes a wide spectrum of disorders, ranging from airway and pleural diseases, bronchiectasias, and nodules, to infection and drug toxicity[104].

Among pulmonary complications, interstitial lung disease (ILD) is one of the most frequent[104].

Although increasing data suggest a strong impact of ILD in both quality of life and overall prognosis of RA patients, diagnosis is still delayed[105]. Moreover, the management of RA-ILD is often challenging due to lack of evidence-based approaches or international recommendations.

The aim of this paper is to provide a comprehensive review of clinical, radiological, histological data about RA-ILD and to analyse the state of the art of the available therapeutic approach.

Definition and epidemiology

The term ILD comprises a complex group of pulmonary disorders principally characterised by varying degrees of inflammation and/or fibrosis of the lung parenchyma[106].

In the last years, increasing evidence suggest that ILD can occur in any stage of RA with varying frequency and severity, sometimes preceding joint disease. In a large Danish national study, more than 75% of ILD patients were diagnosed within 5 years after RA diagnosis, up to 5 years before it, demonstrating that ILD is an early complication of RA[107].

Prevalence of RA-ILD largely varied according to the heterogeneity of the populations, ILD definitions, as well as the diagnostic tools employed in the studies[108–110]. Moreover, epidemiology of RA-ILD has been mainly investigated only in retrospective studies providing no conclusive data.

Although clinically evident ILD is usually recorded in 7-10% of RA patients[105,107], the prevalence of subclinical ILD was higher when consecutive patients were evaluated by high-resolution computed tomography (HRCT)[111]. In this regard, Dawson identified 19% of 150 consecutive RA patients, of which only 54% with low grade dyspnoea and 14% with restrictive syndrome at lung function tests (LFT)[111]; Gochuico observed a “preclinical” ILD at HRCT in one third of the study population, without dyspnoea or cough with long-standing disease[112]; finally, Gabbay identified abnormalities compatible with ILD in 33% of patients with recent onset RA[113]. In an ongoing prospective study evaluating epidemiology of RA-ILD (LIRA study, Lung Involvement in Rheumatoid Arthritis), preliminary data showed a prevalence of 20.1%[114].

Data about annual incidence of RA-ILD are reported in a few studies.
A population-based cohort study conducted in the United States reported a lifetime incidence of RA-ILD of 7.7%[6], while another analysis from the same country found a 10-year incidence of 5% in RA patients diagnosed between 1995 and 2007[115].
Another population study from England reported a yearly incidence of RA-ILD of 4.1/1,000 patients/year, while 15-year cumulative incidence was 62.9/1,000[116].
Finally, a recent study from United States showed annual incidence rates ranging from 2.7 to 3.8 per 100,000 people, with a stability during the period of time from 2004 to 2013[105].

Risk factors and biomarkers

Despite only limited and retrospective data, male sex, older age at RA onset and ever-smoking resulted strictly correlated with RA-ILD in the majority of studies[108,109,116–120], mainly for patients with a usual interstitial pneumonia (UIP) pattern[109,118–120].
Among serological features, ACPA has been associated to extraarticular manifestations of RA, including ILD[109,117–121]. In particular, Correia reported a correlation between ACPA titer and the risk to develop ILD[121]. Moreover, Doyle observed that a combination of older age, male sex, ever-smoking, RF and ACPA was strongly associated with RA-ILD[119]. On the contrary, many studies showed no association between ACPA and ILD, but these different results are probably due to the heterogeneity of ACPA specificities and search methodology[116,122]. Among ACPA specific sub-types, anti-citrullinated alpha-enolase peptide 1 and anti-citrullinated heat shock protein 90 (HSP90) have been associated with RA-ILD (11–14) with a specificity up to 90% for serum autoantibodies targeting HSP90 alpha or beta[123].
Recently, other biomarkers have also been investigated as risk factors for ILD in RA patients, namely LDH, CA-125, CXCL10, fibronectin and serum soluble programmed death ligand 1[120,124–127].
Matrix metalloproteinase 7, pulmonary and activation-regulated chemokine, and surfactant protein D (SP-D) have been recently included in a clinical and serological model able to identify patients with both clinical and subclinical RA-ILD with high accuracy[119].
Finally, the usefulness of serum Krebs von den Lungen-6 (KL-6) has been evaluated in many forms of ILDs and its sensitivity and specificity versus RA-ILD were 68% and 83%, respectively[128]. The combination of KL-6, SP-D and CCL18 furtherly improved the diagnostic accuracy, with increased sensitivity and specificity up to 77% and 97%, respectively[119]. Moreover, in a small group of French RA-ILD patients, baseline KL-6 serum levels were predictive of ILD progression and the degree of ILD progression on HRCT was proportional to baseline KL-6 concentrations[128].

Pathogenesis

RA-ILD pathogenesis is only partially understood. However, some genetic and environmental factors are supposed to have a role[129,130].
In the last years, two different pathways of possible link between lung and joint involvement have been suggested to explain pathogenesis of RA-ILD[131]. In the former, hypothetically associated to inflammatory non–UIP patterns of disease, an immune-response against citrullinated proteins firstly recognized in the synovial tissue successively cross-reacts with similar antigens in the lung. As confirmation, RF and ACPA are associated to airway changes[132] with a higher incidence in long-standing RA, suggesting that the inflammatory burden of the disease might mainly contribute to these modifications[133].
The second pathway, mainly attributable to UIP pattern, is based on a model in which immune alteration begins in the lung. In this regard, toll-like receptor-4 (TLR4) pathway has been investigated

as possible common pathogenetic mechanism in both idiopathic and RA-related UIP pattern[134,135]. In fact, despite some conflicting data[136,137], a pro-fibrotic role has been associated to TLR4 activation. An increased activity of TLR4 has been demonstrated in RA-UIP and a link between TLR4 stimulation and the adaptive autoimmune response has been suggested in RA patients, including a role in ACPA production[135]. Smoking or other environmental or infectious triggers would locally induce citrullination of proteins[134,138,139] and the consequent immune activation would stimulate bronchus-associated lymphoid tissue formation and antibodies production, including ACPA and RF. In RA-ILD patients, high concentration of citrullinated peptides may be detected in the lung parenchyma and this model can explain the possibility that the appearance of arthritis might follow lung involvement by many years[134,139].

All these mechanisms bring back to a pathogenetic model in which an environmental trigger (smoking or infectious pathogens) can cause oxidative stress inducing itself inflammatory process with the contribution of post-translational modifications and immune response. In conjunction with growth factors, many cytokines promote fibroblasts differentiation and proliferation, providing a potential link between inflammation and fibrosis[139]. At the same time, matrix metalloproteinases elaborated from damaged epithelia promote cellular recruitment as well as activation of cytokines and pro-fibrotic mediators, thereby contributing to the cross-talk between inflammatory cascades and tissue remodelling pathways[139].

Genetic associations

Some gene polymorphisms have been associated with an increased risk of developing RA-ILD[140].

The single nucleotide polymorphism rs35705950(G>T) in the promoter region of MUC5B, encoding mucin 5B, was reported to be strongly associated with familial interstitial pneumonia and IPF[141]. This promoter polymorphism increases the risk for ILD by 3-fold among patients with RA and it was found to be specific for the UIP pattern of RA-ILD[142].

Other genes have also been implicated in RA-ILD, however none is as strongly associated as the MUC5B promoter variant[143]. Recently, in Japanese patients, an association between RA-ILD and RPA3-UMAD1 locus has been described. Moreover, genetic variant of RTEL1 and TERT, coding region mutation leading to telomere shortening have been described as related to the onset of RA-associated ILD at a younger age[130,143]. Even the expression of non-coding RNA, such as microRNA and long non coding RNA, have been investigated in RA-ILD[144,145]. For example, expression levels of hsa-miR-214-5p and hsa-miR-7-5p are higher in RA patients with ILD than in those without[144].

Finally, several human leukocyte antigen (HLA) alleles variants have been associated with ILD in RA patients, including HLA-B54, HLA-DQB1*0601, HLA-B40, HLA-DRB1*15, HLA-DRB1*16 and HLA-DR4[140,143,146].

Clinical manifestations and natural history

Clinical manifestations of RA-ILD largely mirror those reported by patients with idiopathic interstitial pneumonias (IIPs)[147].

Exertional dyspnoea and dry cough often represent the presenting symptoms of RA-ILD; however, dyspnoea evaluation could be underestimated in long-standing RA associated to limited mobility[148].

Clubbing is frequent in advanced stages[149], but tachypnoea and bibasilar inspiratory crackles are considered very common[150,151].

All patients with ILD are at risk of acute exacerbation (AE-ILD) defined as an acute worsening or development of dyspnoea, not fully explained by cardiac failure or fluid overload, associated with new bilateral ground-glass opacities and/or consolidations at HRCT superimposed on the previous

ILD pattern[152]. Diagnosis of AE-ILD in the context of rheumatic diseases could be difficult in clinical practice, since many confusing factors have to be considered in differential diagnosis, such as opportunistic infections[153].
Advanced age and severe functional deterioration seem to be risk factors for the occurrence of AE[154]; moreover, lung biopsy can precipitate an AE in ILD patients[153]. Among rheumatic diseases related ILD, RA has the highest reported rate of AE, estimated between 7% to 11% and similar to IIPs[154,155], with a mortality of at least 50% at 3 months from onset[156]. AE is more frequently described in association with UIP pattern, but also detectable in patients with different radiologic patterns[153].
The HRCT imaging in AE-ILD is similar to other forms of adult respiratory distress syndrome and characteristically demonstrates different combinations of patterns of ground glass opacities and consolidations (peripheral, multifocal, or diffuse) superimposed to reticulation or honeycombing[157]. Histologically, it generally consists in diffuse alveolar damage superimposed on a chronic ILD[153].

Screening and diagnosis

Diagnosis of lung involvement in RA patients can be difficult only on the basis of respiratory symptoms: in fact, patients can be asymptomatic at early stages of the disease, and some suggestive clinical manifestations, such as fatigue, dyspnoea and cough, can also derive from extra-pulmonary causes, namely arthritis, long-term deformities and sicca syndrome in patients with secondary Sjogren's syndrome[104,158]. Chest X-ray is considered insensitive in identifying ILD and it is mainly used to identify pulmonary complications, such as pleural effusion, infection, or lung cancer[111,113,151].
High-resolution computed tomography (HRCT) remains the gold standard for diagnosis, and it is mandatory in case of suspected ILD[159]. Nevertheless, a routine use of HRCT for screening programs is not advisable for both high cost and X-ray exposure[159].
Therefore, although it may be unremarkable in some cases, physical lung examination has been proposed as an easy and repeatable screening for the early diagnosis of interstitial pneumonia, both idiopathic and secondary to other diseases[160,161]. In fact, lung auscultation can reveal fine bibasilar, end-inspiratory, "velcro-like" crackles, which may precede the development of clinically overt ILD[111,113,160]. Recently, an algorithm named VECTOR (VElcro Crackles detecTOR) has been demonstrated to be able to recognize velcro crackles in pulmonary sounds from RA patients with a diagnostic accuracy of 83.9%[151].
In the last years, lung ultrasound examination has been proposed as a useful, feasible, non-invasive, imaging technique with high sensitivity and specificity for the screening of ILD in patients affected by CTDs, mainly systemic sclerosis[162]. In RA, published data are scarce and lung ultrasound reproducibility and usefulness have not been established yet[163,164].
In patients with RA-ILD, LFT may detect a restrictive ventilatory failure, characterized by reduced forced vital capacity (FVC), increased forced expiratory volume in 1 second (FEV1), with a normal FEV1/FVC ratio, together with a decreased diffusing capacity of the lung for carbon monoxide (DLCO), even in absence of symptoms[165]. Sometimes, ILD and airway disease may be concomitant in RA patients, for example in combined pulmonary fibrosis and emphysema[166]; in these cases, spirometry can be normal, and only a reduction in DLCO may occur[166] and may discriminate disease extension and progression of lung disease. Since DLCO is highly sensitive in detecting ILD, in early involvement, LFT impairment may be characterized only by DLCO reduction, whereas FVC may be more useful for assessing disease extension[167]. In some patients with established ILD, a disproportion between DLCO and FVC can be observed, with reduction of DLCO and stability of FVC. Although rare in RA, in these subjects a pulmonary arterial hypertension should be suspected[168].

FVC is highly reproducible and its changes are specific to ILD, once extrapulmonary restriction due to pleural or muscle diseases has been excluded[169]. A disease progression may be supposed in RA patients by a decline of at least 10% in FVC or of at least 15% in DLCO over 6–12 months[170].

Multidisciplinary approach

Since 2002, multidisciplinary discussion (MDD), based on integration between clinical, radiographic and histopathologic data, replaced the surgical lung biopsy becoming the diagnostic reference standard in many cases of ILD including IPF, idiopathic nonspecific interstitial pneumonia (NSIP), and hypersensitivity pneumonia[171].

Pulmonologist, radiologist and pathologist are the physicians originally included in MDD, while the rheumatologist is generally involved only in selected cases to exclude secondary forms of ILD. So, the role of rheumatologist in MDD has not been widely investigated. In 2018 Levi conducted a prospective study to evaluate the effect of the inclusion of the rheumatologist in the MDD for the assessment of ILD diagnosis concluding that this approach could significantly increase diagnostic accuracy and reduce invasive procedures[172]. This result has recently been confirmed by a systematic review aimed also to evaluate the role of rheumatologist in MDD; even if authors underscored as data cannot be considered conclusive, for the low number of studies, they observed that participation of rheumatologist in diagnostic MDD reduced the risk of mis-classification of ILD patients[173].

Comprehensibly, the routine use of MDD for diagnosis of RA-ILD is not required, nowadays it is quite clear that ILD can precede the occurrence of articular manifestations in RA patients and the involvement of rheumatologist can facilitate the correct diagnostic definition also in patients with UIP pattern and absent or sub-clinic articular involvement[174].

In patients with definite RA-ILD, MDD is fundamental to define radiologic and histologic patterns. In fact, differently from some CTDs, such as systemic sclerosis, where ILD pattern seems to be irrelevant for the prognosis, in RA patients the presence of a UIP pattern seems to have significant prognostic implications[174].

Moreover, RA patients often present more cardiorespiratory comorbidities other than ILD[175]. In these cases, MDD might be helpful in more precise evaluation of LFT, clinical and radiological data, also during follow-up for the assessment of disease severity and progression[174]. Patients with RA typically undergo immunosuppressive treatment with potentially increased infectious risk; when these occur, MDD can become mandatory to discriminate between infection and disease progression[176].

In RA patients, ILD often complicates a systemic disease with severe joint involvement. The choice of the best treatment for each patient is often challenging and MDD may represent the unique possible approach to achieve this goal[176].

Pathologic features

The spectrum of histological abnormalities seen in lung biopsies of patients with rheumatoid arthritis is broad. In RA, this variability is explained both by the possible involvement of any compartment of the lung (airway, vessels, parenchyma and pleura), and by different patterns of injury that may occur[177]. A variable combination of different localizations and different patterns in the same biopsy (namely interstitial fibrosis, cellular infiltrate, pleuritis) is frequent, and in these cases the exact classification may prove difficult[178]. Two other considerations further contribute to complexity: 1) the significance of the histological alterations varies from being a subclinical incidental finding to portending an aggressive behaviour, and generally the difference cannot be predicted from histology alone; 2) changes related to the underlying disease have to be separated from changes due to therapy,

like infections and drug reactions: in the lung, histologic alterations induced by drugs overlap significantly with RA, and the distinction can be particularly challenging[179].

Common features of pulmonary involvement of RA include interstitial lung diseases, parenchymal nodules, pleuritis and bronchiolitis; vascular lesions may occur but are less common.

ILD generally shows the features of UIP pattern. UIP comprises a combination of old scarring having a sharp demarcation with unaffected lung and young fibroblastic foci, with or without honeycombing. In RA, UIP frequently coexists with cellular infiltrate and/or follicular bronchiolitis (sometimes with germinal centers) and/or pleuritis, a combination that should prompt consideration for an underlying CTD. ILD with different patterns may also occur, including fibrosing NSIP, cellular NSIP, organizing pneumonia (OP), diffuse alveolar damage, pleuro-parenchymal fibroelastosis and alveolar haemorrhage[177].

Parenchymal nodules are the most characteristic pulmonary manifestations of RA, but they are less frequent than RA. Rheumatoid nodules are typically septal or subpleural, and consist in central fibrinoid necrosis with a peripheral rim of palisading histiocytes. Albeit sufficiently typical to allow the pathologist to suggest the diagnosis, they overlap other necrotizing granulomas and the definitive diagnosis requires a careful clinico-pathologic correlation with the exclusion of infection[177,178].

Pleural involvement is common, generally consisting in nonspecific active or chronic pleuritis. Occasionally a rheumatoid nodule opens onto the pleural surface, causing a necrotizing pleuritis with palisaded histiocytes quite evocative of RA[177,179].

Small airway disease generally consists in cellular/follicular bronchiolitis, in which a nodular lymphoid infiltrate localizes in the bronchiolar wall. The more clinically severe constrictive bronchiolitis, consisting in scarring variably obliterating the bronchiolar lumen, is rare[178,179].

Some examples of lung biopsies in patients with rheumatoid arthritis are shown in figure 1.

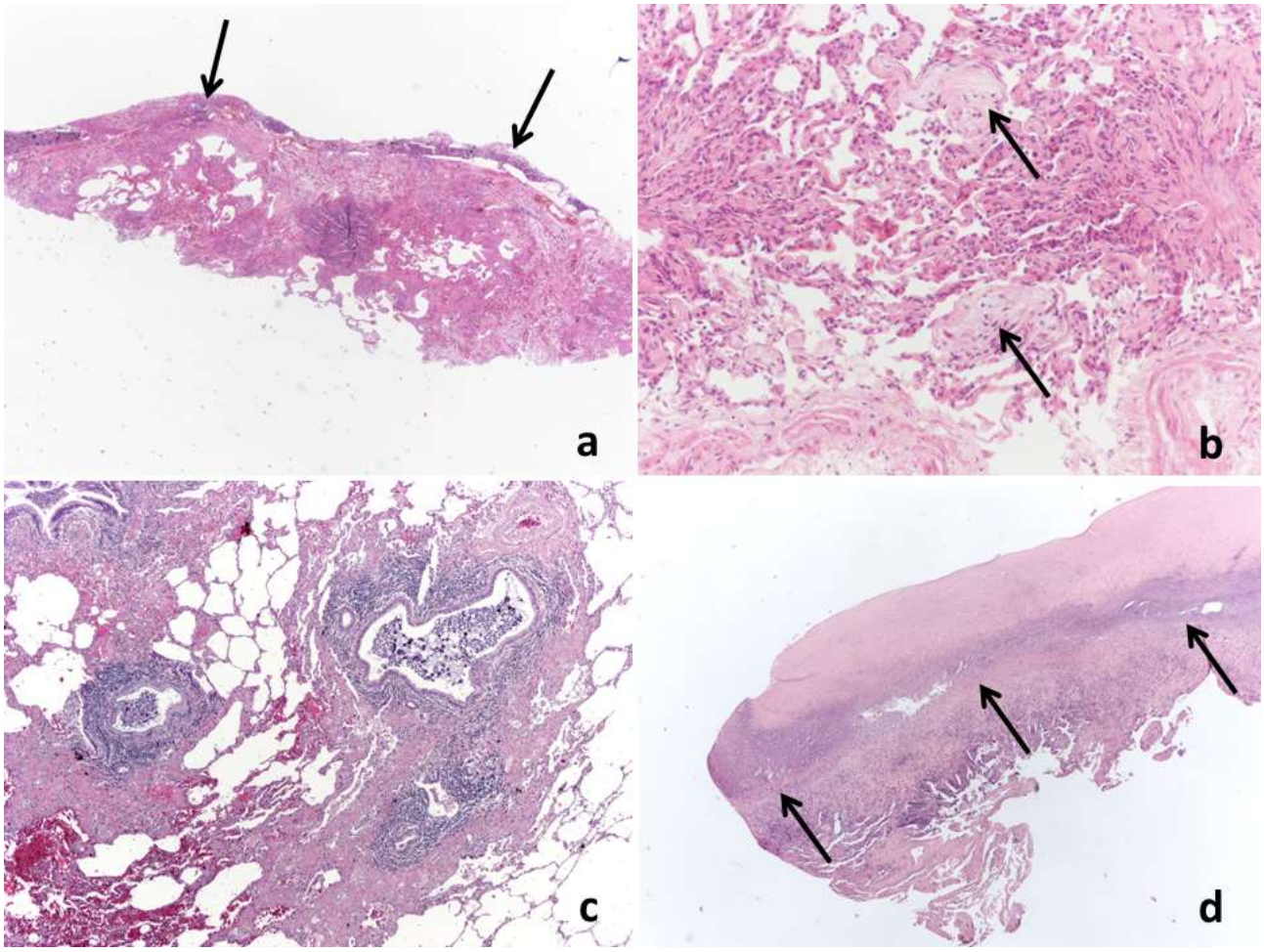


Figure 1. Lung biopsies in patients with rheumatoid arthritis.

a) Surgical lung biopsy showing a scarring process with fibroblastic foci consistent with UIP, associated with pleuritis (arrows). The combination of interstitial lung disease and pleuritis suggests an underlying connective tissue disease (Hematoxylin-Eosin, 20X);

b) Transbronchial biopsy showing intra-alveolar plugs of organizing pneumonia (arrows). In a patient with a known connective tissue disease, this finding rises several possibilities including localization of the underlying disease, infection, drug reaction and aspiration (Hematoxylin-Eosin, 40X);

c) Surgical lung biopsy showing a small airway disease characterized by a combination of cellular bronchiolitis and chronic bronchiolar scarring (Hematoxylin-Eosin, 20X);

d) Pleural decortication in a patient with empyema, showing a necrotizing inflammatory process with a peripheral rim of palisading histiocytes (arrows), reminiscent of a rheumatoid nodule (Hematoxylin-Eosin, 20X).

Radiological classification

In RA patients, HRCT may reveal the presence of multiple disorders, which may not be captured by either LFTs or chest radiography. On the other hand, the specificity of HRCT may be limited by a number of potential confounding factors such as smoking or drugs, which may be both associated with pulmonary abnormalities that mimic those associated with RA itself.

UIP is the most common ILD pattern in RA and it is characterized by basal predominant subpleural reticulation, with or without honeycombing[180]. Other patterns are NSIP and OP[181], while lymphocytic interstitial pneumonia or other uncommon patterns are quite rare[182] (figure 2).

Some HRCT features may suggest RA-ILD in UIP patients. For example, honeycomb cysts located in the mid or upper lungs are infrequently observed in IPF, but are described in patients with RA-ILD[183]. Moreover, bronchocentric fibrosis in the context of UIP has also been reported in a minority of patients with RA-ILD[184].

Chung reported a number of differences between idiopathic and CTD-related-UIP, including RA[185]. In particular, as compared with IPF, they found that three features were more prevalent in patients

with CTD or RA: the *anterior upper lobe* sign (characterized by a concentration of fibrosis in anterior aspects of the upper lobes and relative sparing of the remaining upper lobes but with concomitant lower lobe fibrosis); the *exuberant honeycombing* sign (in which florid honeycomb cysts occupy >70% of fibrotic regions) and the *straight-edge* sign (i.e., the isolation of fibrosis to the lung bases with a sharp demarcation in the craniocaudal plane)[185].

However, using radiologic IPF diagnostic criteria and without any knowledge of clinical history, the majority of patients with RA-UIP are unrecognizable from patients with IPF[171]. Since many patients can present ILD at disease onset before clinical appearance of arthritis, a differential diagnosis between these 2 forms remains an unmet clinical need.

Other than for diagnostic aim, the use of HRCT is fundamental in lung disease staging and severity and for the assessment of associated condition[166].

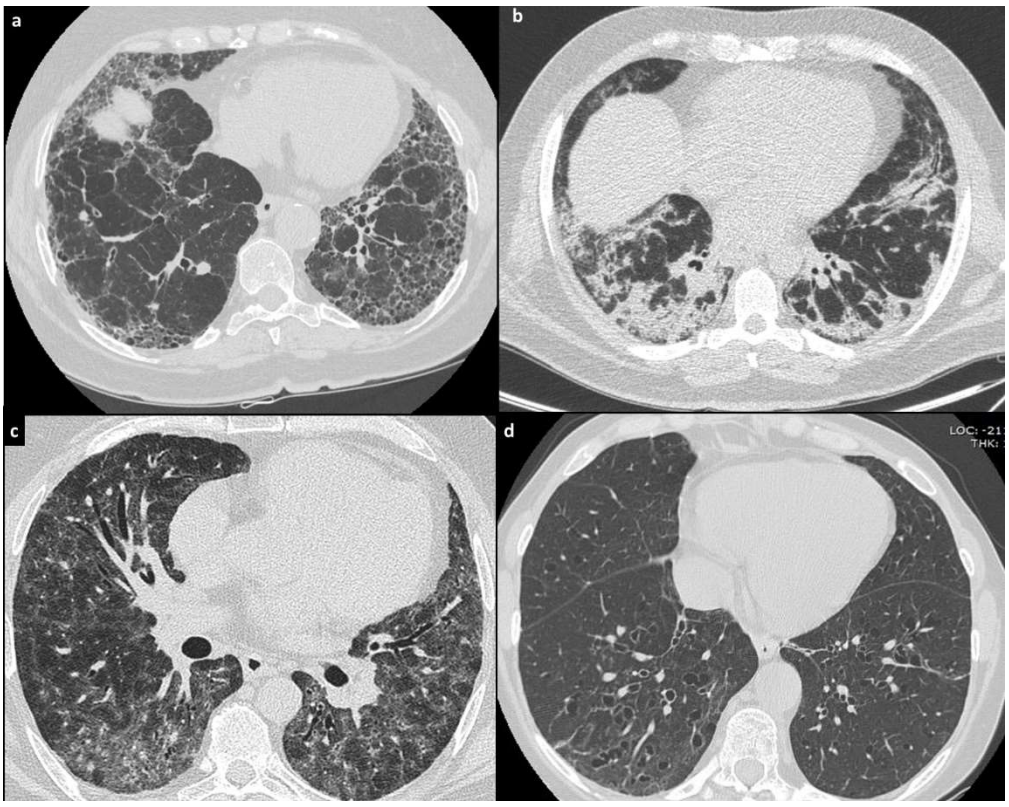


Figure 2. Radiologic patterns of rheumatoid arthritis related interstitial lung disease

a) Usual interstitial pneumonia: subpleural, basal predominance of reticular abnormalities, honeycombing with or without traction bronchiectasis, and absence of extensive ground-glass opacities, nodules, discrete cysts, air trapping, or segmental/lobar consolidation;
b) Organizing pneumonia: bilateral consolidations with peripheral distribution associated to mild ground glass opacities. Polygonal or arcade-like opacities indicating a perilobular distribution are also common;
c) Nonspecific interstitial pneumonia: bilateral basal-predominant ground-glass opacities. Abnormalities are concentrated in lower lobes and fibrosis usually spares the immediately subpleural lung zone. Reticulation and traction bronchiectasias and bronchiolectasias increase with more advanced fibrotic nonspecific interstitial pneumonia;
d) Lymphocytic interstitial pneumonia: numerous thin-walled cysts are randomly distributed throughout the lungs with peribronchovascular distribution associated to mild peripheral ground-glass opacities.

Mortality and prognosis

Patients with RA have an increased rate of mortality when compared with the general population. This is the result of a number of comorbidities that include cardiovascular (CV) diseases, respiratory disorders, mainly due to ILD, malignancies and infectious complications.

In the last years, CV mortality in RA patients is decreasing, while ILD still remains a challenge[115,175]. In a period of time from 1988 to 2004, age-adjusted RA-ILD–associated mortality rates increased 28.3% in women and decreased 12.5% in men, with a higher mortality rate in women than in men for any age group[186].

Mortality of RA-ILD patients is significantly increased compared with RA patients without ILD and the general population, with reported survival rates ranging from 3 to 10 years after ILD diagnosis. In the above-mentioned Danish study, RA-ILD mortality was high already in the first year after diagnosis (13.9%), especially for early AE. In the next years, the hazard rate ratios for death were 2 to 10 times increased for RA-ILD respect to non-ILD in each period of time[107].

Contrasting reports have been published about relationship between HRCT pattern and survival. A study has shown a lower 5-year survival rate for UIP pattern than NSIP (36% and 94%, respectively). In contrast, other studies didn't find any association. Nevertheless, honeycombing would represent the most important radiological finding related to a worse prognosis[183,187–189].

Pulmonary physiology evolution has been reported as an independent predictor of mortality in RA-ILD patients[190]. Patients with worse baseline LFT or disease progression over time are at higher risk of death. AE-ILD and severe infectious pneumonia are known to be the most frequent causes of death in RA-ILD patients, with an earlier fatal outcome in males and elderly patients[190,191].

Differential diagnosis

Signs and symptoms of early RA-ILD, as well as its radiologic/histologic patterns, may be non-specific and a differential diagnosis can be difficult, particularly when lung involvement precedes arthritis and evidence of a systemic disease is minimal or absent[192,193].

Therefore, since in their initial stages many rheumatic diseases can simultaneously show lung and joint involvement, a careful evaluation is mandatory to correctly classify patients[194].

In 2015, the term interstitial pneumonia with autoimmune features (IPAF) has been proposed to describe individuals with interstitial pneumonia and findings suggestive for an underlying systemic autoimmune condition, without meeting current criteria for a specific CTD[195]. The IPAF classification criteria include findings typical for RA, namely arthritis, morning stiffness, rheumatoid factor and ACPA[195,196].

Anti-synthetase syndrome (ASS) is a heterogeneous condition characterized by the clinical triad ILD, myositis and arthritis. Uncomplete forms of the disease and phenotypic variants with positive anti-tRNA-synthetase antibodies and only one or two major clinical manifestations are frequent[197]. ILD frequently represents the only clinical feature in patients with positivity for anti-PL7, -PL12, -OJ and -KS antibodies[198,199]. Therefore, to discriminate ASS and RA could be challenging in these subsets and the search for anti-synthetases antibodies must be part of diagnostic workshop in patients presenting with these features.

Furthermore, ILD may be the first manifestation of primary Sjogren's syndrome (pSS), even before the appearance of sicca syndrome. In these cases, the presence of RF and inflammatory arthralgias or arthritis can complicate an early differential diagnosis between pSS and RA[200,201].

Moreover, in patients with Sarcoidosis the association of pulmonary fibrotic alterations and joint involvement is commonly seen[202].

Finally, a growing number of genetic syndromes characterized by ILD and multisystem immune dysregulation have been described, including joint symptoms[203]. STAT3 gain-of-function syndrome, CTLA4 haplo-insufficiency syndrome and, overall, COPA syndrome are some paradigmatic examples.

COPA syndrome is an autosomal dominant, variably penetrant genetic disease characterized by lung and joint involvement. It can begin in elderly and many patients can show autoantibodies, including RF, ACPA, and antinuclear antibodies[203,204].

Conclusions

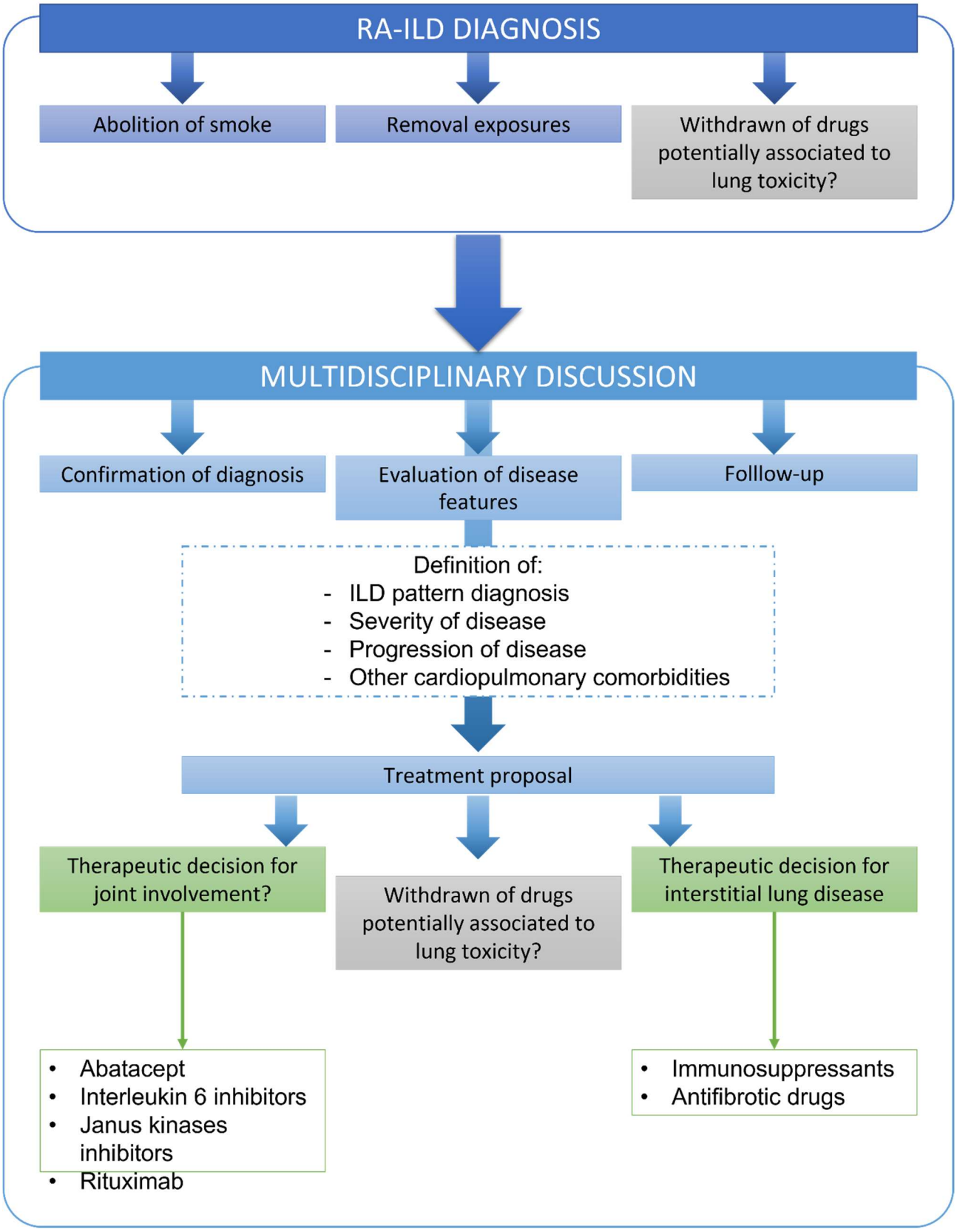
ILD is the most frequent and severe extra-articular manifestation of RA[104,105]. The real prevalence of RA-ILD in still unknown and a systematic search for lung involvement should be always included in the periodic assessment of RA patients.

Many unmet needs remain to be resolved in this field, including the prognostic role of subclinical ILD, that do not appear always to be progressive.

Therefore, prospective studies are desirable to define the natural clinical history of the respiratory disease, the prognostic role of the radiological patterns of ILD and the management of these patients; in particular, safety and possible effectiveness of b- and cs-DMARDs in RA-ILD and the possible association between DMARDs and antifibrotic drugs, will probably be a main research topic for the next years[176].

Finally, the development of multidisciplinary teams involving rheumatologists, pulmonologists and thoracic radiologists might be suitable both for a better management of these patients and for research purposes[174] (figure 3).

Figure 3. Flow-chart proposal for the management of patients with rheumatoid-arthritis-related interstitial lung disease



BACKGROUND, RATIONALE and UNMET NEEDS

Rheumatoid arthritis (RA) is the most common chronic inflammatory disease, affecting 0.5%-1% of the population worldwide. It is a progressive, systemic autoimmune process of undefined etiology, characterized by erosive symmetrical arthritis and progressive disability, often complicated by extra-articular manifestations.
Among them, interstitial lung disease (ILD) is the most common and serious complication of lung involvement in RA, with high rate of morbidity and mortality.

The prevalence of ILD in RA ranges from 4% to 70%. This wide variation reflects differences in study design, study populations and definition of RA-related lung disease. About 10% of the RA population develops a clinically significant ILD that is responsible of 10-20% of all mortality, with a mean survival of 5-8 years.
The real incidence of RA-ILD is unknown, but a prevalence of 7.7% for symptomatic RA-ILD, 67% for radiologic RA-ILD and 80% for biopsy-identified RA-ILD have been reported []. The usual interstitial pneumonia (UIP) is the predominant histological/radiological pattern of RA-ILD, reported in 44-66% of cases []
ILD can occur at any point in the natural history of RA, but its respiratory manifestations usually appear in the late stages of the disease. Most often ILD is identified within the first 5 years of an established RA, however in 10-20% of cases it may precede the onset of articular manifestations with paucisymptomatic or asymptomatic pulmonary disease, leading to a delated diagnosis.
Unfortunately, this complication is underrated, particularly in its earliest stages, and most of the available studies on this topic are retrospective, including small series.
Therefore, there is an unmet need of prospective studies to clarify some crucial points such as the incidence and prevalence of ILD, its clinical features (onset features and clinical evolution), radiological characteristics, the possible predictive factors and the causal relationship with some drugs commonly used for the treatment of RA.

Moreover, an early diagnosis of ILD is challenge, to avoid an under-estimation of the ILD prevalence, in particular in its earliest stages. Although lung involvement represents the second cause of death in RA patients and ILD is associated with worsening of the quality of life and the overall prognosis, there are no randomized screening approaches or management guidelines.
The increase of the opportunities to diagnose ILD could improve the quality of life of patients and decrease the mortality and the high utilization of healthcare resources that ILD entails.
The diagnosis of ILD is based on the radiological finding obtained by high-resolution CT (HRCT), which has the disadvantage of not being used routinely as a screening test in all patients with RA, either because it is burdened by exposure to high doses of radiation for the patient, and for high costs and long waiting lists.
High resolution computed tomography (HRCT) represents the gold standard for the diagnosis of this extra-articular manifestation, but ILD can appear in any stage of RA entailing the need for systematic assessment of lung involvement, and a routine use of HRCT for screening program is not advisable for both the high cost and X-rays exposure.
Therefore, the use of reliable and non-invasive tools may improve early diagnosis and a better management of the disease.

Velcro sound is a pulmonary sound defined as a fine crackle soft and short in duration. The detection of this typical sound has been proposed as an easy and repeatable screening for the early diagnosis of idiopathic pulmonary fibrosis, a disease that shares many similarities with RA-ILD.
The presence of velcro crackles, persistent dry cough and / or dyspnea can support clinicians in requiring the execution of HRCT to diagnose ILD.
Therefore, the systematic use of clinical parameters such as non-cardiogenic dyspnea, persistent dry cough and the presence of Velcro rales can allow a correct screening of RA patients, reducing the improper requests of HRCT and providing a reliable estimate of prevalence and incidence of ILD in the course of this pathology.

Several therapeutic agents have been suggested in literature, but nowadays there are no large randomized controlled clinical trials to support therapeutic guidelines for RA-ILD.
Since no controlled studies are available, the therapeutic approach to RA-ILD is still debated and based on empirical approaches dependent on retrospective studies and case series.
To further complicate this scenario, both conventional and biologic disease modifying anti-rheumatic drugs (DMARDs) have been implicated in the development of drug-related pulmonary toxicity with conflicting data.
The latest ACR and EULAR guidelines for the management of RA do not specifically consider patients with RA-ILD, suggesting the need for a multidisciplinary approach [].
Due to the absence of evidence for RA-ILD treatment and its potential adverse effects, the decision to treat should be based on the balance between its benefits and burden of the disease in each single patient.
Lung disease progression and severity are the two main factors to consider when a decision-making on treatment is needed; other factors to be evaluated include patient's age, gender, histopathologic or HRCT subtype of ILD, worsening of symptoms, pulmonary function tests (PFTs). []
The decision to start therapy is also influenced by the presence of comorbidities that might increase the risk of adverse events (diabetes mellitus, osteoporosis, etc.).
In asymptomatic patients with non-progressive ILD a see and wait approach I s usually recommended.
To identify patients with a progressive disease, a clinical, functional and radiologic follow-up of the lung is mandatory in RA patients. The radiographic or biopsy evidence of non-UIP pattern seems to be a positive prognostic factor to therapy response [].

In this background, there are some urgent unmet need in the field of ILD-RA:

1. We don’t know the real epidemiology of ILD in RA patients.
2. Accurate and early diagnosis is challenging but crucial to ensure that each patient receives ad-hoc treatment. The recent proposal for the use of easy and non-invasive tools for a screening program of interstitial pulmonary involvement in RA patients could improve early diagnosis, in order to avoid an under-estimation of the ILD prevalence and to allow a better management of the disease.
3. Finally, nowadays there are no randomized controlled clinical trials to support therapeutic decisions in RA-ILD patients.

Thus, AIMS OF our THE STUDY PROJECT are:

1) To discuss about therapeutic options in patients with RA-ILD.
   In particular, to review the current literature on the treatment of ILD in RA patients and outline the unsolved problems regarding this challenging patient cohort; and to analyse the evolution of ILD in RA patients treated with some specific bDMARDs as tocilizumab and abatacept.
   In addition, we suggest a framework for the management of RA-ILD and outline a research agenda to fill the gaps in our knowledge.

2) To investigate the possibility of automatic detection of velcro crackle in lung sounds by analyze them using a suitably developed algorithm. The devised algorithm represents an enabling technology for a novel approach to the diagnosis of interstitial lung diseases in patients affected by rheumatoid arthritis; and to validate the diagnostic accuracy of the new algorithm in a larger population of RA patients.

3) To perform an international prospective multicentre observational study to:
   a. evaluate incidence and prevalence of ILD in patients with RA
   b. assess radiological features, clinical onset, and natural history of ILD-RA**,** as well as the risk factors for the development of ILD in RA patients

TREATMENT OF RA-ILD: RECENT ADVANCES AND UNRESOLVED ISSUES

Original article 2[176]**:**

Review: Treatment of Rheumatoid Arthritis-Associated Interstitial Lung Disease: Lights and Shadows.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting 0.5%-1% of the population worldwide[103]. It is characterized by symmetrical erosive synovitis and progressive disability, often complicated by extra-articular manifestations. Among them, lung involvement is common, and it can include a wide spectrum of disorders, ranging from airways and pleural disease, bronchiectasis and nodules, to infection and drug toxicity (**Table 8**, p. 49)[104,158,205].

Interstitial lung disease (ILD) is a serious pulmonary complication in RA, with negative impact on overall prognosis and utilization of healthcare resources[105,107,108,186]. About 10% of the RA patients develops a clinically significant ILD that is responsible for 10-20% of mortality, with a mean survival of 5-8 years[105,107,108,186]. However, the real incidence of RA-related ILD (RA-ILD) is still unknown, and a variable prevalence has been reported in literature[105,107,108,186]. The usual interstitial pneumonia (UIP) is the predominant histological/radiological pattern of RA-ILD, reported up to 66% of cases[178,206–211] (**Table 9**, p. 51). ILD can occur at any point of the natural history of RA, sometimes before the appearance of joint involvement[139,212]. Since its clinical manifestations usually appear in the advanced stages of the lung disease, an early diagnosis of RA-ILD is challenging.

Moreover, in patients with non-symptomatic RA-ILD, a clinical, functional and radiologic follow-up of the lung is mandatory to identify patients with progressive disease.

In fact, the progression and the severity of lung involvement are the two main factors to consider when a decision-making on treatment is needed. Patient's age, gender, histopathologic or radiologic ILD pattern, the worsening of symptoms or pulmonary function tests (PFTs) must be carefully evaluated[139,212–219].

The decision to start a treatment is also influenced by the presence of comorbidities that might increase the risk of adverse events (diabetes mellitus, osteoporosis, etc.).

The therapeutic approach to RA-ILD patients is furtherly complicated by some unresolved matters. First, both conventional and biologic disease modifying anti-rheumatic drugs (DMARDs) have been implicated in the development of drug-related pulmonary toxicity with conflicting data (**Table 8** p. 49; drug toxicity)[139,192,215,220–222]; secondly, there are no evidences that the treatment of RA could be effective also on lung involvement. On the contrary, immunosuppressive drugs employed in connective tissue diseases (CTD) or antifibrotic drugs approved for idiopathic pulmonary fibrosis (IPF) are not effective on arthritis.

Summarizing, to treat ILD secondary to RA is not the same as treating RA in patients with concomitant ILD.

In absence of controlled studies, the therapeutic approach to RA-ILD is still debated and based on empirical approaches dependent on retrospective studies and case series. Several therapeutic agents have been suggested, but nowadays there are no therapeutic recommendations for the treatment of RA-ILD.

The latest ACR and EULAR guidelines for the management of RA do not specifically consider patients with RA-ILD, suggesting the need for a multidisciplinary approach[223,224], while the National Institute for Health and Care Excellence (NICE) and Spanish Society of Rheumatology have proposed

national recommendations, suggesting the use of abatacept and rituximab in patients with RA-ILD, and advising against the use of TNF inhibitors[225,226].
Due to the absence of evidence for RA-ILD treatment and its potential adverse effects, the decision to treat should be based on the balance between its benefits and burden of the disease in every single patient. In asymptomatic patients with non-progressive ILD a "wait and see" approach is usually recommended[213–215].

From this perspective, we review the current literature on the treatment of patients with RA-associated ILD and discuss the unsolved problems regarding this challenging patient cohort.
To achieve our purpose, we reviewed the published studies describing the pulmonary effects of drugs (immunosuppressants, conventional, biological and target synthetic DMARDs and antifibrotic agents) in patients with RA and ILD, focusing on the articles where lung involvement was specifically investigated.
In addition, we suggest a framework for the management of RA-ILD and outline a research agenda to fill the gaps in our knowledge on this field.

Table 8. Lung involvement in Rheumatoid Arthritis.

Interstitial lung disease
UIP
NSIP, OP, DIP, LIP, mixed disease
Airways disease
Bronchiectasis
Bronchiolitis
Bronchiolitis obliterans
Follicular bronchiolitis
Panbronchiolitis
Chronic small airway obstruction
Cricoarytenoid arthritis
Rheumatoid nodules
generally, in subpleural areas, single or multiple, solid or cavitary, range in size
Pleural disease
Pleuritis
Pleural effusion
Pleural thickening
Lung entrapment and trapped lung
Pneumothorax
Vascular disease
Pulmonary hypertension
Primary (related to underlying vasculitis)
Secondary (associated to ILD)
Vasculitis
Haemorrhagic alveolitis
Venous thromboembolism
Caplan syndrome

it occurs in patients with both RA and pneumoconiosis
Lower respiratory tract infection
Common bacterial
Opportunistic infection (pneumocystis jirovecii)
Fungal
Mycobacterial
Amyloidosis
Apical fibrobullous disease
Lung cancer
Drug toxicity
NSAIDs
Diffuse pulmonary infiltration
Eosinophilic pneumonia
ARDS
Bronchospasm
Infection/Pneumonitis
Noncardiogenic pulmonary edema
Glucocorticoids
Infection/Pneumonitis
Cyclophosphamide and Mycophenolate mofetil
Infection/Pneumonitis
Fibrosis
Noncardiogenic pulmonary edema
Methotrexate
Hypersensitivity pneumonitis
Infection
New onset or exacerbation of ILD
Noncardiogenic pulmonary edema
Bronchospasm
Leflunomide
Hypersensitivity pneumonitis
Infection
New onset or exacerbation of ILD
Other conventional DMARDs
New onset or exacerbation of ILD
Infection/Pneumonitis
Obliterative bronchiolitis
Drug-induced lupus
Biologic DMARDs
New onset or exacerbation of ILD
Infection/Pneumonitis
Noncardiogenic pulmonary edema
Drug-induced lupus

Table 9. Histologic classification and typical features of IIPs, applicable to RA-ILD[178,206–211].

Histologic Patterns	Prevalence in RA	Pattern of distribution	Radiographic findings
UIP: Usual interstitial pneumonia	8-66%	Peripheral, subpleural, basal	Reticular opacities; honeycombing; minimal ground-glass opacity; architectural distortion
NSIP: Nonspecific interstitial pneumonia	19-57%	Peripheral, basal, symmetric	Extensive ground-glass opacity; irregular linear opacities; traction bronchiectasis; subpleural preservation
RB: Respiratory bronchiolitis	0-42%	Principally upper fields, centrilobular	Bronchial wall thickening; centrilobular nodules; ground-glass opacities
Mixed forms and Unclassifiable interstitial pneumonia	0-11%		Coexisting patterns of interstitial fibrosing and other lung disease, e.g. emphysema
OP: Organizing pneumonia	0-11%	Subpleural, peribronchial	Focal ground-glass opacities; consolidations; reversed halo sign
DAD: Diffuse alveolar damage	0-11%	Diffuse or focal	Consolidations; ground-glass opacities; traction bronchiectasis
DIP: Desquamative interstitial pneumonia	rare	Lower fields, predominantly peripheral	Ground-glass attenuation; cysts; reticular opacities
LIP: Lymphoid interstitial pneumonia	rare	Predominantly in the upper lung fields	Thin-walled cysts; centrilobular nodules; ground-glass attenuation; peribronchovascular septal thickening
PPFE: Idiopathic pleuroparenchymal fibroelastosis	rare	Peripheral, upper fields	Pleural thickening; subpleural fibrotic changes

1. IMMUNOSUPPRESSANTS

Panther study demonstrated an increase in mortality and infections in patients with IPF treated with immunosuppressive drugs[227]. The role of immunosuppressant in usual interstitial pneumonia (UIP) in RA or CTD has been not clarified, but a better response in ILD patterns different by UIP has been suggested by some retrospective studies[179,187,228].
Therefore, RA-ILD with nonspecific interstitial pneumonia (NSIP) or organizing pneumonia (OP) patterns could have a more favorable response to immunosuppressive therapy than UIP pattern[179,187,228].

1.1.Corticosteroids

The effect of corticosteroids on patients with an UIP pattern remains unclear. In the retrospective study by Song et al, 50% of 84 patients with UIP pattern treated with corticosteroids and

immunosuppressants presented improvement or stabilization of lung function, but without significant differences with the untreated group[229].
In a recent retrospective case series including 11 RA patients, a therapy with pulse intravenous methylprednisolone followed by oral prednisone and tacrolimus appeared to be effective and well tolerated[230].
On the other hand, corticosteroids increased the risk of serious infections in patients with RA-ILD. Zamora-Legoff found that a mean daily dose of prednisone higher than 10 mg was associated with higher rate of infections, despite the combination with DMARDs[231].
In our cohort of RA patients, respiratory infections were associated to ILD, steroids and use of biologic DMARDs (bDMARDs). Among 33 patients with ILD, a combination therapy with b-DMARDs, methotrexate, and corticosteroids was significantly more frequently recorded in patients with infections[232].

1.2.Cyclophosphamide and Mycophenolate mofetil

Cyclophosphamide (CYC) demonstrated a modest advantage in systemic sclerosis-related ILD (SSc-ILD) and other CTD-ILD[233–236], especially in combination with methylprednisolone pulses, although a metanalysis doubted the efficacy of CYC in SSc-related lung fibrosis[237].
There are no controlled clinical trials for CYC in RA-ILD, but it is used in clinical practice despite its limited efficacy data[229,238–240], especially in case of rapidly progressive ILD (**Table 10**, p. 54). Recently, a Chinese retrospective study analyzed the factors associated with progression and survivals in 266 RA-ILD patients, observing a better survival in the group treated with CYC[241].
Since CYC shows a poor benefit on RA joint involvement, it is usually associated with corticosteroids or other immunosuppressants[229,238–241].
Mycophenolate mofetil (MMF) is considered the main alternative to CYC as a first line agent or a possible maintenance therapy in CTD-ILD, with a lower rate of side effects than CYC[240,242–244].
No studies directly compare these two drugs in RA-ILD patients, as well as no data are available to recommend MMF in RA-ILD. Saketkoo et al described a clinical improvement and stability of functional and radiological lung assessment in a small case series of 3 RA-ILD patients[244]. In another retrospective study, MMF induced a stability of forced vital capacity (FVC) and the diffusing capacity of the lungs for carbon monoxide (DLCO)[243].
In 2016, a retrospective study from the UK found a better survival in patients treated with MMF than azathioprine (AZA). The relative risk of death for any cause was increased for patients on prednisone, unaltered for AZA and decreased for MMF. The Authors suggested a better outcome with MMF rather than CS or AZA for the treatment of RA-ILD[245]. Unlikely, both CYC and MMF are ineffective for the articular manifestations of the disease.

2. CONVENTIONAL DISEASE MODIFYING ANTIRHEUMATIC DRUGS (cDMARDs)

Disease modifying antirheumatic drugs, both conventional (cDMARDs) and biologic (bDMARDs), have been demonstrated to improve the joint involvement of RA, but their impact on extra-articular manifestations of the disease, mainly ILD, is unclear. Case reports, case series, and data from registries or retrospective studies demonstrated a wide spectrum of pulmonary effects (**Table 8** p. 49; drug toxicity), including improvement, but also development and worsening of ILD[220,229,246].
Only few reports describe the use of cDMARDs as a treatment for ILD in patients with RA (**Table 10**, p. 54).

2.1.Methotrexate

Methotrexate (MTX) has been associated to acute hypersensitivity pneumonia and to chronic ILD. However, recent studies and meta-analyses suggested that MTX-hypersensitivity pneumonia is less common than previously thought, and interestingly, no episodes of MTX related hypersensitivity pneumonia have been recorded in controlled trials after 2001[247]. Moreover, the association between MTX and ILD development has been recently questioned[108,247–249].

Kiely described data by ERAN and ERAS registries, showing no increased risk of ILD in RA patients treated with MTX; even better, exposure to MTX was associated with a significantly reduced risk of incident RA-ILD[249].

In 2014, a meta-analysis including 8584 participants from 22 double-blind, randomized, controlled trials demonstrated an increased risk of total adverse respiratory events relative to comparator agents. In particular, MTX was associated with an increased risk of total infectious adverse respiratory events, but not with noninfectious respiratory adverse events, including ILD and MTX-related pneumonitis[250]. Finally, Rojas Serrano have recently observed a longer survival in RA-ILD patients treated with MTX compared to other cDMARDs[251].

One paper by the same Authors describes the use of MTX and leflunomide (LEF) for the treatment of ILD in 40 RA patients. Patients received prednisone 1 mg/kg/day associated to MTX in 18 patients and LEF or AZA, or both, in 22. After a 4-month follow-up, FVC improved in both groups[246].

Although recent studies questioned the role of MTX as a causative agent in lung involvement[108,247–251], it may be cautious a tight monitoring of lung function in patients with an established diagnosis of ILD in treatment with MTX[251,252]. However, MTX remains one of the central drugs in the treat-to-target approach to RA, so treatment should not be delayed or limited in active and progressive RA[223].

2.2.Leflunomide

Leflunomide has been associated with rapid onset hypersensitivity pneumonia and new onset or progression of pre-existing ILD, with discordant published data.

In a Japanese cohort, 1.2% of 5054 RA patients who received LEF had a new onset and/or exacerbation of ILD. Pre-existing ILD was the most important risk factor for LEF-induced ILD[253]. Similar results were achieved by Ju et al. in 1,010 Korean patients, but no deaths due to ILD were detected[254].

In 2006, Suissa reported an increased risk of worsening or new onset of ILD with LEF, but only in patients with previous use of MTX or preexisting ILD[255].

Two systematic reviews found conflicting results. Conway et al. showed no association between LEF and increased risk of total or infectious respiratory adverse events in 8 controlled trials[256]; on the contrary, a previous systematic review demonstrated association between the appearance or worsening of ILD and LEF. Bilateral ground glass opacities and diffuse alveolar damage were the most common radiologic and histopathologic findings of ILD secondary to leflunomide[257].

2.3.Azathioprine

In 1977 a case report described a patient with RA biopsy-proven ILD improved after azathioprine (AZA) administration[258]. More recently, two retrospective studies described RA-ILD-UIP patients treated with corticosteroids and cDMARDs, including AZA, without conclusive results[229,246].

On the other hand, pulmonary toxicity has been also described for AZA[259]. In 2016, Oldham et al. studied adverse events related to AZA in patients with fibrotic CTD-ILD, including 15 patients with

RA-ILD. Finally, AZA was compared with MMF, demonstrating a marginal better efficacy but a higher rate of side effects[260].

2.4.Sulfasalazine, Hydroxychloroquine and Penicillamine

Lung toxicity is a rare side effect of sulphasalazine. In the past decades, numerous case reports have been published implicating sulphasalazine in acute lung toxicity, namely interstitial pneumonitis and eosinophilic pneumonia. Many patients with suspected sulphasalazine-induced lung disease improved within a few weeks after drug withdrawal[261]. No data are available regarding pulmonary toxicity of hydroxychloroquine. Although D-penicillamine could induce acute hypersensitivity pneumonitis[262,263], its use in treatment of RA-ILD has been also anecdotally described[264].

2.5.Calcineurin inhibitors (Cyclosporin, Tacrolimus)

Ciclosporin has been used in the treatment of RA-ILD with slight efficacy[229,265–268]. Some case reports described improvement or stability of ILD in a total of 4 RA patients treated with cyclosporin[259,265–267].

Tokano et al. describe a case series of 25 patients with various rheumatic diseases and steroid-resistant ILD, treated with cyclosporin A. Of the 4 patients with a diagnosis of RA, only 1 showed a transient response, while 2 patients died and the latter showed no response[268].

Tacrolimus has been successfully used in patients with ILD related to inflammatory myositis, such as dermatomyositis and anti-synthetase syndrome, also when presenting as acute respiratory distress syndrome[269–271].

In 2018, Yamano et al treated 26 patients with ILD, including 11 with RA, with tacrolimus and steroids. After a 12-month follow-up, PFTs and dyspnea significantly improved, without remarkable life-threatening adverse events[230].

However, the use of calcineurin inhibitor is often limited by their side effects and their efficacy in RA-ILD remains undefined and needs more dedicated studies.

Table 10. Pulmonary effects of immunosuppressants and cDMARDs in RA-ILD patients: review of the literature.

CYCLOPHOSPHAMIDE		
		Number of patients 89
Author, year (ref.)	*Article type*	
Chang HK, 2002 [265]	case report	1
Schupp JC, 2016 [238]	retrospective study	7
Fu Q, 2018 [241]	retrospective study	81
*Other articles**		
Song JW, 2013 [229]	na	84
Zhang G, 2015 [240]	na	23 CTD-ILD
MYCOPHENOLATE MOFETIL		
		Number of patients 29
Author, year (ref.)	*Article type*	
Saketkoo LA, 2008 [244]	case series	3
Fischer A, 2013 [243]	retrospective study	18
Oldham JM, 2016 [260]	retrospective study	8
*Other articles**		

Zhang G, 2015 [240]	na	23 CTD-ILD
	METHOTREXATE	
		Number of patients 72
Author, year (ref.)	*Article type*	
Rojas-Serrano J, 2012 [246]	retrospective study	18
Rojas-Serrano J, 2017 [251]	retrospective study	54
	LEFLUNOMIDE	
		Number of patients 12
Author, year (ref.)	*Article type*	
Rojas-Serrano J, 2012 [246]	retrospective study	12
	AZATHIOPRINE	
		Number of patients 27
Author, year (ref.)	*Article type*	
Cohen JM, 1977 [258]	case report	1
Ishida T, 2012 [259]	case report	1
Rojas-Serrano J, 2012 [246]	retrospective study	10
Oldham JM, 2016 [260]	retrospective study	15
*Other articles**		
Song JW, 2013 [229]	na	84
	PENICILLAMINE	
		Number of patients 7
Author, year (ref.)	*Article type*	
van der Schee AC, 1989 [264]	open trial	7
	CYCLOSPORINE	
		Number of patients 8
Author, year (ref.)	*Article type*	
Puttick MP, 1995 [267]	case report	1
Ogawa D, 2000 [266]	case report	1
Tokano Y, 2002 [268]	pilot study	4
Chang HK, 2002 [265]	case report	1
Ishida T, 2012 [259]	case report	1
*Other articles**		
Song JW, 2013 [229]	na	84
	TACROLIMUS	
		Number of patients 11
Author, year (ref.)	*Article type*	
Yamano Y, 2018 [230]	retrospective case series	11

* Cumulative data on more diseases or drugs. Patients not included for the evaluation of lung outcome
Legend: na=not available.

3. BIOLOGICAL DISEASE MODIFYNG ANTIRHEUMATIC DRUGS (bDMARDs)

Almost all of the bDMARDs have been associated with lung toxicity; however, their ability to improve lung function and stabilize pulmonary symptoms have been also described[220–222].

The possible effectiveness of bDMARDs in RA-ILD has been described only in few retrospective studies and as anecdotical reports (**Table 10-Table 14**). Most of the available data on this field in current literature describe the pulmonary effect of bDMARDs used for RA in patients with concomitant ILD.

3.1.Tumour necrosis factor alpha inhibitors

Tumour necrosis factor alpha inhibitor (TNFi) may have both profibrotic and antifibrotic effects, the imbalance between these two roles might trigger fibrosis or stabilize ILD[272–274].

In fact, transgenic mice over-expressing TNF-alpha develop interstitial pneumonitis resembling IPF. TNF-alpha upregulates the expression of transforming growth factor beta 1 in vitro and in animal model, resulting in chronic inflammation and lung fibrosis[272]; but, on the contrary, the TNF-alpha supplementation ameliorates the lung function and architecture in TNF-alpha (-/-) mice with bleomycin-induced lung fibrosis[274].

TNFi has been associated by many Authors to new onset or exacerbation of RA-ILD[275–283], and the British Society of Rheumatology specifically cautioned prescribing TNFi to patients with RA-ILD[284]. Recently, the NICE and Spanish Society of Rheumatology contraindicated TNFi in this population[225,226].

Despite these observations, other studies confuted a lung toxicity for TNFi and showed that these drugs can stabilize or even improve pulmonary interstitial disease[220,285,286] (**Table 11**, p. 58). For example, an American cohort study observed that, compared with cDMARDs, the use of TNFi didn't increase the occurrence of ILD among RA patients[285].

A British national prospective observational study of 367 patients with pre-existing RA-ILD found that the mortality in patients with RA-ILD was not increased by treatment with TNFi compared with cDMARDs. However, the proportion of deaths attributable to RA-ILD was higher in patients treated with TNFi therapy (34%)[275].

Finally, in the only prospective study available, Detorakis evaluated, in RA patients with or without ILD, the effects of TNFi on lung parameters, observing that the ILD extent score remained unchanged both in TNFi than in cDMARDs group. There was no exacerbation of ILD, nor new ILD onset in patients without pre-existing ILD. Moreover, TNFi induced an improvement of small airways disease[287].

On the contrary, Nakashita described a potential negative role of TNFi in RA-ILD patients. He described 14 interstitial disease events on 46 RA-ILD patients treated with TNFi; among them, 4 patients developed generalized lung disease and 2 died for ILD progression[288]. The same Authors didn't observe an increase of the prevalence of ILD progression in patients treated with tocilizumab and abatacept, whereas a prevalence of 3% of new ILD appearance and 24% of ILD worsening were described in TNFi users[288].

Curtis didn't find significant differences in the risk of ILD and its related complications among RA patients treated with a second-line biologic therapy after TNFi, comparing a second-line TNFi agents or bDMARDs with other mechanisms of action[289].

3.1.1. Infliximab

Only few case reports describe a positive effect of infliximab on RA-ILD. Vassallo described an improvement of dyspnea and a stabilization of PFTs in a patient with RA-ILD refractory to corticosteroid, after 12 months of infliximab treatment[286]. Bargagli reported another similar case in 2004[290], while Antoniou et al. identified a good response to infliximab in a case series of 3 previously progressive RA-ILD patients[291].

Otherwise, there are many reports about the possible iatrogenic role of infliximab in development or exacerbation of RA related ILD[276,280]. In a post-marketing surveillance study in Japanese RA patients, interstitial pneumonitis was observed in 25 patients (0.5%), after a mean of 2.8 infusions of infliximab[282] and respiratory disorders were the most common serious adverse drug reactions.

Adalimumab

As for the other TNFi, data derive by post-marketing surveillance report. The Japan College of Rheumatology, on 3,000 RA patients treated with adalimumab, described the occurrence of interstitial pneumonia in 0.6% of patients[277]. In another retrospective Japanese study on 200 RA patients treated with adalimumab, respiratory disorders were the third most common adverse event, represented by interstitial lung lesions in 3 patients and organizing pneumonia in 2[292].

A case report in 2011 described conflicting actions of adalimumab in the same patient with RA-ILD, suggesting that the drug might be effective against RA-ILD, but may also have caused drug-induced ILD[293]. Case reports describe also anecdotal association between ILD and the use of adalimumab[294,295].

3.1.2. Etanercept

Etanercept has been evaluated in a randomized controlled trial in the treatment of IPF, but without obtaining significant differences from placebo in disease progression nor the change of predicted FVC from baseline[296].

Only 2 case reports described a possible effectiveness of etanercept in females with RA-ILD[297,298]. In the first, treatment with etanercept improved symptoms and physical capacities in a girl with juvenile chronic arthritis and pulmonary interstitial disease[297]. More recently, Wang et al described a sustained improvement in symptoms, PFTs and high-resolution computer tomography (HRCT) findings after etanercept treatment in a 52-year-old woman with RA-ILD refractory to corticosteroids and azathioprine[298].

In 2012, a short review described 12 RA-ILD patients treated with etanercept, 6 with pre-existing ILD and 6 with new-diagnosed ILD. Among them, 8 patients developed a severe ILD (without concomitant use of MTX) and 2 patients died[299].

Moreover, exacerbation of pre-existing ILD during etanercept therapy in RA patients were described[300–302]. In real-life surveillance report published in 2011, among 13894 patients, the most frequent serious adverse events were pneumonia (0.8%) and interstitial lung disease (n=77, 0.6%)[303]. Two years later, the same Authors observed that etanercept in association to MTX showed significantly lower incidence rates for total adverse events, including ILD, than etanercept alone or associated to DMARDs different by MTX[304].

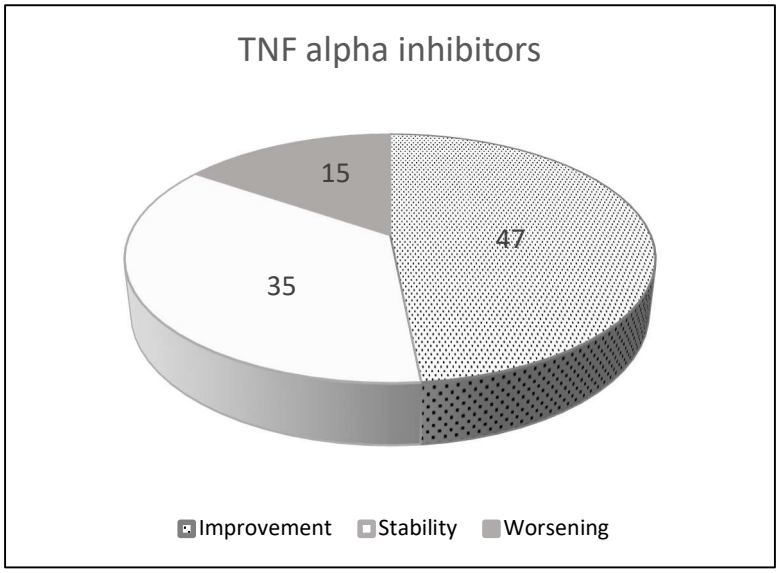
3.1.3. Golimumab and Certolizumab

There are no reports describing the use of certolizumab or golimumab in the treatment of RA-ILD patients, but, on the contrary, a possible relationship between these drugs and new onset or acute exacerbation (AE) of ILD has been described[279,305–308]. In 2017 a post-marketing surveillance study from 2579 Japanese patients treated with certolizumab reported an event rate of ILD of 1.22 per 100 patient-year[309].

Table 11. Pulmonary effects of TNFi in RA-ILD patients: review of the literature.

TNF alpha inhibitors		
		Number of patients 96
Improvement	47	48.4%
Stability	35	36.1%
Worsening	15	15.5%
Author, year (ref.)	*Article type*	*n*
Schultz R, 2001 [297]	case report	1
Vassallo R, 2002 [286]	case report	1
Bargagli E, 2004 [290]	case report	1
Antoniou KM, 2007 [291]	prospective case series	3
Wang Y, 2011 [298]	case report	1
Komiya K, 2011 [293]	case report	1
Nakashita T, 2014 [288]	retrospective review	46
Detorakis EE, 2017 [287]	prospective study	42
*Other articles**		
Kurata I, 2019 [310]	retrospective study	30

* Cumulative data on more diseases or drugs. Patients not included for the evaluation of lung outcome



3.2.Abatacept

An increasing interest on abatacept in RA-ILD is emerging in the last years (**Table 12**, p. 59).

In a murine model, abatacept (ABA) significantly reduced fibrogenic marker levels, T-cell proliferation, and M1/M2 macrophage infiltration in lungs of Fra-2 mouse model, characterized by ILD and pulmonary vascular remodeling leading to pulmonary hypertension[311]. Moreover, ABA improved ILD, significantly reducing the lung density on chest HRCT and fibrosis histological score[312].

In 2014 Mera-Valera et al used ABA in a case series of 4 RA-ILD patients, observing no adverse events nor deterioration of respiratory function tests[313]. However, in a previous case report, ILD worsened 2 days after the administration of ABA and subsequently improved after drug

discontinuation in a 55-year-old man enrolled in a trial of phase III of ABA in Japan. Interstitial shadows worsened on HRCT scans taken on day 13, and the patient withdrew the trial[314].

Ye used corticosteroids and ABA to control both joint and pulmonary disease in a RA patient who developed ILD during treatment with rituximab and MTX. The PFTs parameters improved despite a reduction of the steroid dose to 5 mg daily[315].

Nowadays, there are 6 retrospective studies that investigate the role of ABA in patient with RA-ILD. Nakashita retrospectively evaluated effectiveness and safety of abatacept in 16 RA-ILD patients. None of them experienced a worsening of ILD after 1 year, while 2 patients showed complete resolution of the pulmonary lesions[316].

As above reported, in 2015 Curtis et al. evaluated the incidence of ILD and the risk of hospitalization in a large cohort of RA patients exposed to TNFi or other biologic drugs. They found no significant differences in the risk of ILD and its related complications between patients exposed to tocilizumab, rituximab, or abatacept compared with TNFi therapies[289].

In a Spanish, retrospective, multicenter, non-controlled study on 63 RA patients with ILD treated with ABA, two-thirds of them remained stable, while one-quarter experienced improvement of the dyspnea after a mean follow-up of 9.4 ± 3.2 months. In the meantime, FVC remained stable in almost two-thirds of patents and improved in one out of five patients assessed. Also, DLCO remained stable in almost two-thirds and showed improvement in a quarter of the patients assessed. At 12 months, ILD was stable at HRCT in 11/22 patients in whom chest scan was performed, improved in 8 and worsened in 3[317].

Mochizuki T. showed deterioration of ILD in 8.4% of 131 RA patients treated with ABA for at least 1 year. On the other hand, ILD improved in 14.5% of 55 patients with ILD at baseline. Worsening of ILD was associated to the concomitant use of MTX at multivariate logistic regression analysis[318].

Recently, Kurata et al. evaluated the association between different bDMARDs and new-onset or worsening of RA-airway disease and RA-ILD. Pre-existing airway disease was an independent risk factor for ILD exacerbation or appearance after the start of bDMARDs, namely TNFi, tocilizumab and ABA. Moreover, ABA was an independent protective factor for RA-ILD exacerbation[310].

Finally, in 2020, we published data from a retrospective multicenter Italian study evaluating the evolution of ILD in 44 Italian RA-ILD patients treated with abatacept for at least six months. FVC and DLCO remained stable or increased in 86.1% and 91.7% of patients, respectively, while HRCT was stable or improved in 81.4% of them. Previous and concurrent treatments, serology, age, sex, joint and lung disease duration were not associated with the outcome at univariate analysis[319].

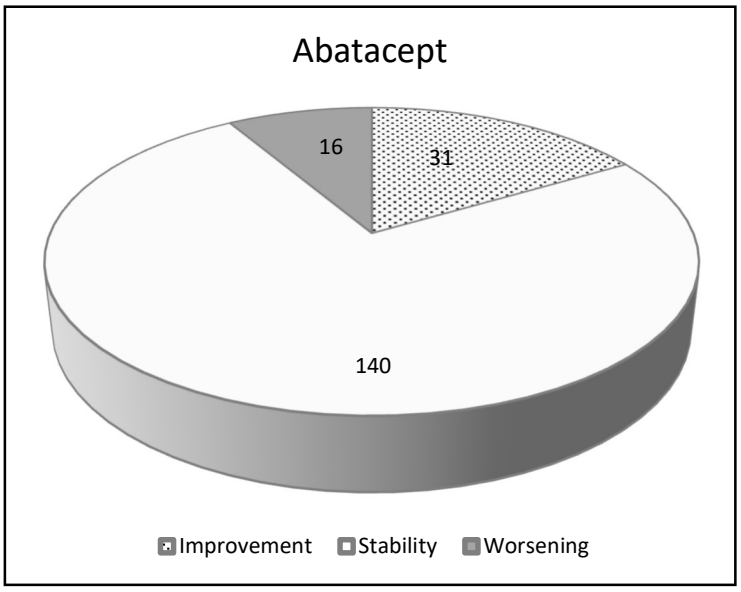
Of interest, a preliminary small clinical trial is ongoing to assess the feasibility of larger controlled study to evaluate the safety of ABA in RA-ILD (APRIL study, NCT03084419).

Table 12. Pulmonary effects of abatacept in RA-ILD patients: review of the literature.

ABATACEPT		
		Number of patients 187
Improvement	31	16.6%
Stability	140	74.9%
Worsening	16	8.5%
Author, year (ref.)	*Article type*	
Wada T, 2012 [314]	case report	1
Mera-Varela A, 2014 [313]	case series	4
Nakashita T, 2014 [288]	retrospective review	3

Nakashita T, 2016 [316]	retrospective study	16
Ye W, 2017 [315]	case report	1
Fernández-Díaz C, 2018 [317]	retrospective study	63
Mochizuki T, 2018 [318]	retrospective study	55
Cassone G, 2020 [319]	retrospective study	44
*Other articles**		
Kurata I, 2019 [310]	retrospective study	12

*Cumulative data on more diseases or drugs. Patients not included for the evaluation of lung outcome



3.3.Interleukin-6 inhibitors

3.3.1. Tocilizumab

The proinflammatory cytokine IL-6 shows profibrotic effects antagonizable by IL-6R blockade[320], suggesting a potential benefit of this therapeutic strategy in RA-associated pulmonary fibrosis. Anyway, data on its use in RA-ILD is anecdotal and conflicting (**Table 13**, p. 61).

For example, tocilizumab (TCZ) as monotherapy was found to stabilize or even improve ILD in a case-series of 4 RA patients[321], and 2 previous case reports described similar observations[322,323].

An improvement or stabilization of lung function in 75% of cases was described also in a retrospective national multicenter study of 28 RA-ILD patients treated with TCZ with or without MTX[324].

On the other hand, adverse lung effects have been also reported after use of TCZ. In particular, Wendling described the worsening of pre-existing ILD in a patient after 23 infusions of TCZ as monotherapy and subsequent improvement of symptoms and HRCT findings after its withdrawal[325].

Moreover, other reports correlate TCZ with AE of pre-existing interstitial lung disease, even with fatal outcome[326,327]. The retrospective case-control study by Akiyama et al. aimed to identify risk factors for AE of ILD during TCZ treatment in patients with RA. Of 78 patients, 6 developed AE. Univariate analysis showed that only disease activity was a risk factor for AE[327].

Data from real-life post-marketing surveillance show a good safety profile for TCZ in Japanese population of RA-ILD patients[303,328].

In an interim analysis, the presence of ILD was a risk factor for AE and serious infections[303]. In 2014, among 7901 patients, ILD was recorded in 38 (22 patients had ILD at baseline, while 16 developed ILD during treatment). Twenty-four of 38 patients had previously received other biologics. Of the 38 patients, 14 improved, 12 recovered and 7 died. At multivariate logistic regression analysis, the risk

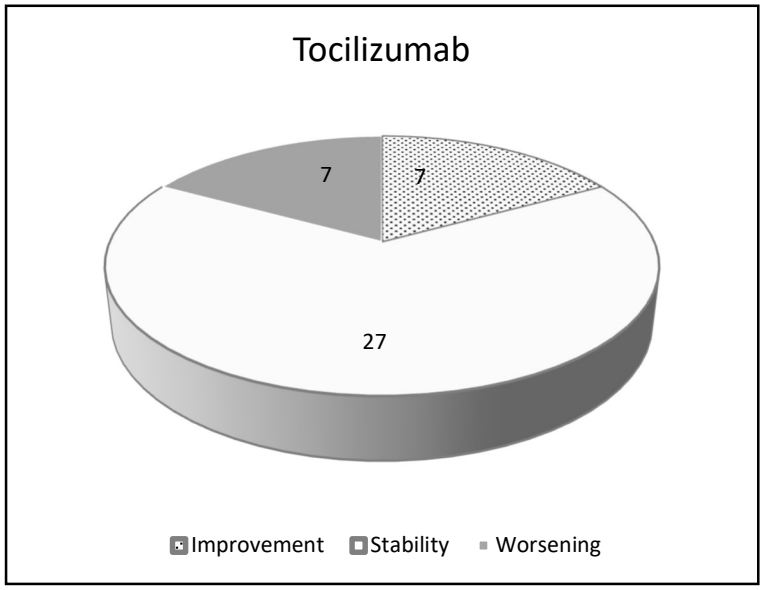
factors for ILD deterioration were advanced age (≥ 65 years) and previous or concurrent ILD at baseline[328].

Of interest, the incidence rate of ILD (0.5%) found in Japan for TCZ was similar to that recorded for infliximab (0.5%), adalimumab (0.6%) and etanercept (0.6%)[277,282,303].

Table 13. Pulmonary effects of tocilizumab in RA-ILD patients: review of the literature.

TOCILIZUMAB		
		Number of patients 41
Improvement	7	17.0%
Stability	27	65.8%
Worsening	7	17.0%
Author, year (ref.)	*Article type*	
Mohr M, 2011 [323]	case report	1
Wendling D, 2013 [325]	case report	1
Nakashita T, 2014 [288]	retrospective review	9
Picchianti Diamanti A, 2017 [322]	case report	1
Manfredi A, 2018 [321]	case series	4
Manfredi A, 2020 [324]	retrospective study	28
*Other articles**		
Koike T, 2014 [328]	postmarketing data	22
Kurata I, 2019 [310]	retrospective study	7

* Cumulative data on more diseases or drugs. Patients not included for the evaluation of lung outcome



3.3.2. Sarilumab

No new onset of ILD were described in RA patients treated with sarilumab during pre-marketing clinical trials. However, all the enrolled patients were evaluated for the presence of lung disease and a pre-existing ILD was considered as an exclusion criterion.

3.4.Rituximab

According to some retrospective data e anecdotal case reports[329–331] (**Table 14**, p. 62), rituximab (RTX) is usually considered a safe therapy for ILD including severe refractory forms[332]. However, a meta-analysis of biological therapies in CTD noted that RTX was associated with an increase of non-infectious parenchymal lung disease[333]. Furthermore, lung toxicity is widely described for RTX in hematological patients[334–337].

In a prospective study of 33 RA patients, the use of RTX resulted in a DLCO decline in 22% of the patients. Even if no cases of symptomatic lung injury were observed, the progressive DLCO decline suggested the presence of subclinical RTX-induced pulmonary toxicity[338].

In 2012 Hartung et al. firstly described a 66-year-old patient with severe RA-ILD successfully treated with RTX after failure of prednisolone and CYC[330].

In the retrospective study by Keir et al., 33 patients received RTX for ILD related to CTD, 2 of them with RA. The Authors concluded that RTX may be an effective therapeutic option in these cases, even if the highest proportion of patients with a categorical improvement was seen in the group with IIM. Data on RA patients can't be deduced[339].

In 2019, Duarte et al. described 17 RA-ILD patients treated with RTX. After a 12-month follow-up, all patients with OP or NSIP (n=12) demonstrated improvement or stability of PFTs and HRCT. Regarding patients with UIP pattern, 2/3 of patients had a decline in FVC and half had HRCT worsening[211].

Moreover, Chartrand described a highly variable response in clinical status of 15 RA-ILD patients, without significant variations of FVC over time nor a corticosteroid-sparing effect[340].

A 10-year study by Yusof et al. assessed the effects of RTX in 700 RA patients, of whom 56 (8%) had a previous diagnosis of ILD and 44 had data on lung function; pulmonary involvement improved or remained stable in 68% of cases, while 18 patients (32%) showed a progression of ILD and half of them (16%) died because of progressive ILD. Factors associated with ILD progression were radiologic UIP pattern, a previous history of lung progression and DLCO <46% of predicted before the therapy. During the follow-up period, only 3 patients developed incident cases of RA-ILD (incidence of 0.4%)[331].

In 2017, Druce et al. retrospectively analyzed 352 patients with RA-ILD treated with either RTX or TNFi as first-line biologic therapy, observing no differences in survival and cause of death between the 2 groups[341].

In 2020, Fui et al, in another retrospective study on 14 RA-ILD patients, observed a possible effect of RTX in reducing lung function deterioration after 6 and 12 months[342].

On the contrary, Matteson showed improvement of ILD only in 1/10 RA-ILD patients treated with RTX in an open-label pilot study[343].

A high rate of side effects was reported also by Dass in 48 patients with RA-ILD treated with RTX: 3 patients died, one because of pneumonia and possible acute progression of ILD. Five patients had a decline of DLCO >10% (abstract). In another abstract, 53 patients with RA-ILD treated with RTX were analyzed. There was no substantive or significant reduction in FVC and DLCO over time; 11 patients received also CYC. Only 3 patients were diagnosed with new ILD after RTX. Nine patients died because of progressive ILD[331].

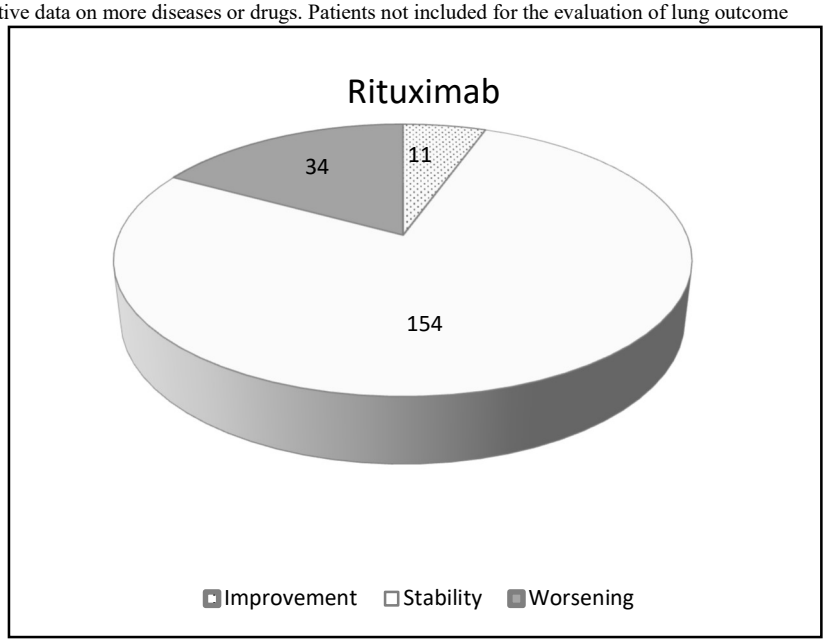
Table 14. Pulmonary effects of rituximab in RA-ILD patients: review of the literature.

RITUXIMAB		
		Number of patients 201
Improvement	11	5.4%

Stability	154	76.6%
Worsening	34	16.9%

Author, year (ref.)	*Article type*	*n*
Dass S, 2011	abstract	48
Matteson EL, 2012 [343]	open-lable pilot study	7
Hartung W, 2012 [330]	case report	1
Kabia A, 2015	abstract	53
Chartrand S, 2016 [340]	case series	15
Yusof, 2017 [331]	retrospective observational study	44
Fui A, 2020 [342]	retrospective study	14
Duarte AC, 2019 [211]	retrospective study	17
*Other articles**		
Becerra E, 2012	abstract	19
Keir GJ, 2014 [339]	retrospective study	2

* Cumulative data on more diseases or drugs. Patients not included for the evaluation of lung outcome



4. TARGETED SYNTHETIC DISEASE MODIFYNG ANTIRHEUMATIC DRUGS (tsDMARDs)

Tofacitinib and baricitinib have been recently licensed for the treatment of RA. Tofacitinib selectively inhibits the janus-kinase (JAK) 1 and 3, while baricitinib blocks JAK1 and JAK2 pathways.
Data regarding the relationship between JAK inhibitors and RA-ILD in real life are limited[344].
In RA clinical development programs of tofacitinib and baricitinib, 0.1% of the patients developed ILD and some of them were de novo ILD.
Successful use of tofacitinib has recently been described for ILD associated to anti–melanoma differentiation–associated protein 5 (anti-MDA5)–positive amyopathic dermatomyositis[345,346].
Phase III trials of tofacitinib in combination with MTX have reported only few cases of new-onset ILD and pulmonary sarcoidosis[347], and a combination of pulmonary fibrosis and chronic obstructive pulmonary disease have been observed in trials using tofacitinib as monotherapy[348].

A very low rate of ILD was recorded in the open-label extension of pre-marketing trials and in post-marketing surveillance of tofacitinib: 18/2631 patients developed ILD in combination therapy with MTX and 9/1543 in monotherapy in the open-label extension of clinical trials and 15 cases on 34223 patients/year in post-marketing surveillance, respectively[349,350]. An interim analysis of the Japanese post-marketing surveillance program of tofacitinib identified 14 cases (0.5%) with serious ILD, of which 3 died (abstract).
Recently, tofacitinib demonstrated its ability to facilitate the expansion of myeloid-derived suppressor cells (MDSC) and ameliorate arthritis in SKG mice, a murine model developing not only arthritis but also ILD. In SKG mice, tofacitinib significantly suppressed the progression of ILD compared to control, by increasing myeloid-derived suppressor cells and suppressing Th17 cells proliferation and differentiation[351]. On the contrary, in another in-vitro study, the JAK2 inhibition, but not the selective JAK1/JAK3 pathway, significantly reduced IL-17A-induced fibrogenic response in RA-ILD patients[352].

5. ANTIFIBROTIC AGENTS

RA-ILD shares some similarities with IPF, especially in patients with a UIP pattern. It shows a similar clinical behavior, often with a progressive fibrosing phenotype, and a comparable prognosis and survival[192]. Some authors suggest that RA-ILD and IPF might also overlap in disease pathogenesis[131]. Moreover, genetic risk factors, previously well characterized in IPF, are increasingly being linked to RA-ILD. For example, the MUC5B promoter variant rs5705950, telomerase complex mutations and short telomere lengths are also linked to an increased susceptibility to UIP pattern in RA-ILD[142,192,353].
The parallelisms between UIP in RA-ILD and IPF may suggest a plausible rationale in the use of antifibrotic therapy in these patients in order to treat the fibrotic process, improve outcomes and reduce lung disease progression. Moreover, given both the fibrotic and inflammatory components of this systemic disease, the combination of immunosuppressive and antifibrotic treatment can potentially be a possible future approach to this spectrum of the disease.
The INBUILD trial recently assessed the efficacy and safety of nintedanib in patients with a diagnosis of ILD other than IPF, including RA[354]. Moreover, several trials are planned or ongoing to assess the efficacy and safety of antifibrotic agents in the treatment of fibrosing ILDs other than IPF, including patients with RA (**Table 15**, p. 65)[354–357].

5.1.Pirfenidone

In Europe, pirfenidone is approved for the treatment of IPF[358].
Interestingly, Pirfenidone reduces the levels of IL6 and TNF-alpha, both cytokines related to the activation of macrophages and with a proven role in RA pathogenesis[359]. Recently, it also showed an inhibitory effect on fibroblast to myofibroblast transition in RA-ILD[360].
Pirfenidone is currently under investigation in patients with RA-ILD (TRAIL1)[356]. This phase II study (NCT02808871) estimates to enroll 270 RA-ILD patients to treat with pirfenidone three times daily (2403 mg) as add-on to existing treatment. It will evaluate a composite primary end-point with PFTs (⩾10% decline in FVC or death) and other secondary outcomes (relative decline in DLCO, FVC, incidence of AE, dyspnea scores, safety and tolerability). No preliminary data are available yet.

5.2.Nintedanib

Nintedanib is approved for the treatment of IPF, it has been shown to slow down decrease in FVC and to reduce the number of AE[358]. In vitro, nintedanib demonstrated its efficacy in reducing both pulmonary fibrosis and joint disease in female SKG mice with RA[361].
Recently, interesting results have been observed in the INBUILD study. This double-blind, placebo-controlled, phase 3 trial aimed to evaluate efficacy and safety of nintedanib in progressive fibrosing ILD secondary to other condition than IPF. The most frequent diagnoses were chronic hypersensitivity pneumonitis (26.1%) and autoimmune ILD (25.6%), including also RA-ILD patients. The patients who received nintedanib had a slower annual rate decline of FVC over a 52-week period ILD than placebo. Of interest, the results were similar in patients with UIP-like fibrotic pattern or other radiological/histological patterns. However, data on specific diseases associated to ILD are not still available[354].
In 2019, a first case report described a 74-year-old man diagnosed with RA-ILD (UIP pattern) treated with nintedanib. The use of nintedanib resulted in decreased coughing together with a reduction in FVC decline, from −11.6%/year to −5.2%/year[362].

Table 15. Clinical trials of antifibrotic agents for the treatment of fibrosing ILDs other than IPF, including patients with RA.

TRIAL NUMBER [ref.]	STUDY NAME	PHASE, DESIGN, POPULATION	PATIENTS	DURATION	STATE
NCT02999178 (*extension NCT03820726*) [354]	**INBUILD**	Phase III efficacy and safety of **nintedanib** in patients with **PF-ILD**	663	52 w	Completed Extension in fieri
EudraCT 2014–000861-32 DRKS00009822 [355]	**RELIEF**	Phase II Efficacy and safety of **pirfenidone** as **add-on to existing treatment** for **progressive, non-IPF lung fibrosis**	374	48 w	Completed
NCT02808871 [356]	**TRAIL1**	Phase II Efficacy and safety of **pirfenidone** as **add-on to existing treatment** in patients with **RA-ILD**	270 estimated	52 w	Recruiting
NCT03843892 [357]	na	Expanded access program to provide **nintedanib** to patients with **non-IPF ILD** who have no alternative treatment possibilities	na	na	Available

Legend: na= not available.

6. CONSERVATIVE THERAPY

Conservative treatment may be advisable for patients with mild and non-progressive disease or contraindications to pharmacological treatments, such as multiple comorbidities, advanced age or frailty syndrome. Non-pharmacological treatments usually include pulmonary rehabilitation, psychological and educational support.
The smoking cessation should be strongly encouraged. The support of anti-smoking counselling centres and the possible use of nicotinic replacement therapy should be considered in all patients with RA.

7.1. Pulmonary rehabilitation

The usefulness of pulmonary physical rehabilitation in RA-ILD is yet undefined. However, in idiopathic ILD, it has a short-term beneficial effect on dyspnea, functional exercise capacity and quality of life[363,364]. However, in RA-ILD patients, pulmonary rehabilitation may be compromised by the functional joint limitations related to the underlying disease.

7.2. Oxygen supplementation

Oxygen supplementation can be a major palliative therapy to improve quality of life in patients with severe lung disease, reducing respiratory symptoms during daily activities.

No data directly address the use of long-term oxygen supplementation in patients with IPF or RA-ILD.

7.3. Vaccination

Corticosteroids and immunosuppressants, as well as the presence of ILD, are associated with high risk of serious infection in RA patients[231,232].

Influenza and anti-pneumococcal vaccines should be proposed to all RA patients. Some authors also recommend prophylaxis against pneumonia by Pneumocystis Jirovecii for all patients in immunosuppressive therapy[104].

7.4. Comorbidities

A specific treatment is recommended in case of comorbidities that can worsening the clinical course of the disease, for example pulmonary hypertension, chronic obstructive pulmonary disease (COPD), gastro-oesophageal reflux ad sleep apnoea.

7. LUNG TRANSPLANT

Lung transplantation may be an option in end-stage RA-ILD. However, there are few studies evaluating post-transplant outcome in RA-ILD patients. The survival rates of 10 patients with RA-ILD undergone to lung transplantation were similar to patients with IPF[365].

In ILD related to CTD or RA, other extrapulmonary disease manifestations may complicate or contraindicate transplant procedures.

Recently, in a Northern Spanish study, CTD-ILD patients (including RA) showed a lower frequency of acute graft rejection than IPF, but also a lower 5-year cumulative survival rate[366].

Finally, a retrospective cohort compared survival, acute and chronic rejection, and extrapulmonary organ dysfunction after transplantation in patients with non-scleroderma connective tissue-related lung disease (NS-CTLD) (including RA) and IPF. The Authors found no significant between NS-CTLD and IPF. So, in appropriately selected candidates, NS-CTLD should not be considered a contraindication to lung transplantation[367].

8. ACUTE EXACERBATION OF RA-ILD

Acute exacerbation (AE) is a life-threatening condition defined as rapidly deteriorating respiratory symptoms within 1-month period with newly developed bilateral ground-glass opacities and/or consolidations on chest CT scans, superimposed on a background pattern consistent with fibrosing

ILD[368]. Other than IPF, AE can complicate also secondary forms of ILD, such as RA, CTD and chronic hypersensitivity pneumonia[155,156,369–375].

In RA-ILD patients, older age at ILD diagnosis, UIP pattern and MTX have been reported as the major risk factors for AE development[374]. AE of RA-ILD can occur at any time during the disease, and occasionally it can represent the onset manifestation of ILD [196-202]. It has a poor prognosis and high mortality, similar to AE in IPF. Therefore, an early diagnosis and referral might be important for the patients' prognosis.

Currently, there is no evidence-based data on effective therapies in AE-ILD. Usually, corticosteroid therapy is empirically used, with or without immunosuppressive agents and antibiotics[155,156,369–373,375–377].

Ota et al.[376] retrospectively reviewed 12 RA-ILD patients with AE treated with corticosteroids. Tacrolimus was added in 3 cases, cyclosporine in 4 and CYC in other 5 patients. Pulmonary function and HRCT alterations significantly improved in all cases, but the CYC group had the better life prognosis, while two patients in cyclosporine group and one patient treated with corticosteroids alone died for a relapse of AE.

Toyoda retrospectively reviewed 10 patients with CTD-ILD and AE, including 6 RA-patients. All patients were treated with antimicrobial agents and high dose corticosteroids, whereas CYC or tacrolimus were added only when a poor response to corticosteroids was observed. The median survival time after onset AE was significantly longer in patients treated with corticosteroids only[372].

In 2019, we investigated incidence of AE in a population of patients with CTD-ILD; in this context, 2 patients with RA and AE were enrolled and treated with high dose of corticosteroids: 1 patient died while the other survived[156].

Finally, two patients with AE successfully treated with nintedanib without corticosteroids or immunosuppressants have been described[377,378].

9. PROPOSAL FOR PATIENT MANAGEMENT AND TREATMENT

The optimal therapeutic regimen of RA-ILD has not been determined as no large randomized controlled trials are yet available.

Treatment options for RA-ILD are further complicated by the implication of almost all drugs used for RA in pulmonary toxicity, and the lack of evidence for their efficacy in the treatment of ILD. Moreover, immunosuppressive drugs employed in CTD or antifibrotic drugs approved for IPF are not effective on the articular manifestation of the disease.

Furthermore, the substantial variability in RA-ILD clinical presentation (subclinical, progressive, slow progression, non-progressive, chronic, acute exacerbation, etc.), histopathologic subtypes, and disease course makes it difficult to speculate about one milestone therapeutic approach.

Therefore, development of guidelines for RA-ILD treatment remains an open challenge.

The treatment of RA-associated ILD should be tailored for each patient after the evaluation of:

-age, gender, comorbidities;

-progression and severity of the lung involvement (symptoms, PFTs, DLCO, HRCT);

-histopathologic or HRCT pattern of ILD;

-activity and severity of joint disease;

-other extra-articular manifestations.

A multidisciplinary approach, including at least rheumatologist, pulmonologist and radiologist, is necessary to optimize therapy and follow-up strategies. Multidisciplinary evaluation has been confirmed as having a high level of confidence in particular for the diagnosis of IPF and CTD-ILD including RA-ILD[379].

Moreover, all RA patients should be considered at risk for ILD and the evaluation of lung involvement during the routine clinical assessment is mandatory. Indeed, an early diagnosis is needful to ensure that each patient receives appropriate treatment for his particular clinical phenotype and to avoid the use of drugs potentially involved in ILD worsening. In this regard, we recently proposed the use of VECTOR as simple, non-invasive and inexpensive tool for the screening of RA patients suspected for ILD[380].

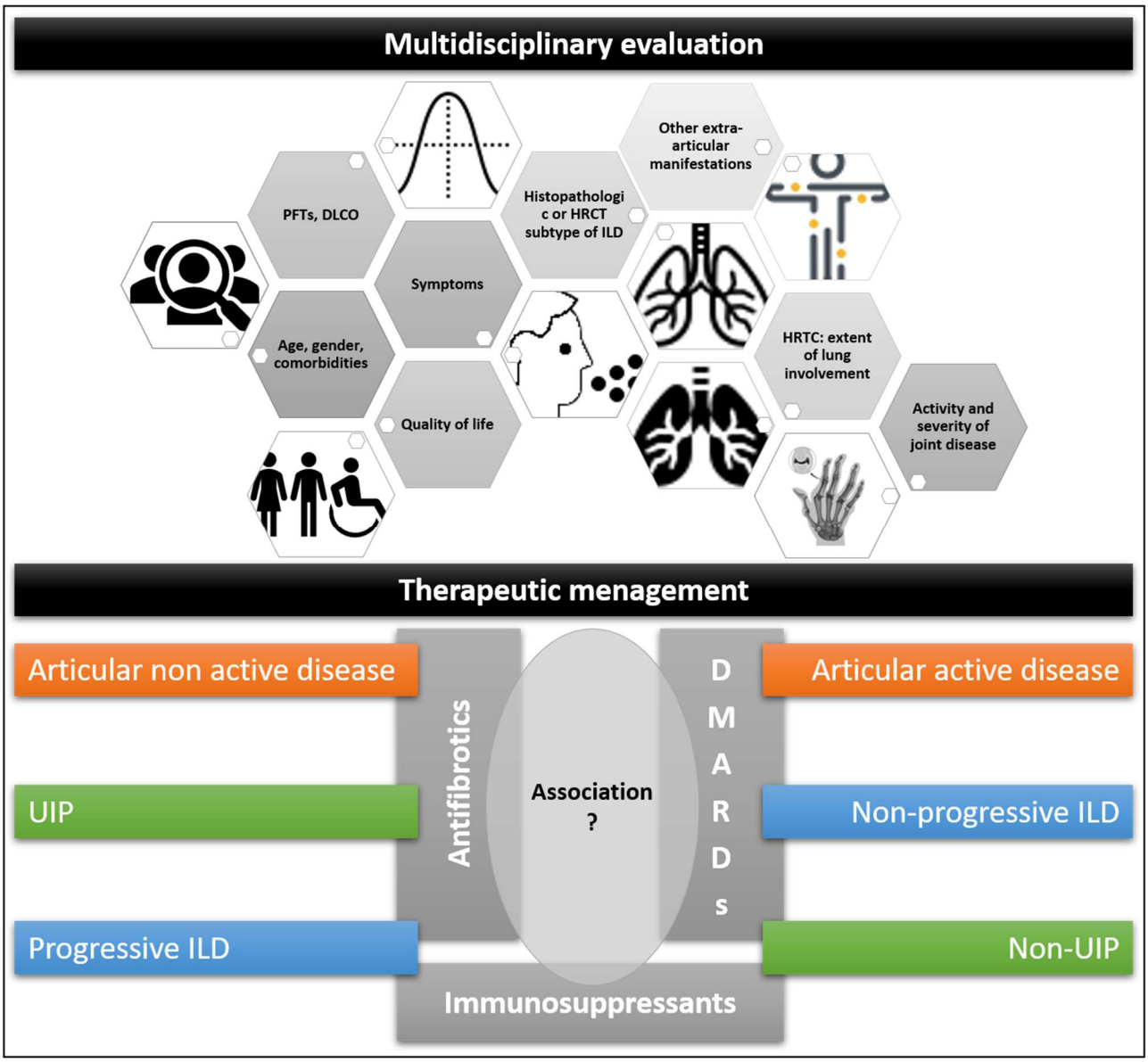
A tight follow-up must be recommended in RA-ILD patients, by means of periodic assessment of respiratory symptoms, PFTs, DLCO and HRCT.

In patients with active joint disease and subclinical non-progressive ILD, current therapy with DMARDs (including MTX and TNFi) should be continued to achieve low disease activity; while in patients starting a new DMARD, the use of ABA, JAK inhibitors, IL6 inhibitors or RTX could be appropriate[225,226,288]. However, we caution about the use of RTX in patients at high risk of infections of lower respiratory tract[231,232]. The association with MTX should evaluated in every single patient.

In patients with progressive lung disease and mild articular involvement, immunosuppressants, such as CYC and MMF, should be considered[234,235,237,240,242–244,381,382]. On the other hand, the recent data about nintedanib allow us to suppose the future use of antifibrotic agents in ILD secondary to RA[354].

Finally, in patients with progressive ILD and active joint disease a combination therapy with antifibrotic agents and bDMARDs could represent an interesting future research field (**Figure 4**).

Figure 4. Proposed framework for the management and treatment of RA-ILD patients.



10. CONCLUSIONS AND RESEARCH AGENDA

ILD is one of the most common extra-articular manifestation of RA, and its management is challenging, for the deterioration of quality of life, the high mortality and utilization of healthcare resources.

Unfortunately, ILD is often underrated, particularly in its early and subclinical stages, and the majority of the available studies on this topic are retrospective and based on low quality data.

The real epidemiology of ILD in RA patients is unknown, and no proteomic or serologic biomarkers are available to improve our armamentarium for both diagnostic and prognostic purpose. Non-homogeneous and sometimes discordant results regarding risk factor for RA-ILD have been described and, finally, randomized controlled clinical trials to support therapeutic decisions in RA-ILD patients are still missing.

In summary, there is an urgent need of prospective studies to clarify these crucial points in the field of RA-ILD.

In this framework, possible future directions of research include the prognostic value of sub-clinical RA-ILD; the development of screening programs in order to achieve early diagnosis of RA-ILD; prospective studies to discover biomarkers and predictors of lung involvement in RA.

Moreover, well-designed therapeutic trials are mandatory, and future research could move to a more personalized management and treatment of RA-ILD patients, for example to evaluate the possible concomitant use of DMARDs and anti-fibrotic agents.

Recently, antifibrotic medications are supposed to have relevance across various ILD subtypes, not only in UIP pattern (INBUILD). Ongoing clinical trials in patients with non-IPF fibrosing ILDs[354–357,383] and RA-ILD patients[354–357] (**Table 15**) will provide valuable insights into the progression of these diseases in well-characterized populations.

Finally, the cooperation between multidisciplinary groups with different experiences may be advisable for further well-designed studies on this topic. Efforts to develop a research network comprising dedicated centers with both respiratory and rheumatology interest in RA-ILD should also be made, in order to deliver important new knowledge of this condition.

Original article 3[384]:

Tocilizumab therapy in rheumatoid arthritis with interstitial lung disease: a multicentre retrospective study.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease, characterized by synovial joint swelling and tenderness, with progressive disability and joint destruction[103].

The interstitial lung disease (ILD) is the most severe extra-articular manifestation of RA, with impact on both therapeutic strategy and overall prognosis and survival[228].

About 10% of the RA population develops a clinically significant ILD that is responsible for decreased quality of life and progressive chronic disability, but also of 10-20% of all mortality associated to the disease, with a mean survival of 5-8 years[108,109,186,385].

Although both genetic and environmental factors have been investigated, the pathogenesis of RA-associated ILD (RA-ILD) remains unclear[213,386].

Moreover, the majority of conventional and biologic diseases modifying anti-rheumatic drugs (DMARDs) have been associated to the development or progression of ILD[220,222].

For these reasons, since no controlled studies are available, the therapeutic approach to RA-ILD is still debated and often empirical[110,213,214,224]. Some limited reports have evaluated the safety and the efficacy of tocilizumab (TCZ), a humanized anti-interleukin 6 (IL6) antibody, in the treatment of patients with RA-ILD[321,322].

In this retrospective study, we analysed the evolution of ILD in a population of RA patients treated with TCZ.

2. Patients and methods

In a national multicenter study, we retrospectively collected patients with ILD associated to RA treated with TCZ. All RA patients attending the Rheumatology Units of 6 Italian centers after 2008 and treated with TCZ for at least 6 months were retrospectively evaluated to identify patients with ILD.

RA was diagnosed according to the 1987 or 2010 classification criteria depending on the year of diagnosis[387,388]. The study was approved by the local Institutional Review Board.

The different patterns of interstitial lung involvement, defined by pulmonary biopsy or chest high resolution computer tomography (HRCT), were classified according to the standardized criteria of the American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias[208] as follows: 1) definite or probable usual interstitial pneumonia (UIP), 2) non-specific interstitial pneumonia (NSIP); and 3) organizing pneumonia (OP) and mixed patterns.

RF was determined by nephelometry; anti-cyclic citrullinated peptides antibodies (ACPA) were detected by standard commercial enzyme-linked immunosorbent assays (ELISA).

The results of pulmonary function tests (PFT) were expressed as percentages of the predicted value of each parameter and corrected for age, gender and height. Pulmonary function was considered as abnormal if forced vital capacity (FVC) was <80% of predicted values. Single-breath diffusing capacity of the lung for carbon monoxide (DLCO-SB) and DLCO adjusted by the alveolar volume (DLCO-VA) were used to assess gas transfer. The last HRCT and the last PFT performed before starting TCZ were recorded as baseline.

2.1 Outcome Variables

A variation of 10% of FVC or DLCO compared to baseline was considered clinically significant[389]. Improvement, worsening or stability of HRCT was centrally evaluated in a blinded manner by an experienced thoracic radiologist (GDC). PFTs were collected at baseline and periodically assessed and for all patients was recorded the last available value (within 3 months from the end of follow-up). All patients but one repeated HRCT at the end of follow-up.

2.2 Statistical Analysis

Results were expressed as median and interquartile range (IQR). Continuous variables were compared using unpaired or paired nonparametric tests (Mann Whitney or Wilcoxon test, respectively). A p value less than 0.05 was considered significant. Statistical analyses were performed using the SPSS statistical software, version 17.0 (SPSS Inc., Chicago, IL, USA).

3. Results

We included 28 RA-ILD patients (18 females and 10 males, median age 64, IQR 15) treated with TCZ. The drug was administered at the standard dose, both intravenous (8 mg/kg every 4 weeks) and subcutaneously (162 mg weekly). For all patients, HRCT was available in the previous 12 months before the beginning and at the end of the therapy with TCZ, while PFTs were available in 25/28 patients.

Baseline characteristics of RA-ILD patients included in the study are summarized in Table 16.

The median follow-up was 30 months (range 6-90). All patients were positive for RF and all but 2 for ACPA.

An UIP pattern was described in 14/28 patients (50%), while a NSIP pattern was identified in other 13 patients. In the last case a combined pattern pulmonary fibrosis and emphysema was recorded.

All patients experienced therapies with synthetic or biologic DMARDs before TCZ. Twenty-five patients (89.3%) have been previously treated with methotrexate (MTX) and 10 with leflunomide (37%); among biologic DMARDs, 10 patients (37%) experienced a therapy with TNF inhibitors, 7 with rituximab (25.9%) and 3 with abatacept (10.7%).

Twenty-three patients taken TCZ as monotherapy, while in 5 patients TCZ was associated to MTX; on the other hand, 20 patients were treated with a low dose of prednisone (5 mg daily or equivalent).

All patients but 3 were treated with subcutaneous TCZ, and 6 patients were switched from intravenous to subcutaneous route of administration.

The evolution of lung function and radiology are summarized in Figure 5.

PFTs were available at baseline and at the end of the follow-up in 25 patients. After a median follow-up of 30 months, FVC remained stable in 14 patients (56%), improved in 5 (20%) and worsened in 6 (24%). Mean FVC was stable during follow-up (99%, IQR 27 at baseline and 96%, IQR 26 at the end of follow-up).

DLCO showed a similar trend, remaining stable in 14 patients (56%), improving in 5 (20%) and worsening in 6 (24%), even though in 3 patients DLCO and FVC showed an opposite trend. Also mean DLCO remained stable during follow-up (58.5%, IQR 23 at baseline and 57%, IQR 31.5 at the end of follow-up).

HRCT was performed at the end of the follow-up in all 28 patients, it was stable in 25 cases, worsened in 2 and improved in the latter. The worsening was recorded in patients with UIP pattern, while the only case of improvement was observed in a patient with NSIP pattern.

No differences were recorded according to the duration of follow-up neither to the previous therapies.

During the follow-up period, TCZ was withdrawn in 6/28 patients: for inefficacy in 3 cases and for adverse events in the other 3 (no adverse events were correlated to the treatment). No withdrawals were recorded for a worsening of ILD or for infections.

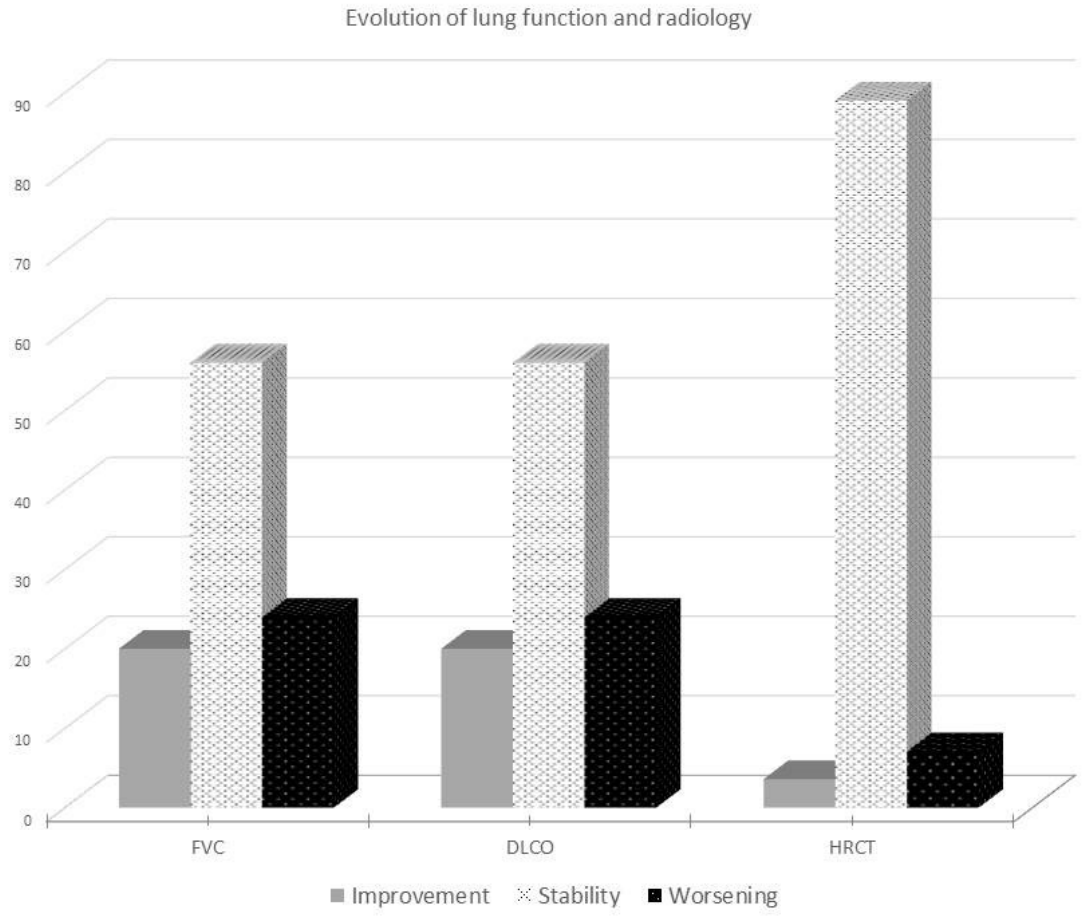
Table 16. Demographic, clinical and serological features of patients at baseline

Mean age	64 (15)
Female/Male ratio	2.25/1
Disease duration	11.5 (13)
ILD duration before TCZ therapy (months)	12 (34)
Follow-up (months)	30 (44)
Rheumatoid factor	28 (100%)
ACPA	26 (92.8%)
HRCT pattern	
UIP	14 (50%)
NSIP	13 (46.5%)
CPFE	1 (3.5%)
Forced vital capacity (%)	99 (27)
Diffusion lung CO (%)	58.5 (23)
Use of cDMARDs before TCZ	28 (100%)
Mehotrexate	25 (89.3%)
Leflunomide	10 (37%)
TNFalpha inhibitors	10 (37%)
Rituximab	7 (25.9%)
Abatacept	2 (7.4%)
TCZ mono-therapy	23 (82.1%)
TCZ + methotrexate	5 (17.8%)
Corticosteroids	20 (71.4%)

Continuous data are reported as median (IQR)

ACPA: anticiclic citrullinated peptides antibodies, UIP: usual interstitial pneumonia, NSIP: nonspecific interstitial pneumonia, CPFE: combined pulmonary fibrosis and enphisema, cDMARDs: conventional diseases modifying anti-rheumatic drugs, TCZ: tocilizumab, IQR: interquartile range

Figure 5. Evolution of lung function and radiology during follow-up.



4. Discussion

Treatment of RA-ILD is challenging, due to the possible role of DMARDs in the progression of the disease and in the development of acute exacerbation (AE). In fact, both methotrexate and leflunomide have been associated to ILD progression and development; recently, Conway demonstrated a mild increased risk of respiratory adverse events in RA patients treated with MTX compared with other conventional and biologic DMARDs[250].

Moreover, some Authors described a possible class effect of all anti-tumor necrosis factor inhibitors (TNFi) in the new onset or exacerbation of ILD secondary to RA[275–282]. Perez-Alvarez and colleagues[280] and the British Society of Rheumatology has specifically cautioned prescribing TNFi to patients with RA-ILD for the supposed increased risk of exacerbation of the ILD[284].

Nakashita didn't observe an increase of the prevalence of ILD progression in patients with TCZ and abatacept, whereas a prevalence of 3% of new ILD appearance and 24% of ILD worsening were described in TNFi users[277,282,284,288]. On the other side, Curtis et al. found no significant differences in the risk of ILD incidence and its related complications between patients exposed to tocilizumab, rituximab, or abatacept compared with TNFi therapies[289]. Moreover, some case reports have been reported about acute worsening of pre-existing RA-ILD in patients treated with TCZ[325,326].

Despite the lack of evidences, the use of MTX is poorly indicated in patients with RA-ILD[251,252]. In this regard, TCZ could represent a possible safe drug in these patients, considering its efficacy in RA also as monotherapy[390].

In our population the majority of the patients showed a stability of pulmonary function and about 20% showed an improvement of PFTs and less than a quarter of patients showed a deterioration of lung function. At the same time, only 2/28 patients showed a worsening of HRCT.
On the whole TCZ demonstrated a good safety profile in patients with RA-ILD and a good efficacy on the stabilization of the lung involvement[108,322]. In small case series, other Authors observed similar efficacy in RA-ILD patients treated with other biologic DMARDs. In particular, Md Yusof showed the improvement or the stability of ILD in 30/44 RA patients treated with rituximab, however describing a high number of infectious adverse events[331]; more recently, Fernández-Díaz et al described a high rate of improvement of ILD in 63 RA patients treated with abatacept with or without conventional DMARDS[317]. Data on abatacept were confirmed in 55 Japanese RA-ILD patients, despite the Authors observed a deterioration of lung function in patients treated with a combination therapy with MTX[41]. Finally, no reports have been reported until now about possible involvement in ILD appearance or deterioration for the Janus Kinases inhibitors[349].

5. Conclusions

In conclusion, we cannot exclude that some biologic DMARDs, such as TCZ, abatacept, RTX, poorly influence the natural clinical history of ILD and our results, in line with recent literature data, could reflect the natural evolution of lung involvement in RA. It should be essential, to minimize the risk of progression and acute exacerbation of ILD, reduce the risk of infection, providing the available vaccinations to all patients.
The management of RA-ILD patients remains a critical unmet medical need. Waiting for prospective controlled studies, in patients with RA-ILD should be preferred biologic DMARDs, namely IL-6 inhibitors, abatacept, and probably Janus kinases inhibitors, that have demonstrated a good safety profile in these specific population[109,110,322,349].
Finally, an early diagnosis of ILD in RA patients is mandatory to understand the natural history of ILD, its possible predictive factors, and to evaluate the real involvement of some DMARDs, such as MTX, in the development and progression of this severe extra-articular complication[380].

Original article 4[319]:

Safety of Abatacept in Italian Patients with Rheumatoid Arthritis and Interstitial Lung Disease: A Multicenter Retrospective Study.

1. Introduction

Interstitial lung disease (ILD) is a severe extra-articular manifestation of rheumatoid arthritis (RA), deeply impacting quality of life, overall prognosis and survival[103,139].

Although prevalence of ILD in RA patients was unclear, it is responsible for decreased quality of life and progressive chronic disability in a significant proportion of patients, but also of 10-20% of all cause of death associated to the disease, with an estimated mean survival of 5-8 years[105,107,108,186].

The pathogenesis of RA-associated ILD (RA-ILD) remains unclear[386], but both genetic and environmental factors have been investigated.

Moreover, almost all the conventional and biologic diseases modifying anti-rheumatic drugs (DMARDs) have been associated to ILD development or progression[215,220,222].

Waiting for controlled studies, the therapeutic strategy in RA-ILD patients is still debated and empirical[139,192,214,215,386]; in fact, the treatment of joint involvement in this subgroup of patients should be effective, but safe on the lung manifestation of disease.

Abatacept (ABA) is a soluble fusion protein, comprising cytotoxic T-lymphocyte-associated protein 4 and an Fc portion of immunoglobulin G1 that inhibits T-lymphocyte co-stimulation, approved for the treatment of moderate to severe RA[223]. In the last years, an increasing interest on ABA in RA-ILD is emerging, based on its capacity to improve ILD in mice models[311,312]. Recently, some Authors described the possible effectiveness and safety of abatacept in the treatment of patients with RA-ILD[289,313,315–318].

In this multicenter retrospective study, we analysed the evolution of ILD in a population of RA patients treated with ABA.

2. Patients and methods

In a national multicenter study, we retrospectively collected patients with RA-ILD treated with ABA.

All RA patients attending the Rheumatology Units of 6 Italian Centers between 2012 and 2018 and underwent to ABA therapy for at least 6 months were retrospectively evaluated to identify patients with ILD.

RA was diagnosed according to the 1987 or 2010 classification criteria depending on the year of diagnosis[387,388]. The study was approved by the local Institutional Review Board.

The different patterns of interstitial lung involvement, defined by pulmonary biopsy or chest high resolution computer tomography (HRCT), were classified according to the standardized criteria of the American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias[208] as follows: definite or probable usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP) and mixed patterns.

Rheumatoid factor (RF) was determined by nephelometry; anti-cyclic citrullinated peptides antibodies (ACPA) were detected by standard commercial enzyme-linked immunosorbent assays (ELISA).

The results of pulmonary function tests (PFT) were expressed as percentages of the predicted value of each parameter and corrected for age, gender and height. Pulmonary function was considered as abnormal if forced vital capacity (FVC) was <80% of predicted values. Single-breath diffusing

capacity of the lung for carbon monoxide (DLCO-SB) was used to assess gas transfer. The last HRCT and the last PFT performed before starting ABA were recorded as baseline.

2.1 Outcome Variables

A variation of 10% of FVC and 15% of DLCO compared to baseline was considered clinically significant[389]. Improvement, worsening or stability of HRCT was centrally re-evaluated in a blinded manner by an experienced thoracic radiologist (GDC). PFTs were collected at baseline and periodically assessed and for all patients was recorded the last available value (within 3 months within the end of follow-up). All patients but one repeated HRCT at the end of follow-up.

2.2 Statistical Analysis

Results were expressed as median and interquartile range (IQR). Continuous variables were compared using unpaired or paired nonparametric tests (Mann Whitney or Wilcoxon test, respectively). A p value less than 0.05 was considered significant. Statistical analyses were performed using the SPSS statistical software, version 17.0 (SPSS Inc., Chicago, IL, USA).

3. Results

We included 44 RA-ILD patients (32 females and 12 males, median age 65 years, IQR 11) treated with ABA. The drug was administered at the standard dose, both intravenous (every 4 weeks) and subcutaneously (125 mg weekly). At the time of ABA initiation, the median of RA duration was 89 months (IQR 142), while ILD predated by a median of 20 months (IQR 58).

For all patients, HRCT was available in the previous 12 months before the beginning and at the end of the therapy with ABA, while PFTs were available in 42/48 patients (87.5%).

Baseline characteristics of RA-ILD patients included in the study are summarized in Table 17.

The median follow-up was 26.5 months (range 6-116, IQR 38). A high percentage of patients was positive for RF (38/44 patients, 86.4%) and for ACPA (40/44, 90.1%).

At the end of follow-up, RA showed a remission or a low disease activity in all patients but 3.

Table 17. Demographic, clinical and serological features of patients at baseline

Mean age	65 (11)
Female/Male ratio	2.7/1
Disease duration	7.4 (11.8)
ILD duration before ABA therapy (months)	20 (58)
Follow-up (months)	26.5 (38)
Rheumatoid factor	38 (86.4%)
ACPA	40 (90.1%)
HRCT pattern	
UIP	19 (43.2%)
NSIP	22 (50%)
CPFE	2 (4.5%)
OP	1 (2.3%)
Forced vital capacity (%)	88.5 (18.5)
Diffusion lung CO (%)	66.4 (34.5)

Use of cDMARDs before TCZ	44 (100%)
Mehotrexate	32 (72.3%)
Leflunomide	20 (45.5%)
TNFalpha inhibitors	19 (43.2%)
Tocilizumab	9 (20.5%)
Rituximab	5 (11.4%)
Janus kinases inhibitors	3 (6.8%)
ABA mono-therapy	9 (20.4%)
ABA + methotrexate	17 (38.6%)
Corticosteroids	33 (75%)

Continuous data are reported as median (IQR).

ACPA: anti-cyclic citrullinated peptides antibodies, UIP: usual interstitial pneumonia, NSIP: nonspecific interstitial pneumonia, OP: organizing pneumonia; CPFE: combined pulmonary fibrosis and emphysema, cDMARDs: conventional diseases modifying anti-rheumatic drugs, ABA: abatacept, IQR: interquartile range.

3.1 Previous treatments

All patients experienced therapies with synthetic and/or biologic DMARDs before ABA.

In particular, all patients but 5 were previously treated with methotrexate (MTX) or leflunomide (LFN), namely 32 (72.7%) with MTX and 20 (45.5%) with LFN. Twelve patients were previously treated with both drugs, alone or in combination.

Abatacept was the first biologic DMARD in 19 patients (43.2%). Twenty-five subjects were previously treated with other biologic DMARDs, in particular 19 subjects (43.2%) with a tumour necrosis factor inhibitor (TNFi), 9 (20.5%) with tocilizumab, 5 (11.4%) with rituximab and 3 (6.8%) with a Janus kinases inhibitor. In 34 cases (77.3%), ABA was the first or second biologic DMARD.

3.2 Current treatments

Only 4 patients (9.1%) were treated with intravenous ABA, while 3 (6.8%) have been switched by intravenous to subcutaneous route of administration. ABA was prescribed in combination with MTX in 17 patients (38.6%) or with other DMARDs in 18 (40.9%); monotherapy with ABA was recorded in the other 9 patients (20.4%), all in combination with low dose of steroids. Finally, a low dose of prednisone (usually ≤ 5 mg daily) was prescribed in 33 patients (75%).

3.3 ILD radiologic patterns

All patients had a HRCT in the 12 months before starting ABA. Usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) were the 2 prevalent HRCT pattern (43.2% and 50%, for UIP and NSIP, respectively), while a combined pulmonary fibrosis and emphysema (CPFE) was described in 2 patients (4.5%) and an organizing pneumonia in the latter (2.3%).

3.4 Pulmonary function tests

PFTs were available at baseline in 39/44 patients. The median of FVC was 89% (IQR 18) and it was normal at baseline in 82.1% (32/39). DLCO was available in 38/44 patients and was normal in less than 50% of patients (44.7%, 17/38), with a median of 66.4% (IQR 34.5).

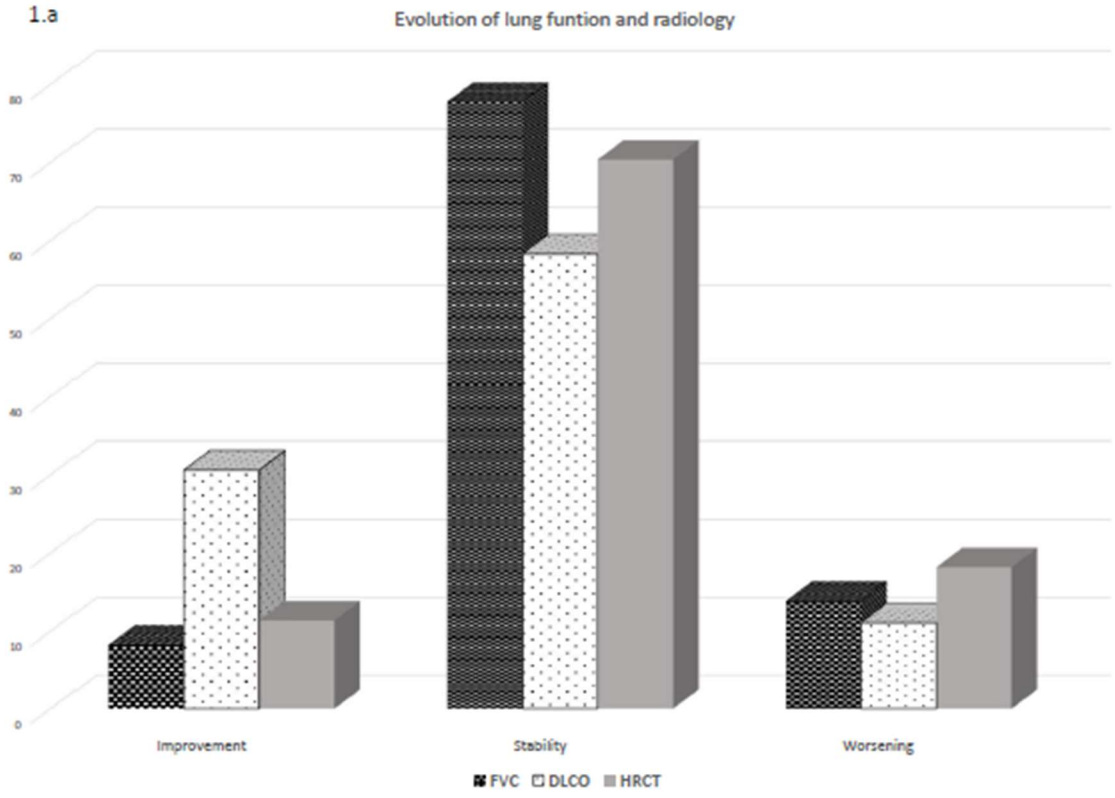
3.5 Evolution of lung function and HRCT

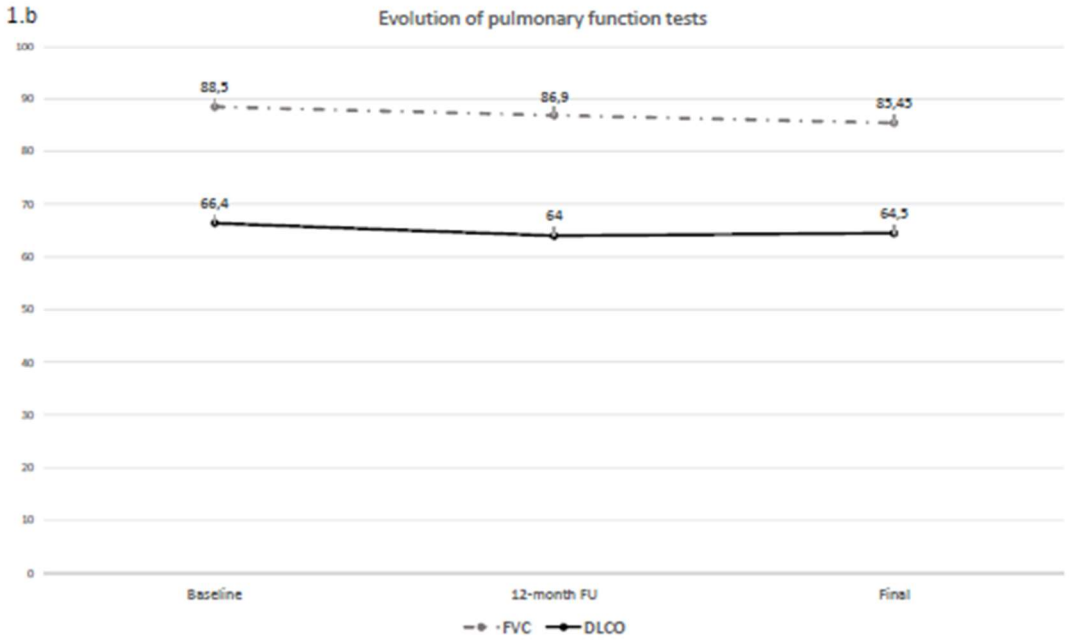
The evolution of lung function and radiology are summarized in Figure 6a and 6b.

PFTs were available after 1-year and at the end of the follow-up in 36 patients. The median of FVC was 86.9% (IQR 28.8) and 85.45% (IQR 21.5) after one year and at the end of follow-up, respectively; After 1-year follow-up, FVC remained stable in 28/36 patients (77.8%), improved in 3 (8.3%) and

worsened in 5 (13.9%). The trend of FVC didn't change at the end of follow-up, FVC stable, improved and worsened in 28, 3, and 5 patients, respectively.
The median of DLCO was 64% (24.3) and 64.5% (27.5) after one year and at the end of follow-up, respectively; after 1 year, DLCO remained stable in 50% of patients (18/36), worsened in 11.1% (4/36) and improved 14 patients (38.9%). At the end of follow-up, 3 patients, initially improved, showed a decrease of DLCO up to the baseline values.
HRCT was performed at the end of the follow-up in all patients, it was stable in 31/44 cases (70.4%), worsened in 8 (18.2%) and improved in 5 patients (11.4%). The worsening was recorded in 6 patients with UIP and 2 with NSIP pattern, while, on the contrary the 5 cases of improvement was observed in 4 patients with NSIP pattern and only one with UIP pattern.
On the whole, HRCT in patients with UIP pattern worsened in 6 cases, remained stable in 12 and improved in the latter; NSIP remained stable in 16 patients, improved in 4 and worsened in 2.
Univariate analysis didn't show any differences in patients with worsening and stability or improvement of lung disease, regarding previous therapy with MTX or LFN, previous biologic DMARDs, combination therapy with MTX, positivity for ACPA or rheumatoid factor, age at disease onset, joint and lung disease duration.
A trend for a worst FVC evolution was observed in male patients ($p=0.07$).
During the follow-up period, ABA was withdrawn in only 4 patients: for loss of efficacy on RA in 3 patients and for a non-respiratory infectious adverse event in the fourth case.

Figure 6a and 6b. Evolution of lung function and radiology during follow-up.





4. Discussion

Treatment of RA-ILD is challenging, due to the possible role of DMARDs in the progression of the disease and in the development of acute exacerbation of ILD (AE)[139,192,214,215,220,222].

Recently, some Authors described in case reports and retrospective studies the possible effectiveness and safety of abatacept in the treatment of RA patients complicated by ILD, showing a stability of lung function during the follow-up period and the absence of severe adverse events[313,318] in particular

no cases of AE of ILD were described during the therapy (only a case of AE 2 months later ABA discontinuation has been described in literature[314]).

ABA was associated to the improvement of FVC and DLCO in 20% and 25%, respectively, in 63 RA-ILD patients from a Spanish retrospective cohort[317], while Mochizuki described an improvement in 14.5% of 55 RA-ILD patients. Worsening of ILD was associated to the concomitant use of MTX at multivariate logistic regression analysis[318].

Moreover, Nakashita recorded new appearance in 3% and the worsening of pre-existing ILD in 24% of RA patients treated with TNF alpha inhibitors (TNFi) compared with no events in ABA and tocilizumab group[288,316]. On the other side, Curtis et al. found no significant differences in the risk of ILD incidence and its related complications in a large cohort of patients in second-biologic line after a first-line treatment with TNFi, among patients exposed to tocilizumab, rituximab, or ABA compared with TNFi therapies[289].

Kurata et al. recently found that abatacept was an independent protective factor for RA-ILD exacerbation after the initiation of bDMARDs[310] [30].

Finally, a small clinical trial to assess the safety of abatacept in patients with RA-ILD is ongoing (APRIL study, NCT03084419). The investigators underline that it's a small clinical trial to assess the feasibility of performing a larger randomized controlled trial.

Our data confirm the safety of ABA in the treatment of RA-ILD patients, showing a good safety on lung involvement of disease. MTX seems to be safe in our RA-ILD patients, although, due to the low number of patients, the possible role of MTX as possible factor associated to ILD evolution cannot be fully evaluated and prospective studies should be scheduled in this regard.

In Japanese series MTX has been suspected to be involved in lung disease progression[318]; on the contrary, we systematically evaluated previous and concurrent therapy to ABA without highlighting any role for MTX or other conventional DMARDs in progression of ILD in Italian RA patients.

Until the definition of the possible lung toxicity of MTX in controlled study, a cautious use of this drug in RA-ILD patients should be considered and, in these cases, the use of ABA as monotherapy should be considered. The main limit of our study is represented by the retrospective design of the study, but the rigorous recording of PFT and the centrally re-evaluation of HRCT ensure the quality of our data.

Available data didn't allow us to postulate an efficacy of ABA in the treatment of ILD in RA patients, but our data furtherly reinforce our knowledge about the safety of ABA in the management of RA complicated by ILD. Moreover, ILD is associated to a high risk of infectious complications and the safety profile of ABA with regard to infection could represent another point to encourage the use of this drug in RA-ILD patients[232]. Other biologic DMARDs, such as interleukin 6 and Janus-kinases inhibitors, seem to be associated to a good safety profile in RA patients complicated by ILD[322,324,349].

In conclusion, the management of RA-ILD patients remains a critical unmet medical need. Waiting for prospective controlled studies, in patients with RA-ILD should be preferred biologic DMARDs, such as ABA, that have demonstrated a good safety profile in these specific population [17-22], and avoided conventional DMARDs, namely leflunomide and MTX, until the exact definition of their possible role in ILD worsening.

Finally, an early diagnosis of ILD in RA patients should be encouraged for increase our knowledge on the natural history of ILD, its possible predictive factors, and the possible involvement of DMARDs, in the development and progression of this RA complication[380].

Original article 5[391]**:**

Case report: Pirfenidone for the treatment of interstitial lung disease associated to rheumatoid arthritis: a new scenario is coming?

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease, affecting 0.5%-1% of the population worldwide. It is a systemic disease, characterized by typical joint involvement with symmetrical erosive synovitis and progressive disability[103].

Interstitial lung disease (ILD) is a frequent extra-articular manifestation of RA, with negative impact on overall prognosis and utilization of healthcare resources[103,105,107,108,139,186,205]. The real incidence of RA-ILD is unknown, but a prevalence of 7-10% for symptomatic RA-ILD has been reported, that is responsible of 10-20% of all mortality, with a mean survival of 5-8 years[105,107,108,186].

The predominant histological/radiological pattern of RA-ILD is usual interstitial pneumonia (UIP) reported in 44-66% of cases[209]. The UIP pattern demonstrated having a poorer prognosis than other forms, sharing many analogies with idiopathic pulmonary fibrosis (IPF)[217,392]. Moreover, clinical, etiopathogenetic and genetic similarities between RA-ILD, especially with UIP pattern, and IPF have been described[119,125,131,139,142,219,353,393].

Several therapeutic agents have been suggested for the treatment of RA-ILD, but nowadays there are no randomized controlled clinical trials to support therapeutic guidelines; therefore, the role of immunosuppression remains uncertain. On the other hand, antifibrotic drugs have been shown to reduce the decline in lung function in patients with IPF and their use is now recommended for the treatment of this progressive fibrosing ILD[358].

This background may suggest a plausible rationale in the use of antifibrotic therapies, such as pirfenidone, in RA-ILD patients, especially in UIP pattern. Moreover, the concomitant use of anti-fibrotic agents and biological or conventional DMARDs represents an emergent gap of knowledge.

To date, there is only one ongoing clinical trial evaluating safety and efficacy of pirfenidone in RA-ILD (TRAIL1), and no other published data are available on this topic[356].

We describe for the first time two RA-ILD patients successfully treated with pirfenidone.

CASES PRESENTATION

Patient 1.

In 2014, a 70-year-old man presented to the pneumological unit of our Hospital for persistent dry cough. His past clinical history revealed the presence of metabolic syndrome (type 2 diabetes mellitus, increased blood pressure, high levels of cholesterol and triglyceride, and a BMI of 32) and a post-surgical hypothyroidism for a diffuse multinodular goiter. He was a current smoker (60 pack/years), and before retiring he worked as a construction worker and foundry worker.

Chest X-ray showed a diffuse thickening of the lung, and a subsequent high-resolution computed tomography (HRCT) was diagnostic for a diffuse ILD with typical UIP pattern: basal and subpleural reticular opacities, honeycombing and traction bronchiectasis, associated with some areas of pleural thickening of the right lung, were recorded (Figure 7 A).

Pulmonary function tests (PFT) described a mild restrictive ventilatory defect with slight reduction of forced vital capacity (FVC) and normal value of single-breath diffusing capacity of the lung for carbon monoxide (DLCOsb) (FVC 81%, DLCOsb 80%).
With the exception of bilateral velcro crackles at pulmonary clinical evaluation, the patient's physical examination was unremarkable: no arthralgias or arthritis, no Raynaud phenomenon, no sicca syndrome or other signs or symptoms suggestive for connective tissue diseases (CTD) were detected. Schirmer's test was negative.
Routine laboratory examinations and immunological texts, including anti-nuclear antibodies (ANA), rheumatoid factor (RF) and anti-cyclic citrullinated peptide antigen (ACPA) were negative.
After a multidisciplinary discussion including pulmonologist, rheumatologists and radiologists, in April 2014 lung environmental exposures (in particular possible exposure to asbestos) were excluded and a diagnosis of idiopathic pulmonary fibrosis (IPF) was made. The patient started an antifibrotic therapy with pirfenidone 2403 mg daily. Afterwards, the treatment was reduced to 2136 mg/die for symptoms of gastrointestinal intolerance. Dry cough and general clinical conditions improved gradually.
During the following two years, PFT showed an improvement of FVC greater than 10% of the baseline value and a slight decrease of DLCOsb (FVC 94%, DLCOsb 65%). Chest HRCT images showed a stabilization of the lung fibrosis. No oxygen desaturation at 6-minute walking test was reported (520 m of walking).
In January 2017, the patient referred to our multidisciplinary outpatient of the university-based Center for Rare Pulmonary Diseases for the occurrence of inflammatory arthralgias, polyarticular morning stiffness and bilateral swelling of the wrists. The ultrasound sonography confirmed an arthritis involving wrists and III proximal interphalangeal joint of the left hand.
Laboratory test were repeated and revealed: increased erythrocyte sedimentation (57 mm) and C-reactive protein (2.05 mg/dl), ANA 1:80 speckled, RF 18 U/ml (normal value < 14) and ACPA 522 U/ml (normal value < 20). Extractable nuclear antigens (ENA), anti-synthetase antibodies and antineutrophil cytoplasmic antibodies were negative; C3 and C4 were normal. Screenings for hepatitis virus C and B were negative, while QuantiFERON TB Gold test was compatible with latent tuberculosis infection, in absence of X-Ray signs of disease.
Patient satisfied the EULAR/ACR classification criteria for RA and treatment with methylprednisolone 16 mg/die, gradually tapered to 4mg/die, and hydroxychloroquine 400 mg/die was started. Considering the clinical, functional and radiological stabilization of the ILD with the use of pirfenidone, the antifibrotic therapy was maintained in association with anti-rheumatic therapy. Finally, a treatment regimen for latent TB infection using isoniazid 300 mg/die was started.
Few months later, the patients experienced an improvement of articular manifestations and reached an inactive disease activity without worsening of respiratory symptoms. In November 2017, a chest HRCT was repeated, showing mild progression of the lung fibrosis, with interstitial subpleural thickening of the lower lung lobes, traction bronchiectasis and multiple cysts (Figure 7 B). Simultaneously, PFTs confirmed a stabilization of the lung function (FVC 95% and DLCOsb 59%).

Clinical history of patient 1 is summarized in Figure 8.

Figure 7. Chest high-resolution computed tomography images of patients 1 (A: at baseline; B: at follow-up).

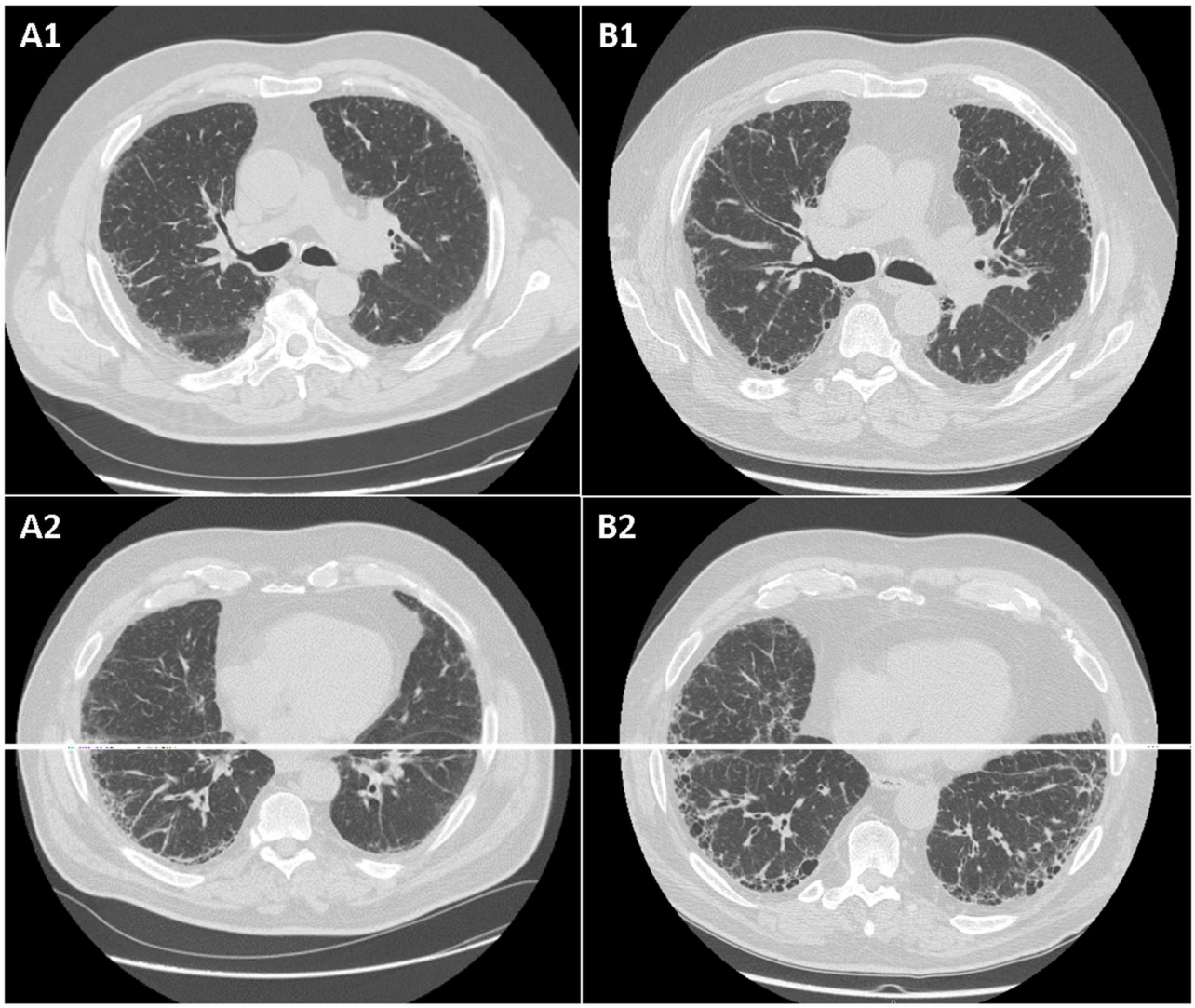
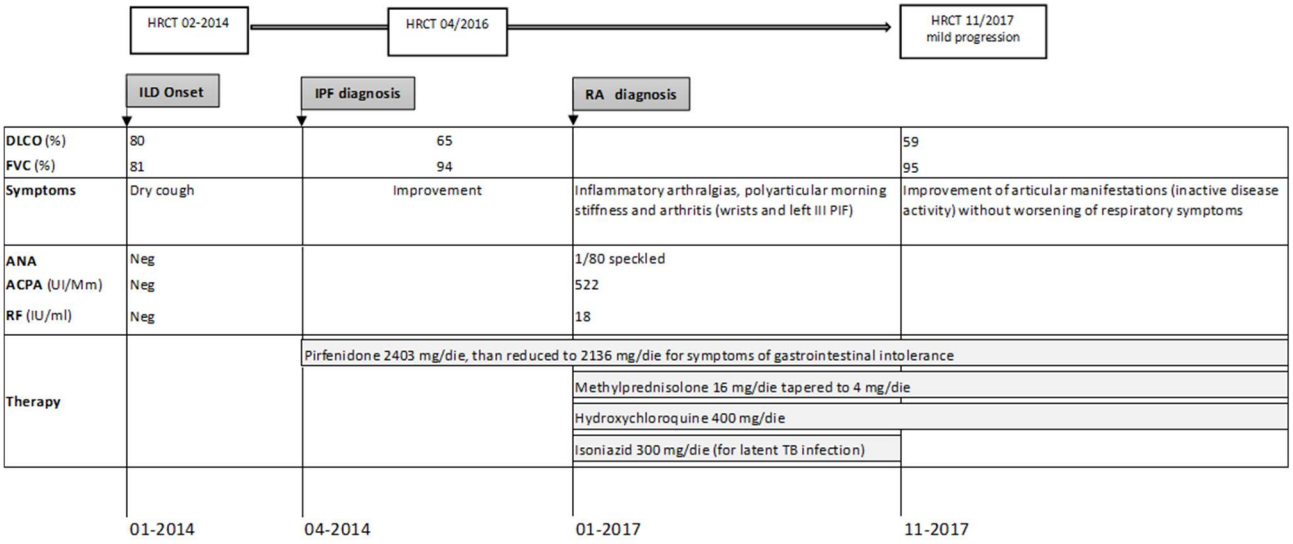


Figure 8. Clinical case summary patient 1



HRCT: high resolution computer tomography; ILD: Interstitial lung disease; RA: Rheumatoid arthritis; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide test; UIP: usual interstitial pneumonia; ACPA: anti-citrullinated peptides antibodies ; RF: rheumatoid factor; TB: tuberculosis.

Patient 2.

In 2015, a 69-year-old man referred to the pneumological unit of our Hospital for dyspnea.

He reported a past clinical history of type II diabetes mellitus, hypertension and at least 3 cardiac surgery procedures of coronary artery bypass. He worked as a mail carrier and no environmental exposure were detected during the clinical interview. He was a former smoker (45 pack/years until 1995).

Patient's physical examination revealed fine velcro crackles in bilateral lower lung fields. Routine laboratory examinations and immunological texts, including anti-nuclear and anti-neutrophil cytoplasmic antibodies, RF and ACPA were negative.

HRCT showed parenchimal consolidation areas, cysts, ground-glass opacities and interlobular septal thickening, as well as bronchiectasis. These abnormalities were consistent with an UIP pattern (Figure 9 A), and a diagnosis of IPF was made.

PFT confirmed a mild restrictive ventilatory defect (FVC 96%, TLC 71%) with reduction of DLCOsb (51%). In march 2015, the patient started pirfenidone 2403 mg/die, without adverse events.

At 6-month follow-up, the patient reported a clinical improvement and PFTs also revealed stability of pulmonary function (FVC 90%, TLC 80%, DLCOsb 43%). An echocardiogram excluded the presence of indirect signs of pulmonary hypertension.

However, at 18-month follow-up, a decrease of DLCOsb was recorded (33%) without worsening of clinical symptoms. The patient also reported erythematous skin lesions in photo-exposed areas of the body, possible side effect of pirfenidone. Clinicians suggest to repeat a chest HRCT and PFTs, they informed the patient about the importance of sun protection during the assumption of pirfenidone, and the antifibrotic treatment was continued. A stabilization of lung function (FVC 84%, TLC 71% and DLCO sb 44%) and of the ILD at chest HRCT was assessed.

In may 2017, for persistent arthralgias and polyarticular morning stiffness, the patient referred to our rheumatologic unit. He reported a past clinical history of inflammatory arthralgias with anecdotal episodes of swelling joints. He denied sicca syndrome, Raynaud's phenomenon, purpuric skin lesions

or photosensitivity skin reactions and oral ulcers. Physical articular examination revealed an arthritis of the II metatarsophalangeal joint of the left foot, left wrist and right ankle, confirmed by articular ultrasound.
A positivity for type III cryoglobulins, RF (118 U/l) and ACPA (7579 U/l) was detected. ANA were also positive with a speckled pattern and a title of 1:160, while ENA and anti-Synthetase antibodies were negative.
Schirmer's Test was negative, and no major abnormalities were detected at nailfold videocapillaroscopy. However, minor salivary glands' biopsy showed a lymphocytic sialadenitis with 2 lymphocytic foci (focus score >1[394]).
A diagnosis of Rheumatoid arthritis and secondary Sjogren syndrome was performed by our rheumatology-pulmonology multidisciplinary team, according to clinical and laboratory data. We started prednisone 25 mg/die, progressively tapered to 5 mg/die, and hydroxychloroquine 400 mg/die. According to the stability of the interstitial pulmonary disease, we also decided to continue pirfenidone.
Few months later, because of an articular exacerbation of the joint disease, tocilizumab 162 mg/week was started and quickly (after 4 weeks) withdrawn for leukopenia till 2400/mmc white cells.
Subsequently, our patient remained asymptomatic, both for articular and respiratory manifestations, despite the withdrawal of corticosteroid therapy. A chest HRCT in August 2017 showed a slight progression of the fibrosing ILD with a definite UIP pattern (Figure 9 B). Nevertheless, no decrease of FVC or DLCO (FVC 92% and DLCO sb 36%) as well as no desaturation at 6-minute walking test were reported.

Clinical history of patient 2 is summarized in Figure 10.

Figure 9. Chest high-resolution computed tomography images of patients 2 (A: at baseline; B: at follow-up).

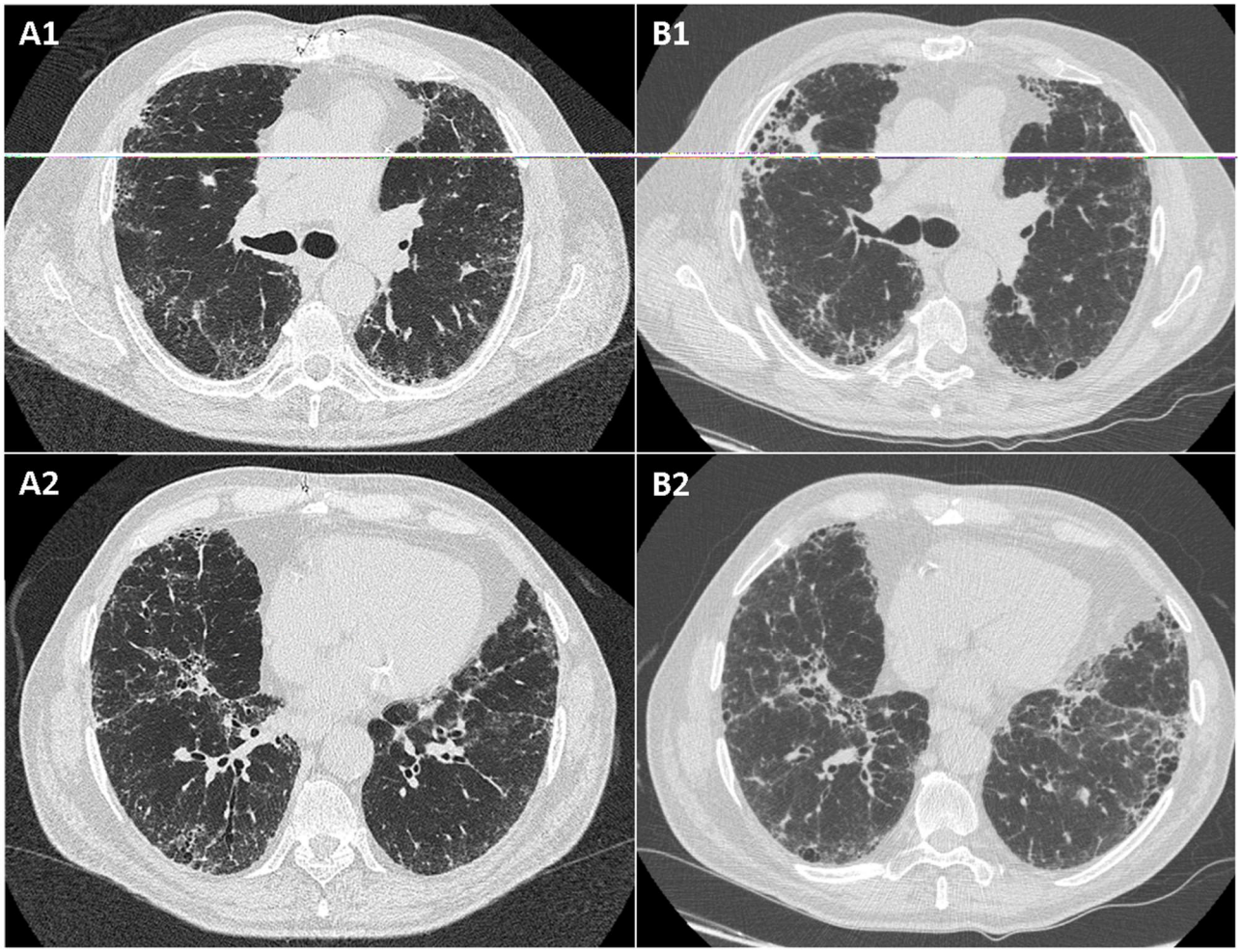
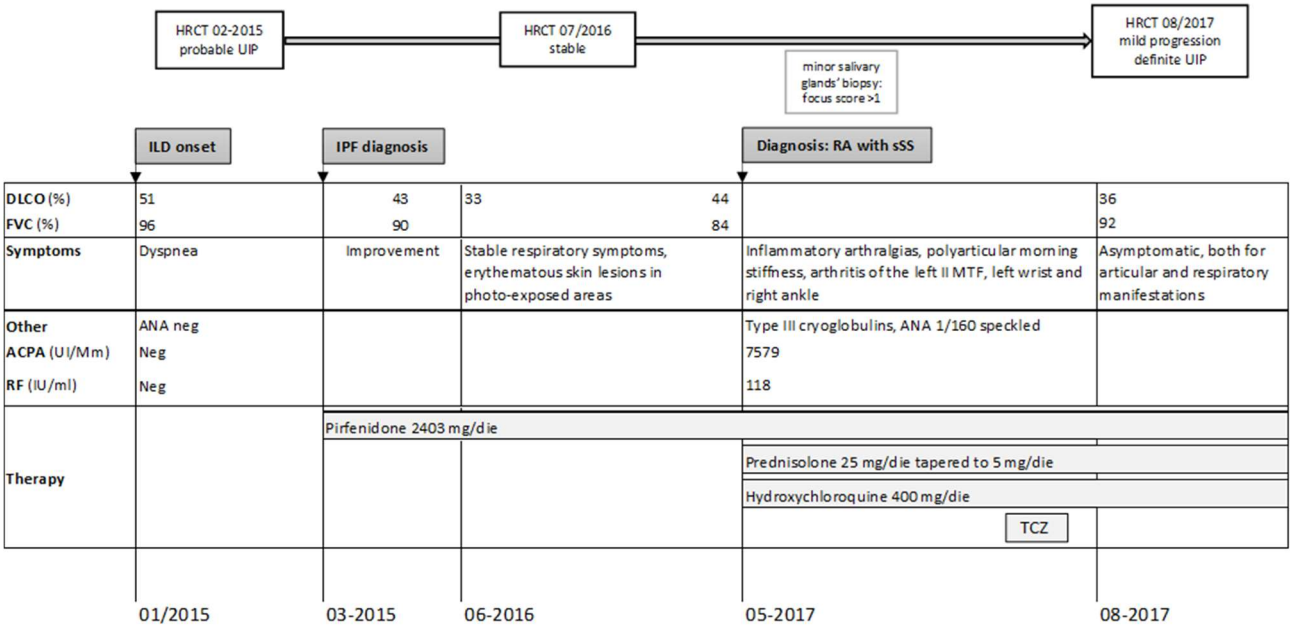


Figure 10. Clinical case summary patient 2



HRCT: high resolution computer tomography; ILD: Interstitial lung disease; RA: Rheumatoid arthritis; sSS: secondary Sjogren syndrome; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide test; UIP: usual interstitial pneumonia; ACPA: anti-citrullinated peptides antibodies ; RF: rheumatoid factor.

DISCUSSION

In absence of randomized controlled trials, the optimal treatment of RA-ILD has not been determined.
Treatment of RA-ILD is furtherly complicated by the association between almost all DMARDs and lung toxicity; however, their ability to improve lung function and improve pulmonary symptoms have also been described in anecdotal reports[220–222,246].
Moreover, treatment of RA-ILD patients with active articular disease should be continued to achieve low disease activity, and the use of any DMARDs to control joint symptoms remains mandatory[223].
RA-ILD shares some similarities with IPF, first of all the predominant UIP pattern and its association with a genic variant of MUC5B[142,209,217,392,393]. It also shows a similar clinical behavior, often with a progressive fibrosing phenotype, and a comparable prognosis and survival[105,107,108,131,139,186,205,219].
These analogies between RA-ILD and IPF may suggest a possible role of antifibrotic therapy in these patients, in order to treat the fibrotic process, improve outcomes and reduce lung disease progression[192,395].
Moreover, some Authors questioning if new trajectories in the treatment of ILD will focus to treat the disease or to treat the underlying pattern[192].
In this regard, antifibrotic drugs are recently supposed to have relevance across various ILD subtypes, not only in UIP pattern (INBUILD). The INBUILD study assessed the efficacy and safety of nintedanib versus placebo in 663 patients with a diagnosis of ILD other than IPF, including RA, despite the radiological or histological pattern[354].
Pirfenidone is an oral antifibrotic and anti-inflammatory drug approved for the treatment of mild to moderate IPF. It demonstrated its efficacy in reducing the rate of absolute decline of percent predicted FVC and the decline in 6MWT distance from baseline, and also in reducing the risk of all-cause mortality[396–398].
Interestingly, Pirfenidone reduces the levels of IL6 and TNF-alpha, both key-cytokines in RA pathogenesis[359] and recently, an inhibitory effect on transition from fibroblast to myofibroblast has been also showed in RA-ILD[360].
Therefore, a potential therapeutic role of pirfenidone in RA-LD is supposable.
A number of trials are planned or ongoing to assess the efficacy and safety of pirfenidone in the treatment of fibrosing ILDs other than IPF, including CTD-associated lung fibrosis, unclassifiable PF-ILD, fibrotic idiopathic NSIP, IPAF[399,400], pulmonary fibrotic sarcoidosis and ILD related to ANCA antibodies or dermatomyositis [NCT03385668; NCT03260556; [401]].
Recently, in a double-blind, randomized, placebo-controlled, phase 2 trial, pirfenidone showed an acceptable safety and tolerability profile in 253 patients with unclassifiable progressive fibrosing ILD. Over 24 weeks predicted mean change in FVC was lower in patients treated with pirfenidone compared to placebo (p=0.002). Compared with the placebo group, patients treated with pirfenidone were less likely to have a decline in FVC of more than 5% (p=0.001) or more than 10% (p=0.011)[400].
At last, to underline the increasing interest on other possible therapeutic potentiality of this drugs, pirfenidone is currently under investigation as a therapeutic option for patients with RA-ILD (TRAIL1)[402].
Nowadays, with the exception of one case report describing the successful use of nintedanib, there are no published data supporting the use of antifibrotic therapies in RA-ILD[362].
Our case report describes for the first time two patients with a diagnosis of RA-ILD treated with pirfenidone in association with hydroxychloroquine. The association of these two drugs allowed a stabilization of both articular and lung manifestations, without adverse events.
When considering therapeutic options for RA-ILD, both pulmonary and extra-thoracic disease manifestations and degrees of activity should be assessed and taken into consideration.

Further, considering both fibrotic and inflammatory components of this systemic disease, the combination of immunosuppressive and antifibrotic treatment can potentially be the future approach to this spectrum of the disease.

Moreover, developing guideline treatment for RA-ILD has proven challenging given the undefined natural history of the disease, the unknown real prevalence of asymptomatic/subclinical RA-ILD, the lack of proven risk factors and biomarkers predictive of disease progression.

Future prospective research might change RA-ILD management, moving to a more personalized approach based on the identification of different phenotypes of the disease (underlying pattern, clinical behavior, genetic and biomarkers risk factors, etc.).

Anyhow, the heterogeneity in disease presentation, the multiple manifestation that may be present, and the broad range of disease severity, makes it difficult to speculate about one milestone therapeutic strategy, so a multidisciplinary approach including rheumatologists, pulmonologists, and other health care providers is essential[379,403].

Multidisciplinary cooperation may be advisable also for developing further prospective studies to clarify the best treatment approach in RA-ILD patients.

Efforts to develop a research network comprising dedicated centers with both pneumological and rheumatological expertise in RA-ILD also should be made, in order to fill the gap of our knowledge of such challenging disease.

Original article 6[404]:

Case report: Combination Therapy with Nintedanib and Sarilumab for the Management of Rheumatoid Arthritis Related Interstitial Lung Disease.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease affecting 0.5-1% of the population worldwide. It's characterized by chronic symmetrical erosive synovitis and sometimes by extra-articular manifestations[228]. Among them, lung involvement is common and includes a wide spectrum of disorders ranging from airways and pleural disease, bronchiectasis and nodules, to infection and drug toxicity[228].

Interstitial lung disease (ILD) is the most common lung involvement, with an estimated prevalence ranging from 4 to 30%, and significantly affects therapeutic approach, quality of life, morbidity and mortality of RA patients[108,151]. The treatment of RA-ILD is still debated and it mainly based on corticosteroids and immunosuppressants[215]. Differently by connective tissue diseases (CTDs), usual interstitial pneumonia (UIP) is the more frequent ILD pattern recorded in RA. Although RA-UIP is frequently reported to have a better prognosis than idiopathic pulmonary fibrosis (IPF), its role on the prognosis of RA-patients isn't yet well defined[392].

Nintedanib is a small molecule triple tyrosine kinase inhibitor approved as anti-fibrotic agent for the treatment of IPF[405]. Nintedanib has shown a significant efficacy in reducing the annual rate of decline of forced vital capacity (FVC) in subjects with IPF in comparison to placebo[405] and very recently showed efficacy also in the treatment of fibrosing ILD different by IPF[354].

Here we present the case of a patient with RA-ILD treated with nintedanib in association to a biologic anti-rheumatic drug.

Case Report

A 75 years old man, former smoker (40 pack-years, until 2007), was referred to the Respiratory Unit of our university hospital because of the appearance of a persistent and productive cough associated to worsening dyspnea on exertion in November 2016. His past clinical history revealed the presence of ischemic heart disease treated with triple percutaneous transluminal coronary angioplasty, type 2 diabetes mellitus, systemic arterial hypertension, and benign prostatic hyperplasia.

He underwent high resolution computer tomography (HRCT) with the detection of reticular ILD characterized by bibasal thickening of the interstice and interlobular septa associated to traction bronchiectasis.

At the time of diagnosis, FVC was normal (FVC 109%), while the diffusion capacity for carbon monoxide test (DLCO) was severely reduced (DLCO Sb 35%). Echocardiography was not suggestive for pulmonary arterial hypertension. The patient showed digital clubbing at physical examination and the chest auscultation revealed velcro crackles.

For the detection of low-titer anti-citrullinated peptides antibodies (ACPA) (89 UI/Mm), he was referred to our Rheumatology Unit. The patient didn't complain arthritis, sicca syndrome, Raynaud phenomenon or other symptoms or sign related to inflammatory arthritis or CTDs. Both Schirmer test and nailfold capillaroscopy were negative. Erythrocyte sedimentation rate (ESR), C reactive protein (CRP), antinuclear antibodies (ANA) including extractable nuclear antigen (ENA), and anti-granulocyte antibodies (ANCA) and rheumatoid factor (RF) were all negative.

A surgical lung biopsy confirmed the presence of an UIP pattern, showing an altered architecture due to "honeycombing" aspects accompanied by mild to moderate chronic interstitial inflammation. A

diagnosis of IPF was performed, and the patient began a treatment with nintedanib (150 mg twice daily), that was well tolerated.

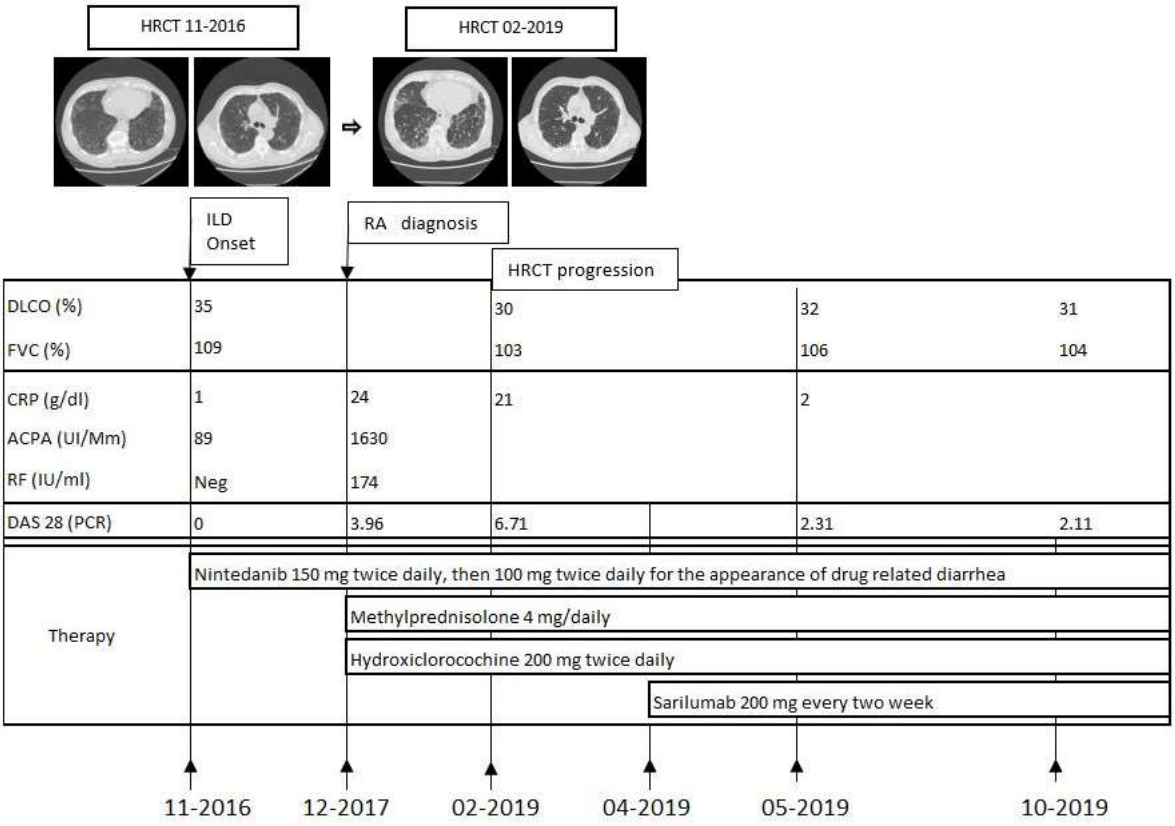
In December 2017 he was newly referred to our Rheumatology Unit for the appearance of inflammatory arthralgias involving small joints of the hands and swelling of left wrist associated to increase of ESR, CRP (30 mm/h and 24 mg/l, respectively) and the presence of rheumatoid factor (174 IU/ml) besides ACPA. Disease activity score on 28 joints (DAS-28-CRP) was 3.96 (moderate disease activity). Ultrasound confirmed the presence of bilateral arthritis of the wrists with power-doppler positivity. A diagnosis of RA was performed according to 2010 ACR/EULAR criteria [8] and we started a low dose steroid therapy (methylprednisolone 4 mg/daily) and hydroxycloroquine (200 mg twice daily), in association with nintedanib, decreased to 100 mg twice daily because of the appearance of drug-related diarrhea.

In February 2019 an arthritis relapse occurred involving small joints of the hands and the knees. ESR and CRP (36 mm/h and 21 mg/l, respectively) increased again (DAS 28 6.71).

A suspected progression of lung fibrosis at HRCT was also observed, with an increase of fibrosis in the mid-basal and in the subpleural and peri-scissural areas, an increase in traction bronchiectasis and honeycombing aspects, even if symptoms and respiratory function remained stable (figure 11). X-Rays of the hands showed typical bone erosions in several metacarpophalangeal joints.

In April 2019, indeed, we proposed the association with anti IL6 receptor antagonist sarilumab (200 mg every two week) achieving a regression of articular involvement (DAS 28-PCR 2.31 one month after), that persisted after 6 months.

Figure 11. Clinical case summary



HRCT: high resolution computer tomography; ILD: Interstitial lung disease; RA: Rheumatoid arthritis; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide test; CRP: C reactive protein; ACPA: anti-citrullinated peptides antibodies ; RF: rheumatoid factor; DAS 28-PCR: Disease activity score on 28 joints;

Discussion

ILD has a significant impact on morbidity and mortality and represents a current challenge in the therapeutic approach to RA. Treatment, mainly based on corticosteroids and immunosuppressants[215], is not well defined and efficacy data are not still available. On the other hand, the supposed role of many conventional and biologic disease modifying antirheumatic drugs (DMARDs) in the onset or worsening of preexisting ILD in RA further complicates the therapeutic choice for these patients[110,151,252].

Nintedanib is an antifibrotic agent approved for the treatment of IPF and recently its efficacy has been demonstrated also in secondary forms of fibrosing ILD[354,405]. It inhibits signal transmission at vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and fibroblast growth factor receptors associated with proliferation, migration, and transformation of fibroblasts[405]. There's an increasing interest about the possible role of nintedanib in the treatment of progressive ILD other than IPF. Because of clinical and radiological similarity between RA-ILD and IPF, it's expected that nintedanib could produce similar effects in slowing the progression of the disease. Preclinical data support a possible effect of nintedanib in fundamental processes of lung fibrosis and that the antifibrotic activity is independent of the cause of the fibrosing lung disease[361]. Furthermore, the frequent association between UIP and RA allows us to speculate that nintedanib might also have efficacy in RA-ILD[406,407].

A randomized, double-blind, placebo-controlled, phase III trial (INBUILD trial) recently assessed the efficacy and safety of nintedanib (150 mg twice daily) versus placebo in 663 patients with a diagnosis of ILD other than IPF, including subjects affected by RA[408]. Patients eligible for the study presented features of diffuse fibrosing lung disease affecting more than 10% of lung volume on HRCT; moreover, they showed disease progression in the last two years before the screening, according to FVC, respiratory symptoms, or HRCT. In particular, the study population included a sub-group of patients with UIP-like pattern, namely patients with reticular abnormalities, traction bronchiectasis with or without honeycombing on HRCT (412 patients, 62.1%)[354].

The patients who received nintedanib showed a slower progression of ILD compared to placebo, as shown by lower decline in annual rate of FVC over the 52-week period, both in overall population and in UIP-like fibrotic patterns group. Interestingly, the absolute treatment effect of nintedanib in this study was similar in magnitude to those observed in pooled data from the INPULSIS trial[354].

To our knowledge, this is the second report of a patient with RA-ILD treated with nintedanib and, for the first time, we describe the association between nintedanib and a biologic DMARD.

Kakuwa et al. described for the first time a 74-years old man presenting UIP pattern at HRCT who was diagnosed with IPF and subsequently developed an inflammatory articular involvement typical of RA, with positivity of ACPA and RF. The patient was successfully treated with nintedanib[362] [18].

In our patient, treatment with nintedanib allowed a maintenance of lung function along the follow-up period, despite HRCT showed a progression of fibrotic features of disease. On the other side, we obtained the remission of the joint involvement, observing a good safety profile of the combination therapy, without observing any other side effects. Finally, we need data from specific controlled trials to evaluate the safety and effectiveness of nintedanib in RA related ILD[354,362], and the possible association with conventional, biological, and targeted-synthetic DMARDs.

Original article 7[409]:

Case report: Tofacitinib for the Treatment of Severe Interstitial Lung Disease Related to Rheumatoid Arthritis.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease affecting 0.5-1% of the population worldwide. It's characterized by chronic symmetrical erosive synovitis and sometimes by extra-articular manifestations[228], including Interstitial lung disease (ILD), which represents the most common lung involvement[108]. ILD significantly affects therapeutic approach, quality of life, morbidity and mortality of RA patients, with an estimated prevalence ranging from 4 to 30%[108,380].
Among the main risk factors for the development of AR-ILD we consider high titles of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), male sex and cigarette smoking history[410]. Sometimes lung interstitial involvement is early and represents the only sign of disease. In these cases, a clinical and serological follow up may lead to evidence of autoimmune disease later in time[411].
In RA patients with lung involvement, radiological UIP pattern is the most frequent one (about 60-70%) but also the most associated with poor prognosis[228,412].
The treatment of patients with RA and concomitant ILD is nowadays challenging and mainly based on glucocorticoids (GC) and immunosuppressants[176]. Therapeutic options in these patients are complicated by the possible pulmonary toxicity of many disease modifying anti-rheumatic drugs (DMARDs) and by their unclear efficacy on pulmonary involvement[176]. The scientific community is constantly looking for therapeutic alternatives to control RA activity avoiding lung toxicity and, possibly, influencing the natural history of RA-ILD. Furthermore, RA-ILD treatment should be safe and easy to manage in case of infectious adverse events, giving the higher infectious risk in ILD patients[413].
Small-molecule Janus Kinase inhibitors (JAK-i), namely tofacitinib baricitinib and upadacitinib, are the latest drug class of DMARDs commercialized for the treatment of RA with a good safety profile[344,414–417].
Here, we present the case of a patient affected with progressive RA-ILD successfully treated with tofacitinib.

Case report

A 52 years old man, former smoker (45 pack years), was referred to our multidisciplinary outpatient clinic for rheumatic and rare lung diseases for an active RA associated to progressive ILD. His past clinical history revealed systemic arterial hypertension, dyslipidaemia, non-alcoholic fatty liver disease, class II obesity (BMI 37).
Diagnosis of RA was performed in April 2012. RF and ACPA were positive (42 and 300 U/mL, respectively), while antinuclear antibodies (ANA), extractable nuclear antigens (ENA) and anti-neutrophil cytoplasmic antibodies (ANCA) were negative.
Arthritis was aggressive and rapidly erosive at hands and wrists. The patient had been initially treated with methotrexate (MTX) 15 mg weekly, effective but replaced with hydroxychloroquine (HCQ) 400 mg daily for the desire of paternity in December 2012. Since HCQ became ineffective, etanercept (ETA) 50 mg weekly was added in April 2014.
Fourteen months later, ILD was casually detected, and ETA was replaced with subcutaneous tocilizumab (TCZ) 162 mg weekly. This latter drug was stopped after few months for relapsing infections, mainly involving urinary and lower respiratory tract.

In October 2017, due to a deterioration of respiratory symptoms he was referred for the first time our multidisciplinary outpatient clinic, which includes rheumatologist and pulmonologist. At that time he presented severe restrictive ventilatory impairment, with a forced vital capacity (FVC) of 52% of the predicted value, and a severe reduction in gas exchange with a diffusion capacity for carbon monoxide (DLCO) of 33% of the predicted value. Moreover, he desaturated at 6-minute walking test (Nadir reached after two minutes with oxygen saturation of 87%). As far as RA activity he showed arthritis of wrists and II-III right metacarpophalangeal; C reactive protein (CPR; 50 mg/L) and erythro-sedimentation rate (ESR; 50 mm/h) were both increased, with a 28 joints-disease activity score (DAS-28 CRP) of 5.27.

At chest high resolution computed tomography (HRCT) a pattern of usual interstitial pneumonia was described, characterized by reticular abnormalities and honeycombing aspects, in particular at right lower lobe.

At that time, he was taking HCQ and low dose of prednisone (5 mg daily).

According to the clinical picture, we prescribed oxygen supplementation and proposed treatment with rituximab (1000 mg every other week for 2 intravenous infusions), performed in December 2017, maintaining treatment with prednisone and HCQ. Two months later, arthritis was still active, involving bilateral MCF and proximal interphalangeal joints of hands, wrists and ankles associated to ESR and CRP elevation (45 mm and 60 mg/L, respectively).

After multidisciplinary discussion with pulmonologist, in March 2018 we prescribed tofacitinib 5 mg twice daily. Vaccination for varicella zoster virus (VZV) was not performed, because of the immunosuppressive condition of the patient.

One month later, the patient presented an infection of upper respiratory tract, successfully treated with antibiotic therapy; tofacitinib was discontinued for ten days. Despite other few respiratory and urinary infectious episodes, RA remission was obtained after 3 months. Disease flares appeared when tofacitinib was discontinued, but every time a rapid arthritis control was obtained with the re-introduction of tofacitinib.

From August 2018 to March 2020, we observed a stable RA remission and no other infections were reported by the patient.

Despite an initial radiological progression detected at HRCT in November 2018, respiratory symptoms improved and lung function (FVC and DLCO) remained stable over the time.

Discussion

ILD is a serious pulmonary complication of RA, characterized by a significant impact on morbidity and mortality and representing a current therapeutic challenge, since the possible pulmonary toxicity of many traditional and biological DMARDs, their unclear efficacy on pulmonary disease and the higher infectious risk in comparison to non-ILD RA patients[176,413].

JAK-is have recently emerged in clinical practice for the treatment of RA and they are recommended by European league against rheumatism (EULAR) in patients failing an initial treatment with MTX or other conventional DMARDs with poor prognostic factors[418].

Despite limited data, no relevant safety concerns in relation to both ILD onset and progression are emerged for tofacitinib[344,415,419,420] .

A post hoc analysis on 7061 RA patients receiving tofacitinib from clinical trials and long-term extension studies reported an incidence rate for ILD with both tofacitinib doses of 0.18 per 100 patient-years[421].

Few real-life data are up to now available. Among 15 RA-ILD patients treated with tofacitinib, none showed worsening of dyspnoea, while improvement was reported in some cases; moreover,

respiratory function and DLCO remained stable in the majority of subjects evaluated, while 4 patients improved[422].

In another study, 3 RA-ILD patients were successfully treated with tofacitinib without pulmonary adverse events in an 8-12 month period[423].

About the possible effect on ILD, some case reports have recently been published in which tofacitinib appears to be effective on ILD related to anti-melanoma differentiation-associated 5 gene antibody-positive dermatomyositis and anti-synthetase syndrome[424–427].

Tofacitinib has been demonstrated to be able in reducing the progression of zymosan-induced ILD in SKG mice, a murine model of RA. Tofacitinib significantly suppressed the progression of ILD compared to control by expanding myeloid-derived suppressor cells and suppressing Th17 cells proliferation and differentiation, suggesting a potential therapeutic effect of tofacitinib for RA-ILD[351].

However, other in vitro studies reported that the inhibition of JAK2, but not the selective JAK1/JAK3 pathway, significantly reduced IL-17A-induced fibrogenic response in fibroblast from IPF and RA-ILD patients[428].

Rituximab was proposed as a therapeutic option for RA-ILD, even if it has been associated to an increased risk of infections in patients with RA-ILD.

Unfortunately, in our patient rituximab was ineffective on arthritis and ILD and it could have contributed to the infectious adverse events showed by the patient in the next six months[429].

The short half-life and rapid-acting of tofacitinib are two characteristics that we have considered for the treatment of our patient. Moreover, we took advantage by an intermittent therapy when the infectious events appeared obtaining a rapid clearance of the drug. On the other side, the patient also showed a rapid flare of disease after tofacitinib discontinuation, needing a temporary increase of prednisone dose.

Conclusion

Despite limited data from clinical trials and real-life, tofacitinib could represent a therapeutic option for RA-ILD patients, with a good safety profile. Longitudinal studies are required to confirm this encouraging report.

EARLY DIAGNOSIS OF RA-ILD: THE ROLE OF VELCRO-CRACKLES

Original article 8[430]:

Analysis of pulmonary sounds for the diagnosis of interstitial lung diseases secondary to rheumatoid arthritis.

INTRODUCTION

Idiopathic interstitial pneumonia (IIP) denote a class of lung diseases which is particularly difficult to diagnose and cure as the pathogenesis is mainly unknown[431]. Particular attention has been devoted in the last decade to idiopathic pulmonary fibrosis (IPF) since, by the time a diagnosis is made, the median survival time is on the order of 2 − 4 years[431], just little better than that of inoperable lung cancers[432]. The prevalence of IPF over the population is very low, on the order of 14 − 43 cases over 100.000 persons[431,433], however it would be ranked as the eighth most prevalent cancer in the world if it was classified as a malignancy[432]. In practice IPF appears as a chronic inflammation of the lungs, where the lung parenchyma is progressively replaced by fibrotic tissue leading to death for respiratory failure.

Luckily, recent drug therapies based on pirfenidone and nintedanib have shown some positive effects in limiting the disease progression and improving the survival rate[161,434], provided that an early diagnosis is available[160,161,432,434]. However, the early diagnosis of IPF is still an open issue; in fact, patients may feel quite healthy at the early stage of the disease when fibrosis is limited to the peripheral of lungs, as well as the first symptoms, like cough and dyspnoea, are common in seniors. Up-to-date (2011) guidelines identify three core requirements for the diagnosis of IPF[431], namely a) the exclusion of other possible causes of interstitial lung disease, b) the specific findings of usual interstitial pneumonia (UIP) on computer tomography (CT) and c) the UIP findings on lung biopsy. As a result, it is highly unlikely that patients are examined by specialists at the early stage of the disease, as well as the complex diagnostic procedure can take several months. For these reasons, the delay between the first symptoms and the IPF diagnosis can be as large as 2 − 3 years[161] and this can definitely reduce the survival rate of the patient.

Besides the above mentioned core requirements, velcro crackle (VC) has recently emerged as a reliable

marker of IPF[160,161,432–434]. VC is considered to be generated by the abnormal flow of air in the fibrotic tissue and its name stems from the sound produced by separating two joined strips of velcro[161]. Unlike the UIP radiological pattern known as honeycombing[431] that can be found only at an advanced stage of the disease, VC can be heard on auscultation in the basal areas of the lung even at the early stage of the fibrosis process.

In principle, a massive screening campaign based on low dose chest CT could evidence IIP at an early stage, however the very low prevalence of these diseases makes such approach practically unfeasible. Then, the only viable solution to early diagnosis of IPF is currently represented by lungs auscultation. Information and communication technologies (ICT) could play a crucial role in this field, however the few efforts devoted to this orphan disease have been focused only on the development of decision support systems[435] and on the quantitative analysis of UIP radiological patterns on the CT outcome.

In this paper we investigate the problem of automatic detection of velcro crackles in lung sounds. In practice 211 patients have been auscultated with a digital stethoscope before undergoing CT. Then the lung sounds are digitized, saved in a file and processed through the novel algorithms. This experimental set-up has been properly conceived to devise the ground truth from the CT[160], in the

sense that the CT outcome has been exploited to determine whether the patient is affected by an interstitial disease or not; however, no attempt has been accomplished to quantify the UIP radiological pattern in case of interstitial disease, since this requires huge efforts from the radiology specialists as well as it can introduce subjective factors in our study. For these reasons we have focused our work on developing binary classifiers that can be fairly compared with the ground truth devised as described above. In particular, two different algorithms suitable for the automatic detection of velcro crackles have been developed, both relying on the empirical observation that the bandwidth of VC is larger than that of the healthy breath sound. The first solution is based on a parametric estimator which basically compares the bandwidth of the acquired lung sounds with a fixed threshold. The second approach consists of a neural network processing the bandwidth of the acquired lung sounds. Indeed, the output of both algorithms is given by a boolean index inferring the presence (or not) of an interstitial disease in the patient.

The developed algorithms have the potential to shorten the time necessary for the diagnosis of IIP for two main reasons. Firstly, a sedentary lifestyle may mask dyspnoea[161], so that our tool can be adopted for "self-auscultation" to reduce the delay between the appearance of symptoms and the consultation of a specialist. Secondly, our tool can raise diagnostic suspicions and can help community physicians in recognizing IIP. Furthermore, the very limited computational complexity of the proposed algorithms allows an easy implementation on commercial smartphones, tablets and personal computers, as well as the delivery of the proposed solutions through the cloud can enable an ubiquitous access to this technology. This paper is organized as follows. The experimental study is presented in Section II, whereas the algorithms suitable to the automatic detection of VC are described in Section III. The experimental results are shown in Section IV and, finally, some conclusions are offered in Section V.

DESCRIPTION OF THE EXPERIMENTAL STUDY

This work represents a byproduct of the study designed by Cottin and Richeldi aimed at investigating the correlation between lung sounds and CT patterns[160]. The population considered in this work includes patients undergoing chest CT at the general hospitals of Modena and Baggiovara (Italy). For the sake of fairness, the CTs have been requested by physicians independent of this research and the patients have not been suitably selected, i.e. all the patients scheduled in the given CT session have been included in the database. The lung sounds have been collected while the patient is waiting to enter the CT scanner and this environment has proved to be very harsh for number of reasons, e.g. the patient may be uncooperative because of stress entailed by the CT, the patient may need to talk with the radiologist or other persons in the room, the physician may be rushed by the strict time schedules of CT and so on. Nonetheless this scenario can be deemed absolutely realistic and the performance shown in Section IV can be easily achieved in any other medical facility.

In the study designed by Cottin and Richeldi, besides recording the lung sounds, the physician is required also to collect demographic data, medical history, respiratory signs and symptoms of the patient. In particular the questionnaire adopted in that research includes a proper entry requiring the physician to report the presence (or absence) of VC in the auscultations. This specific entry is exploited to devise the performance of specialized physicians in the detection of VC through auscultation as shown in Section Furthermore, the CTs have been analyzed by radiologists and pulmonologists to devise a diagnosis for each patient; then the set of diagnosis encompassing the whole database is exploited as ground truth for the performance assessment of the algorithms presented in Section III. It is worth noting that the considered ground truth is "binary", in the sense

that radiologists and pulmonologists have detected the presence of IIP, but the entity of the related radiological patterns have not been quantified.

The electronic stethoscope Littmann 3200 has been employed to record the lung sounds of each patient at Na = 6 auscultation points, namely paravertebral middle lobe, paravertebral lower lobe and axillary lower lobe[160]. Each auscultation is digitized and is saved as a WAV file over the memory onboard the stethoscope. Then the set of Na audio files acquired for each patient are transferred to a personal computer through a Bluetooth link. The employed electronic stethoscope is characterized by a sampling frequency fs = 4 kHz.

The database exploited in this work collects the lung sounds of 211 people auscultated over a period of 18 months. CTs have shown that 67 patients are affected by an interstitial disease, whereas the remaining 144 are considered healthy for the scope of this study (even if they may be affected by a pulmonary disease whose origin is not interstitial).

Finally, it is worth pointing out that different types of lung sounds are related to distinct pulmonary diseases, however we focus our efforts on the automatic detection of VC, since it is a robust indicator of an interstitial disease.

ALGORITHMS FOR THE DETECTION OF VELCRO CRACKLES

In this Section we present two algorithms suitable to identify velcro crackles. Both techniques rely on the empirical evidence that velcro crackles are characterized by a frequency spectrum wider than that of healthy breath sounds. To this aim, the pre-processing techniques suitable to mitigate the noise affecting the auscultations and to compute the bandwidth of the lung sounds are described in detail in Section III-A. The first algorithm for the detection of VC is introduced in Section III-B and represents the most simple approach to binary classification; in fact the bandwidth of the lung sounds is estimated and compared to a fixed threshold with the scope of discriminating healthy persons from patients affected by an interstitial disease. Hence this technique can be referred as a (unsupervised) parametric estimator. The second algorithm is shown in Section III-C and consists of a (supervised) neural network. This approach has been adopted because of its better accuracy with respect to unsupervised estimators, even if other mathematical tools, like for instance kernel machines and principal component analysis, could be employed, at least in principle. Finally the computational complexity of the proposed solutions is analyzed in Section III-D.

Pre-processing

The flow chart illustrating the pre-processing performed over the lung sounds of each patient is shown in Figure 12. Firstly, the audio signals si [n], with i = 1, 2, ..., Na and n = 0, 1, ..., N − 1, undergo a short time Fourier transform (STFT) for time-frequency analysis; this yields the quantities Si [m, k], with i = 1, 2, ..., Na, m = 0, 1, ..., M − 1 and k = 0, 1, ..., K − 1. Non-overlapping Hamming windows have been used, so that N/M represents the time resolution of the STFT Si [m, k], as well as 2K denotes the order of the discrete Fourier Transform (DFT) performed over the window of dimension N/M . As a consequence, the indeces m and k denote time and frequency, respectively, whereas the index i is used to relate the devised quantities with one of the Na auscultations acquired over the same patient.

It is well known that velcro crackles are generated by sudden opening of small airways during inspiration, although some rales can be heard even during expiration[161,436,437]. In our work inspiration periods are identified through an heuristic approach, which is based on the empirical observation that the energy of lung sounds associated with inspiration is larger than that related to expiration. In practice the energy associated with each time bin Ei [m] is computed as

$$E_i[m] = \sum_{k=k_1}^{K-1} |S_i[m,k]|^2, \qquad (1)$$

With i= 1, 2, ..., Na and 0 <k1 <K, whereas the mean energy per time bin Ei is devised as

$$\bar{E}_i = \frac{1}{M} \sum_{m=0}^{M-1} E_i[m] \qquad (2)$$

With i= 1, 2, ..., Na. Note that the first k1 frequency bins are discarded in the computation of Ei [m] (1), since we have experimentally found that several interfering (unwanted) sounds are characterized by a significant power spectral density at low frequencies (e.g. rales generated by pulmonary edema and heart failure, rubbing and beating the stethoscope on the skin, ...). The tentative inspiration periods are identified as the set

$$T\tilde{}i = \{m|Ei[m] > \alpha E\bar{}i\} \qquad (3)$$

including all the time bins associated with an energy Ei [m] larger than a given fraction α of the average
energy E¯i. Unluckily, we have also found that some interfering sounds (like, for instance, coughing,
speaking, hisses) evidence a significant power spectral density at high frequencies, so that further filtering is necessary to reject unwanted signals. In particular, lung sounds too short with respect to usual inspiration time can be discarded, since they are related to artifacts or interfering signals with high probability. This idea can be mathematically formulated defining the set of inspiration periods as

$$Ti = \{m \in T\tilde{}i | m + p \in T\tilde{}i \ \vee\ m - p \in T\tilde{}i,\ p = 1, 2, ..., Lmin, \} \qquad (4)$$

so that sounds shorter than NLmin/Mfs seconds are not accounted for.
Finally, the bandwidth of the inspiration sounds is evaluated as

$$B_i = \frac{f_s}{2K} \left[\arg\min_{\tilde{k}} \left(\sum_{m \in T_i} \sum_{k=k_2}^{\tilde{k}} |S_i[m,k]|^2 > 0.99 \hat{E}_i \right) \right] \qquad (5)$$

For i= 1,2,…, Na, where

$$\hat{E}_i = \sum_{m \in T_i} \sum_{k=k_2}^{K-1} |S_i[m,k]|^2 \qquad (6)$$

denotes the energy of the lung sounds associated to the inspiration periods. It is worth pointing out that expression (5) does not strictly follow the definition of the 99% bandwidth, as the parameter k2 is exploited to neglect the lower portion of the spectrum which is more affected by noise and interfering sounds; nonetheless, the bandwidth Bi is employed to measure the contribution of high frequencies to the lung sounds within the ith auscultation.

Parametric estimator

The bandwidths Bi (5) (with i = 1, 2, ..., Na), generated by the analysis of the Na auscultations per patient, are compared with a given threshold Bth to devise the boolean indicator I, where I = 0 and I = 1 denotes the absence and presence of an interstitial disease, respectively. Further information about the threshold Bth is provided in Section IV. In practice, the decision strategy can be expressed as

$$\begin{cases} I = 1 & \text{if } \sum_{i=1}^{N_a} (B_i > B_{th}) \geq 3 \\ I = 1 & \text{if } \sum_{i=1}^{N_a} (B_i > B_{th}) \geq 2 \text{ and } \frac{1}{N_a} \sum_{i=1}^{N_a} B_i > B_{th} \cdot \\ I = 0 & \text{otherwise} \end{cases} \tag{7}$$

The rationale behind this heuristic approach is very pragmatic: bandwidths Bi (5) (with i = 1, 2, ..., Na) larger than Bth are interpreted as an indicator of the presence of velcro crackles, otherwise the acquired audio signals are considered as healthy breath sounds, at least for the scope of this work (the patient might be affected by a pulmonary disease whose origin is not interstitial). In particular, we have experimentally found that when 3 or more audio signals are characterized by a bandwidth larger than Bth, the patient is affected by an interstitial disease with very high probability. Furthermore, an average bandwidth larger than Bth (provided that at least 2 lung sounds are characterized by a bandwidth larger than Bth) is considered an indication of an interstitial disease as well, since in some patients velcro crackles are well identifiable in a couple of auscultations but is not detectable in the others. We suspect that this behavior can be entailed by two main conditions: (a) at early stage of the fibrosing process, velcro crackles can be heard only in limited regions of the pulmonary lower lobes; (b) at late stage of the fibrosing process, some patients are not able to support deep inspirations for all the Na = 6 auscultation points.

Neural network

Besides the heuristic decision strategy (7), a supervised neural network characterized by Nh = 10 hidden nodes and No = 1 output node has been developed to analyze the lung sounds. In practice, this approach consists of a binary classifier, where the input is represented by the bandwidths Bi (with i = 1, 2, ..., Na) computed through (5), whereas two possible outputs I = 0 and I = 1 are generated to identify an healthy person and a patient affected by an interstitial disease, respectively.

A training data set has been properly devised from the whole database of lung sounds, in order to balance the number of auscultations referring to healthy people and to patients affected by an interstitial disease. Then the neural network is trained through the gradient backpropagation algorithm. Finally the performance of the trained neural network is evaluated over the whole database of lung sounds.

In this Section the computational complexity involved by the techniques described in Sections III-A, III-B and III-C is analyzed.

The STFT performed on non-overlapping windows requires the computation of N/M DFTs of order 2K, so that the computation of the spectrogram involves a computational complexity of O((N/M)2K log(2K)). The identification of the inspiration periods (see eqs. (1)-(4)) entails a computational complexity of O(MK), since the whole STFT Si [m, k] of the audio signal need to be parsed. The complexity of bandwidth computation can be upper bounded by O(MK), as the energy included in the K subbands needs to be evaluated over the subset of time bins Ti (see eqs. (5)-(6)).

Finally, the decision strategy (7) involves a complexity negligible with respect to the previous steps, whereas the neural network requires additional processing whose computational complexity can be upper bounded as O(NaNh).

EXPERIMENTAL RESULTS

The database exploited in this study collects the auscultations of Np = 211 persons, where Na = 6 audio files have been registered for each person (see Section II). Moreover, the CT of each person is available as reference for ground truth (the whole database of CTs has been interpreted by physicians specialized in radiology and/or pulmonology as described in Section II).

Generally speaking, distinct auscultations are characterized by different time support because of the intrinsic variability of the scenario in which the lung sounds are acquired; for instance, the length of the CT queue varies from day to day, as well as the number of deep breaths that can be acquired closely depends on the health conditions of the patient. Therefore the physician cannot know a priori the time available for the auscultation, i.e. for data acquisition. Experimental results have shown that the time support of the acquired lung sounds lies in the range $7 - 30$ s and, as a consequence, the length N of the related sequence can vary from 28 ksamples to 120 ksamples. The variability of the length N of the audio signal affects the computational complexity (see Section III-D) and defines the maximum time-frequency resolution that could be achieved. Luckily we have found from preliminary experimental tests that time and frequency resolution can be set to tr = 50 ms and fr = 10 Hz, respectively, independently to the specific auscultation. In fact these results have evidenced that a typical expiration period is not shorter than $400 - 500$ ms and negligible performance variations have been observed changing the bandwidth threshold Bth (see (7)) of few tens of Hz. As a consequence the dimension of the Hamming window used in the STFT is W = fstr = 200 yielding M = [N/W ♩. Moreover, we have found that the main portion of the energy associated with lung sounds is in the band $0 - 800$ Hz, so K = 800/fr = 80 and 2K < W . Analyzing the results of Section III-D on the basis of the derived parameters, it can be easily inferred that the computational complexity of the proposed solutions is very limited and simple programmable hardware, like a low-end personal computer, can be used to run the algorithms described in Section III. The results shown in Figs. 13 have been devised setting k1 = 400 Hz, k2 = 40 Hz and $\alpha = 0.5$, whereas Lmin = 10 has been adopted to discard sounds shorter than 500 ms. In addition, the bandwidth threshold Bth = 100 Hz necessary to implement the decision strategy (7) has been selected optimizing the performance of the parametric estimator with respect to the ground truth provided by CTs. It is worth

noting that this value is not far from the average bandwidth $\bar{B}$ = 115 Hz computed over the whole

database; this result denotes that, at least in principle, sounds with band larger than the average band $\bar{B}$ can be identified as representatives of an interstitial disease with a significant probability.

The performance of the parametric estimator shown in Fig. 13 can be fairly compared to the performance of physicians illustrated in Fig. 14. The overall reliability of the developed algorithm is 64.4% whereas that of physicians is 76.4%. This performance gap is due mainly to the measurement setup: the physicians can base their diagnosis on both the clinical history of the person and the auscultation through the stethoscope, either mechanical or digital. In addition, physicians can repeat the auscultation process until the lung sounds are perceived clearly enough to yield a diagnosis. On the other hand, the developed tool can only rely on a subset of data, in the sense that the lung sounds are digitized only once the (tentative) diagnosis has been identified by the physician.

False decisions taken by the parametric estimator amount to 35.6%, whereas the failure probability of physicians is 23.6%. This performance gap is mainly related to the artifacts which are not filtered out by the pre-processing (see Section III-A). Indeed, the missed diagnosis common to both parametric estimator and physicians stem from well known scenarios, for instance the person does not breath deeply enough, lung sounds are covered by other sounds like cough or voice and so on.

The neural network (see Section III-C) has been trained through a data set collecting the lung sounds of 39 healthy people and 39 patients affected by an interstitial disease. The training set has been populated firstly including the patients whose auscultations clearly evidence the presence of velcro crackles, then the data set has been balanced including also people characterized by healthy breath sounds. In practice the clear presence of velcro crackles in the available audio signals have been subjectively assessed by both physicians and engineers belonging to the research team. Then the trained neural network has been employed to assess the performance of the system over the whole database collecting the auscultations of the Np = 211 persons. The target of the optimization process consists of reproducing the percentage of false negative achieved by physicians, which is a measure, in some sense, of their capability to diagnose an interstitial disease. The performance of the trained neural network is illustrated in Fig. 15. The success probability provided by the neural network is 72.1% and is very close to the 76.4% achieved by physicians. This performance increasing compared to the parametric estimator is basically entailed by the supervised classifier which can significantly outperform the heuristic decision strategy (7). In fact, the false positives decreases from 21.3% to 18.5%, as well as the false negatives decreases from 14.2% to 9.5%. As a result, the performance of the neural network is very close to that achieved by physicians.

CONCLUSIONS AND FUTURE WORKS

The problem of automatic detection of velcro crackles in lung sounds has been investigated through a properly designed clinical experiment. The developed algorithms have been tested over a cohort of 211 persons waiting for CT. Experimental results have evidenced that the proposed neural network can achieve a success probability of 72.1%, which is very close to that offered by physicians (76.4%) in the diagnosis of interstitial diseases. Indeed, the reliability of the developed technology can pave the way for a massive screening campaign focused on the early detection of IIP. This, in turn, can appreciably shorten the time necessary for the diagnosis of IPF and can improve the survival rate of patients.

Future works concern the implementation of soft decision strategies that could be very useful to quantify velcro crackles and monitor the progression of the disease, provided that the UIP radiological pattern can be objectively quantified for ground trut.

Figure 12. Flow chart illustrating the pre-processing performed over the Na auscultations of each patient

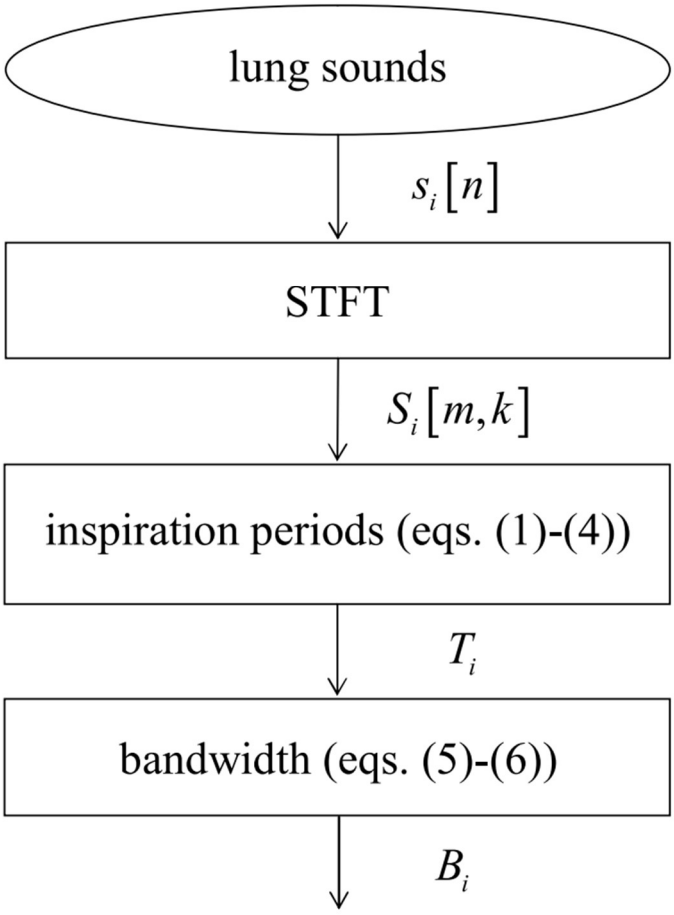


Figure 13. Performance provided by the parametric estimator.

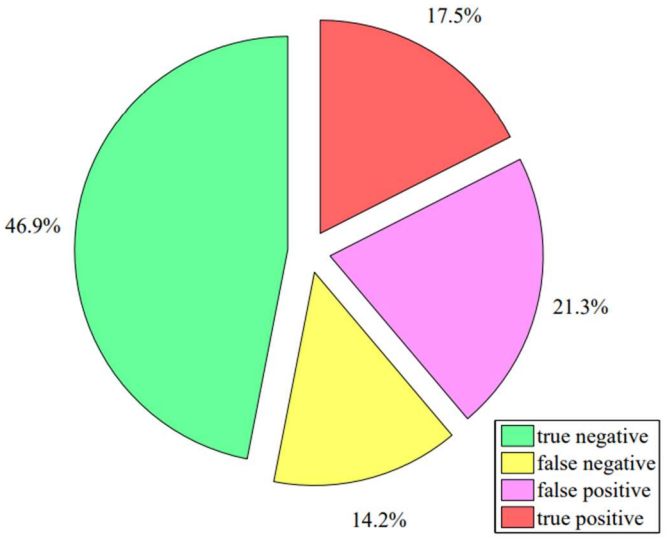


Figure 14. Performance provided by phisicians.

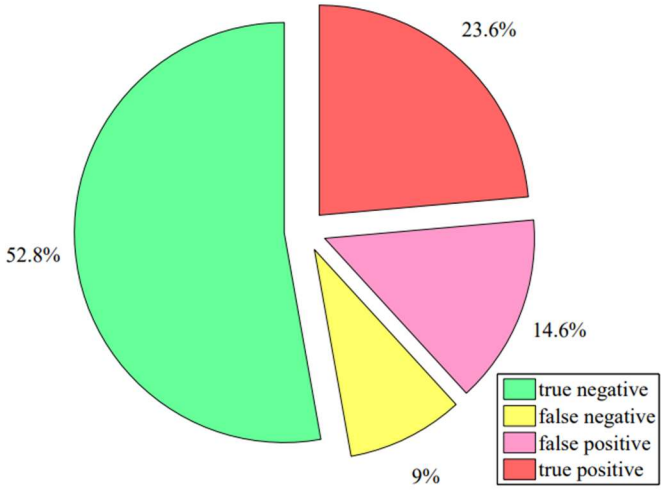
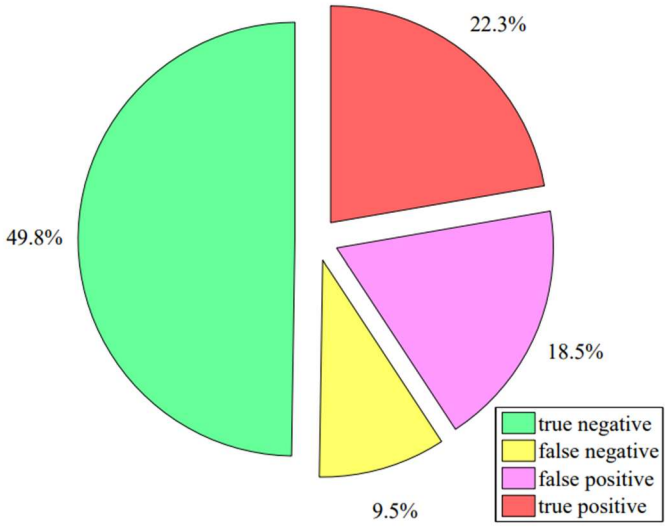


Figure 15. Performance provided by the trained neural network.



Original article 9[380]:

Diagnostic accuracy of a velcro sound detector (VECTOR) for interstitial lung disease in rheumatoid arthritis patients: the INSPIRATE validation study (INterStitial pneumonia in rheumatoid ArThritis with an electronic device).

Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease, secondary to immune-system dysfunction, characterized by synovial joint swelling and tenderness, with joint destruction and progressive disability. RA is often complicated by extra-articular manifestations, and, among them, interstitial lung disease (ILD) is one of the most frequent and deleterious complication with negative impact on both therapeutic approach and overall prognosis[109,206,228].

About 10% of the RA population develops a clinically significant ILD and that is responsible for decreased quality of life and progressive chronic disability, but also of 10-20% of deaths associated to the disease, with a mean survival of 5-8 years[108,213].

Since no controlled studies are available, the therapeutic approach to RA-ILD is still debated and further complicated by the supposed role of many conventional and biologic disease modifying anti-rheumatic drugs (DMARDs) in onset or worsening of pre-existing ILD[110,220]. In this regard, the British Society of Rheumatology has specifically cautioned prescribing TNFi to patients with RA-ILD, while, in 2008, the American College of Rheumatology (ACR) contraindicated methotrexate for the treatment of these patients[252]. Actually, current literature data are not able to fill the gap of knowledge in this intriguing matter. Considering the possible severity of this complication and the therapeutic implications, to investigate a better approach to obtain an early diagnosis is mandatory.

High resolution computed tomography (HRCT) represents the gold standard for the diagnosis of this extra-articular manifestation, but ILD can appear in any stage of RA entailing the need for systematic assessment of lung involvement, and a routine use of HRCT for screening program is not advisable for both the high cost and X-rays exposure[159].

In this background, a delayed diagnosis could be responsible for possible severe complications; therefore, the use of reliable and non-invasive tools may improve early diagnosis and a better management of the disease.

Velcro sound is a pulmonary sound defined as a fine crackle soft and short in duration, similar to the sound heard when the joined strip of jogging shoes is slowly separated. The detection of this typical sound, generally present throughout the inspiratory time and persisting after several deep breaths, has been proposed as an easy and repeatable screening for the early diagnosis of idiopathic pulmonary fibrosis and other forms of ILD[160,161]. Recently, we developed an algorithm, named VECTOR (VElcro Crackles detecTOR), to detect the presence of velcro crackles in pulmonary sounds recorded by an electronic stethoscope (ES) and that showed good results in a low sample of RA patients. In this preliminary study diagnostic accuracy of VECTOR was 90%, with a sensitivity of 92.6% and a specificity of 88.4%[430].

The aim of the study was to validate the diagnostic accuracy of VECTOR in a larger population of RA, compared with the reference standard of HRCT, from a multicenter study.

Patients and Methods

The study InsPIRAtE (INterStitial Pneumonia in Rheumatoid ArThritis with an Electronic device) involved seven Italian tertiary rheumatologic Centers with clinical experience in rheumatic disorders and interstitial lung diseases, after approval in local ethical committee. All patients were evaluated

by mean of VECTOR and the result (presence or absence of velcro crackles) compared in a blind manner with HRCT (presence or absence of ILD).

Inclusion criteria

All consecutive RA patients, classified according to 1987 or 2010 ACR classification criteria[387,388], with a recent HRCT evaluation were eligible for the study and enrolled in a six-month period. According to clinical history, the HRCT should have been performed within 12 months in absence of subsequent appearance or variation of signs or symptoms suggestive for lung disease (cough, dyspnea, velcro sound at routine clinical examination)

The reason for HRCT prescription was not a selection criterion for the participation to the study.

Exclusion criteria

Exclusion criteria were represented by:

- a significant variations of the respiratory symptoms after HRCT executions (when possible, a new HRCT was requested);
- presence of pleural effusion or pneumothorax at HRCT;
- an overlap diagnosis with connective tissue disease

Study design

According to our previous experience, respiratory sounds were recorded in 4 pulmonary fields bilaterally (2 at the basal fields, 1 at the medium fields and 1 at the upper field; see figure 16) in a silent environment with a commercial ES (Littmann 3200^{TM} 3M, USA). Then, audio files acquired for each patient were digitized, coded, saved as a WAV and analyzed by mean of VECTOR.

Moreover, all HRCT images were transferred on DICOM format, anonymized, coded and evaluated in a blind manner by an expert thoracic radiologist for the assessment of ILD.

Moreover, for all patients the value of forced vital capacity (FVC), diffusion lung of CO (DLCO), the result of x-Ray thorax, the presence of velcro crackles at thorax examination and the presence of cough or dyspnea at baseline were recorded.

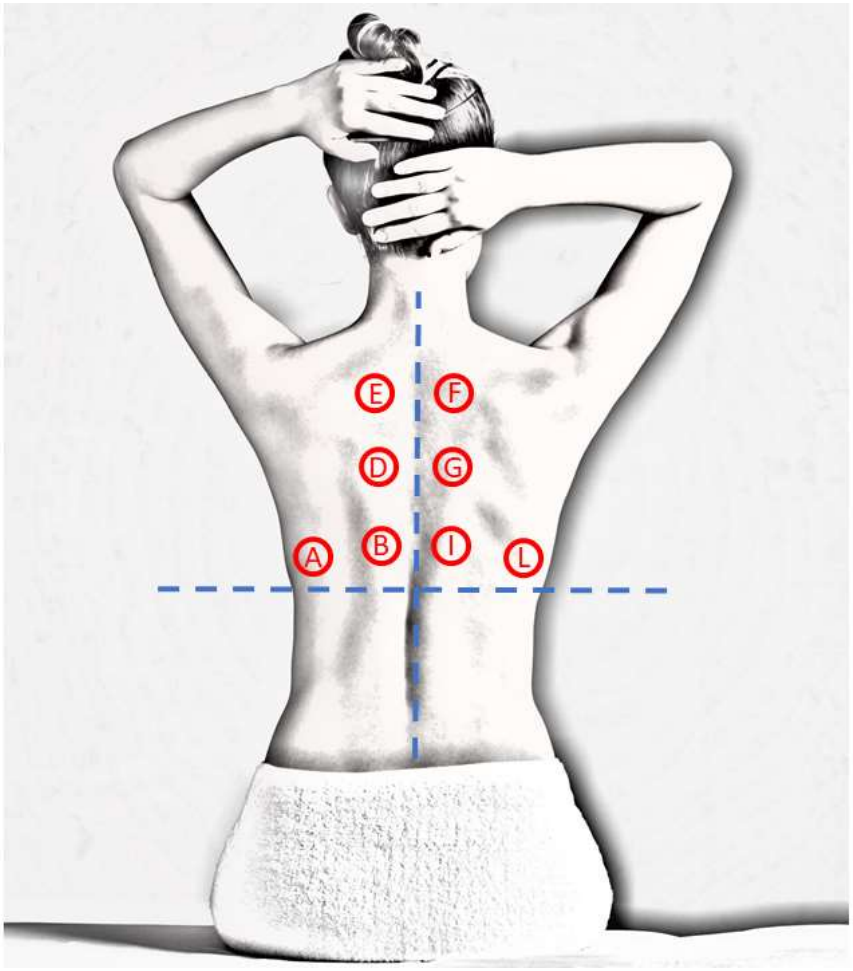


Figure 16.
All patients were auscultated bilaterally in 4 pulmonary fields at dorsal level: 2 at the basal fields, 1 at the medium fields and 1 at the upper field.

Assessment of lung involvement

1. Radiological

All HRCT exams were performed by using different multidetector scanners with a slice thickness of less than 2 mm, from the lung apices to below the costophrenic angles, reconstructed by using an edge-enhancing algorithm. The scan was performed in the supine position at full inspiration. All images were viewed at window setting optimized for assessment of lung parenchyma (width 1500 HU; level -700 HU). HRCT scans were assessed by an expert chest radiologist who interpreted the radiologic pattern ILD according to American Thoracic Society, European Respiratory Society, Japanese Respiratory Society and Latin American Thoracic Association statement on the diagnosis of idiopathic pulmonary fibrosis (IPF)[207,208]. The pattern of disease was recorded as definite, possible and inconsistent with UIP (see table 18). If an inconsistent with UIP pattern was noted, we specified if it was compatible with a nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP) or lymphoid interstitial pneumonia (LIP)[438,439]. When radiologic findings were not suggestive of any ILD, the radiologist recorded the precence of nodules, pleural effusion or other isolated manifestations of pulmonary disease such as consolidation.

2. Functional

The results of pulmonary function tests were expressed as percentage of the predicted value of each parameter and corrected for age, gender and height. Pulmonary function was considered as abnormal

if FVC was <75% of predicted values. Single breath DLCO was used to assess gas transfer. A cut-off of 47% was chosen for identify a severe reduction of DLCO according to previous data[156].

Statistical analysis

Data were analyzed using STATA statistical software (version 11. StataCorp LP, College Station, Texas, USA). Categorical variables were analyzed by chi square test and differences between the means were determined using Mann-Whitney or Student's t-test test for unpaired samples. Accordingly, diagnostic accuracy, specificity and sensitivity of the clinical and instrumental diagnostic tools were calculated. P values ≤0.05 were considered statistically significant.

Results.

General data

One hundred and forty RA patients were enrolled for the study. Three patients were excluded for the low quality of the recorded lung sounds. The indications for the HRCT were: dyspnea accompanied or not by fine crackles at lung auscultation (25.4%), a suggestive thorax X-Ray in 17.4%, the presence of fine crackles at lung auscultation in 12.3% and cough (4.3%). The remaining 56 patients underwent HRCT for other reasons (i.e. monitoring of lung nodules, infections, screening for tumor or other lung diseases).

Clinical and serological features of the 137 patients investigated are reported in table 18. An ILD was detected in 59 patients (43.1%). No differences were observed between patients with or without ILD with regard to sex, autoantibodies, smoking habit, spirometry (FVC), mean age at disease onset, and disease duration. On the contrary, patients with ILD were older, and showed a lower DLCO than non-ILD patients (table 18).

Diagnostic accuracy of VECTOR

VECTOR correctly classified 115/137 patients (83.9%), showing a sensitivity and specificity of 93.2% and 76.9%, respectively. Only 4/59 patients with ILD were not identified by VECTOR, while false positive cases were 18/78. Diagnostic accuracy of VECTOR in detecting ILD was higher than dyspnea (64.6%), cough (58.3%), DLCO (54.9%), FVC (52.8%) and chest X-ray (71.3%) (see table 19). The rheumatologist (GC, not blinded) correctly identified crackles in 69.1% patients with ILD (versus 93.2% of VECTOR), but also detected crackles in 34.2% of patients without ILD (versus 23.1% of VECTOR).

VECTOR correctly identified patients with ILD despite their radiological pattern (table 20). The 4 false negative patients showed an OP in two cases and an UIP pattern in the other two. The 2 patients with UIP pattern had an advanced and clinically evident lung fibrosis, with difficulty to properly deeply breath. Patients with OP had a not typical distribution of the lung involvement that could interfere with a proper auscultation. The possible patchy distribution of OP could explain the missing detection of these patients. About false positive cases, 12/18 showed an airways disease, mainly bronchiectasis chronic bronchitis, and obliterative bronchiolitis.

The diagnostic accuracy of VECTOR was not influenced by the duration of lung disease and by the extension of lung involvement.

Table 18. Clinical and serological features of 137 patients with rheumatoid arthritis

	Total	ILD -	ILD +	p
Nr.	137	78	59	
Smoke (%)	37.2	39.7	34	ns
Sex M/F	1/1.83	1/2.54	1/1.31	ns

ACPA (%)	77.2	77.1	77.2	ns
Rheumatoid factor (%)	78.6	81.1	75.4	ns
Forced vital capacity (%±SD)	91.8±22.3	93.1±21.3	90.3±23.7	ns
DLCO (%±SD)	59.9±18.0	65.7±20.4	54.4±13.6	0.015
Disease duration (years±SD)	11.1±9.5	10.4±7.8	12.1±11.3	ns
Mean age at disease onset (years±SD)	56.1±12.9	55.3±12.3	57.0±13.6	ns
Mean age at study entry (years±SD)	67.9±9.9	66.5±10.3	69.8±9.1	0.049

ILD: interstitial lung disease; M: males; F: females; ACPA: anti-citrullinated peptide antibodies; DLCO: Diffusion lung capacity of CO; SD: standard deviation

Table 19. Diagnostic accuracy of clinical and instrumental variables

	Total	ILD -*	ILD +*	p	diagnostic accuracy	specificity	sensitivity
Dyspnoea	29.1	18.7	41.2	0.004	64.6	81.3	41.2
Dry cough	12.1	10.8	15.1	ns	58.3	89.2	15.1
Thorax X-Ray	35.1	20	57.8	<0.001	71.3	80	57.8
DLCO < 47%	26	20	30.8	ns	54.9	80	30.8
FVC < 70%	18.9	17.9	20	ns	52.8	82.1	20
Velcro crackles°	49.2	34.2	69.1	<0.001	67.2	65.7	69.1
VECTOR	52.9	23.1	93.2	<0.001	83.9	76.9	93.2

* percentage of positive patients; °presence of velcro crackles according to rheumatologist's auscultation (AM)

Table 20. Diagnostic accuracy according to HRCT pattern

	Nr	%	Diagnostic accuracy (%)
UIP	30	21.7	93.5
NSIP	11	8	100
OP	8	5.8	75
LIP	1	0.7	100
Other	10	7.2	100
Normal	78	56.5	81.8

HRCT: high resolution computerized tomography; UIP: usual interstitial pneumonia; OP: organizing pneumonia; LIP: lymphocitic interstitial pneumonia; NSIP: nonspecific interstitial pneumonia

Discussion

The present multicenter study confirmed the high sensitivity, specificity and diagnostic accuracy of VECTOR on the presence of ILD in patients with RA.

RA-ILD is a field of great interest for both rheumatologists and pulmonologists. In the last years, many studies have been conducted to elucidate different facets of this harmful clinical problem, but they are all retrospective with substantial bias due to diagnostic methodologies[217,440,441].

An early diagnosis of RA-ILD is mandatory since it represents one of the most severe and challenging extra-articular manifestations in RA patients, associated to very low quality of life and poor overall prognosis[109,206,228]. Given its significant impact, there is a need to develop strategies to increase the diagnosis of ILD before symptoms occurrence. Moreover, ILD can occur at any stage of the disease; for this reason, lung evaluation should always be included in the clinical assessment of RA patients, regardless the disease duration or activity.

At the moment, a screening for RA-ILD is not feasible mainly because of the low diagnostic accuracy of any method other than HRCT, resulting in mis- or delayed diagnosis[108,110,159].

This limitation was already suggested in 2001, by Dawson et al. who showed the low diagnostic accuracy of clinical and functional features in RA-ILD patients. Among cases with HRCT evidence of ILD, only the presence of bilateral basal chest crackles was significantly associated of ILD, while restrictive pulmonary function tests, and bilateral chest radiographic signs of ILD showed a very low diagnostic accuracy for ILD. Also, DLCO was associated to ILD, but at the same time 52% of patients had a reduced DLCO without having ILD[442]. On the other hand, to study the possible risk factors for ILD appearance or progression, the natural evolution of the lung disease and its prognosis, it is crucial to assess the whole clinical history of ILD, identifying also patients with subclinical lung involvement. VECTOR could represent the first validated tool for the screening of RA patients suspected for ILD and who should be directed to HRCT for the diagnosis.

Our software, in combination with an ES, showed a sensitivity and specificity of 93.2% and 76.9%, respectively, and a very good diagnostic accuracy (83.9%), higher than any other method available to date, except for the HRCT, but without any radiological exposure. Diagnostic accuracy of VECTOR was also higher than the capability of an expert rheumatologist to detect velcro-sound by means of a pneumatic stethoscope, allowing to reduce the prescription of needless HRCT and increase the diagnosis of ILD before clinical manifestations become evident. Of interest, in our population, less than half of the patients correctly identified by VECTOR showed clinical symptoms or a reduction of functional lung test, confirming the usefulness of VECTOR in the identification of subclinical forms of ILD (table 19).

RA is the most frequent inflammatory rheumatic disease with a high risk of developing ILD, but up-to-date a systematic approach to this problem is not a routinely engaged in clinical practice[110,170,213,228]. The algorithm proposed could represent an opportunity for all rheumatologists to improve the screening of patients to direct to HRCT. It can be combined with an ES and allow a real-time detection of velcro-crackles during a routine clinical examination.

The main limit of our study is its retrospective design, and it could justify a number of false positive cases, probably due to transient conditions. Another possible explanation is the appearance of ILD subsequently to the HRCT used for the study. For example, in a patient with an apparent false positive result, a HRCT repeated after 10 months highlighted the presence of an initial ILD, not visible in the previous evaluation.

We are aware that our population are not completely comparable with general RA population, where we can suppose a lower rate of ILD, but also of comorbidities, that could affect sensitivity and specificity of the test. We think that sensitivity is a greater priority than specificity in diagnosis of RA-ILD and a possible reduction in specificity in a real-world setting could be justify by the correct identification of patients with ILD. However, although VECTOR performed well in the studied population, further researches are needed to confirm its efficacy as a screening tool in patients with early lung disease and in real-world setting of RA.

In conclusion, VECTOR, associated to an ES, could allow at rheumatologist a real-time screening of patients with ILD and it could be really helpful in the design of prospective studies, in which RA-ILD patients are identified with the help of this non-invasive method and followed during all disease course.

EPIDEMIOLOGY OF RA-ILD: STILL AN UNMET NEED

Study protocol to prospectively evaluate epidemiological features and risk factors of interstitial lung disease related to rheumatoid arthritis (LIRA Study).

AIMS OF TH STUDY

LIRA is an international prospective multicentre observational study. Its purpose is to evaluate incidence and prevalence of ILD in patients with RA. Moreover, it aims to assess radiological features, clinical onset and natural history of ILD-RA**,** as well as the risk factors for the development of ILD in RA patients.

Objectives:

- ✓ To evaluate prevalence of ILD in patients with RA
- ✓ To evaluate incidence of ILD in patients with RA
- ✓ To assess radiological features of RA-ILD
- ✓ To assess clinical onset and evolution of RA-ILD
- ✓ To assess risk factors for the development of ILD in RA patients

STUDY DESING AND METHODS

LIRA is an international prospective multicentre observational study enrolling all consecutive patients with a diagnosis of RA and evaluating the possible presence of pulmonary interstitial involvement.
It is a European study that mainly involves Italian rheumatologic centers and some Spanish and French centers.

Study population

Inclusion criteria:
All consecutive patients with a diagnosis of Rheumatoid Arthritis (RA) satisfying EULAR/ACR criteria, aged more than 18-year-old, will be enrolled.
Exclusion criteria**:** patients aged less than 18-year-old or patients not giving their informed consent for the study.
Number of patients (sample size) and Time schedule of the project:
We supposed to include a total of 500 patients. The number of patients recruited in the prospective study has been estimated on the mean number of RA patients per year diagnosed at the clinical centres. The enrolment stage will take 1 years, the duration of the study (follow-up for each patient) will be 5 years per subject.

Methods

All RA patients will be screened for signs or symptoms suggesting for the pulmonary involvement (cough, dyspnoea, velcro crackles, suspected ILD in a chest x-ray performed for other reasons, etc.) during the outpatient visit at rheumatologic centre.
Patients with suspicion of pulmonary disease will undergo a high-resolution computed tomography (HRCT), the gold standard for the diagnosis of ILD. No additional HRCT will be required in patients whom already have a diagnosis of ILD.
The HRCT images, acquired in digital "DICOM" format, will be centrally evaluated by an expert radiologist, in order to confirm the presence of ILD and to classify it according to the current radiological classification.

The images will be anonymized, coded and uploaded to the Coordinator Center by mean of a dedicated server whose access will be protected by password.
The following data will be collected at time of enrolment and during follow-up for each patient:

- Demographic data (age, sex, disease duration)
- Ongoing therapy: corticosteroids, conventional, targeted synthetic and biologic DMARDs
- Previous therapies type of drug (corticosteroids, cDMARDs, sDMARDs, bDMARDs), treatment duration and reason for discontinuation
- Respiratory symptoms (dyspnoea, dry cough, comorbidities potentially responsible for respiratory symptoms)
- Any instrumental investigations regarding respiratory assessment based on clinical needs (chest X-ray, respiratory function tests, BAL, lung biopsy, etc.)
- RA signs and symptoms

According to the different purposes of the study, the observational study will proceed as follows:
- Assessment of the prevalence: all patients will be evaluated in a cross-sectional study. The prevalence will be estimated as the ratio between the number of RA patients enrolled and the number of patients with RA-ILD diagnosed by HRCT.
- Assessment of the incidence: patients without signs or symptoms suggesting pulmonary involvement will be evaluated every 6 months. The incidence will be estimated as the ratio between the number of RA patients enrolled and the number of new cases of ILD diagnosed by HRCT in a year.
- Evaluation of the predictive factors and the onset of ILD with respect to the natural history of RA: all patients with newly diagnosed RA will be evaluated prospectively every 6 months for a period of 5 years.
Prevalence and incidence will be provided along with their 95% confidence intervals.

TRIAL STATUS

Submission of the study protocol to the Ethics Committee was set in February 2019; the study protocol was then approved in April 2019.
A total of 10 participating centers throughout Italy were activated. Moreover, two Spanish and a French rheumatologic center have been involved in the study.
The duration of the study (follow-up for each patient) will be 5 years per subject, the study completion date is estimated in 2024.

FIRST UPDATE 01/2020

Original article 10[114]:

Abstract: Interstitial lung disease related to rheumatoid arthritis. What do we don't know? The LIRA study (Lung Involvement in Rheumatoid Arthritis).

Background:
Interstitial lung disease (ILD) is one of the more frequent and potentially severe extra-articular manifestation of rheumatoid arthritis (RA). ILD significantly decreases the survival and quality of life of patients and influences the treatment approach to the patient.
Despite its clinical relevance, the prevalence, incidence and survival of RA-ILD is unknown and supposed on the base of retrospective data or registry-based studies.

Objectives:

For the first time, the Lung Involvement in Rheumatoid Arthritis (LIRA) study aims to investigate epidemiology, features and prognosis of RA-ILD patients in a prospective international multicentre study.

Methods:
All RA patients referring to the involved centres will be evaluated every six months with a digital stethoscope and a software able to identify velcro crackles with a diagnostic accuracy of 83.9% (VECTOR). In fact, velcro crackles are virtually identified in all stages of fibrosing alveolitis like RA-ILD, and their search is as a simple and reliable method to screening patients to be undergone to high resolution computed tomography (HRCT).
For each patient, clinical and serological data are recorded at baseline and every six months; when velcro crackles or other conditions suspicious for ILD, such as cough or dyspnoea, are detected, a HRCT is requested to confirm ILD. Patients with ILD periodically perform pulmonary function tests to monitor lung function evolution.

Results:
205 RA patients have been enrolled (female/male 161/44, mean age 64.8±12.9 years, mean disease duration 14.2±8.9 years), anti-citrullinated peptides antibodies (ACPA) and rheumatoid factor (RF) were positive in 77.1% and 78.1%, respectively. The prevalence of ILD was 21% (43 patients). In other 13 patients the HRCT is ongoing; therefore, we could suppose up to a prevalence of 27.3%. Patients with ILD were symptomatic in 53.5% of cases (23 patients), they are more frequently males and were older than patients without ILD (mean age 73.2±7.4 and 62.7±13.2; $p<0.0001$, female/male ratio 139/23 vs 22/21; $p<0.0001$) without significant differences regarding disease duration, positivity for ACPA or RF.

Conclusion:
The prevalence and the incidence of RA-ILD is still not well defined. Preliminary data of our study confirm a prevalence of ILD higher than 20%, patients are asymptomatic in almost the half of cases and more frequently males and elderly. Our study can help to define the clinical history of these patients, the possible association with clinical and serological features and the supposed role of some drugs.

CONCLUSION AND RESEARCH AGENDA

Interstitial lung disease is one of the most common extra-articular manifestations of RA, and its management is a challenge, to improve quality of life and decrease mortality and high utilization of healthcare resources.

Unfortunately, this complication is often underrated, particularly in its earliest and subclinical stages, and most of the available studies on this topic are retrospective.

As a result, we don't know the real epidemiology of ILD in RA patients, no proteomic or serologic biomarkers are available to augment our armamentarium for both diagnostic and prognostic purpose, non-homogeneous and sometimes discordant results regarding the proposed risk factor associated with RA-ILD have been described and, finally, randomized controlled clinical trials to support therapeutic decisions in RA-ILD patients are still missing.

In summary, there is an urgent need of prospective studies to clarify these crucial points in the field of RA-ILD. Overcoming these gaps of knowledge is compulsory for the design of target therapies and to improve patient management and quality of life.

In this framework, possible future directions include studies of sub-clinical RA–ILD, randomized trials stratified by RA–ILD subtypes, studies to detect easy and non-invasive tools for screening programs of interstitial lung involvement in RA patients, and other prospective studies to discover biomarker and predictors of lung involvement in RA, biomarkers to clinically phenotype patients, and well-designed treatment trials.

Perhaps future research will lead to changes in the diagnostic approach and management of ILD. One possibility includes moving away from the classification of ILD by specific disease, to a more personalized approach involving the identification of the underlying pattern, clinical behavior, genetic and biomarkers risk profile. So, well-designed therapeutic trials are mandatory, for a more personalized management and treatment of RA-ILD patients.

The substantial variability in RA-ILD clinical presentation (subclinical, progressive, slow progression, non-progressive, chronic, acute exacerbation, etc.), histopathologic subtype, and disease course makes it difficult to speculate about one milestone therapeutic approach. Further, studies to elucidate the possible concomitant use of DMARDs, immunosuppressants and anti-fibrotic agents are needed. Recently, antifibrotic medications are supposed to have relevance across various ILD subtypes, not only in UIP pattern (INBUILD). The INBUILD study showed that the utilization of nintedanib in patient with progressive fibrotic non-UIP phenotype that shows functional deterioration could also make sense. Maybe, the associations of both immunosuppressants and anti-fibrotic agents can potentially be the future of treatment in this spectrum of the disease.

In conclusion, taken together our works aim to fil the gap of knowledge in this newsworthy topic, considering every aspect of the issue, from epidemiology to diagnosis and therapy.

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