Tocilizumab for the treatment of patients with rheumatoid arthritis and interstitial lung diseases: a case series.

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Sir,

Rheumatoid arthritis (RA) related interstitial lung disease (ILD) represents one of the first cause of death in RA, with a mean survival of 2.6 years after diagnosis (1). The correct therapeutic approach to RA-ILD is still debated, since no controlled studies are available (2). The choice of the treatment is further complicated by the supposed role of many DMARDs in onset or worsening of pre-existing ILD (1, 2). Recently, Picchianti Diamanti et al, reported a case report of a patient with RA-ILD efficaciously treated with tocilizumab (TCZ), speculating about its possible role in this sub-group of patients (2).

In this background, here we report our experience of 4 patients with RA-ILD treated with tocilizumab monotherapy, in which remission of RA and stability or improvement of ILD were obtained (see table for clinico-serological data).

Patient 1: treated with methotrexate (MTX) and rituximab (RTX) from 2001 to 2009, when a high resolution computerized tomography (HRCT) showed a thickening of the interstitium of the right lower lobe. Treatment with abatacept was performed until 2013, when, for a low disease control of

RA (DAS28 4.77), he underwent to intravenous TCZ (560 mg monthly). At that time, HRCT showed a worsening of ILD (reticular lung fibrosis compatible with usual interstitial pneumonia). Joint involvement quickly improved (DAS28 2.64 after 6 months) and after an initial decrease of FVC, the lung function and the extension of reticular lung involvement remained stable along the next 3 years.

Patient 2: treated with sulfasalazine (SFZ) and MTX since 2008. In 2015, ILD was diagnosed, with a nonspecific interstitial pneumonia (NSIP) pattern at HRCT. The patient was asymptomatic, FVC was normal, while DLCO was 38%. Because of moderate activity of RA (DAS28 4.87), TCZ was started in 2016, and SFZ and MTX were stopped. After 16 months of therapy, RA was in remission (DAS28 2.53), while lung involvement remained unchanged (no dyspnea, stable HRCT).

Patient 3: overlap syndrome RA-systemic sclerosis, ILD known since 1998, with NSIP pattern at HRCT. She was treated with leflunomide, MTX, SFZ, etanercept and RTX, until 2013, when intravenous TCZ was started for RA high disease activity (DAS28 6.01). Joint involvement rapidly improved. After 30 months, lung involvement was unchanged, but TCZ was stopped for patient's choice.

Patient 4: treated with leflunomide since 2001. In 2008 a combined pulmonary fibrosis and emphysema was diagnosed. In 2016, when the patient underwent to our observation, a mild restrictive lung disease was recorded. At January 2017, leflunomide was replaced with TCZ for a low disease control of RA (DAS28 5.44). After 6 months, the patient showed a low disease activity (DAS28 3.03), while no changes were observed in respiratory symptoms and function.

Although the link ILD/MTX is not clearly defined, the use of MTX is nowadays not indicated in patients with RA-ILD (2-4), while it is largely recommended for the management of RA, as first line therapy or in association with biologic DMARDs (5). TCZ could represent a possible safe drug in these patients, considering its efficacy in RA also as monotherapy (6). Moreover, Interleukin-6 plays a key role synovial cell proliferation, but it is also potentially involved in extra-articular manifestations of RA and other connective tissue diseases (7-9).

The management of RA-ILD patients remains a critical unmet medical need. Prospective studies on larger populations are required to define if biologic or conventional DMARDs could really influence the evolution of ILD in RA patients (2, 10). Moreover, the enrollment of RA patients with an early diagnosis of ILD is mandatory to perform ad hoc studies and clinical trials required to define the best clinical management of a such severe complication in RA patients (11).

References

1. O'Dwyer DN, Armstrong ME, Cooke G, Dodd JD, Veale DJ, Donnelly SC. Rheumatoid Arthritis (RA) associated interstitial lung disease (ILD) Eur J Intern Med. 2013; 24: 597-603
2. Picchianti Diamanti A, Markovic M, Argento G, Giovagnoli S, Ricci A, Laganà B, D'Amelio R. Therapeutic management of patients with rheumatoid arthritis and associated interstitial lung disease: case report and literature review. Ther Adv Respir Dis. 2017; 11: 64-72
3. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 2008; 59: 762-84
4. Saravanan V, Kelly C. Reducing the risk of methotrexate pneumonitis in rheumatoid arthritis. Rheumatology 2004; 43: 143–7.
5. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res. 2016; 68: 1-25
6. Jones G, Wallace T, McIntosh MJ, Brockwell L, Gómez-Reino JJ, Sebba A. Five-year Efficacy and Safety of Tocilizumab Monotherapy in Patients with Rheumatoid Arthritis Who Were Methotrexate- and Biologic-naive or Free of Methotrexate for 6 Months: the AMBITION Study. J Rheumatol. 2017; 44: 142-6

7. McInnes IB, Schett G. Pathogenetic insights from the treatment of rheumatoid arthritis. Lancet. 2017; 389: 2328-37
8. Barsotti S, Stagnaro C, d'Ascanio A, Della Rossa A. One year in review 2016: systemic sclerosis. Clin Exp Rheumatol. 2016; 34: 3-13
9. Denton CP. Systemic sclerosis: from pathogenesis to targeted therapy. Clin Exp Rheumatol. 2015; 33: S3-7
10. Iqbal K, Kelly C. Treatment of rheumatoid arthritis-associated interstitial lung disease: a perspective review. Ther Adv Musculoskelet Dis. 2015; 7: 247-67
11. Manfredi A, Sebastiani M, Cassone G, Fedele AL, Venerito V, Trevisani M, et al. New perspectives in diagnosis of interstitial lung disease related to rheumatoid arthritis. validation study of an electronic stethoscope and ad hoc software for detection of pulmonary crackles. Ann Rheum Dis. 2017; 76 (supp 2), 248