Rheumatol Ther
https://doi.org/10.1007/s40744-025-00805-2

ORIGINAL RESEARCH

Filgotinib Effectiveness in Rheumatoid Arthritis: Observational Analysis of a Large Multicenter Cohort

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Received: June 20, 2025 / Accepted: October 15, 2025

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40744-025-00805-2.

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Published online: 04 December 2025

ABSTRACT

Introduction: The efficacy and safety of filgotinib (FIL) for the treatment of patients with rheumatoid arthritis (RA) have been evaluated in a number of randomized controlled trials. However, there is a scarcity of real-world studies evaluating the effectiveness, persistence, tolerability, and safety of FIL in everyday clinical practice. This study aimed to assess the effectiveness and retention rate of FIL in a real-world cohort of patients with RA.

Methods: A multicenter retrospective cohort study of patients with RA treated with FIL was conducted in 27 Italian tertiary referral rheumatology centers. The drug retention rate (DRR) was estimated by the Kaplan–Meier method, while multivariate Cox regression was used to detect potential factors affecting drug survival and persistence in therapy. Disease activity score (DAS28-CRP) was assessed at baseline and after 6 and 12 months.

Results: We enrolled 204 patients (80% female). The DRR of FIL was 90.2% (95% confidence interval (CI) 86–94.6%), 75.1% (95% CI 68.5–82.4%), and 64.7% (95% CI 56.3–74.3%) at months 6, 12, and 18, respectively. The DRR was negatively associated with the line of treatment and the presence of rheumatoid factor. Effectiveness was evaluated as DAS28-CRP response. At 6 months, DAS28-CRP remission was observed in 65 (36.1%) patients, and remission or low disease activity in 98 (54.4%). At 12 months, DAS28-CRP remission was observed in 64 (50.0%) patients, and remission or low disease activity in 81 (63.2%).

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Conclusions: This analysis of real-world patients with RA demonstrated the effectiveness of FIL with a good DAS28-CRP response and high DRR at follow-up.

PLAIN LANGUAGE SUMMARY

Filgotinib is a selective Janus kinase 1 inhibitor that has been approved in Europe for the treatment of moderate to severe active rheumatoid arthritis in adult patients who are unresponsive or intolerant to one or more disease-modifying antirheumatic drugs. The efficacy and safety of filgotinib for the treatment of patients with rheumatoid arthritis have been evaluated in a number of randomized controlled trials. However, real-world data could offer valuable insights into the effectiveness, persistence, and safety of filgotinib in routine clinical practice. This study, therefore, looked at how long patients with rheumatoid arthritis from a large Italian cohort continued treatment with filgotinib, and how effective it was at achieving disease remission or at least low disease activity. A total of 204 patients were included in this study. More than half of the patients (64.7%) remained on treatment at 18 months. At 12 months, disease remission was observed in 50.0% of patients, whereas remission or low disease activity was experienced by 63.2% of patients. In conclusion, this real-world study demonstrates that filgotinib is effective and safe for the treatment of patients with rheumatoid arthritis in routine clinical practice.

Keywords: bDMARD; csDMARD; Drug retention rate; Efficacy; Effectiveness; Filgotinib; JAK inhibitor; Rheumatoid arthritis; Safety; tsDMARD

Key Summary Points

Why carry out this study?
The efficacy and safety of filgotinib (FIL) for the treatment of patients with rheumatoid arthritis (RA) have been evaluated in a number of randomized controlled trials.
However, there is a scarcity of real-world studies evaluating the effectiveness, persistence, tolerability, and safety of FIL in everyday clinical practice.
The goal of this multicenter retrospective study was to assess the effectiveness, retention, and safety of FIL in a real-world cohort of patients with rheumatoid arthritis.
What was learned from the study?
A total of 204 patients with RA (80% female) were included in the study. The results showed effectiveness in terms of disease activity score (DAS28-CRP) remission or low disease activity both at 6 and 12 months. The FIL retention rate was considered satisfactory with more than half of the patients continuing treatment at month 18. Retention rate was found to be negatively associated with the line of treatment and the presence of rheumatoid factor (RF).
Overall, the findings of this real-world study support the favorable clinical profile of FIL for the treatment of RA and may inform clinical practice and guideline recommendations.

INTRODUCTION

Rheumatoid arthritis (RA) is one of the most common chronic inflammatory diseases, primarily affecting the joints and presenting with extra-articular manifestations such as rheumatoid nodules, lung involvement or vasculitis, as well as other systemic comorbidities [1]. This

disease causes a decline in physical function, reduced work capacity, and decreased social participation, leading to reduced quality of life and increased cumulative risk of comorbidities, representing a significant burden for both the individual and society [2].

The incidence of RA in Italy is 0.5–1%, with an apparent decrease from North to South and from urban to rural areas [3]. A positive family history increases the risk of RA by approximately 3–5 times, implicating genetic factors in the pathogenesis, as confirmed by increased concordance rates in twins [4].

Nowadays, treatment goals include rapid achievement of remission or low disease activity to prevent structural damage and consequent disability. The early initiation of therapy in the course of the disease can prevent radiographic progression, most of which occurs within the first few months of disease onset. The primary role of disease-modifying antirheumatic drugs (DMARDs) is well established, with conventional synthetic DMARDs (csDMARDs, such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) still used as first-line therapy today, in addition to their non-selective immunosuppressive mechanism of action. The introduction of biologic DMARDs (bDMARDs) in the 1990s represented a major change in the management of RA. They can be used as monotherapy or in combination with csDMARDs, with a sensible improvement in achieving remission or obtaining low disease activity of RA. They are specific, targeting a precise pathway of the immune system, and are used as second-line therapy. The most representative class of bDMARDs is the tumor necrosis factor (TNF) inhibitors (TNF-i), such as infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol. While only 30% of patients treated with csDMARDs achieve remission, up to 50.0% of those treated with TNF-i in a treat-to-target strategy achieve remission at 6–12 months. However, despite treatment with csDMARDs and bDMARDs, up to 20–30% of patients with RA do not achieve or fail to maintain a good response over time [5].

In recent years, the development and authorization of Janus kinase (JAK) inhibitors (JAKis), small molecules belonging to the class of targeted synthetic DMARDs (tsDMARD), have further improved treatment options for RA.

JAKis are cytoplasmic proteins that link cytokine signaling from membrane receptors to transcription factors, known as signal transducers and activators of transcription (STATs). This allows for optimal control of the inflammatory response, making it a valuable resource for the management of autoimmune diseases [6]. There are four members in the JAK family (JAK1, JAK2, JAK3, and tyrosine kinase 2, TYK2), and seven types of STATs (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, STAT6), that can be targeted by JAKis [7].

In addition to their good efficacy and safety profiles, other important advantages of JAKis are their oral route of administration and lower production costs compared to bDMARDs [7].

Four JAKis—tofacitinib, baricitinib, upadacitinib, and filgotinib (FIL)—have been approved in Europe for the treatment of moderate-to-severe RA after failure of first- and second-line therapy [8]. Tofacitinib and baricitinib are considered pan-JAK inhibitors, being able to simultaneously interact with different JAKis, blocking their downstream signaling pathway, while upadacitinib and FIL are preferentially blockers of JAK1 over the other molecules.

FIL is a competitive and reversible inhibitor of adenosine triphosphate in the JAK family, and is currently indicated in the EU both as monotherapy and also in combination with methotrexate for the treatment of moderate-to-severe active RA in adults with an inadequate response or intolerance to one or more DMARDs [9]. Specifically, FIL has been shown to preferentially inhibit JAK1/3, JAK1/2, and JAK1/TYK2 (Tyrosine Kinase 2), with a functional selectivity for cytokine receptors that signal via JAK2 or JAK2/TYK2 pairs [10].

The efficacy of FIL in the treatment of moderate-to-severe active RA was initially investigated in the phase II DARWIN 2 trial [11], as well as in the phase II DARWIN 1 trial [12] in combination with methotrexate (MTX), demonstrating an improvement in symptoms among patients with an inadequate response to methotrexate.

Subsequently, its efficacy was further evaluated in phase III trials, including: (a) FINCH 1 [10], which assessed the efficacy of FIL versus

placebo or adalimumab in patients with inadequate response to MTX; (b) FINCH 2 [13], which showed a significantly greater proportion of patients achieving clinical response at week 12 in patients with active RA who had an inadequate response or intolerance to one or more bDMARDs; and (c) FINCH 3 [14], which demonstrated the efficacy of FIL plus or without MTX compared to MTX alone. Notably, FINCH 3 also showed a rapid decrease in pain after only 2 weeks of treatment, which was maintained up to 24 weeks.

FIL was generally well tolerated in patients with RA across clinical trials, with the most frequently reported adverse reactions being nausea, upper respiratory tract infection (URTI), urinary tract infection (UTI), and dizziness. Moreover, the frequency of serious infection associated with FIL remained low and stable with longer-term exposure [15]. However, patients in real-world clinical practice often differ from those selected for registration trials. For this reason, real-world clinical data on efficacy, safety, and adherence are particularly valuable. To date, however, data supporting the efficacy and safety of FIL in patients with RA from real-life studies are still scarce [16, 17].

On this basis, our study aims to further evaluate the effectiveness and safety of FIL in real-world patients with RA from a large Italian cohort. To our knowledge, this is the first real-world study to assess the effectiveness of FIL in patients with RA with an 18-month follow-up. Thanks to its large sample size and the involvement of multiple centers across Italy, this study offers a comprehensive snapshot of FIL's effectiveness in clinical practice nationwide.

METHODS

This multicenter retrospective cohort study involved 27 tertiary referral rheumatology centers in Italy. The study is part of the BIRRA (BIologics Retention Rate Assessment) project, which aims to investigate the long-term retention of innovative antirheumatic drugs. The study was approved by the ethics committee of Comitato Etico dell'Area Vasta Emilia Nord (protocol code 34,713, approved on 28 August 2019) as well as by the ethics committees of the remaining 26 centers involved (see Supplementary Material, Table S1) and was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. All participants provided written consent to participate in the study and for publication.

Patient data were extracted from the clinical databases of each participating center in the study. The diagnosis of RA was made according to the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) criteria [18]. All patients were aged ≥ 18 years and were treated with FIL as monotherapy or in combination with csDMARDs, with or without the addition of steroids. The patient cohort was followed for 18 months, from May 2021 to December 2023. Demographic characteristics, smoking habits, previous and ongoing treatments, comorbidities, and laboratory data, including positivity for rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), were recorded. Comorbidities considered were diabetes, dyslipidemia, history of major adverse cardiovascular events (MACEs), cancer, and hypertension. Disease activity at baseline, 6 months, and 12 months was assessed in all patients by calculating the disease activity score 28-CRP (DAS28-CRP); FIL retention rate, and any reasons for discontinuation of therapy were then analyzed.

Statistical Analysis

Median and interquartile range (IQR) were calculated for variables with nonparametric distributions. Categorical data were expressed as numbers and percentages. Cox regression analysis was used to identify predictors of FIL discontinuation. These data were presented as the hazard ratio (HR) and the corresponding 95% CI. The FIL retention rate curve was constructed using the Kaplan–Meier method. Logistic regressions were used to determine whether there were factors associated with the achievement of DAS28-CRP low disease activity or remission at 6 and 12 months. These data were presented as odds ratio (OR) and the corresponding 95%

CI. We performed univariate regression analysis on all variables and included those with a p value < 0.1 in multivariate regression analysis to determine independent prognostic factors. The effectiveness outcomes were analyzed using the intention-to-treat approach, with the last observation carried forward where appropriate. A p value ≤ 0.05 was considered statistically significant. All statistical analyses were two-sided and were performed using Jamovi statistical software version 2.3.21 (http://www.jamovi.org).

RESULTS

We included 204 patients with RA treated with FIL. The demographic and clinical characteristics of the patients studied are detailed in Table 1.

A total of 163 (79.9%) patients were female, and the median disease duration was 22 months (IQR 8–135). The median age at the start of FIL treatment was 62 years (IQR 54–69) and the median IQR body mass index (BMI) was 25.9 (23.0–28.3). A total of 133 (62.2%) patients had a positive RF and 115 (56.4%) a positive ACPA. FIL was used as monotherapy in 119 (58.3%) patients, while concomitant csDMARDs were reported in 85 (41.7%) patients (69 methotrexate, 12 leflunomide, and four hydroxychloroquine); 99 (48.5%) patients were taking corticosteroid at baseline, with a median (IQR) prednisone equivalent dose of 5 mg/day (5–5). FIL was used in 53 (25.9%) patients after the failure of csDMARDs. With regard of prior treatments, 122 (59.8%) patients had received at least one anti-TNF, 42 (20.6%) an IL6R inhibitor, 50 (24.5%) abatacept, seven (3.4%) an IL1R antagonist, 15 (7.3%) rituximab and 71 (34.8%) a prior JAK inhibitor. The median DAS28-CRP at baseline was 5.17 (IQR 4.21–5.86). Smoking history data were available for 187 patients: 35 (18.7%) patients were current smokers, and 27 (14.4%) were former smokers. Among comorbidities, hypertension was the most common [97 (47.5%) patients]. At baseline, 23 (11.3%) patients had diabetes mellitus, 68 (33.3%) had dyslipidemia, and 12 (5.9%) had a history of cancer.

Retention Rate and Predictors of Retention Rate

The DRR of FIL was reported using the Kaplan–Meier curve over 18 months (Fig. 1).

At months 6, 12, and 18, the DRR was 90.2% (95% CI 86–94.6%), 75.1% (95% CI 68.5–82.4%), and 64.7% (95% CI 56.3–74.3%), respectively.

Predictive independent variables of FIL retention rate were analyzed using univariate and multivariate Cox regression expressed as HR and 95% CI. These data are summarized in Table 2.

Age (p = 0.59), sex (p = 0.57) and BMI (p = 0.46) did not affect the DRR of FIL in our cohort. The presence of diabetes mellitus (p = 0.18), hypertension (p = 0.73), and dyslipidemia (p = 0.22) did not affect the DRR. Finally, we observed a high risk of discontinuation in patients with rheumatoid factor positivity [HR 2.23 (95% CI 1.12–4.45; p = 0.02)] and in those with an increasing number of treatment lines [HR 1.15 (95% CI 1.03–1.28; p = 0.01)].

During the observation period, 50 (24.5%) patients discontinued treatment with FIL, 27 for lack or loss of efficacy, 20 for adverse events, and three for unknown reasons. Of the 20 patients who experienced adverse events, four had mild infections not requiring hospitalization, four discontinued the drug due to dyslipidemia, three due to the onset of leucopenia and two following a cancer diagnosis. The reasons for discontinuation and all the adverse events are detailed in Table 3.

DAS28-CRP Response and Predictors of DAS28-CRP Response

Among the 204 patients treated with FIL, we analyzed the DAS28-CRP response in 180 patients at 6 months, and in 128 patients at 12 months, using the intention to treat-to-target approach. At 6 months DAS28-CRP remission was observed in 65 (36.1%) patients, while remission or low disease activity was observed in 98 (54.4%) patients. At 12 months DAS28-CRP remission was observed in 64 (50.0%) patients, whereas remission or low disease activity in 81 (63.2%).

Table 1 Baseline characteristics

Characteristic	
Age, year, median (IQR)	62 (54–69)
Sex, *n* (%)	
Female	163 (80%)
Male	41 (20%)
BMI, kg/m^2, median (IQR)	25.9 (23–28.3)
Smoker status, *n* (%)	
Yes	35/187 (18.7%)
Former	27/187 (14.4%)
Never	125/187 (66.9%)
Disease duration, months, median (IQR)	22 (8–135)
RF positive, *n* (%)	133 (62.2%)
ACPA positive, *n* (%)	115 (56.4%)
DAS28-CRP, median (IQR)	5.17 (4.21–5.86)
Line of treatment, *n*, median (IQR)	2 (1–3.5)
Concomitant csDMARDs, *n* (%)	
MTX	69 (33.8%)
LFN	13 (6.4%)
HCQ	4 (2%)
Concomitant corticosteroid, *n* (%)	99 (48.5%)
Steroid (PDN-Eq) dose, mg/day, median (IQR)	5 (5–5)
Previous usage of bDMARDs, *n* (%)	
Anti-TNFα	122 (59.8%)
Anti-IL6R	42 (20.6%)
IL1Ra	7 (3.4%)
CD80/CD86 inhibitor	50 (24.5%)
Anti-CD20	15 (7.3%)
Previous usage of tsDMARDs, *n* (%)	71 (34.8%)
One	62 (30.4%)
Two	6 (2.9%)

Table 1 continued

Characteristic	
Three	3 (1.5%)
Comorbidities, *n* (%)	
Diabetes	23 (11.3%)
Dyslipidemia	68 (33.3%)
Previous MACE	16 (7.8%)
Hypertension	97 (47.5%)
History of cancer	12 (5.9%)

IQR median and interquartile range, *BMI* body mass index, *RF* rheumatoid factor, *ACPA* anti-citrullinated protein antibody, *DAS28-CRP* disease activity score 28-CRP, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *MTX* methotrexate, *LFN* leflunomide, *HCQ* hydroxychloroquine, *PDN-Eq* prednisone equivalent, *bDMARD* biologic disease-modifying antirheumatic drugs, *Anti-TNFα* anti-tumor necrosis factor alpha, *Anti-IL6R* anti-interleukin-6 receptor, *IL1Ra* interleukin-1 receptor antagonist, *CD80/CD86 inhibitor* cytotoxic t-lymphocyte antigen 4 (CTLA-4) Ig fusion protein inhibitor of CD80/CD86 costimulatory molecules, *Anti-CD20* anti-cluster of differentiation 20 monoclonal antibody, *tsDMARDs* targeted synthetic disease-modifying antirheumatic drugs, *MACE* major adverse cardiovascular events

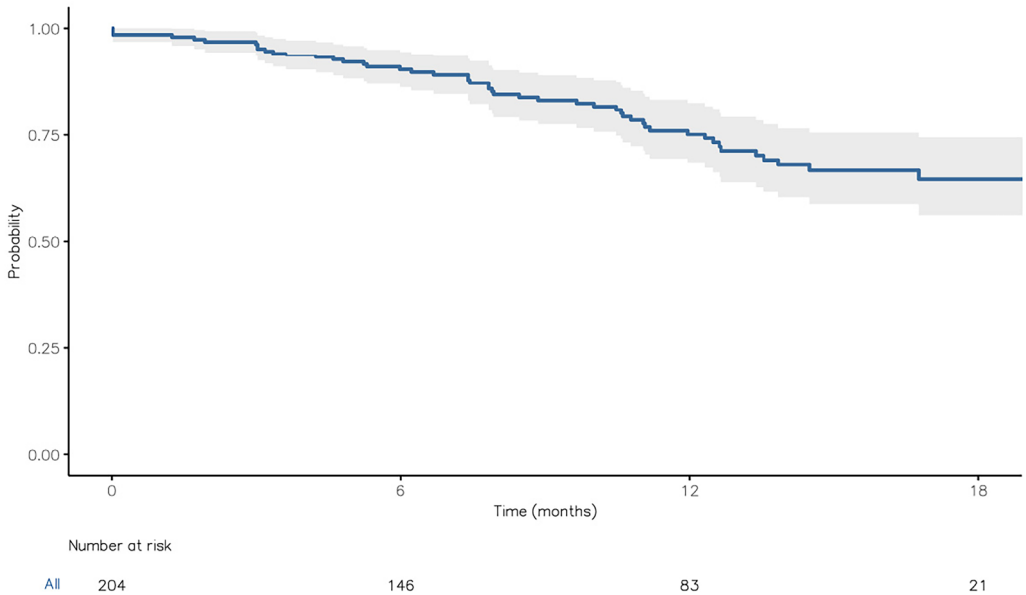

Fig. 1 Survival curves for overall based on Kaplan–Meier estimates

Predictive independent variables for FIL DAS28-CRP remission or low disease activity at 6 and 12 months were analyzed using univariate and multivariate logistic regression expressed as OR and 95% CI (Table 4 for 6 months, Table 5 for 12 months).

At 6 months, disease duration was associated with achievement of remission or low disease activity (OR 1.00; 95% CI 1.00–1.01; $p=0.027$). At 12 months, however, lower BMI was associated with achievement of remission or low disease activity (OR 0.91; 95% CI 0.85–0.99; p 0.049).

Table 2 Analysis of predictive factors of FIL retention rate

	Univariate	Multivariate
Age	1.01 (0.98–1.03), $p = 0.59$	
Sex (M vs. F)	0.81 (0.39–1.67), $p = 0.57$	
BMI	0.97 (0.91–1.04), $p = 0.46$	
Smoke		
Current vs. Never	1.61 (0.81–3.20), $p = 0.17$	
Former vs. Never	0.80 (0.32–1.99), $p = 0.51$	
Line of treatment	1.10 (0.99–1.22), $p = 0.06$	**1.15 (1.03–1.28), $p = 0.01$**
Disease duration	1.00 (1.00–1.00), $p = 0.47$	
RF (present)	1.83 (0.95–3.50), $p = 0.06$	**2.23 (1.12–4.45), $p = 0.02$**
ACPA (present)	1.24 (0.70–2.20), $p = 0.45$	
DM (present)	0.46 (0.14–1.47), $p = 0.18$	
Hypertension (present)	1.10 (0.63–1.93), $p = 0.73$	
Dyslipidemia (present)	0.67 (0.35–1.28), $p = 0.22$	
Previous MACE	0.98 (0.30–3.15), $p = 0.97$	
Previous Neoplasm	0.65 (0.16–2.67), $p = 0.54$	
Current csDMARDs	1.08 (0.61–1.89), $p = 0.79$	
Basal DAS28	0.95 (0.75–1.2), $p = 0.65$	

FIL filgotinib, *M* male, *F* female, *BMI* body mass index, *RF* rheumatoid factor, *ACPA* anti-citrullinated protein antibody, *DM* diabetes mellitus, *MACE* major adverse cardiovascular events, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *DAS28-CRP* disease activity score 28-CRP. The values in bold indicate statistical significance with $p < 0.05$

DISCUSSION

This real-life analysis of FIL retention aimed to assess the effectiveness and persistence of therapy over an 18-month period. Data collected from this multicenter study demonstrated good effectiveness of FIL in patients with RA in a real-world setting, as evidenced by high DRR rates and statistically significant reductions in DAS28-CRP at 6- and 12-month follow-up.

Furthermore, major predictive factors such as comorbidities, use in combination therapy, and baseline patient characteristics did not significantly affect DRR, supporting the efficacy of FIL even as monotherapy. In this context, real-world evidence supporting its effectiveness as a standalone treatment provides a valuable therapeutic option when combination therapy is not indicated.

In addition, our data identified RF titer and multiple prior treatment failures as negative predictive factors for DRR, in line with recent evidence from the literature [19].

The observed reduction in DAS28-CRP at 6 months further supports a rapid onset of action with FIL, consistent with findings from RCTs [14] and other real-life studies [16, 20].

Regarding safety, no MACEs were reported, even among patients aged over 65 years, despite 16 patients (7.8%) having a previous history of cardiovascular events. In these cases, FIL was

Table 3 Causes of discontinuation of FIL treatment

No. of cases (%)	
Primary failure	7 (3.4%)
Secondary failure	20 (9.8%)
Cancer	2 (0.9%)
Infection	4 (1.9%)
Leukopenia	3 (1.4%)
Dyslipidemia	4 (1.9%)
Nightmares	1 (0.4%)
Xerophthalmia	1 (0.4%)
Retinal thrombosis	1 (0.4%)
Tachycardia	2 (0.9%)
Headache	1 (0.4%)
Cutaneous calcinosis	1 (0.4%)
Unknown	3 (1.4%)

FIL filgotinib

initiated prior to the updated recommendations regarding cardiovascular risk. Only two patients were diagnosed with malignancy, leading to treatment discontinuation.

In real-world settings, other JAK inhibitors (tofacitinib, baricitinib, and upadacitinib) have all demonstrated meaningful clinical effectiveness and varying DRR levels. Observational data indicate baricitinib persistence rates of approximately 66.5% at 12 months and 56.4% at 24 months in a 139-patient prospective cohort. In a larger Italian cohort ($n=478$), baricitinib retention rates were 94.6% at 12 months, 87.9% at 18 months, 81.7% at 24 months, and 53.4% at 48 months [21, 22].

Similarly, data from the UPHOLD observational cohort showed upadacitinib achieving DAS28-CRP remission rates between 46.5% and 55.3% at 6 months [23], while results from the Italian GISEA registry reported drug retention rates of 91.6% at 6 months, 84.6% at 12 months, 80.3% at 18 months, and 80.0% at 24 months in 215 patients with RA [24].

For tofacitinib, a large Australian retrospective cohort ($n=650$) matched with 1300 bDMARD users showed DAS28 remission at 18 months in 57.8% of tofacitinib-treated patients versus 52.4% with bDMARDs, with median treatment persistence of 34.2 months—comparable to the bDMARD group (33.8 months) [25]. In Italy, a multicenter retrospective study across 23 tertiary rheumatology centers ($n=213$) reported retention rates of 86.5% at 12 months, 78.8% at 24 months, 63.8% at 36 months, and 59.9% at 48 months [26].

Overall, our findings with FIL are consistent with the existing body of evidence reported for other JAK inhibitors in similar patient populations. Despite inherent study limitations, the efficacy outcomes observed in our cohort are broadly comparable to those reported for tofacitinib, baricitinib, and upadacitinib, particularly in terms of clinical response and DRR. Likewise, the safety profile did not reveal any new or unexpected signals, aligning with the established tolerability of the class. FIL's preferential inhibition of JAK1 (over JAK2, JAK3, and TYK2) may translate into a differentiated clinical profile compared with less selective JAK inhibitors. By sparing JAK2, FIL is less likely to interfere with erythropoietin and thrombopoietin signaling, potentially reducing the risk of anemia or thrombocytopenia. Reduced activity on JAK3 and TYK2 may also limit interference with common γ-chain cytokines (e.g., IL-2, IL-4, IL-7) and type I interferons, which could result in a more favorable infection and lipid profile. Clinically, this selectivity may enable effective modulation of inflammatory pathways driven by IL-6 and interferon-γ (key JAK1-dependent cytokines), while minimizing hematologic and metabolic side effects, offering a potentially safer

Table 4 Analysis of predictive factors of DAS28-CRP remission or low disease activity at 6 months

	Univariate	Multivariate
Age	1.00 (0.97–1.02), $p = 0.88$	
Sex (M vs. F)	0.65 (0.31–1.34), $p = 0.24$	
BMI	0.91 (0.85–0.99), $p = 0.03$	0.92 (0.85–1.00), $p = 0.057$
Smoke		
Current vs. Never	1.20 (0.54–2.67), $p = 0.64$	
Former vs. Never	0.55 (0.22–1.37), $p = 0.20$	
Line of treatment	0.98 (0.85–1.14), $p = 0.87$	
Disease duration	**1.00 (1.00–1.01), $p = 0.02$**	**1.00 (1.00–1.01), $p = 0.027$**
RF (present)	1.02 (0.55–1.90), $p = 0.92$	
ACPA (present)	1.00 (0.55–1.81), $p = 0.99$	
DM (present)	1.24 (0.50–3.07), $p = 0.64$	
Hypertension (present)	1.27 (0.70–2.28), $p = 0.43$	
Dyslipidemia (present)	1.46 (0.78–2.74), $p = 0.23$	
Previous MACE	3.33 (0.89–12.36), $p = 0.07$	3.71 (0.66–20.77), $p = 0.13$
Previous neoplasm	1.50 (0.42–5.32), $p = 0.53$	
Current csDMARDs	0.81 (0.44–1.47), $p = 0.49$	
Basal DAS28	0.76 (0.58–0.99), $p = 0.04$	0.72 (0.51–1.01), $p = 0.059$

M male, *F* female, *BMI* body mass index, *RF* rheumatoid factor, *ACPA* anti-citrullinated protein antibody, *DM* diabetes mellitus, *MACE* major adverse cardiovascular events, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *DAS28-CRP* disease activity score 28-CRP. The values in bold indicate statistical significance with $p < 0.05$

long-term option for patients requiring chronic immunomodulation.

While the study provides valuable insights into FIL use in real-world clinical practice, its findings should be interpreted with caution due to several methodological and contextual limitations.

First, the retrospective nature of the study inherently limits the ability to establish causal relationships and may introduce selection bias. Additionally, missing DAS28-CRP data at 12 months and the absence of a comparator group restrict the depth of interpretation and preclude direct comparisons of efficacy and safety.

The observation period (May 2021–December 2023) also implies that not all patients completed a full 12-month follow-up. Specifically, 52 patients did not reach the 12-month endpoint, either due to early treatment discontinuation or insufficient observation time within the study window. This could introduce attrition bias, as outcomes among these patients may differ from those who completed the follow-up. Furthermore, the lower treatment persistence observed among patients with multiple prior therapeutic failures highlights the ongoing challenge of managing this difficult-to-treat population.

Finally, the relatively small sample size and the lack of evaluation regarding glucocorticoid tapering during therapy further limit the generalizability of our findings.

Future prospective, controlled studies with larger cohorts are warranted to confirm these results and better define the long-term role of FIL in clinical practice.

Table 5 Analysis of predictive factors of DAS28-CRP remission or low disease activity at 12 months

	Univariate
Age	0.99 (0.96–1.02), $p = 0.47$
Sex (M vs. F)	0.89 (0.39–2.05), $p = 0.76$
BMI	**0.91 (0.85–0.99), $p = 0.049$**
Smoke	
Current vs. Never	0.83 (0.29–2.28), $p = 0.71$
Former vs. Never	0.98 (0.36–2.62), $p = 0.96$
Line of treatment	1.02 (0.84–1.23), $p = 0.86$
Disease duration	1.00 (0.99–1.01), $p = 0.56$
RF (present)	1.19 (0.58–2.44), $p = 0.63$
ACPA (present)	1.58 (0.78–3.19), $p = 0.21$
DM (present)	0.71 (0.27–1.85), $p = 0.48$
Hypertension (present)	0.70 (0.35–1.42), $p = 0.32$
Dyslipidemia (present)	1.10 (0.52–2.33), $p = 0.79$
Previous MACE	1.69 (0.43–6.71), $p = 0.45$
Previous neoplasm	3.87 (0.45–33.12), $p = 0.22$
Current csDMARDs	1.15 (0.56–2.38), $p = 0.69$
Basal DAS28	0.82 (0.61–1.13), $p = 0.24$

M male, *F* female, *BMI* body mass index, *RF* rheumatoid factor, *ACPA* anti-citrullinated protein antibody, *DM* diabetes mellitus, *MACE* major adverse cardiovascular events, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *DAS28-CRP* disease activity score 28-CRP. The values in bold indicate statistical significance with $p < 0.05$

CONCLUSIONS

The results of this multicenter retrospective cohort study of real-world patients with RA support the effectiveness and safety of FIL therapy in everyday clinical practice. The real-world data collected from this analysis demonstrate the good effectiveness of FIL in terms of high retention rates observed up to 18 months and significant reductions of DAS28-CRP at 6- and 12-month follow-ups. Overall, the findings of this study support the favorable clinical profile of FIL for the treatment of RA and may inform clinical practice and guideline recommendations.

ACKNOWLEDGEMENTS

We sincerely thank all patients with RA who participated in this multicenter study. Their valuable contribution, coming from centers across Italy, made this research possible.

Medical Writing/Editorial Assistance. Editorial support provided by Dr. Daniela De Feo, Momento Medico srl (Milan, Italy), was funded by an independent grant from Alfasigma S.p.A.

Author Contributions. All authors (Eleonora Celletti, Myriam Di Penta, Alarico Ariani, Simone Parisi, Romina Andracco, Bernd Raffeiner, Aurora Ianniello, Alberto Lo Gullo, Aldo Biagio Molica Colella, Marta Priora, Marino Paroli, Federica Lumetti, Viviana Ravagnani, Francesco Girelli, Rosetta Vitetta, Alessandro Volpe, Palma Scolieri, Alessandra Bezzi, Francesca Ometto, Elisa Visalli, Antonella Farina, Patrizia Del Medico, Elena Bravi, Matteo Colina, Maddalena Larosa, Francesca Serale, Veronica Franchina, Francesco Molica Colella, Giulio Ferrero, Gilda Sandri, Olga Addimanda, Massimo Reta, Fabio Mascella, Maria Cristina Focherini, Alessia Fiorenza, Guido Rovera, Cecilia Giampietro, Simone Bernardi, Natalia Mansueto, Dario Camellino, Rosalba Caccavale, Valeria Nucera, Emanuela Sabatini, Pietro Del Biondo, Maria Chiara Ditto, Ilaria Platè, Giuditta Adorni, Eleonora Di Donato, Daniele Santilli, Gianluca Lucchini, Giorgio Amato, Francesco De Lucia, Ylenia Dal Bosco, Roberta Foti, Gianluca Smerilli, Gerolamo Bianchi, Rosario Foti, Eugenio Arrigoni, Antonio Marchetta, Riccardo Bixio, Vincenzo Bruzzese, Enrico Fusaro, Dilia Giuggioli, Carlo Salvarani, Francesco Cipollone,

Andrea Becciolini) have made substantial contributions to the conception or design of the work, drafted the manuscript or revised it critically for important intellectual content and approved the version to be published; Andrea Becciolini performed statistical analysis; Eleonora Celletti, Pietro Del Biondo and Myriam Di Penta prepared the first draft of the paper.

Funding. Support for editorial assistance and for the journal's Rapid Service Fee was funded by an independent grant from Alfasigma S.p.A; the authors of the manuscript were solely responsible for manuscript development and content.

Data Availability. The data underlying this article are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Alarico Ariani has received honoraria as a speaker and an advisory board member of Amgen, Bristol-Myers Squibb, Boehringer, Bruno Farmaceutici, Janssen, Lilly, Novartis, Novo Nordisk, Sanofi, and Zentiva. We would also like to note that Alarico Ariani's new institutional affiliation is "Rheumatology Unit, AUSL Bologna, Policlinico S. Orsola, AOU-IRCCS di Bologna, Bologna—Italy"; Francesca Serale's new institutional affiliation is "Unit of Rheumatology, ASL VC Ospedale S. Andrea, Vercelli - Italy" and Alberto Lo Gullo's new institutional affiliation is "Rheumatology Unit, Azienda Ospedaliera Papardo, Messina - Italy" Federica Lumetti has received honoraria as an advisory board member of Amgen. Eleonora Celletti, Myriam Di Penta, Simone Parisi, Romina Andracco, Bernd Raffeiner, Aurora Ianniello, Alberto Lo Gullo, Aldo Biagio Molica Colella, Marta Priora, Marino Paroli, Viviana Ravagnani, Francesco Girelli, Rosetta Vitetta, Alessandro Volpe, Palma Scolieri, Alessandra Bezzi, Francesca Ometto, Elisa Visalli, Antonella Farina, Patrizia Del Medico, Elena Bravi, Matteo Colina, Maddalena Larosa, Francesca Serale, Veronica Franchina, Francesco Molica Colella, Giulio Ferrero, Gilda Sandri, Olga Addimanda, Massimo Reta, Fabio Mascella, Maria Cristina Focherini, Alessia Fiorenza, Guido Rovera, Cecilia Giampietro, Simone Bernardi, Natalia Mansueto, Dario Camellino, Rosalba Caccavale, Valeria Nucera, Emanuela Sabatini, Pietro Del Biondo, Maria Chiara Ditto, Ilaria Platè, Giuditta Adorni, Eleonora Di Donato, Daniele Santilli, Gianluca Lucchini, Giorgio Amato, Francesco De Lucia, Ylenia Dal Bosco, Roberta Foti, Gianluca Smerilli, Gerolamo Bianchi, Rosario Foti, Eugenio Arrigoni, Antonio Marchetta, Riccardo Bixio, Vincenzo Bruzzese, Enrico Fusaro, Dilia Giuggioli, Carlo Salvarani, Francesco Cipollone and Andrea Becciolini have nothing to disclose.

Ethical Approval. The study was approved by the ethics committee of "*Comitato Etico dell'Area Vasta Emilia Nord*" (protocol code 34,713, approved on 28 August 2019) as well as by the ethics committees of the remaining 26 centers involved (see Supplementary Material, Table S1) and was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments, and good clinical practice guidelines. All participants provided written consent to participate in the study.

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