Effectiveness and safety of filgotinib in rheumatoid arthritis: a real-life multicentre experience

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Abstract

Objective

We investigated the effectiveness and safety of filgotinib in a real-life multicentre cohort of rheumatoid arthritis (RA) patients.

Methods

RA patients were evaluated at baseline and after 12 and 24 weeks and were stratified based on previous treatments as biologic disease-modifying anti-rheumatic drug (bDMARD)-naive and bDMARD-insufficient responders (IR). Concomitant usage of methotrexate (MTX) and oral glucocorticoids (GC) was recorded. At each timepoint we recorded disease activity, laboratory parameters and adverse events.

Results

126 patients were enrolled. 15.8% were bDMARD-naive (G0), while 84% were bDMARD-IR (G1). In G0, 45% of patients were in monotherapy (G2) and 55% were taken MTX (G3). In G1, 50% of patients were in monotherapy (G4) and 50% used MTX (G5).A significant reduction in all parameters at 12 weeks was observed; in the extension to 24 weeks the significant reduction was maintained for patient global assessment (PGA), examiner global assessment (EGA), visual analogue scale (VAS) pain, VAS fatigue, disease activity score (DAS)28- C-reactive protein (CRP) and CRP values. Filgotinib in monotherapy showed better outcomes in bDMARD-naive patients, with significant differences for patient reported outcomes (PROs) and DAS28-CRP. At 12 weeks, low disease activity (LDA) and remission were achieved in a percentage of 37.2 % and 10.7 % by simplified disease activity index (SDAI), 42.6 % and 5.7 % by clinical disease activity index (CDAI), 26.8 % and 25.2 % by DAS28-CRP, respectively. A significant decrease in steroid dose was evidenced in all patients. We observed a major adverse cardiovascular event in one patient and an increase in transaminase in another. No infections from Herpes Zoster were reported.

Conclusion

Our real-world data confirm the effectiveness and safety of filgotinib in the management of RA, especially in bDMARD-naive patients.

Key words

rheumatoid arthritis, therapeutics, filgotinib, JAK inhibitors, effectiveness, safety

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Introduction

The therapeutic approach to rheumatoid arthritis (RA) has dramatically evolved in the last few years thanks to the development of a treat-to-target strategy to guide patients management (1-3). Current treatments should aim to rapidly achieve remission or low disease activity (LDA) and prevent structural damage and consequent disability through the tailored use of disease-modifying anti-rheumatic drugs (DMARDs) (4).

In the rheumatologists' armamentarium Janus kinase (JAK) inhibitors (JAKi), small molecules belonging to targeted synthetic DMARDs (tsDMARDs) are the latest available treatment option. Four JAKi, tofacitinib, baricitinib, upadacitinib and filgotinib have been approved so far to treat moderate-to-severe RA in Europe, after failure of first line therapy, mostly methotrexate (MTX) (5, 6). Among JAKi, tofacitinib and baricitinib are considered pan-JAK inhibitors, being able to simultaneously interact with different JAK, blocking their downstream signalling pathway; while upadacitinib and filgotinib are more selectively blocking JAK1 over the other molecules (7). Filgotinib efficacy and safety was extensively studied in phase 2 and phase 3 trials, at both 200 mg and 100 mg daily dose, in combination or not with conventional DMARDs (cDMARDs) (8).

To date, data regarding filgotinib in RA derive only from randomised control trials (RCTs), and information from real-life clinical practice are still lacking. We present herein the first real-world cohort of RA patients treated with filgotinib obtained from a multicentre study. The co-primary objectives of the study were to assess the effectiveness and the safety of treatment with filgotinib in our cohort of RA patients after 12 weeks. We present data even at 24 weeks for patients that reached this timepoint in the extension study.

Materials and methods

Patients

In this retrospective observational study, we included 126 patients from 10 Sicilian rheumatology centres (AOUP Paolo Giaccone, Palermo; AO Papardo, Messina; AOUP Gaetano Martino, Messina; AO Cannizzaro, Catania; ARNAS Civico, Palermo; Ospedali Riuniti Villa Sofia-Cervello, Palermo; AOP Vittorio Emanuele, Catania; PO Sant'Antonio Abate, Trapani; Ospedale Busacca di Scicli, Ragusa; ARNAS Garibaldi, Catania), fulfilling the American College of Rheumatology (ACR) 2010 revised criteria for RA (9), and starting treatment with filgotinib (200 mg/day) between December 2021 and December 2022. Inclusion criteria for patients were the followings: age ≥18 years old, availability of complete clinical and laboratory data with a follow up of at least 12 weeks of treatment. Exclusion criteria included age under 18 years old, history of active cancer or stroke/thromboembolic disease, absence of complete clinical and laboratory data in the clinical records.

Methods

Patients were divided into groups: the bDMARD-naive [group 0 (G0)] or bDMARD-IR [group 1 (G1)] status and the concomitant use of MTX: G0 without MTX [group 2 (G2)], G0 with MTX [group 3 (G3)], G1 without MTX [group 4 (G4)], G1 with MTX [group 5 (G5)] (Fig. 1).

At baseline (T0), patients' demographic characteristics, serological data [Rheumatoid Factor (RF), anti-citrullinated peptides antibodies (ACPA)], data on treatments [previous bDMARD, concomitant cDMARDs, concomitant glucocorticoids (GC)], comorbidities and previous Herpes Zoster (HZ) infections were collected.

At T0, and then after 12 weeks (T1) and 24 weeks (T2) of therapy with filgotinib, we reported serological data [cell blood count (CBC), creatine phosphokinase (CPK), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)] and clinical data [number of tender joints (TJ) and swollen joints (SWJ), visual analogue scale (VAS) pain, VAS fatigue, physician's (EGA) and patient's (PGA) assessment of disease activity]. Biochemical data were retrieved from clinical records in which we reported all parameters at each visit. Disease activity was assessed by Disease Activity

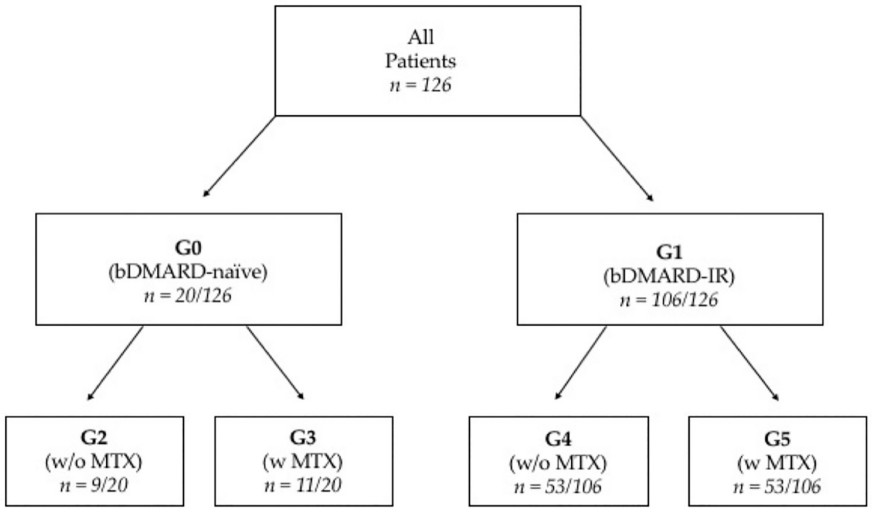

Fig. 1. Study flowchart.
bDMARD: biological disease-modifying anti-rheumatic drug; bDMARD-IR: bDMARD-insufficient responder; MTX: methotrexate; n: number; w/o: without; w: with.

Score 28 (DAS28-CRP), Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) that were calculated according to published literature (10). Remission and low disease activity (LDA) were defined according to DAS28, CDAI and SDAI definitions.Concomitant GC use and dose was collected for each patient at every timepoint. Occurrence of adverse events (AE) was evaluated at T1 and T2.

Ethics

The study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki principles (n. 08/21 dated 09/15/2021). All subjects gave their written informed consent for inclusion in this study.

Statistical analysis

Different subgroups were compared using the either parametric and not parametric test. Particularly, Wilcoxon, the Mann-Whitney and the Pearson's Chi-square tests were used as appropriate. All analyses were two-tailed and performed using STATA for Macintosh (Stata Corp. College Station, TX); *p*-values ≤0.05 were considered as statistically significant.

Results

Patients

From December 2021 and December 2022, 126 consecutive RA patients from 10 Sicilian rheumatology centres started treatment with filgotinib 200 mg daily. The median age of the cohort was 56.5±11.7, the majority were female (110; 87,3%) and the mean disease duration was 29 years.

Twenty patients (15.8%) were bDMARD-naive (G0), while 106 patients (84%) were bDMARD-IR (G1). In G0, 9 patients (45%) were not treated with concomitant MTX (G2) and 11 patients (55%) were taken MTX (G3). In G1, we reported 53 patients (50%) without concomitant MTX and 53 patients (50%) with concomitant MTX.

There was no age difference between G0 and G1, while disease duration was higher in G1(14.4 years *vs*. 6.3 years).

Table I summarises the demographic, clinical and serological features of the enrolled patients at baseline.

Effectiveness evaluation

At baseline our two cohorts of patients, G0 and G1, were homogeneous, without any significant difference in clinical and laboratory parameters used to assess disease activity.

When considering the entire population, a significant reduction in all disease monitoring parameters at 12 weeks was observed, as shown in Table II. At the extension to 24 weeks the significant reduction was maintained for PGA, EGA, VAS pain, VAS fatigue, DAS28-CRP and CRP values.

The analysis conducted stratifying according to the bDMARD status evidenced some differences at T1. Specifically, the reduction in SDAI, CDAI, DAS28-CRP and DAS28-ESR between bDMARD-naive and bDMARD-IR (10.1±6 *vs*. 13.8±8.6; 9.3±4.9 *vs*. 13.38.3±; 2.8±1.3 *vs*. 3±1.6; 3.2±1.8 *vs*. 3.9±2) was significantly higher ($p<0.05$) in G0. Data at T2 confirmed our results for SDAI and CDAI.

Among bDMARD-naive patients no differences were found at baseline with regard to the presence of background MTX. On the other hand, at T0 in G1 patients under concomitant MTX a slight increased score for composite indexes of disease activity (SDAI and CDAI) was highlighted.

After 12 weeks of active treatment in G2 and G3 no differences in clinical outcomes were found while in bDMARD-IR under filgotinib (G4) without MTX Tj, SDAI and PGA (5.2±4.8 *vs*. 3.2±3.1; 15.8±9.7 *vs*. 12.3±7.3 ; 13.8±18.2 *vs*. 6.1±9.7) resulted significantly higher ($p<0.05$) with respect to MTX co-treated patients (G5).

Filgotinib in monotherapy showed better outcomes in bDMARD-naive patients, with significant differences ($p<0.05$) for PROs: PGA, VAS pain and VAS fatigue; and for DAS28-CRP. Combo therapy (filgotinib + MTX) lead to an improvement in disease activity parameters without significant differences between G3 and G5. The extension at T2 confirmed T1 data in all groups except for G5, in which PGA and EGA worsened. The data on efficacy across different groups are given in Table II.

Overall, at 12 weeks, LDA and remission were achieved in a percentage of 37.2% and 10.7% by SDAI, 42.6% and 5.7% by CDAI, 26.8% and 25.2% by DAS28-CRP, respectively. At 24 weeks, LDA and remission were achieved in a percentage of 50% and 11.3% by SDAI, 55.5% and 1.6% by CDAI, 20.3% and 50% by DAS28-CRP, respectively.

The differences in LDA and remission percentages between the two timepoints could be due to fewer patients evaluated at T2 (66/126, 52.4%). However, the achieved higher remission rate by DAS28-CRP in T2 was statistically significant compared to T1.

Table I. Baseline characteristics of RA patients receiving filgotinib.

		bDMARD-naive			bDMARD-IR		
	Total n=126	Total n=20/126 (15.8%)	Without MTX n=9/20 (45%); n=9/126 (7.1%)	With MTX n=11/20 (55%); n=11/126 (8.7%)	Total n=106 (4.1%)	Without MTX n=53/106 (50%); n=53/126 (42%)	With MTX n=53/106 (0%); n=53/126 (42%)
Demographics							
F:M	110:16	13:7	5:4	8:3	97:9	48:5	49:4
Age mean (years range)	56.5 (21-80)	58 (27-76)	59 (52-63)	57.7 (27-76)	56.2 (21-80)	56.7 (21-80)	55.7 (31-75)
Disease duration mean (years range)	29 (1-36)	6.3 (1-19)	6.2 (1-10)	6.3 (2-19)	14.4 (1-36)	15.6 (1-36)	13.3 (1-27)
Smoker n (%)	22 (17.4%)	1 (5%)	1 (11%)	0 (0%)	21 (19.8%)	11 (20.7%)	10 (18.8%)
Ex smoker n (%)	17 (13.4%)	5 (25%)	2 (22%)	3 (27.2%)	12 (11.3%)	4 (7.5%)	8 (15%)
BMI (range)	25.4 (17.3-46.3)	24.6 (18-35.4)	24.7 (20.2-35.4)	24.6 (18-30)	25.1 (17-46)	25.1 (18.5-31)	26 (17-46)
Disease features							
ACPA+ n (%)	76 (60.3%)	12 (60%)	4 (44.4%)	8 (72%)	64 (60.3%)	33 (62.2%)	31 (58.4%)
RF+ n (%)	91 (72.2%)	10 (50%)	4 (44.4%)	6 (54.5%)	81 (76.4%)	41 (77.3%)	40 (75.4%)
Erosion n (%)	66 (52.3%)	4 (20%)	1 (11.1%)	3 (27.2%)	62 (58.5%)	33 (62.2%)	29 (54.7%)
Extra-articular manifestation n (%)	22 (17.4%)	3 (15%)	3 (33.3%)	0 (0%)	19 (17.9%)	11 (20.7%)	8 (15%)
Comorbidities							
Cardiomyopathy n (%)	1 (0.7%)	1 (5%)	1 (11.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypercholesterolaemia n (%)	26 (20.6%)	3 (15%)	2 (22.2%)	1 (9%)	23 (21.6%)	14 (26.4%)	9 (16.9%)
Hypertension n (%)	37 (29.3%)	4 (20%)	1 (11.1%)	3 (27.2%)	33 (31.1%)	17 (32%)	16 (30.1%)
Diabetes n (%)	12 (9.5%)	2 (10%)	1 (11.1%)	1 (9%)	10 (9.4%)	2 (3.7%)	8 (15%)
Cancer n (%)	5 (3.9%)	1 (5%)	0 (0%)	1 (9%)	4 (3.7%)	3 (5.6%)	1 (1.8%)
Previous HZ n (%)	3 (2.3%)	0 (0%)	0 (0%)	0 (0%)	3 (2.8%)	2 (3.7%)	1 (1.8%)

ACPA: anticitrullinated peptides antibodies; bDMARD: biological DMARDs; BMI: Body Mass Index; HZ: herpes zoster; IR: insufficient response; mg: milligrams; MTX: methotrexate; n: number; RA: rheumatoid arthritis; RF: rheumatoid factor. *p<0.05.

Considering the bDMARD status, at T1 higher rates of LDA were evidenced in G0 versus G1, confirming the effectiveness data reported above. Specifically, in G0, LDA was reported in a percentage of 57.8 % by SDAI, 68.4% by CDAI, 52.6 % by DAS28-CRP *versus* G1 (33.3%, 31.7% and 22.1%). Interestingly, the difference between the percentages of remission at T2 in the two groups were more pronounced (9.09 by SDAI and CDAI in G0 *vs*. 11.8 by SDAI and 5.8 by CDAI in G1) (Fig. 2).

A significant decrease in GC dose was observed at 3 months in the whole cohort, as shown in Figure 3, with the number of patients on GC that decreased from 92/126 (73%) to 51/126 (40.5%) at T0 and T1, respectively. In bDMARD-naive patients the reduction of GC daily dose was higher and statistically significant than in bDMARD-IR, despite a baseline equal or superior mean dose in the first group. At 24 weeks the 50% of patients was still taking a low GC daily dose, that was comparable to the one reached at 12 weeks. Of note, GC use was almost exclusively evidenced in bDMARD-IR at 24 weeks (Table III).

The whole cohort reached the first timepoint with complete evaluation available at 12 weeks; 66 (52.3%) patients were evaluated at T2. At T1 7/126 (5.6%) patients stopped filgotinib: i) 4/126 (3.2%) for inefficacy; ii) 1 for personal reason; iii) 2 (1.6%) for AE. At T2 6/66 (9.1%) patients discontinued filgotinib for inefficacy.

Safety evaluation

Two patients reported at least one AE that in both cases were the reason for treatment discontinuation. Withdrawal was due to the occurrence of a major adverse cardiovascular events (MACE) in one patient and to the evidence of increase AST and ALT (75 and 101 UI/l, respectively) in another.

Among haematological parameters in the G2 and G4 groups we observed a trend towards mild worsening of leukopenia, neutropenia, lymphopenia, thrombocytopenia and anaemia at T1 in 16 patients that was considered not significant and filgotinib was not discontinued. In G3 and G5 groups, at least one alteration in CBC was retrieved in 9 patients at T1, all parameters were stable across the different timepoints, except for neutropenia that was evidenced in 5 patients at T0 and persisted only in one at T1. No alterations in the platelet count were observed in the filgotinib plus MTX treated patients. CPK values were within the range at every timepoint in all patients.

At T2, 4 patients in the monotherapy group and 5 patients in the combination therapy group presented at least one mild haematological alteration, respectively. One patient in the bDMARD-IR group experienced a MACE within the first trimester of treatment with filgotinib, specifically a myocardial infarction. Of note, the patient was a 48-year-old female with long-standing and persistently active disease, and unresponsive to treatment.

We did not record any case of HZ infection or reactivation; of the 126 patients, 51 were vaccinated with the new antigenic HZ vaccine. No thromboembolic events occurred in our cohort.

Discussion

JAKi are the latest available drugs to treat RA. Their mechanism of action has revolutionised the approach to RA, including small molecules among

Table II. Clinical and laboratory features by groups in the different timepoints.

		T0 n=126		T1 n=126		T2 n=66	
		G0 n 20	G1 n=106	G0 n=20	G1 n=106	G0 n=10	G1 n=10
Tender joints	Total	8 ± 5.9	8.7 ± 5.3	2.4 ± 2.2	4.1 ± 4.5	1.3 ± 2.2	2.9 ± 3.6
	w/o MTX	9.4 ± 7.7	8.2 ± 5.1	2.4 ± 2.6	5.2 ± 4.8*	2.2 ± 4	3.2 ± 4.2
	w/ MTX	6.9 ± 3.8	9 ± 5.4	2.4 ± 1.9	3.2 ± 3.1	0.9 ± 1.1	2.4 ± 2.8
Swollen joints	Total	5.2 ± 4.5	5.1 ± 3.8	0.9 ± 1.4	1.5 ± 2.1	0.7 ± 2.2	1 ± 1.7
	w/o MTX	6.5 ± 5.9	5 ± 4	1.3 ± 1.5	1.7 ± 2.3	1.7 ± 4	0.7 ± 1.2
	w/ MTX	4.2 ± 2.9	5.2 ± 3.6	0.5 ± 1.3	1.4 ± 1.9	0	1.4 ± 2.1
PGA	Total	7.1 ± 1.3	7.2 ± 1.6	8.6 ± 14.7	9.9 ± 15.4	7.1 ± 6.9	9 ± 14.3
	w/o MTX	7.3 ± 1.3	7.5 ± 1.4*	8.7 ± 15.6*	13.7 ± 18.1*	8.7 ± 8.9	9.4 ± 14.8
	w/ MTX	6.9 ± 1.3	6.9 ± 1.7	8.5 ± 14.6	6.1 ± 9.7	5.9 ± 6.3	8.1 ± 14
EGA	Total	5.5 ± 2.1	6.1 ± 2.2	3.8 ± 6.7	4.9 ± 8.7	1.5 ± 2.1*	5.4 ± 9.6
	w/o MTX	6.2 ± 2.3	6.2 ± 2*	2.2 ± 2	7 ± 11.6	2 ± 3.8	5.2 ± 8.9
	w/ MTX	4.8 ±1.8	5.8 ± 2.4	5 ± 8.8	2.7 ± 1.8	1 ± 0.8	5.2 ± 10.6
VAS pain	Total	7,4 ± 1.5	7.5 ± 1.4	4.3 ± 1.4	4.9 ± 2.2	3.8 ± 2.2	4.4 ± 2.3
	w/o MTX	7.5 ± 1.6	7.7 ± 1.3	4.4 ± 1.3*	5.6 ± 2.1	4.2 ± 2.7	4.3 ± 2.2
	w/ MTX	7.2 ± 1.5	7.3 ± 1.5	4.2 ± 1.6	4.4 ± 2.1	3.7 ± 2.2	4.5 ± 2.5
VAS fatigue	Total	6.7 ± 2.1	7.1 ± 1.7	4.2 ± 2.1	4.7 ± 2.3	3.4 ± 2.1	4.1 ± 2.5
	w/o MTX	6.4 ± 2.4	7 ± 1.8	3.8 ± 1.9*	5.3 ± 2.1	3.7 ± 1.5	4.3 ± 2.4*
	w/ MTX	6.9 ± 1.9	7.2 ± 1.7	4.6 ± 2.3	4.1 ± 2.3	3.4 ± 2.4	4.3 ± 2.7
SDAI	Total	24.9 ± 12.3	28.2 ± 13.9	10 ± 6*	13.8 ± 8.6	7.5 ± 8*	11.4 ± 7.9
	w/o MTX	26.6 ± 14.7	27.8 ± 14.8*	11.2 ± 7.3	15.8 ± 9.7*	10.5 ± 14.8	10.8 ± 7.7
	w/ MTX	23.6 ±10.6	28.5 ± 12,5	9.2 ± 4.9	12.3 ± 7.3	5.5 ± 2.4	11.8 ± 8.2
CDAI	Total	25.6 ± 13.8	27.7 ± 10.7	9.3 ± 4.9*	13.3 ± 8.3	7.5 ± 7.5*	11.3 ± 7.8
	w/o MTX	29.4 ± 18.4	27.3 ± 10.2*	9.8 ± 6	15 ± 9.3	10.2 ± 2.9	10.9 ± 7.9
	w/ MTX	22.2 ± 7.3	28.1 ± 11.4	8.9 ± 4.1	11.8 ± 6.9	5.9 ± 1.9	11.5 ± 7.8
DAS28ESR	Total	5.1 ± 2.3	5.4 ± 2.5	3.2 ± 1.8*	3.9 ± 2.1	3.1 ± 1.7	3.7 ± 2.1
	w/o MTX	5.6 ± 2.9	5.5 ± 2.8	4.2 ± 2.4	4.3 ± 2.4	4.3 ± 2.4	3.8 ± 2.2
	w/ MTX	4.8 ± 1.8	5.3 ± 2.1	2.8 ± 1.3	3.6 ± 1.7	2.7 ± 1.2	3.6 ± 1.9
DAS28CRP	Total	4.7 ± 1.9	4.8 ± 1.9	2.8 ± 1.3*	3 ± 1.6	2.4 ± 1.4	2.6 ± 1.5
	w/o MTX	4.7 ± 2.2	4.7 ± 2.2	2.9 ± 1.4*	3.1 ± 1.8	3 ± 2.5	2.4 ± 1.6
	w/ MTX	4.7 ± 1.6	4.8 ± 1.6	2.6 ± 1.2	3 ± 1.3	2 ± 0.9	2.7 ± 1.4
ESR (mmIh)	Total	36.9 ± 35.8	31.7 ± 24.9	19 ± 13.5	23.4 ± 18.6	22.9 ± 20.3	24.4 ± 22
	w/o MTX	47.8 ± 42.3	32.6 ± 24.1	25 ± 13.7	24.4 ± 20.9	25.2 ± 15.1	26 ± 22.8
	w/ MTX	27.2 ± 28.2	30.6 ± 26.1	13.8 ± 11.6	22.4 ± 16.4	19.6 ± 22.4	20.7 ± 20
CRP (mg/L)	Total	11.7 ± 14.8	10 ± 15.8	3.1 ± 3.3	5.1 ± 7.3	1.9 ± 2.1	5.7 ± 8.3
	w/o MTX	4 ± 3.7	13 ± 19.9	3.2 ± 4.1	5.8 ± 7.4	0,5 ± 0,7	5.8 ± 9.1
	w/ MTX	17.5 ± 18.9	7.7 ± 10.7	2.9 ± 2.6	4.7 ± 7.3	2.3 ± 2.4	5.1 ± 7.3

CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: Disease Activity Score 28; ESR: erythrocyte sedimentation rate; MTX: methotrexate; n: number; SDAI: Simplified Disease Activity Index; w/o: without; w: with. *p<0.05.

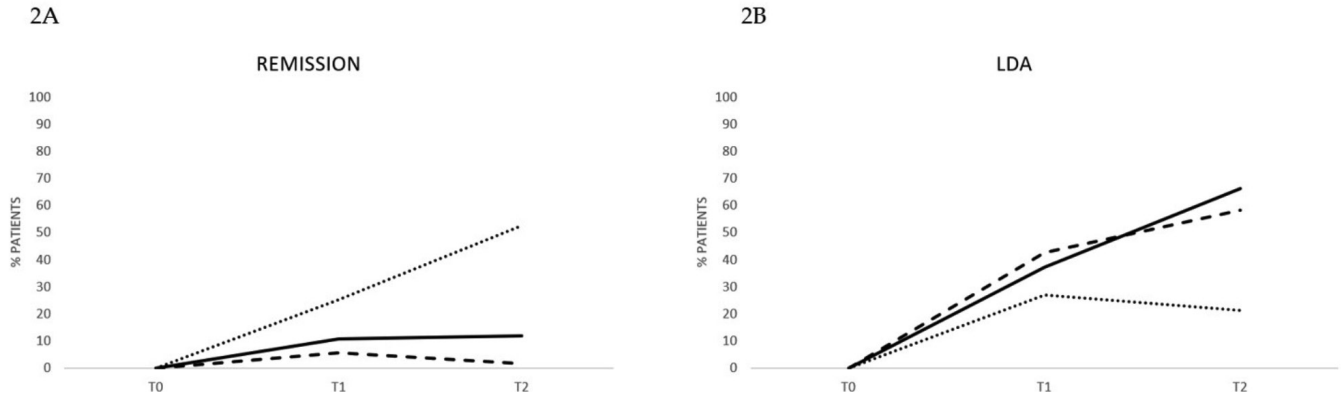

Fig. 2. Percentage of RA patients achieving remission (2A) and low disease activity (2B) according to SDAI, CDAI and DAS28-CRP at the different time-points: T0: baseline; T1: 12 weeks; T2: 24 weeks.
CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: Disease Activity Score 28; SDAI: Simplified Disease Activity Index.

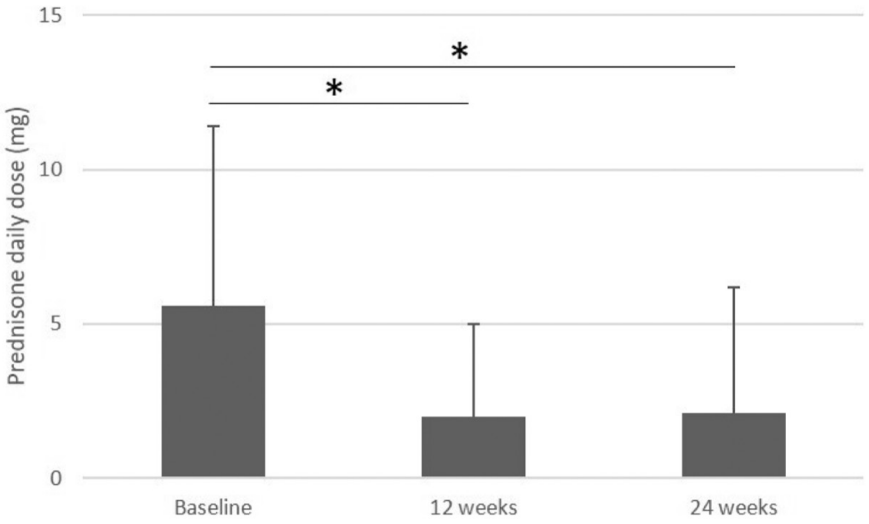

Fig. 3. Oral glucocorticoid dose (expressed as mg/day of prednisone) in patients at baseline, 12 and 24 weeks of treatment with filgotinib. *p<0.05.

treatment options for patients. Filgotinib is a second generation JAKi, with *in vitro* potent and selective inhibition of JAK1 (11).

To our knowledge no reports on filgotinib use in real-life are available. Our study is the first multicentric study designed to evaluate effectiveness and safety of filgotinib in an Italian cohort of RA patients (Table IV). Patients were arrayed according to previous exposure to bDMARD and concomitant MTX use.

The clinical programme evaluating filgotinib in patients with moderately-to-severely active RA consists of three phase 2b (DARWIN 1-3) and four phase 3 (FINCH 1-4) studies.

In the phase 3 studies, the use of filgotinib was evaluated in combination with cDMARDs in MTX-IR patients (FINCH 1) and in bDMARD-IR patients (FINCH 2), and in monotherapy in MTX-naive patients (FINCH 3) (12-14); while the long-term extension study (FINCH 4) is still ongoing (NCT03025308) (15).

Subpopulation analyses reported the efficacy of filgotinib in Japanese patients up to week 24 in three Phase 3 RCTs, showing an acceptable safety and tolerability profile in terms of opportunistic infections, MACE, venous thromboembolism (VTE), and haematologic changes. Efficacy and safety of filgotinib were maintained through week 52 in the long term extension trials (16).

Data from RCTs demonstrated that filgotinib induced LDA and remission at 12 weeks, as assessed by DAS28-CRP, in the 70% and 52% of patients, respectively, in FINCH 1 (12), and in the 40.8% and 22.4%, respectively, in FINCH 2 (17). In our cohort the percentages of LDA and remission at 12 weeks, by using DAS28-CRP, were 52.6% and 21% in bDMARD-naive, and 22.1% and 25.9% in bDMARD-IR. Moreover, at 12 weeks, when using SDAI, LDA was achieved in the 57.8% of bDMARD- naive patients and in the 33.3 % of bDMARD-IR patients.

It should be noted that our cohort had a long disease duration, exceeding 20 years in most patients, with a small number of subjects evaluated. Thus, achieving the LDA after 12 weeks in a range of one-third to one-half of patients could be considered an acceptable goal in a real-word setting.

One of the main goals of treatment is the reduction up to discontinuation of GC. The optimal control of disease activity and inflammation should grant a progressive rapid tapering of GC, as recommended by European league against rheumatism (EULAR) guidelines (1), in order to prevent AE related to steroid chronic use (18). In our cohort, filgotinib determined a significant decrease of the GC daily dose across all groups of RA patients at 12 weeks, that was maintained at 24 weeks observation. At 3 months 50% of patients had discontinued GC with an impressive response in bDMARD-naive patients, independently of the MTX additional use. In this regard and in line with

Table III. GC use at baseline, 12 weeks and 24 weeks in RA patients treated with filgotinib; patients are stratified according to bDMARD and MTX use.

		Steroid dose (mg/day)^			n. patients on GC		
		Baseline (n=126)	12 weeks (n=126)	24 weeks (n=66)	Baseline	12 weeks	24 weeks
All patients		5.6 ± 5.8	2 ± 2.9*	2.1 ± 4.1*	92/126 (73%)	51/126 (40.5%)	23/66 (34.9%)
bDMARD-naive	Total	6.4 ± 5.6	1.3 ± 2.1*	0.5 ± 1.6	18/20 (90%)	6/20 (30%)	1/10 (10%)
	w/o MTX	7.8 ± 8.2	1 ± 2	0 ± 0	7/9 (77.8%)	2/9 (22.2%)	0/3 (0%)
	w MTX	5.2 ± 1.8	1.6 ± 2.3	0.7 ± 1.9	11/11 (10%)	4/11 (36.4%)	1/7 (14.3%)
bDMARD-IR	Total	5.5 ± 5.9	2.2 ± 3*	2.4 ± 4.3	74/106 (69.8%)	45/106 (42.5%)	22/56 (39.3%)
	w/o MTX	5.3 ± 6.3	2.6 ± 3.5	2.6 ± 5	34/53 (64.2%)	24/53 (45.3%)	13/31 (42%)
	w MTX	5.7 ± 5.6	1.8 ± 2.4	1.9 ± 3.3	40/53 (75.5%)	21/53 (39.6%)	9/25 (36%)

bDMARD: biological DMARDs; GC: glucocorticoid; IR: insufficient response; mg: milligrams; MTX: methotrexate; n: number; RA: rheumatoid arthritis; w/o: without; w: with.
^steroid dose is expressed in prednisone equivalents; *p<0.05.

Table IV. Key messages.

What is already known on this topic?	JAKi are the latest available drugs to treat RA. Filgotinib, a JAK1 inhibitor preferentially blocking the JAK1 molecule, has recently been approved for the treatment of RA and data from clinical trials evidenced its efficacy and safety.
What this study adds?	We demonstrated the effectiveness and safety of filgotinib in a real-life multicentre study that included 126 RA patients. We evidenced an improvement in main disease activity scores, PROs and a reduction in GC intake. Only one MACE was observed and no HZ infections were reported.
How this study might affect research, practice or policy?	Filgotinib stands out as an effective and safe drug to treat moderate-to-severe RA in our real-world experience. The absence of HZ infection was probably related to the vaccination with the recombinant HZ vaccine that the 40.5% of our patients underwent, emphasising that this prophylactic measure should be strongly encouraged.

GC: glucocorticoid; HZ: herpes zoster; JAKi: JAK inhibitors; MACE: major adverse cardiovascular events; PROs: patient reported outcomes; RA: rheumatoid arthritis.

literature on other JAKi (19, 20), the prompt administration of filgotinib in the early stage of active disease should be encouraged as it rapidly optimises disease management and simultaneously allows GC tapering. However, even in bDMARD-IR, the objective of reducing GC seems achievable using filgotinib, and in such patients could be very important because of the long-standing use of GC and related cumulative potential toxicities (21).

The effect of filgotinib goes beyond inflammation control. We observed a profound reduction in PGA, VAS pain and VAS fatigue after 12 weeks of treatment, especially in bDMARD-naive patients, that was uncoupled with concomitant decrease in inflammatory parameters (ESR and CRP), clearly pointing out that JAKi exert a pleiotropic effect and may act through different mechanism to halt pain (22). The rapid response to filgotinib may then be related to the resolution of pain with consequent improvement in patients' quality of life. Notably, we report for the first time the real-life effect of filgotinib on PROs that is in line with data coming from a recent post hoc analysis of the FINCH programme studies (23).

Beside effectiveness, filgotinib presented an overall good safety profile. No hospitalisation, death, severe infections were reported. Surprisingly, with respect to published data on JAKi, no patient experienced reactivation of HZ. Our patients were advised to undergo HZ antigenic vaccination before starting treatment and, indeed 40.5% did so, allowing us to speculate that a proper prophylaxis measure successfully prevents HZ infection and needs to be always carefully considered (24). Because of JAK1 preferential selectivity, filgotinib is estimated to not interact with the signalling pathways related to erythropoietin, thrombopoietin and colony-stimulating factors with a consequent weak impact on CBC parameters (25). However, in our real-world cohort laboratory test highlighted a trend towards the occurrence of mild leukopenia and anaemia that were never clinically significant and did not require suspension of filgotinib.

Among serious events, we registered a case of myocardial infarction in a female patient with a severe long-standing disease refractory to several lines of treatment. In particular, even under filgotinib, disease activity was persistently high, depicting an important case of difficult-to-treat RA. Literature data account for a strong influence of uncontrolled disease an persistent inflammation as a main driver of cardiovascular event in RA (26, 27), so we cannot conclude that the MACE reported in our cohort is related to filgotinib. Finally, no VTE was reported in our cohort, differently from studies on other JAKi.

The evaluation of safety issues arises one of the main limitations of our study that is related to the short observational period. In 24 weeks it is difficult to draw conclusion on the risk of malignancy, cardiovascular event or other AE possibly associated with chronic intake of a drug. Another important point is the absence of imaging evaluation of our patients, with ultrasound or standard x-ray, to assess the effect of filgotinib on synovial and tenosynovial inflammation as well as to obtain data on radiographic progression. Our cohort belonged to 10 different centres across Sicily and it was difficult to homogenise or centralise the US and x-ray evaluation as, especially the US exam, required a previous reliability exercise to standardise the technique and obtain consistent results. Such questions remain an open topic of research to reinforce our results on filgotinib effectiveness.

To sum up, we demonstrated for the first time the effectiveness of filgotinib in RA patients from a real-life Italian cohort. Filgotinib was proven effective in controlling disease activity, pain, fatigue, especially in bDMARD-naive patients. The concomitant evidence that up to 50% of patients discontinued GC strengthens the importance of filgotinib as a steroid-sparing agent for RA management. The safety profile of filgotinib clearly emerged from the present study, we did not observe any HZ reactivation nor reported hospitalisation or death among our patients.

References

1. SMOLEN JS, LANDEWÉ RBM, BIJLSMA JWJ *et al.*: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020; 79(6): 685-99. https://doi.org/10.1136/annrheumdis-2019-216655
2. SINGH JA, SAAG KG, BRIDGES SL JR *et al.*: 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol* 2016; 68(1): 1-26. https://doi.org/10.1002/art.39480
3. MARIANI FM, MARTELLI I, PISTONE F, CHERICONI E, PUXEDDU I, ALUNNO A: Pathogenesis of rheumatoid arthritis: one year in review 2023. *Clin Exp Rheumatol* 2023; 41(9): 1725-34. https://doi.org/10.55563/clinexprheumatol/sgjk6e
4. ALETAHA D, SMOLEN JS: Diagnosis and management of rheumatoid arthritis: a review. *JAMA* 2018; 320(13): 1360-72. https://doi.org/10.1001/jama.2018.13103
5. ANGELINI J, TALOTTA R, RONCATO R *et al.*: JAK-Inhibitors for the treatment of rheumatoid arthritis: a focus on the present and an outlook on the future. *Biomolecules* 2020; 10(7):1002. https://doi.org/10.3390/biom10071002

6. GARAFFONI C, ADINOLFI A, BORTOLUZZI A *et al*.: Novel insights into the management of rheumatoid arthritis: one year in review 2022. *Clin Exp Rheumatol* 2022; 40(7): 1247-57. https://doi.org/10.55563/clinexprheumatol/1sjgyr
7. SPINELLI FR, MEYLAN F, O'SHEA JJ, GADINA M: JAK inhibitors: ten years after. *Eur J Immunol* 2021; 51(7): 1615-27. https://doi.org/10.1002/eji.202048922
8. WESTHOVENS R: Filgotinib in rheumatoid arthritis. *Expert Rev Clin Immunol* 2023; 19(2): 135-44. https://doi.org/10.1080/1744666X.2023.2149495
9. KAY J, UPCHURCH KS: ACR/EULAR 2010 rheumatoid arthritis classification criteria. *Rheumatology* (Oxford).2012; 51 Suppl 6: vi5-vi9. https://doi.org/10.1093/rheumatology/kes279
10. ANDERSON J, CAPLAN L, YAZDANY J *et al*.: Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. *Arthritis Care Res* (Hoboken) 2012; 64(5): 640-47. https://doi.org/10.1002/acr.21649
11. JEGATHEESWARAN J, TURK M, POPE JE: Comparison of Janus kinase inhibitors in the treatment of rheumatoid arthritis: a systemic literature review. *Immunotherapy* 2019; 11(8): 737-54. https://doi.org/10.2217/imt-2018-0178
12. TANAKA Y, MATSUBARA T, ATSUMI T *et al*.: Efficacy and safety of filgotinib in combination with methotrexate in Japanese patients with active rheumatoid arthritis who have an inadequate response to methotrexate: Subpopulation analyses of 24-week data of a global phase 3 study (FINCH 1). *Mod Rheumatol* 2022; 32(2): 263-72. https://doi.org/10.1093/mr/roab030
13. TAKEUCHI T, MATSUBARA T, ATSUMI T *et al*.: Efficacy and safety of filgotinib in Japanese patients with refractory rheumatoid arthritis: Subgroup analyses of a global phase 3 study (FINCH 2). *Mod Rheumatol* 2022; 32(1): 59-67. https://doi.org/10.1080/14397595.2020.1859675
14. ATSUMI T, TANAKA Y, MATSUBARA T *et al*.: Long-term safety and efficacy of filgotinib treatment for rheumatoid arthritis in Japanese patients naive to MTX treatment (FINCH 3). *Mod Rheumatol* 2023; 33(4): 657-67. https://doi.org/10.1093/mr/roac083
15. TANAKA Y, KAVANAUGH A, WICKLUND J, MCINNES IB: Filgotinib, a novel JAK1-preferential inhibitor for the treatment of rheumatoid arthritis: An overview from clinical trials. *Mod Rheumatol* 2022; 32(1): 1-11. https://doi.org/10.1080/14397595.2021.1902617
16. TANAKA Y, MATSUBARA T, ATSUMI T *et al*.: Safety and efficacy of filgotinib for Japanese patients with RA and inadequate response to MTX: FINCH 1 52-week results and FINCH 4 48-week results. *Mod Rheumatol* 2023; 33(4): 668-79. https://doi.org/10.1093/mr/roac084
17. GENOVESE MC, KALUNIAN K, GOTTENBERG JE *et al*.: Effect of Filgotinib vs placebo on clinical response in patients with moderate to severe rheumatoid arthritis refractory to disease-modifying antirheumatic drug therapy: the FINCH 2 Randomized Clinical Trial [published correction appears in *JAMA* 2020 Feb 4; 323(5): 480]. *JAMA* 2019; 322(4): 315-25. https://doi.org/10.1001/jama.2019.9055
18. KISSIN EY: The "dirty little secret" exposed in the 2013 EULAR recommendations for rheumatoid arthritis therapy. *Clin Ther* 2014; 36(7): 1114-16. https://doi.org/10.1016/j.clinthera.2014.06.012
19. GUIDELLI GM, VIAPIANA O, LUCIANO N *et al*.: Efficacy and safety of baricitinib in 446 patients with rheumatoid arthritis: a real-life multicentre study. *Clin Exp Rheumatol* 2021; 39(4): 868-73. https://doi.org/10.55563/clinexprheumatol/pudtpo
20. IWAMOTO N, SATO S, KURUSHIMA S *et al*.: Real-world comparative effectiveness and safety of tofacitinib and baricitinib in patients with rheumatoid arthritis. *Arthritis Res Ther* 2021; 23(1): 197. https://doi.org/10.1186/s13075-021-02582-z
21. BERGSTRA SA, SEPRIANO A, KERSCHBAUMER A *et al*.: Efficacy, duration of use and safety of glucocorticoids: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2023; 82(1): 81-94. https://doi.org/10.1136/ard-2022-223358
22. PAZMINO S, VERSCHUEREN P, WESTHOVENS R: JAK inhibition and the holy grail for pain control in early RA. *RMD Open* 2022; 8(1): e002068. https://doi.org/10.1136/rmdopen-2021-002068
23. BINGHAM CO 3RD, WALKER D, NASH P *et al*.: The impact of filgotinib on patient-reported outcomes and health-related quality of life for patients with active rheumatoid arthritis: a post hoc analysis of Phase 3 studies. *Arthritis Res Ther* 2022; 24(1): 11. https://doi.org/10.1186/s13075-021-02677-7
24. FURER V, RONDAAN C, HEIJSTEK MW *et al*.: 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2020; 79(1): 39-52. https://doi.org/10.1136/annrheumdis-2019-215882
25. NAMOUR F, DIDERICHSEN PM, COX E *et al*.: Pharmacokinetics and pharmacokinetic/pharmacodynamic modeling of Filgotinib (GLPG0634), a selective JAK1 Inhibitor, in support of phase IIB dose selection. *Clin Pharmacokinet* 2015; 54(8): 859-74. https://doi.org/10.1007/s40262-015-0240-z
26. ENGLAND BR, THIELE GM, ANDERSON DR, MIKULS TR: Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications. *BMJ* 2018; 361: k1036. https://doi.org/10.1136/bmj.k1036
27. CACCIAPAGLIA F, SPINELLI FR, ERRE GL *et al*.: Italian recommendations for the assessment of cardiovascular risk in rheumatoid arthritis: a position paper of the Cardiovascular Obesity and Rheumatic DISease (CORDIS) Study Group of the Italian Society for Rheumatology. *Clin Exp Rheumatol* 2023; 41(9): 1784-91. https://doi.org/10.55563/clinexprheumatol/hyaki6