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Phase III trials of JAK1 selective inhibitors in rheumatoid arthritis

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Abstract

Upadacitinib and filgotinib, two JAK1 selective drugs have undergone extensive phase III clinical trials in RA and have demonstrated rapid improvements in disease activity, function and patient reported outcomes. Six global phase III randomized controlled clinical trials (SELECT phase III program) evaluated the efficacy and safety of upadacitinib and four clinical phase III trials (the FINCH program) evaluated the efficacy and safety of filgotinib. This article is a critical review of all these studies with focus on the therapeutic efficacy in RA. The aim is to display the data that could allow the approval of these new drugs for the treatment of RA (upadacitinib has been already approved in most of the markets around the world).

Key words: rheumatoid arthritis, JAK1 inhibitors, upadacitinb, filgotinib, efficacy

Rheumatology key messages

- Upadacitinib and filgotinib have shown superiority in two different head-to-head clinical trials when compared to the standard of care.
- JAK1 selective inhibitors favourable efficacy data will allow, if safety is proven, to be included in the rheumatoid arthritis treatment arsenal.

Introduction

Since the approval of the first-generation of Janus kinase (JAK) inhibitors, tofacitinib and baricitinib, the search for new innovative JAK inhibitors with more specific selectivity has started. It has been hypothesized that the inhibition of JAK1 will allow the same clinical efficacy as a non-selective pan-JAK inhibitor (or event better as the dose could be increased), but with a better safety profile potentially guaranteed by the non-inhibition of JAK3 [1]. Therefore, upadacitinib and filgotinib, two JAK1 selective drugs have undergone extensive phase III clinical trials in RA and demonstrated rapid improvements in disease activity, function and patient-reported outcomes.

Upadacitinib (UPA) is a JAK inhibitor selective for JAK1 74-fold over JAK2 [2]. Six global phase III randomized controlled clinical trials (SELECT phase III program) evaluated the efficacy and safety of upadacitinib covering different RA subpopulations. There is also information available about radiographic outcomes and extension trials are ongoing.

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Filgotinib is a selective JAK inhibitor with a selectivity for JAK1 *vs* JAK2 of near 30-fold [2]. The FINCH program includes four clinical phase III trials conducted also in different RA patient types that is now under evaluation.

The aim of this article is to review the phase III clinical data for upadacitinib and filgotinib, with focus on the therapeutic efficacy in RA. Critical evaluation of these new drugs is crucial, in order to help clinicians chose the best treatment for their patients.

Upadacitinib

The SELECT Phase III program in RA included six global phase III studies (Table 1). The favourable data on clinical efficacy and the acceptable benefit risk profile allowed the approval of UPA 15 mg once a day (qd) by the United States Food and Drug Administration and the European Medicines Agency for the treatment of moderate to severe RA either as monotherapy or in combination with conventional synthetic DMARD (csDMARDs) for patients who failed MTX. One of the strengths of the SELECT studies was the statistical analysis that was used in data evaluation, like the adjustment for multiplicity and the non-responder imputation. There were also two studies that have demonstrated non-inferiority/

SUPPLEMENT

Table 1 SELECT phase III studies

Study	Early	Monotherapy	Compare	Next	Beyond	Choice
Population	MTX naive	MTX IR	MTX IR	csDMARD IR	bDMARD IR	bDMARD IR
Type of therapy	Mono	Mono	Combo	Combo	Combo	Combo
Background			MTX	csDMARDs	csDMARDs	csDMARDs
Active Comparator	MTX	MTX	Adalimumab			Abatacept
Arms	• 7.5 mg q.d. (Japan) • 15 mg q.d. • 30 mg q.d. • MTX	• 15 mg q.d. • 30 mg q.d. • MTX	• 15 mg q.d. • Placebo • ADA	• 15 mg q.d. • 30 mg q.d. • Placebo	• 15 mg q.d. • 30 mg q.d. • Placebo	• 15 mg q.d. • ABA
Primary end point	• ACR 50 • DAS28 CPR <2.6	• ACR 20 • DAS28 CPR 3.2 or less	• ACR 20 • DAS28 CPR <2.6	• ACR 20 • DAS28 CPR 3.2 or less	• ACR 20 • DAS28 CPR 3.2 or less	• Change DAS 28 CPR
Statistical analysis	Superiority against PBO UNK	Superiority against PBO Adjusted for multiplicity	Non-inferiority/ superiority Adjusted for multiplicity	Superiority against PBO Adjusted for multiplicity	Superiority against PBO Adjusted for multiplicity	Non-inferiority / superiority UNK
Results[a]	NRI • ACR50 52.1% UPA *vs* 28.3% PBO • DAS28 CPR < 2.6 48.3% UPA *vs* 18.5% PBO	NRI • ACR20 68% UPA *vs* 41% MTX • DAS28 CPR ≤3.2 45% UPA *vs* 19% MTX	NRI • ACR 20 71% UPA *vs* 36% PBO *vs* 63% ADA • DAS28 CPR <2.6 29% UPA *vs* 6% PBO *vs* 18% ADA	NRI • ACR20 64% UPA *vs*36% PBO • DAS28 CPR ≤ 3.2 48% UPA *vs* 17% PBO	NRI • ACR20 65% UPA *vs* 28 PBO • DAS28 CPR ≤3.2 43% UPA *vs* 14% PBO	NRI • Change DAS 28 CPR −0.52 (−0.69, −0.35) favours UPA
Duration of Period 1	48 weeks	14 weeks	48 weeks	12 weeks	24 weeks	24 weeks
Sample size	975	600	1500	600	450	550
Radiographic progression	Yes		Yes			

Clinical trials for upadacitinib in RA (SELECT phase III program). [a]Results are reported for the 15 mg dose (approved dose). ABA: abatacept; ACR: American College of Rheumatology improvement response; ADA: adalimumab; bDMARD: biological DMARD; bDMARD IR: biological DMARD insufficient response; csDMARD: conventional synthetic DMARD; csDMARD IR: conventional synthetic DMARD insufficient response; DAS28(CRP): 28-joint disease activity score using CRP; MTX-IR: MTX insufficient response; NRI: non-respond imputation; PBO: placebo; q.d.: once daily; UNK: unknown; UPA: upadacitinib.

superiority of upadacitinib when compared with another biological DMARD (bDMARD).

As combination therapy after inadequate response to cs/bDMARDs

The SELECT NEXT study was a randomized double-blind, placebo-controlled trial (RCT) of 661 patients with active RA with an inadequate response to csDMARDs. RF or anti-citrullinated protein antibody (ACPA) was positive in 80% of the patients, 7.3 years was the mean time since the diagnosis and patients had high disease activity with mean 28-joint disease activity score using CRP [DAS28 (CRP)] of 5.6, mean clinical disease activity index (CDAI) of 38.2, mean swollen joint count (SJC66) of 15.8 and mean tender joint count (TJC68) of 25.4. Patients receiving stable background csDMARDs were assigned to UPA 15 or 30 mg, or placebo (PBO), for 12 weeks. The primary endpoints were the proportion of patients at week 12 who achieved 20% improvement in American College of Rheumatology criteria (ACR20), and DAS28[CRP] of 3.2 or less. At week 12, ACR20 was achieved by 141 (64%; 95% CI: 58, 70) of 221 patients receiving UPA 15 mg and 145 (66%; 60, 73) of 219 patients receiving UPA 30 mg, compared with 79 (36%; 29, 42) of 221 patients receiving PBO ($P < 0.0001$ for each dose *vs* PBO). DAS28[CRP] of 3.2 or less was met by 107 (48%; 95% CI: 42, 55) patients receiving UPA 15 mg and 105 (48%; 41, 55) patients receiving UPA 30 mg, compared with 38 (17%; 12, 22) patients receiving PBO ($P < 0.0001$ for each dose *vs* placebo). Upadacitinib 30 mg seemed to provide only a minimal increase in some efficacy measures [ACR 70, simplified disease activity index (SDAI) and CDAI low disease activity when compared with the 15 mg dose] [3].

SELECT BEYOND was a RCT trial that included 499 patients with RA previously inadequate responders or intolerant to bDMARDs. Patients had long-standing established disease with mean duration since diagnosis of 13.2 years and had high disease activity, with a mean DAS28[CRP] of 5.8, TJC68 of 27.9 and SJC66 of 16.8. Patients were assigned to receive UPA 15 mg or 30 mg or PBO for 12 weeks, followed by UPA 15 mg or 30 mg from week 12 onwards. Both doses of UPA led to rapid and significant improvements compared with PBO over 12 weeks in patients with refractory RA. ACR20 (primary end point) was achieved by 106 (65%; 95% CI: 57, 72) of 164 patients receiving UPA 15 mg and 93 (56%; 49, 64) of 165 patients receiving UPA 30 mg compared with 48 (28%; 22, 35) of 169 patients receiving PBO ($P < 0.0001$ for each dose *vs* placebo). DAS28[CRP] of 3.2 or less (primary end point) was achieved by 71 (43%; 95% CI: 36, 51) of 164 patients receiving UPA 15 mg and 70 (42%; 35, 50) of 165 patients receiving UPA 30 mg *vs* 24 (14%; 9, 20) of 169 patients receiving PBO ($P < 0.0001$ for each dose *vs* PBO) [4].

As monotherapy after inadequate response to methotrexate

Upadacitinib monotherapy showed statistically significant improvements in clinical and functional outcomes *vs* continuing MTX in the SELECT MONOTHERAPY study. Patients with active RA ($n = 648$) despite stable MTX were randomly assigned to switch to once-daily monotherapy of UPA 15 mg or 30 mg or to continue MTX at their existing dose as blinded study drug. Starting from week 14, patients assigned to continue MTX were switched to UPA 15 mg or 30 mg. Patients were ACPA or RF positive in 79% and had high disease activity. At week 14, an ACR20 response (primary end point) was achieved by 89 (41%) of 216 patients (95% CI: 35, 48) in the continued MTX group, 147 (68%) of 217 patients (62, 74) receiving UPA 15 mg, and 153 (71%) of 215 patients (65, 77) receiving upadacitinib 30 mg ($P < 0.0001$ for both doses *vs* continued MTX). DAS28[CRP] 3.2 or lower (primary end point) was met by 42 (19%) of 216 (95% CI: 14, 25) in the continued MTX group, 97 (45%) of 217 (38, 51) receiving UPA 15 mg, and 114 (53%) of 215 (46, 60) receiving UPA 30 mg ($P < 0.0001$ for both doses *vs* continued MTX) [5].

As monotherapy in methotrexate-naive patients

The SELECT EARLY study compared the clinical efficacy of UPA monotherapy *vs* MTX monotherapy, in MTX-naïve patients with moderate to severely active RA. Patients ($n = 94$) were positive for both RF and ACPA and/or had ≥ 1 joint erosion. Patients were randomized to UPA 15 mg or 30 mg, or weekly MTX (titrated by week 8). Separate primary endpoints were ACR50 at week 12 or the proportion of patients achieving DAS 28[CRP] <2.6 at week 24. Significantly more patients receiving UPA 15 mg and 30 mg *vs* MTX achieved ACR50 responses at week 12 (52.1% and 56.4% *vs* 28.3%) and DAS28[CRP] <2.6 at week 24 (48.3% and 50.0% *vs* 18.5%) [6].

Compare to adalimumab

The SELECT COMPARE study evaluated the efficacy of UPA as compared with PBO or adalimumab (ADA) in MTX inadequate response patients. Patients included ($n = 1629$) had active disease and the mean duration of RA since diagnosis was 8 years. Most of the patients (87.5%) were positive for either RF and/or ACPA. They were randomized to receive UPA 15 mg, placebo, or ADA (40 mg every other week) while continuing to take a stable background dose of MTX. This study was designed and powered for superiority against placebo, and to test for the noninferiority and then if achieved, superiority of UPA compared with ADA, as measured both clinically and functionally. At week 12, both primary end points (ACR20 improvement and DAS28[CRP] score <2.6) were met in patients receiving UPA compared with those receiving PBO ($P \leq 0.001$). Upadacitinib was superior to ADA based on the ACR50 response rate, change in pain severity score, and change in the HAQ Disability Index (HAQ DI). At week 26, more patients receiving UPA than those receiving PBO or ADA achieved low disease activity or remission ($P \leq 0.001$) [7].

SELECT COMPARE STUDY, over 48 weeks, demonstrated that the responses were maintained with UPA treatment over 48 weeks and were consistently significantly better than with ADA. Patients who failed to achieve 20% improvement in TJC with ADA or UPA were switched to the other drug. A total of 251 patients (38.6%) were rescued to ADA *vs* 159 (48.6%) to upadacitinib. Following 6 months of switch treatment in patients rescued from adalimumab to UPA, CDAI remission/low disease activity was achieved by 15/53% and DAS28[CRP] $<2.6/\leq 3.2$ by 35/56%; in patients rescued from UPA to ADA, CDAI remission/low disease activity was achieved in 5/41% and DAS28[CRP] $<2.6/\leq 3.2$ was achieved in 21/40% [8]. This is the first data to assess the response on patients who failed to respond to JAKi and were switched to TNFi.

Compare to abatacept in patients with prior inadequate response to biologic therapy

The SELECT-CHOICE was a head-to-head phase 3, double-blind study in bDMARD-IR patients comparing the efficacy and safety of UPA to abatacept (ABA), each in combination with stable background csDMARDs. The study included 613 patients, with long-standing established and active disease, who were randomized to UPA 15 mg q.d. or intravenous ABA in standard doses. The primary end point was the non-inferiority comparison of UPA to ABA in change from baseline in DAS28[CRP] at week 12. The ranked key secondary endpoints were the superiority comparison of UPA to ABA in change from baseline in DAS28(CRP) at week 12 and the superiority comparison of UPA to ABA in proportion of patients

achieving clinical remission based on DAS28(CRP) at week 12.

UPA met the primary end point of non-inferiority *vs* ABA for change from baseline in DAS28(CRP) ($P < 0.001$) and shown to be superior to ABA for change from baseline in DAS28(CRP) ($P < 0.001$) and proportion of patients achieving DAS28(CRP) <2.6 remission ($P < 0.001$) at week 12. A significant difference in the proportion of patients achieving DAS28(CRP) <2.6 was also maintained at week 24 [9]. The SELECT-CHOICE is the first study demonstrating the superiority of a selective JAK inhibitor compared with a standard of care biologic in a population of RA patients with a prior inadequate response to a biologic therapy.

Radiographic responses

The impact of upadacitinib on structural joint damage was assessed during SELECT EARLY and SELECT COMPARE. In the SELECT EARLY trial, at week 24, both doses of UPA monotherapy significantly reduced progression of joint damage as determined by significantly lower change from baseline in modified Total Sharp Score (mTSS) compared with MTX (ΔmTSS UPA 15 mg: 0.03; UPA 30 mg: 0.10; MTX: 0.66; $P < 0.001$ both doses). At week 48, both doses of UPA monotherapy continued to significantly reduce progression of joint damage compared with MTX [6, 10]. In the SELECT COMPARE trial, at week 26, UPA 15 mg + MTX significantly reduced progression of joint damage as determined by significantly lower change from baseline in mTSS compared with PBO + MTX [ΔmTSS UPA 15 mg + MTX: 0.16; ADA + MTX: 0.19; PBO + MTX: 0.94; $P < 0.001$ (*vs* PBO + MTX)]. The change from baseline for UPA 15 mg + MTX was similar to that for ADA + MTX. At week 48, the UPA 15 mg + MTX continued to significantly reduce progression of joint damage [7, 10].

Two years' data was recently presented. In the SELECT EARLY, UPA monotherapy (both doses) continued to demonstrate reduced progression of structural joint damage compared with MTX monotherapy; and in the SELECT COMPARE study, the rate of inhibition of structural progression observed was similar between continuous administration of UPA + MTX or ADA + MTX as measured by a mean change from baseline in mTSS. Following the switch of PBO patients to UPA 15 mg, no further radiographic progression was observed in almost 90% of patients [11].

Patients' reported outcomes

In the SELECT program, patients' reported outcomes such as pain, physical function assessment (HAQ-DI), fatigue (FACIT-F) and quality-of-life (SF-36 PCS) were also significantly improved in patients treated with UPA *vs* PBO [3–8]. The effect of UPA on morning stiffness was seen early. In the SELECT NEXT study by week 1, the severity of morning stiffness was significantly improved for patients receiving either 15 or 30 mg compared with PBO ($P < 0.0001$), and improvements continued over the 12 weeks [3]. In the SELET COMPARE study, UPA was superior to ADA based on the change in pain severity score [mean change −32.1 in the UPA group *vs* −25.6 in the ADA group, difference −6.5 (95% CI: −9.7, −3.3); $P \leq 0.001$] and change in HAQ DI score [mean change −0.60 in the UPA group *vs* −0.49 in the ADA group, difference −0.11 (95% CI −0.18, −0.03); $P \leq 0.01$]. These improvements were maintained through 26 weeks [7].

Filgotinib

The development of filgotinib included four phase III clinical trials, the FINCH phase III program (Table 2). Results from some of the studies have been recently published but still there is a lot of information expected to be presented soon. The long-term extension study is still ongoing.

As combination therapy after inadequate response to methotrexate

The FINCH 1 study was a double blind RCT. MTX-IR patients with active RA on background stable MTX were randomized to oral filgotinib 200 mg or filgotinib 100 mg once daily, subcutaneous adalimumab 40 mg every 2 weeks, or matching placebo up to week 52. Patients receiving placebo at week 24 were re-randomized to receive filgotinib. The primary end point was the proportion of participants who achieve an ACR 20% at week 12. A total of 1417 patients received study drug through week 52. Most of the patients had long-standing disease (mean 7.8 years if diagnosis), 85.3% were RF or anti CCP positive and have active disease (mean DAS28 CPR 5.7). A significantly greater proportion of patients treated with filgotinib 200 or 100 mg achieved ACR 20 at week 12 compared with placebo (76.6%, 69.8%, 49.9% respectively, $P < 0.001$). The proportion of patients achieving DAS28(CPR) <2.6 at week 52 was 54%, 43% and 46% for patients receiving filgotinib 200 mg, filgotinib 100 mg, and adalimumab, respectively (nominal P for filgotinib 200 mg *vs* adalimumab = 0.024). Non-inferiority of FIL 200 mg to ADA was met based on DAS28-CRP ≤3.2. Response rates were numerically similar between patients treated with filgotinib 100 mg *vs* adalimumab. Radiographic progression measured by change from baseline in mTSS *vs* placebo at week 24 was significantly less in filgotinib 200 mg or 100 mg *vs* placebo ($P < 0.001$ and $P = 0.001$, respectively). Overall, filgotinib demonstrated a favourable benefit-risk profile in MTX IR patients with AR [12, 13].

As combination therapy after inadequate response to bDMARDs

The FINCH 2 study compared the effects of filgotinib *vs* placebo for the treatment of patients with moderately to severely active RA and an inadequate response or intolerance to 1 or more prior bDMARDs. Patients were

Table 2 FINCH phase III studies

Study	FINCH 1	FINCH 2	FINCH 3	FINCH 4
Population	MTX IR	bDMARD IR	MTX naive	LTE
Type of therapy	Combo	Combo	Mono *vs* Combo	Combo
Background	MTX	csDMARDs	MTX	csDMARDs
Active comparator	ADA	csDMARs	MTX	
Arms	• FIL 200 mg QD + MTX • FIL 100 mg QD + MTX • ADA +MTX • − PBO +MTX for 24 weeks followed by FIL 100 mg or 200 mg +MTX	• FIL 200 mg QD + csDMARDs • FIL 100 mg QD + csDMARDs • − PBO + csDMARDs	• FIL 200 mg QD + MTX • FIL 100 mg QD + MTX • FIL 200 mg • PBO +MTX	• FIL 200 mg QD • FIL 100 mg QD
Primary end point	ACR 20	ACR 20	ACR 20	Safety
Statistical analysis	Non inferiority Not adjusted for multiplicity NRI	Superiority against PBO Not adjusted for multiplicity NRI	Superiority against PBO Not adjusted for multiplicity NRI	
Results	ACR20 76.6% FIL 200 mg, 77.7% FIL 100 mg *vs* 49.9% PBO	ACR20 66% FIL 200 ng, 57.5% FIL 100 mg *vs* 31.1% PBO	ACR20 81% FIL 200 mg, 80.2% FIL 100 mg *vs* 71.4% MTX	
Duration of Period 1	12 weeks	24 weeks	26 weeks	78 weeks
Sample size	1759	449	1552	2800
Radiographic progression	Yes		Yes	

Clinical Trials for Filgotinib in RA (FINCH phase III program). ACR: American College of Rheumatology improvement response; ADA: adalimumab; bDMARD: biological DMARD; bDMARD IR: biological DMARD insufficient response; csDMARD: conventional synthetic DMARD; csDMARD IR: conventional synthetic DMARD insufficient response; FIL: filgotinib; LTE: Long term extension; MTX-IR: MTX insufficient response; NRI: non-responder imputation; PBO: placebo; QD: once daily.

randomized to once daily filgotinib 200 mg; filgotinib 100 mg; or placebo. In total, 449 patients were included. At week 12, the ACR20 response rates (primary end point) were 66.0% (95% CI: 58.0%, 74.0%) and 57.5% (95% CI: 49.4%, 65.7%) for filgotinib 200 mg and 100 mg, respectively, *vs* 31.1% (95% CI: 23.3%, 38.9%) for placebo [difference *vs* placebo: 34.9% (95% CI: 23.5%, 46.3%) for filgotinib 200 mg, and 26.4% (95% CI: 15.0%, 37.9%) for filgotinib 100 mg; both $P < 0.001$]. At week 24, 30.6% of patients treated with filgotinib 200 mg, achieved disease remission (DAS28-CRP <2.6). Responses with the filgotinib 200 mg dose were numerically higher compared with the 100 mg dose, but no statistical analysis for potential dose response was done. There were no radiographic end points to evaluate structural joint damage [14].

Methotrexate-naive patients

The FINCH 3 trial included MTX naive patients with active RA, randomized to oral filgotinib 200 mg once daily plus MTX, filgotinib 100 mg plus MTX, filgotinib 200 mg monotherapy and MTX ≤20 mg weekly. The primary efficacy end point was proportion of patients achieving ACR20 response at week 24. In total, 1249 received the study drug and were analysed; 1130 completed week 24. 77% of patients were RF or anti CCP positive and 94% of patients had at least one erosion; mean time since RA diagnosis was 2.2 years (median 0.4 years); mean (S.D.) DAS28-CRP was 5.7 (1.0); and 35.9% were using oral steroids at baseline. At week 24, significantly more patients in the FIL 200 mg + MTX (81.0%; $P < 0.001$) and FIL 100 mg + MTX (80.2%; $P < 0.05$) arms achieved an ACR20 response compared with MTX monotherapy (71.4%). In the monotherapy arm, a higher proportion of patients achieved ACR 50/70 with filgotinib 200 mg *vs* MTX, though ACR 20 response was not significantly higher at week 24. Filgotinib efficacy was sustained through week 52. There was less radiographic progression as measured by change in mTSS from baseline at week 52 in patients receiving filgotinib 100/200 mg *vs* MTX monotherapy [15, 16].

The FINCH 4 is a study that is evaluating the long-term safety and tolerability of filgotinib in participants who have completed one of the parent studies of filgotinib in RA. The study is still active and partial results are expected soon [17].

Conclusion

The available data on upadacitinib and filgotinib is very promising. JAK 1 selective drugs have shown to be highly effective in the treatment of RA, following the data of the other pan-JAK inhibitors. The speed of response is a unique characteristic of this family of drugs and was also reflected in the upadacitinib/filgotinib trials. Head-to-head trials are needed if differences in efficacy between JAKi do exist, as present trials have been done with different methodology and patient populations. In the absence of these data, indirect comparison of real-life data from observational registries is crucial for better understanding the real potential benefit of JAK1 selective inhibition over pan-JAK blockade [1], as well as metanalysis [18].

Upadacitinib and filgotinib in two different trials that compared them to a standard of care were able to show superiority. Upadacitinib also demonstrated superiority to another biologic in bDMARD-IR population. Another plus of the studies from the select program was the adjustment for multiplicity in their statistical analysis, something that was not done in the FINCH studies.

Some other issues remain still unanswered as results from long-term studies are need to address the efficacy over time and some safety issues that are controversial, like the thromboembolic events and the relationship between the change in lipid profile and cardiovascular diseases. Also, tapering strategies in patients with clinical remission needs formal testing with these drugs and the question if one JAKi could be use after the failure of another JAKi needs to be answered with proper clinical trials.

Upadacitinib and filgotinib favourable data should allow these drugs to be included in the medical arsenal available for the treatment of RA and could in the future change the guidelines.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

References

1 Biggioggero M, Becciolini A, Crotti C, Agape E, Favalli EG. Upadacitinib and filgotinib: the role of JAK1 selective inhibition in the treatment of rheumatoid arthritis. Drugs Context 2019;8:212595.

2 Bechman K, Yates M, Galloway JB. The new entries in the therapeutic armamentarium: the small molecule JAK inhibitors. Pharmacol Res 2019;147:104392.

3 Burmester GR, Kremer JM, Van den Bosch Kivitz A *et al.* Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti -rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018;391:2503–12.

4 Genovese MC, Fleischmann R, Combe B *et al.* Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Lancet 2018;391:2513–24.

5 Smolen JS, Pangan AL, Emery P *et al.* Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. Lancet 2019;393:2303–11.

6 van Vollenhoven R, Takeuchi T, Pangan AL *et al.* A Phase 3, randomized, controlled trial comparing upadacitinib monotherapy to MTX monotherapy in MTX-naive patients with active rheumatoid arthritis (abstract). Arthritis Rheumatol 2018;70: 891.

7 Fleischmann R, Pangan AL, Song IH *et al.* Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. Arthritis Rheumatol 2019;71:1788–800.

8 Fleischmann RM, Genovese MC, Enejosa JV *et al.* Safety and effectiveness of upadacitinib or adalimumab plus methotrexate in patients with rheumatoid arthritis over 48 weeks with switch to alternate therapy in patients with insufficient response. Ann Rheum Dis 2019;78:1454–62.

9 Rubbert-Roth A, Enejosa J, Pangan A *et al.* Trial of Upadacitinib or Abatacept in Rheumatoid Arthritis. N Eng J Med 2020;383:1511–21.

10 Peterfy C, Genovese M, Song IH *et al.* Inhibition of structural joint damage with upadacitinib as monotherapy or in combination with methotrexate in patients with rheumatoid arthritis: 1 year outcomes from the SELECT phase 3 program. Arthritis and Rheumatol 2019;71:547.

11 Peterfy C, Strand V, Genovese MC *et al.* Radiographic outcomes in patients with rheumatoid arthritis receiving upadacitinib as monotherapy or in combination with methotrexate: results at 2 years from the select-compare and select-early studies. Ann Rheum Dis 2020;79:330–1.

12 Combe B, Kivitz A, Tanaka Y *et al.* Efficacy and safety of filgotinib for patients with rheumatoid arthritis with inadequate response to methotrexate: FINCH 1 primary outcome results. Ann Rheum Dis 2019;78:77–8.

13 Combe B, Kivitz A, Tanaka Y *et al.* Efficacy and safety of filgotinib for patients with rheumatoid arthritis with inadequate response to methotrexate: finch 1 52-week results. Ann Rheum Dis 2020;79:320–1.

14 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. JAMA 2019;322: 315–25.

15 Westhovens R, Rigby W, Van der Heijde D *et al.* Efficacy and safety of filgotinib for patients with rheumatoid arthritis naive to methotrexate therapy: FINCH3 primary outcome results. Ann Rheum Dis 2019;78:259–61.

16 Westhovens R, Rigby W, Van der Heijde D *et al.* Efficacy and safety of filgotinib in methotrexate-naive patients with rheumatoid arthritis: finch 3 52-week results. Ann Rheum Dis 2020;79:1019–20.

17 Long Term Extension Study to Assess the Safety and Efficacy of Filgotinib in Adults With Rheumatoid Arthritis (FINCH 4). US National Library of Medicine, clinical trials. https://clinicaltrials.gov/ct2/show/NCT03025308 (18 July 2020, date last accessed).

18 Pope J, Sawant R, Tundia N *et al.* Comparative efficacy of JAK inhibitors for moderate-to-severe rheumatoid arthritis: a network meta-analysis. Adv Ther 2020;37: 2356–72.