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SPONDYLOARTHRITIS (M KHAN, SECTION EDITOR)

JAK Inhibitors for Axial Spondyloarthritis: What does the Future Hold?

Nurullah Akkoc[1] · Muhammad A. Khan[2]

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Abstract

Purpose of Review To discuss the potential role of JAK inhibitors (JAKis) as a new therapeutic class for the treatment of axial spondyloarthritis (axSpA, including ankylosing spondylitis [AS] and non-radiographic axSpA [nr-axSpA]).

Recent Findings A phase III randomized controlled trial of tofacitinib (a "pan JAKi") in patients with active AS was found to be superior to placebo in achieving the ASAS20 primary endpoint at week 16 (56.4% and 29.4%, $p < 0.0001$, phase II trials of AS). Upadacitinib, a JAK1 inhibitor, has also been evaluated in a phase III trial for its efficacy and safety in AS. The primary endpoint, ASAS40 at week 16, was reached by 52% of the patients randomized to upadacitinib and 26% of the patients receiving placebo ($p = 0{\cdot}0003$). All the important secondary endpoints also improved with both agents. No new changes in their safety profile were noted. However, the more frequent occurrence of cardiovascular and cancer adverse events associated with tofacitinib than with TNFi observed in the very recent post-marketing "ORAL surveillance" safety study, the results of which were released on January 27, 2021, may lead to safety concerns swirling around the whole class of JAKis.

Summary JAKis seem to be effective in treating signs and symptoms of AS but have not been studied in nr-axSpA. Both tofacitinib and upadacitinib have been pre-registered with the FDA for the treatment of AS. Upadacitinib has just recently received approval for this indication in the European Union..

Keywords Axial spondyloarthritis · Ankylosing spondylitis · Upadacitinib · Tofacitinib · Filgotinib · JAK inhibitors

Introduction

Inflammatory cytokines play a major role in the pathogenesis of immune-mediated chronic inflammatory diseases. Cytokines are rarely produced alone and play their role in a complex network with others [1]. They perform many functions and can act synergistically or antagonistically. They can be produced by more than one type of cell and exert redundant and pleiotropic functions, which may be different in different tissues. The release of one cytokine may influence the production of, or response to, several others. These features all point out to the complexity of interplay between different immune cell types and between different cytokine networks involved in the pathogenesis of different chronic inflammatory diseases. Nevertheless, single anti-inflammatory cytokine–targeting strategies, using monoclonal antibodies or receptor constructs against tumor necrosis factor α (TNFα), interleukin (IL)-1, IL-6, IL-17A, and IL-23, have been successful in the treatment of several chronic inflammatory conditions [2–5].

Blocking one single cytokine, like TNFα, is effective in a wide spectrum of chronic inflammatory diseases, including even some seemingly unrelated ones, such as ankylosing spondylitis (AS), rheumatoid arthritis (RA), and hidradenitis suppurativa [2]. This indicates that common inflammatory pathway(s) may be implicated in the pathogenesis of different inflammatory diseases. On the other hand, targeting IL-17 may show efficacy in only a subset of diseases, which are known to respond well to TNF inhibitors (TNFis), but not in all of them [5]. AS, psoriasis, and psoriatic arthritis (PsA) are effectively treated by IL-17 inhibitors, but RA, which is unrelated to spondyloarthritis (SpA), inflammatory bowel disease (IBD), and uveitis, do not respond to anti-IL-17 agents [5].

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✉ Nurullah Akkoc
nurullah.akkoc@gmail.com

Muhammad A. Khan
m.asimkhan@gmail.com

[1] Division of Rheumatology, Department of Medicine, Manisa Celal Bayar University School of Medicine, Manisa, Turkey

[2] School of Medicine, Case Western Reserve University, 1722 Coes Post Run, Westlake, OH 44145, USA

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Targeting IL-23, which is required for the optimal expansion and activation of Th17 cells [6], is very effective in psoriasis but not in AS [5, 7, 8]. Similarly, IL-1 and IL-6 are also among the key regulators in the differentiation of human Th17 cells [6], but blockers of these cytokines have not shown any efficacy in AS [4, 9–11].

All this information suggests that the lack of response to a single anti-cytokine therapy in a chronic inflammatory disease may not entirely exclude a pathogenic role for that cytokine because of the redundant and pleiotropic nature of cytokines. Targeting a combination of such cytokines that have failed as single treatment targets, despite their involvement in the induction and perpetuation of the inflammatory process in that particular disease, may still be an effective therapeutic strategy. To this purpose, targeting Janus kinases (JAKs) can be a potential strategy for the treatment of chronic inflammatory diseases, since they are associated with receptors of numerous cytokines [12].

Cytokine binding to its receptor on the cell surface leads to dimerization of the receptor and activation of the JAKs, which subsequently phosphorylate the tail of receptors on tyrosine, creating docking sites for signaling molecules, especially members of the signal transducer and activator of transcription (STAT) family. Dimers of STATs are then phosphorylated by JAKs and translocate to the nucleus, where they regulate the expression of cytokine-responsive genes (Fig. 1) [13–15].

JAKs are a family of non-receptor protein tyrosine kinases with four members: JAK1, JAK2, JAK3, and Tyrosine kinase 2 (Tyk2). Distinct combinations of homodimers of JAK proteins selectively associate with different cytokine receptors, which consist of multiple (usually two) protein chains (Fig. 2) [13, 15–17]. Hence, the inhibition of each JAK member interferes with the downstream signal transduction of relevant cytokines, which make JAK proteins an attractive target for the treatment of several chronic inflammatory diseases [12, 18, 19].

JAK Inhibitors (JAKis) in AS

A significant proportion of patients with active AS treated with TNFis discontinue their treatment due to failure or inadequate response [20]. Although, IL-17 inhibitors may be effectively used in such patients, response rate is generally lower compared to TNFi-naïve patients [21]. Therefore, there is still a considerable number of patients with AS, whose disease activity cannot be adequately suppressed despite the use of currently approved biologic drugs. Therefore, it is expected that JAKis may reduce the unmet need for treatment options in AS.

Currently, three JAKis, tofacitinib, baricitinib, and upadacitinib, are approved for the treatment of RA in the USA and European Union. JAKis are also being used to tackle other autoimmune disorders, and tofacitinib has been approved also for the treatment of PsA and ulcerative colitis (UC). Even alopecia areata is a possible target, as studies have found that these drugs help trigger new hair growth [17]. Moreover, phase II and phase III trials of tofacitinib [22, 23], a phase II/III trial of upadacitinib [24••], and a phase II trial of filgotinib [25•] all showed good therapeutic response in adults with AS. Interestingly, neither the TNF nor the IL-17A signal through JAK-STAT signaling pathway, whereas IL-23 and IL-6 use JAK-STAT pathway, and phase III trials with monoclonals targeting IL-23 and IL-6 showed no efficacy in AS [7, 8, 10, 11].

Tofacitinib

Tofacitinib mainly inhibits JAK1 and JAK3 and, to a lesser extent, JAK2 but has little effect on TYK2 [13]. It is approved for the treatment of RA, PsA, and UC both in the USA and Europe and polyarticular course juvenile idiopathic arthritis (JIA) in the USA. It is pre-registered with the Food and Drug Administration (FDA) for the treatment of AS, after the positive results of a recent phase III study in adults with active AS [23]. A previous phase II dose ranging study had noted higher Assessment of SpondyloArthritis International Society (ASAS) 20 response rates in adult AS patients treated with 2, 5, or 10 mg twice daily doses of tofacitinib over 12 weeks than with placebo, but the difference did not reach statistical significance in tofacitinib 2 mg and 10 mg groups [22]. In the same study, significant improvements were observed with 5 and 10 mg tofacitinib than placebo, in most of the secondary endpoints assessed, including magnetic resonance imaging (MRI) inflammation scores in the spine and the sacroiliac joints.

After the completion of the phase II study, the manufacturing company Pfizer waited for more than 3 years to initiate a phase III study with tofacitinib for the AS indication, the results of which were presented at the American College of Rheumatology Convergence 2020 meeting and demonstrated its efficacy [23]. This randomized, double-blind, placebo-controlled study enrolled adult patients with active AS who had an inadequate response or intolerance to ≥ 2 non-steroidal anti-inflammatory drugs (NSAIDs). All patients met modified New York Criteria based on centrally read radiographs. Patients with complete ankylosis of the spine were ineligible. About 23% of the patients had prior exposure to TNFis.

A total of 269 patients were randomized in a 1:1 ratio to receive tofacitinib 5 mg twice daily or placebo during the 16-week double-blind phase of the study, after which all patients were switched to open-label tofacitinib for up to week 48 [23]. The primary endpoint was ASAS20 response at week 16. It was achieved by 56.4% and 29.4% of the patients taking tofacitinib and placebo, respectively ($p < 0.0001$). ASAS40 response at the same time point was the key secondary

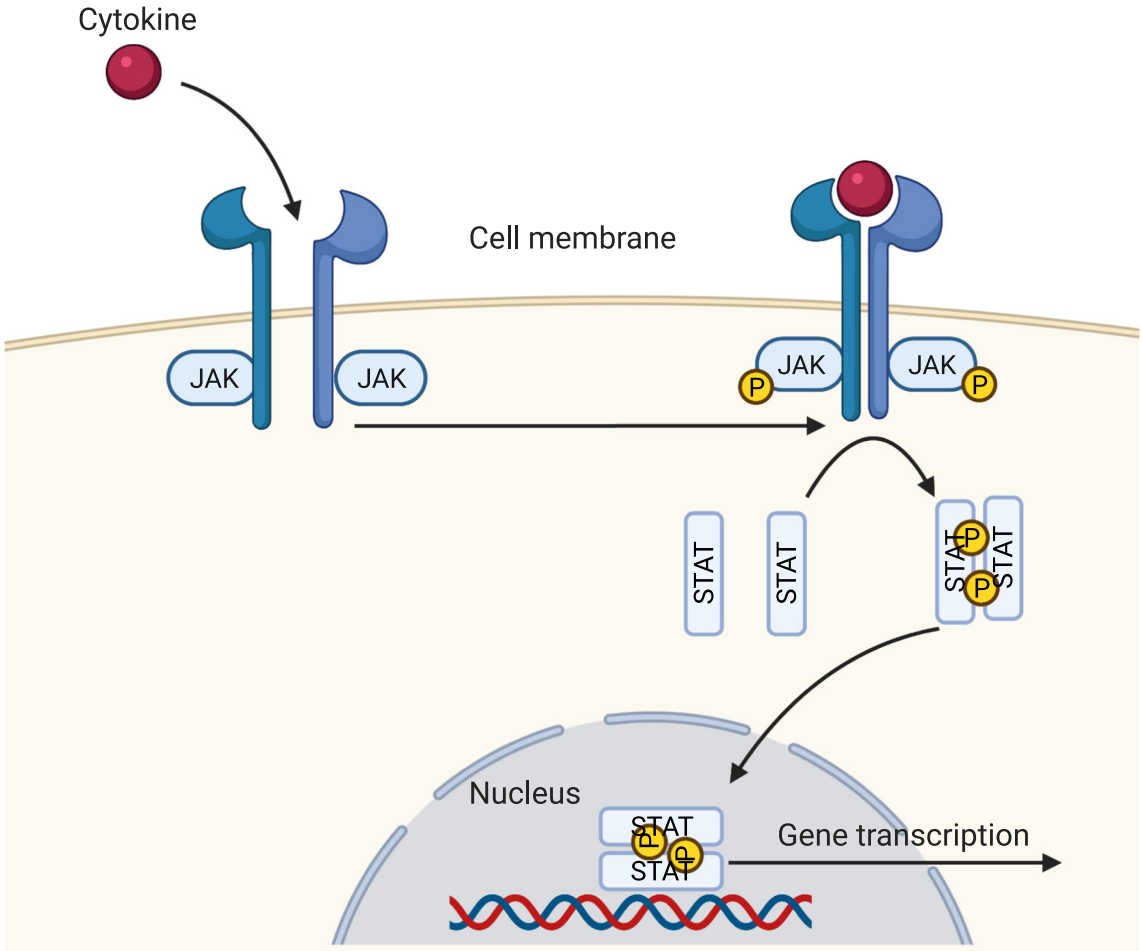


Fig. 1 Cytokine signaling through the Janus kinase–signal transduction and activation of transcription (JAK–STAT) pathway. Cytokine binding to its receptor on the cell membrane leads to activation and phosphorylation of the JAKs and their associated receptors in the cytoplasm. This in turn leads to phosphorylation and recruitment of STATs via their SH2 domains, resulting in activated STATs homodimer or heterodimer forms that translocate to the nucleus. There they bind to their specific DNA-binding sites and initiate gene transcription

endpoint and was met by 40.6% of the patients receiving tofacitinib versus 12.5% of the patients on placebo ($p < 0.0001$) (Fig. 3). Type I error-controlled secondary efficacy endpoints were also improved significantly. Moreover, greater improvements were observed from baseline to week 16 in the tofacitinib group compared with placebo for disease activity (Ankylosing Spondylitis Disease Activity Score–C-reactive protein [ASDAS-CRP]), objective inflammation markers (high-sensitivity CRP), mobility measures (Bath Ankylosing Spondylitis Metrology Index), and patient-reported outcomes related to health status, such as quality of life (Short Form-36 Health Survey Version 2 Physical Component Summary), ankylosing spondylitis quality of life score, and fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue score) (Table 1). ASAS20 responder rates at week 16 in the active treatment versus placebo groups were 61% versus 33% among biologic disease modifying anti-rheumatic drug (DMARD)–naïve patients and 39% versus 16% among biologic DMARD-exposed patients. Improvements in ASAS20 and ASAS40 were evident as early 2 and 4 weeks, respectively. No new safety signals were recorded. Based on these positive results, Pfizer filed an application with the FDA for the indication for treatment of adult patients with active AS.

Upadacitinib

Upadacitinib is a selective JAK1 inhibitor, with a greater selectivity for JAK1 and JAK2 than for JAK3 and TYK2 as shown in a cell-free isolated enzyme assay [27]. It is approved for the treatment of RA by the FDA and the European Medical Agency (EMA). It has just recently received approval from the EMA for the treatment of AS and PsA [28]. It is also preregistered with the FDA for the treatment of AS. The approval from EMA for the AS indication was based on a multicenter, randomized, double-blind, placebo-controlled phase II/III

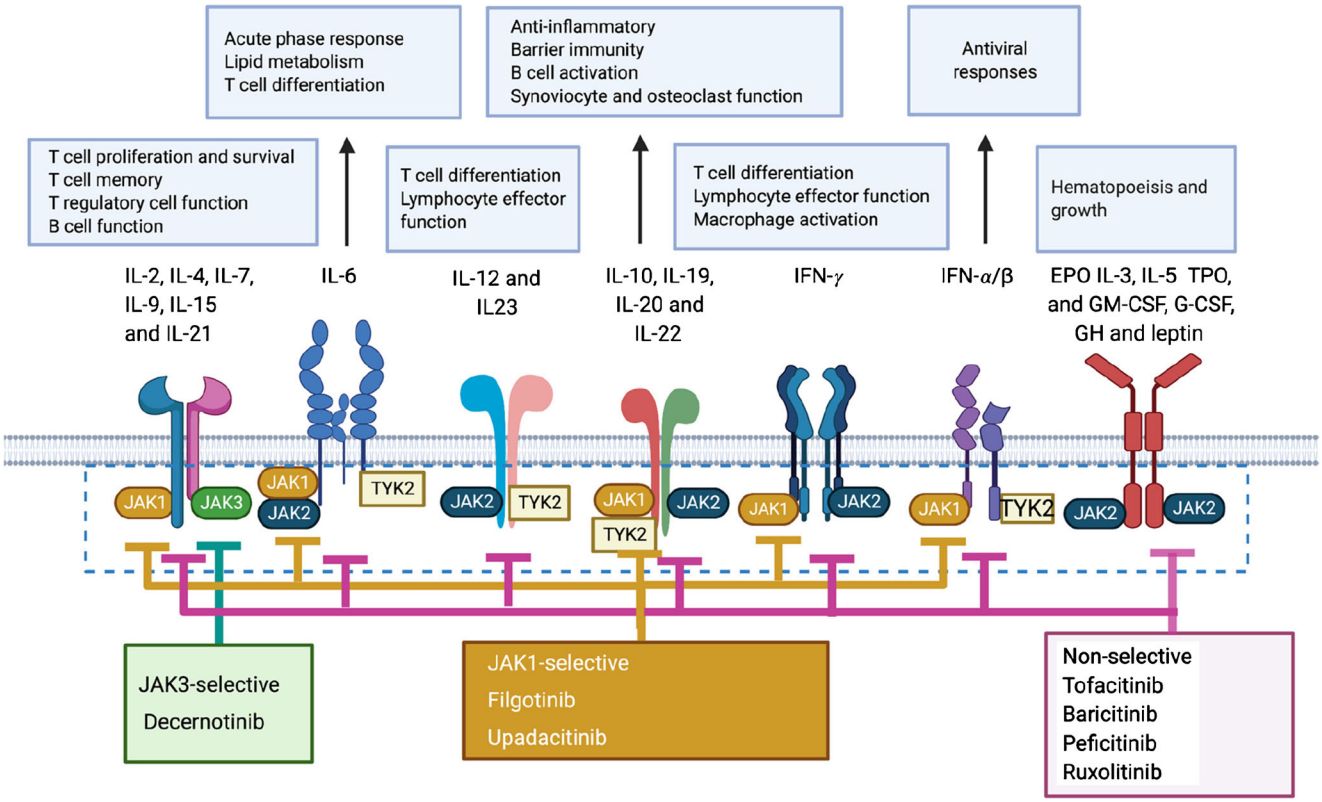


Fig. 2 Consequence of blocking key immunoregulatory cytokines and growth factors by different JAK inhibitors on biologic functions (adapted from reference [15]). EPO, erythropoietin; granulocyte colony-stimulating factor (G-CSF); GH, growth hormone; GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukin; IFN, interferon; TPO, thrombopoietin; TYK, tyrosine kinase

study which evaluated the efficacy and safety of upadacitinib 15 mg once daily ($n = 93$) in comparison with placebo ($n = 94$) in adult patients with active AS [24••]. Study entry eligibility criteria included fulfillment of the modified New York Criteria, inadequate response to maximum tolerated doses of at least two NSAIDs, and no exposure to biologic treatment. Patients with complete ankylosis of the spine were excluded.

The primary endpoint was ASAS40 response at week 14, and it was achieved by 52% of the patients on upadacitinib versus 26% of the patients on placebo ($p = 0{\cdot}0003$) (Fig. 3). Significant improvement in clinical outcomes was noted as early as week 2. Multiplicity-adjusted p values were significant for the differences between upadacitinib versus placebo for the change in ASDAS, Spondyloarthritis Research Consortium of Canada (SPARCC) MRI spine, and Bath Ankylosing Spondylitis Functional Index scores from baseline to week 14 and Bath Ankylosing Spondylitis Disease Activity Index 50 response and ASAS partial remission rates at week 14 (Table 1). ASAS partial remission was reached by 19% and 1% of the patients taking upadacitinib and placebo, respectively ($p < 0.0001$) (Fig. 3). Improvements in Maastricht Ankylosing Spondylitis Enthesitis Score, Bath Ankylosing Spondylitis Metrology Index, Ankylosing Spondylitis Quality of Life, and ASAS Health Index at week 14 were observed with upadacitinib versus placebo (nominal p values < 0.05), as well as in ASAS20 and SPARCC MRI sacroiliac joint scores (nominal $p = 0{\cdot}001$ and $p < 0{\cdot}0001$, respectively) (Table 1) [24, 26]. Higher percentage of patients achieved ASDAS major improvement, ASDAS clinically important improvement, ASDAS low disease activity, and ASDAS inactive disease at week 14 with upadacitinib treatment than with placebo (nominal $p < 0.0001$ for all comparisons). Improvement in the mean ASDAS value and ASDAS major improvement rate were noted as early as 2 weeks. The improvements observed at primary time point were maintained with an upward trend up to week 64. Safety findings were consistent with previous upadacitinib studies in other indications, with no new safety signal [29].

Filgotinib

Filgotinib is a selective JAK1 inhibitor as shown in biochemical assays, with greater than 5-fold higher potency for JAK1 over JAK2, JAK3, and TYK2. It has been approved for the treatment of RA in Europe and Japan, but not in the USA. The FDA has issued a complete response letter in response to the drug maker Gilead's filing for approval of filgotinib in RA and requested safety data from the two ongoing phase II trials

Table 1 Mean change from baseline to endpoint in several secondary efficacy measures with JAK inhibitors as compared with placebo in trials of AS

	Tofacitinib 5 mg twice daily (n = 133) [23]	Placebo (n = 136)	p value
Some of the type I error-controlled secondary endpoints, tested in the sequence below			
ASDAS	− 1.46	− 0.37	< 0.0001
hsCRP (mg/dL)	− 1.05	− 0.09	< 0.0001
ASqOL	− 4.03	− 2.01	0.0001
SF-36v2 PCS	6.69	3.14	< 0.0001
BASMI-linear method	− 0.63	− 0.11	< 0.0001
FACIT-F total score	6.54	3.12	0.0008
Change in ASDAS components, tested in the sequence below			
Patient global assessment	− 2.47	− 0.91	< 0.0001
Total back point	− 2.57	− 0.96	< 0.0001
BASFI	− 2.05	− 0.82	< 0.0001
Inflammation (morning stiffness)	− 2.69	− 0.97	< 0.0001
	Upadacitinib 15 mg once daily (n = 94) [24, 26]	Placebo (n = 93)	p value
Multiplicity-controlled analysis using the Hochberg procedure; test sequence is not shown			
ASDAS	− 1.5	− 0.5	< 0.001*
BASFI	− 2.3	− 1.3	< 0.001*
MASES	− 2.3	− 1.4	0.049
BASMI	− 0.4	− 0.1	0.03
ASqOL	− 4.2	− 2.7	0.016
WPAI	− 18.1	− 12.6	0.19
ASAS HI	− 2.8	− 1.4	0.007
SPARCC MRI Spine	− 6.9	− 0.2	< 0.001*
SPARCC MRI Sacroiliac joints	− 3.9	− 0.2	< 0.0001
hsCRP	− 8.2	0.18	< 0.0001
	Filgotinib (n = 58) [25]	Placebo (n = 58)	p value
BASDAI	− 2.4	− 1.4	0.0052
hsCRP	− 10.8	− 2.2	< 0.0001
ASDAS	− 1.5	− 0.6	< 0.001
BASFI	− 2.5	− 1.2	0.0015
BASMI	− 0.8	− 0.4	0.0093
ASqOL	− 4.8	− 2.2	0.0038
SF36 PCS	8.4	3.8	0.0008
SF36 MCS	4.0	1.0	0.07
SPARCC MRI Spine	− 5.8	− 0.5	0.0066
SPARCC MRI Sacroiliac joints	− 3.5	− 0.1	0.0150

*Significant in multiplicity-controlled analysis. Nominal p values are shown

ASAS20 Assessment of SpondyloArthritis International Society 20 response, *ASAS40* Assessment of SpondyloArthritis International Society 40 response, *ASAS HI* ASAS Health Index, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *ASQoL* ankylosing spondylitis quality of life score, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue, *hsCRP* high-sensitivity C-reactive protein, *MASES* Maastricht Ankylosing Spondylitis Enthesitis Score, *SF36 MCS* Short Form-36 Health Survey Mental Component Score, *SF36 PCS* Short Form-36 Health Survey Physical Component Score, *SF-36v2 PCS* Short Form-36 Health Survey Version 2 Physical Component Summary, *SPARCC* Spondyloarthritis Research Consortium of Canada. *WPAI* work productivity and activity impairment

which aim to assess the testicular toxicity of the drug. Thereupon the drug maker has announced that it will no longer pursue FDA approval for RA and paused the two ongoing phase III trials for AS, as well as the ongoing trials for PsA and uveitis [30]. Thus, it is very unlikely that the company will continue the clinical development for the AS indication.

Efficacy and safety of filgotinib were evaluated in patients with active AS in TORTGUGA phase II trial, which randomized 116 patients in a 1:1 ratio to receive filgotinib 200 mg or

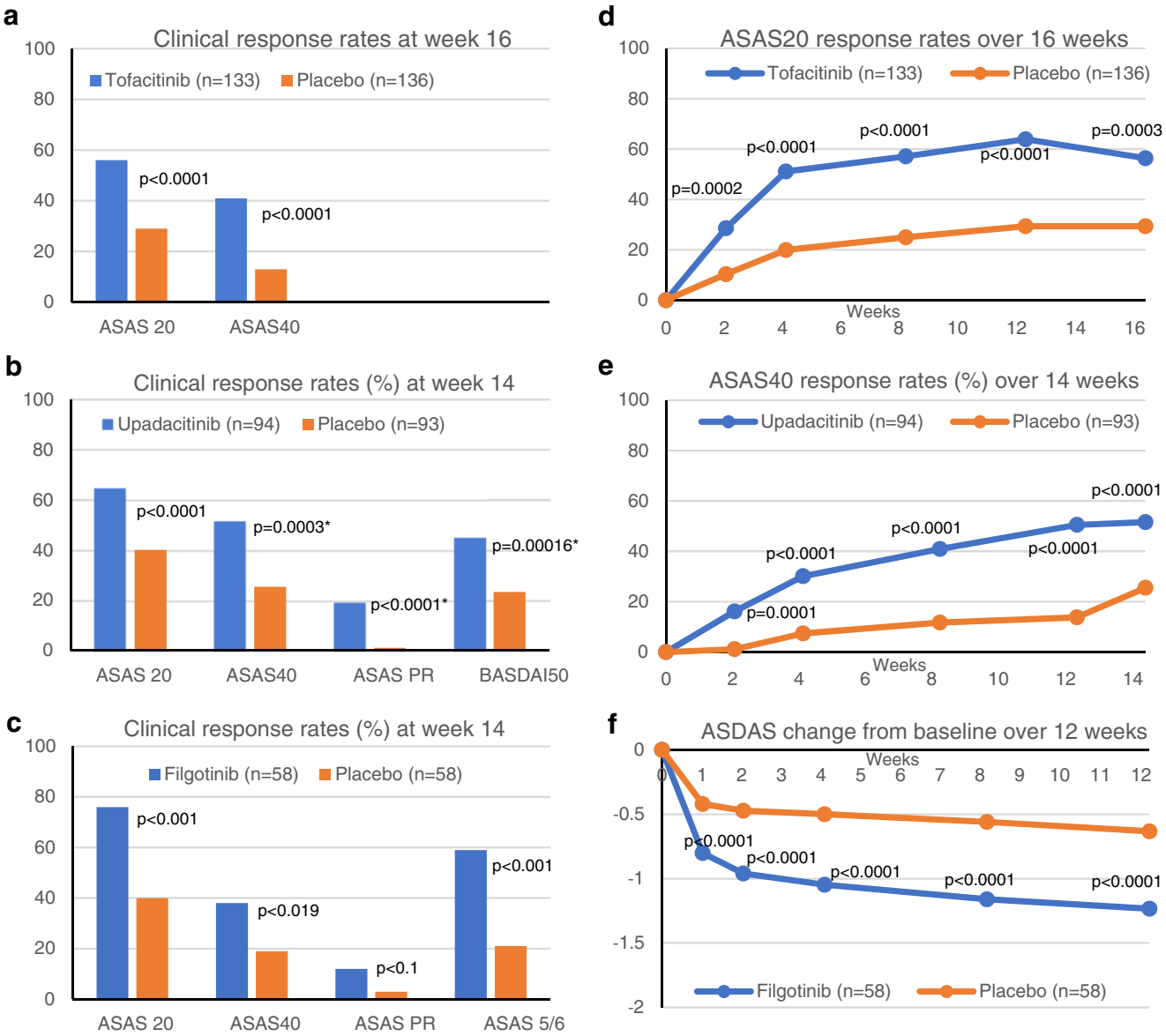


Fig. 3 Clinical response rates with JAK inhibitors in patients with AS and time course of the response of the relevant primary outcome in the individual studies: **a** ASAS20 (primary endpoint) and ASAS40 (key secondary endpoint) responses with tofacitinib 5 mg twice daily versus placebo at week 16. **b** ASAS20, ASAS40 (primary endpoint), ASAS partial remission, and BASDAI50 responses with upadacitinib 15 mg once daily versus placebo at week 14 (*Significant in multiplicity-controlled analysis. Nominal *p* values are shown). **c** ASAS20, ASAS40, ASAS 5/6, and ASAS partial remission with filgotinib 200 mg once daily versus placebo at week 12. **d** ASAS20 response rates with tofacitinib 5 mg twice daily versus placebo over 12 weeks. (e) ASAS40 response rates with upadacitinib 15 mg once daily versus placebo over 14 weeks. (f) ASDAS change from baseline with filgotinib 200 mg once daily versus placebo (primary outcome) over 12 weeks. ASAS20, Assessment of SpondyloArthritis International Society 20 response; ASAS40, Assessment of SpondyloArthritis International Society 40 response; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI50, at least 50% improvement from baseline in Bath Ankylosing Spondylitis Disease Activity Index

placebo once daily for 12 weeks [25•]. Eligible patients were active AS adult patients who had shown inadequate response or intolerance to two or more NSAIDs and who all fulfilled the modified New York criteria. Exclusion criteria included prior use of more than one TNFi and presence of total spinal ankylosis. About 10% of the enrolled patients had prior exposure to TNFis. The primary endpoint was the change in ASDAS from baseline to week 12. Significantly greater change in ASDAS was noted at week 12 in patients treated with filgotinib than with placebo, with a mean change from baseline of − 1.47 (SD 1.04) versus − 0.57 (0.82) ($p < 0.0001$) (Fig. 3F). More patients in the filgotinib arm showed higher response rates for ASAS20 (76% vs 40%, $p < 0.0001$) (Fig. 3) and ASDAS major improvement (33% versus 2%, $p < 0.0001$) at 12 weeks compared with placebo. Improvements in several other clinical outcome measures were also observed (Table 1). The

difference between the placebo and filgotinib in change in ASDAS from baseline was significant by week 1 (Fig. 3). For most improvements, a separation from placebo was noted at 4–8 weeks [25•].

Other JAKis

SHR0302 is a novel, potent, orally administered selective Janus kinase type 1 inhibitor developed in China, and its development program includes a phase II/III study to evaluate its efficacy and safety in active AS patients (NCT04481139). The study was started in October 2020 and is expected to be completed in February 2023. Clinical development programs of any other JAKis do not include AS indication.

Safety

The safety data from AS trials of JAKis include small number of patients with a short follow-up. They showed no new safety signal and were consistent with the previously reported safety profiles in RA and other chronic inflammatory diseases. Considering that patients with AS are more likely to be young and male and are less likely to be using glucocorticoids or methotrexate concomitantly, they may theoretically have a lower risk for some of the adverse effects observed with JAKis in RA patients. On the other hand, because patients with AS often use NSAIDs, they may theoretically be more prone to some other adverse effects, such as gastrointestinal perforation, which is a rare but serious adverse event (AE) of JAKis. The bulk of the available data on the safety of JAKis are derived from the first generation JAKis generated from RA studies, predominantly from tofacitinib, with safety data reported up to 9.5 years [31]. Data with the newer JAKis are much more limited, with safety data available with upadacitinib up to 3 years [32].

There is a large overlap between the safety profiles of different JAKis, despite differences in their JAK selectivity profile [33, 34, 35•, 36]. Changes in laboratory parameters have been observed with all JAKis with some minor differences (Table 2 lists the data in VISUALFORM©, copyrighted by us) [36]. Hematological adverse effects include neutropenia, which is observed with all JAKis [33]. Platelets decrease with tofacitinib and filgotinib treatment within normal ranges. An initial transient increase in platelet counts observed with baricitinib disappears during treatment [37] and minimally changes with upadacitinib treatment [38]. Hemoglobin may initially decrease and then slowly improve with baricitinib, tofacitinib, and filgotinib, while upadacitinib treatment has little impact on hemoglobin [34, 37, 38]. Elevations in liver transaminase, creatine kinase, total cholesterol, and serum creatinine levels are commonly observed with JAKis [33, 36].

Potential serious AEs of JAKis include herpes zoster, serious infections including tuberculosis (TB), major adverse cardiovascular events (MACE), venous thromboembolic events (VTEs), and malignancies (Table 3) [31, 36, 38, 39]. Caution is warranted when comparing the incidence rates of AEs with different JAKis due to the wide variation in patient-years of exposure to each drug. Full appreciation of safety profile of a therapeutic agent requires data from long-term extension studies as well as data from real-world studies. They are as of now available only for tofacitinib and discussed in detail in a recent narrative review [40].

The adverse effects of JAKis have been the target of many recent meta-analyses. A recent meta-analysis on the safety of JAKis, which included trials of RA, IBD, psoriasis, or AS, found no increased risk for serious infection as compared to placebo [41•]. Another metanalysis involving only RA trials demonstrated that serious infection rate was not increased with tofacitinib, 5 mg, twice daily; baricitinib, 2 mg, daily; or upadacitinib, 30 mg, daily but significantly increased with tofacitinib, 10 mg, twice daily; baricitinib, 4 mg, daily; and upadacitinib,15 mg, daily [42]. However, real-world data from RA patients registered in three US databases indicated that the risk of serious infection with tofacitinib treatment was significantly higher than with etanercept; lower than with infliximab; numerically higher than with abatacept, golimumab, and tocilizumab; and similar to adalimumab and certolizumab [43•].

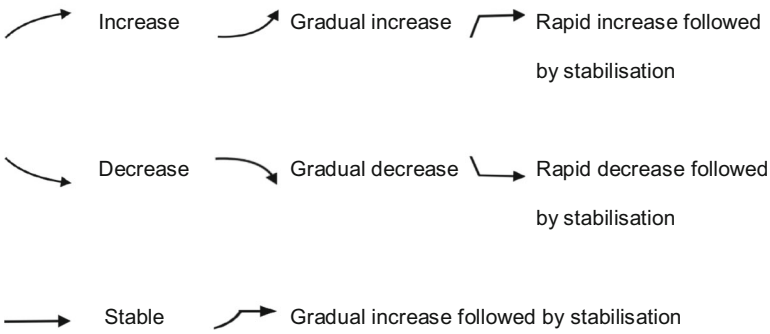
Tofacitinib was associated with a 2-fold higher risk of herpes zoster compared with biologic DMARDs in this and also in an earlier real-world study [43, 44]. Other JAKis also seem to increase the risk of herpes zoster infection relative to the current biologic agents and conventional synthetic DMARDs [32, 35]. Risk factors for zoster infections include older age, female sex, East Asian ethnicity, concomitant use of corticosteroids, diabetes, history of infections, and hospitalizations [35, 44]. Available data suggest that JAK2 and JAK3 inhibition may be associated with a higher risk of zoster infection than JAK1 inhibition. Blocking JAK2 may be associated with the highest risk [35, 45].

Opportunistic infections, particularly TB, are of special concern for patients treated with JAKis. This topic was the focus of a recent systematic review which examined 40 publications [46•]. The authors identified 79 (0.28%) active TB cases among 28,099 tofacitinib-treated patients, 10 (0.23%) among 4310 baricitinib-treated patients, but none among the 3437 and 1326 patients treated with upadacitinib and filgotinib, respectively. All these TB cases except one were from intermediate- or high-TB risk countries. Most TB cases involving tofacitinib had used the 10 mg twice daily dose. Notably, a significant proportion of TB cases had negative quantiferon test at baseline. TB occurred after a median time of 9 months after the initiation of tofacitinib. Absence of any active TB infection in patients receiving upadacitinib and filgotinib may be due to the lower number of enrolled patients, the shorter follow-up period, and limited long-term extension data. Therefore, more long-term observational data with larger number of patients treated

Table 2 Effects of JAK inhibitors tested in AS on laboratory parameters, expressed in a VISUALFORM© (based on data from reference [36])

Laboratory parameters	Tofacitinib	Upadacitinib	Filgotinib
Haemoglobin			
Lymphocyte count			
Platelet count			
Liver transaminases			
Creatinine kinase			
HDL cholesterol			
LDL cholesterol			
Creatinine			

HDL=high-density lipoprotein, LDL=Low-density lipoprotein



with JAK1 inhibitors are needed before concluding that TB risk is dependent on JAK selectivity.

The concern regarding the thromboembolic AEs of JAKis was first raised during the approval process of baricitinib in RA [47, 48]. Regulatory authorities in the USA and Europe highlighted this risk in the Summary of Product Characteristics of JAKis. FDA issued a "black box" warning for the increased risk of thrombosis, including deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis for baricitinib in 2017 and for Tofacitinib 10 mg twice daily (authorized for UC) in 2019 [49]. The latter was based on interim results of the post-marketing "ORAL surveillance" safety study (NCT02092467) comparing the safety of tofacitinib with TNFis in patients with RA aged ≥ 50 years and with ≥ 1 cardiovascular risk factor, which revealed an increased incidence of PE events and all-cause mortality in the 10 mg twice daily dosing of tofacitinib compared with TNFi [50]. The results of a systematic review of the FDA's Adverse Event Reporting revealed increased reporting rates for both tofacitinib and ruxolitinib for pulmonary thrombosis, suggesting the possibility of a class-wide issue [51]. The FDA approval of upadacitinib for RA also came with a boxed safety warning for thromboembolic events [27]. On the other hand, three meta-analyses of randomized controlled trials of JAKis did not reveal significant change in the risks of VTE, PE, and DVT in patients receiving JAKis, compared with placebo [41, 52, 53]. The risk with tofacitinib tended to be lower in the two studies which provided data for individual JAKis [41, 52]. The same studies found no difference between the placebo and JAKis in the incidence of MACE. In one of these studies,

Table 3 Safety profiles of JAK inhibitors in doses proposed for the treatment of ankylosing spondylitis*

Adverse events of special interest	Tofacitinib [31]	Upadacitinib [38]		Filgotinib [39]	
	5 mg BID *N* = 3066 PYE = 8171.3 EAIR (95% CI)	15 mg QD *n* = 2630 PYE = 2655.1 EAIR (95% CI)	Placebo *n* = 1042 PYE = 256.8 EAIR (95% CI)	200 mg QD *n* = 2267 PYE = 4047.7 EAIR (95% CI)	Placebo *N* = 781 PYE = 302.4 EAIR (95% CI)
Serious infection	2.8 (2.5–3.2)	3.8 (3.1–4.7)	3.1 (1.3–6.1)	1.7 (1.3–2.3)	2.3 (0.9–4.8)
Herpes zoster	3.6 (3.4–3.9)	3.7 (3.0–4.5)	1.2 (0.2–3.4)	1.8 (1.4–2.3)	1.0 (0.2–2.9)
Opportunistic infection	0.3 (0.2–0.5)	0.6 (0.4–1)	1.2 (0.2–3.4)	0.3	0
Tuberculosis	0.1 (0.1–0.2)	< 0.1	0	0	0
Malignancies excluding NMSC	0.8 (0.7–0.9)	0.9 (0.5–1.3)	0.4 (0.0–2.2)	0.5 (0.3–0.8)	1.0 (0.2–2.9)
Lymphoma	0.01 (0.00–0.07)	< 0.1	0	ND	ND
GI perforation	0.1 (0.0–0.2)	< 0.1	0	ND	ND
MACE	0.4 (0.3–0.6)	0.6 (0.4–1.0)	1.2 (0.2–3.4)	0.5 (0.3–0.7)	1.0 (0.2–2.9)
VTE	0.2 (0.1–0.4)	0.6 (0.3–1.0)	0.4 (0.0–2.2)	0.2 (0.1–0.4)	0.7 (0.1–2.4)
DVT	0.2 (0.1–0.3)	ND	ND	0.1 (0.1–0.3)	0.7 (0.1–2.4)
PE	0.1 (0.0–0.2)	ND	ND	0.1 (0.1–0.3)	0.0 (0.0–1.2)

*Data presented here are from integrated safety analyses of pooled data from rheumatoid arthritis trials. The safety data from ankylosing spondylitis trials of JAK inhibitors include small number of patients with a short follow-up

BID twice daily, *DVT* deep vein thrombosis, *EAIR* Exposure-adjusted incidence rates, *GI* gastrointestinal, *ND* not described, *MACE* Major adverse cardiovascular event, *NMSC* non-melanoma skin cancer, *PE* pulmonary embolism, *PYE* patient-years of exposure, *QD* once daily, *VTE* venous thromboembolism

dose-dependent impact was observed with only baricitinib, with 2 mg being safer than 4 mg.

The patient population of randomized controlled trials who are selected by strict inclusion/exclusion criteria may lead to lower rates of AEs than in the real world. Incidence rates of DVT, PE, and arterial thromboembolism estimated by analysis of the data from tofacitinib development programs were roughly consistent with the estimates based on the observational data from the US Corrona registries and MarketScan databases [54•]. In conclusion, the available evidence from a range of sources suggests that JAKis are associated with an increased risk of thrombosis, but the risk is low and mostly confined to patients with additional risk factors. More data dealing with the new JAKis are needed to better appreciate whether it is a class effect. Until then, it is reasonable to avoid or use cautiously any JAKi in patients with risk factors for VTE, such as older age, obesity, a medical history of DVT/PE, or surgery and immobilization, in line with the recommendations of regulatory authorities [48, 55, 56]. RA, glucocorticoid use, and NSAIDs should also be kept in mind as potential risk factors for thromboembolic events [47].

Malignancy is one of the major concerns for patients undergoing treatment with JAKis. A recently published meta-analysis which reviewed safety data from both interventional and observational studies of tofacitinib, filgotinib, upadacitinib, and baricitinib conducted in patients with IBD, psoriasis, or AS found no increase in the incidence of malignancy in patients receiving JAKis in the controlled periods [41•]. However, it should be underlined that participants of randomized controlled trials are selected by tight inclusion and exclusion criteria. Moreover, the time frame of the randomized controlled trials may underestimate the AE that require time to develop, like malignancy [41•]. Long-term safety data of tofacitinib for up to 9.5 years collected from RA patients showed a comparable incidence rate of malignancy to those seen with TNFis and other biologic DMARDs [57].

However, just recently, the above-mentioned post-marketing "ORAL surveillance" safety study has been completed, and the results announced by the manufacturer company indicated that tofacitinib missed the trial's co-primary endpoints, which were to show non-inferiority to TNFi in risks for MACE and cancer [58]. FDA has issued an alert upon the preliminary results of this study which showed a higher frequency of MACE (9.8 vs 7.3 per 1000 person-years of drug exposure; HR 1.33, 95% CI 0.91–1.94) and malignancy (11.3 vs 7.7 per 1000 person-years of drug exposure; HR 1.48, 95% CI 1.04–2.09) with tofacitinib at both 5 and 10 mg twice daily dosing, compared to patients treated with a TNFi [58, 59].

JAKis in the Guidelines

Tofacitinib is addressed in the 2019 American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of AS and nr-axSpA [60].

According to these recommendations, tofacitinib should be considered as a last-line therapy after TNFis and IL-17 inhibitors for the treatment of adult patients with active AS despite treatment with NSAIDs. However, tofacitinib should be considered as the choice of therapy in patients with coexisting UC, if anti-TNF therapy is not an option, since tofacitinib is an approved treatment for UC, whereas interleukin-17 inhibitors have not been shown to be efficacious in IBD. The panel based their treatment recommendations on the phase II study of tofacitinib, which showed benefit in clinical and MRI outcomes after treatment for 12 weeks [22]. JAKis might be expected to be addressed more extensively in the next update of these recommendations, due to both the positive results of the recently reported phase III studies of JAKis [23, 24] and the recently safety concerns raised after the announcement of the results of the above-mentioned post-marketing "ORAL surveillance" safety study [58, 59].

European League Against Rheumatism (EULAR) has recently published points to consider for the treatment of immune-mediated inflammatory diseases with JAKis [55••]. These recommendations state that patients should be carefully evaluated before starting treatment with a JAKi and questioned about history of malignancy, diverticulitis, and thromboembolic events. Concomitant medication use, including classical NSAIDs, COX-2 inhibitors, glucocorticoids, and oral contraceptives, are also relevant when screening risk factors for thrombosis. Age, comorbidities such as diabetes mellitus and chronic respiratory diseases, the use of glucocorticoids, and recent serious infection all pose a risk for serious adverse effects.

To avoid serious infection, EMA advises not to use tofacitinib in people older than 65, if an alternative treatment option is available [55••]. EMA also recommends not to use baricitinib at a greater dose than 2 mg daily in patients over 70 years old due to reduced renal function in the elderly. EULAR consensus statement includes laboratory screening prior to treatment with JAKis, and that should include complete blood counts and tests for liver and kidney function and serological tests for HBV and HCV infection. Chest X-rays and interferon-γ-releasing assays should be ordered to detect patients with latent TB infection. Local guidelines should be followed for administering treatment to prevent reactivation of TB infections or hepatitis. Minimal laboratory monitoring during the treatment course should include full and differential blood counts and liver transaminases and renal function tests at months 1 and 3 and on periodically, thereafter, such as every 3 months and lipid levels only at month 3 [55••]. EULAR recommends also annual skin examination (for detection of skin cancer). It should be kept in mind that in patients under treatment with JAKis, CRP and ESR may not increase despite the presence of an infection [55••].

Treatment should not be initiated with tofacitinib or upadacitinib if absolute neutrophil count is less than 1000 cells/mm^3, absolute lymphocyte count is less than 500 cells/mm^3, or hemoglobin (Hb) level is below 9 g/dL for tofacitinib and below 8 g/dL for upadacitinib. Treatment should be interrupted if Hb level falls below 8 g/dL, absolute neutrophil count drops to less 1000 cells/mm^3, or absolute lymphocyte count decreases to less than 500 cells/mm^3 [27, 61]. Treatment may be reinitiated once the values return above the corresponding cut-off levels. Tofacitinib or upadacitinib should not be used in patients with severe hepatic impairment (Child Pugh C). No dose adjustment is needed for mild hepatic impairment (Child Pugh A) [27, 61]. In case of moderate hepatic impairment (Child Pugh B), dose modification is recommended for tofacitinib, but not for upadacitinib [27, 61]. Dosage adjustment of Tofacitinib is recommended in the presence of moderate or severe renal dysfunction but is not needed for upadacitinib [27, 61].

Generics

A generic version of tofacitinib extended-release tablets, 11 mg, used to treat UC in the USA received a tentative market approval from the FDA in October 2020. Apparently, even if tofacitinib gains its expected approval from the FDA for the treatment of AS in 2021, it will have only four years before its constraining patent expires in 2025 in the USA.

Concluding Remarks

A considerable number of patients with AS do not respond to or tolerate the currently available biologics. Therefore, the positive results obtained in the recent phase III trials of tofacitinib and upadacitinib have given hope that these novel agents would provide the unmet need for treatment of such patients. Their efficacy appears to be comparable to each other as well as to TNF or IL-17 inhibitors. JAKis have not, as yet, been studied in nr-axSpA. With regard to their safety profile, the more frequent occurrence of cardiovascular and cancer adverse events associated with tofacitinib than with TNFi observed in the very recent post-marketing "ORAL surveillance" safety study that prompted the February 2021 FDA Drug Safety Communication about tofacitinib may lead to safety concerns swirling around the whole class of JAKi [58, 59]. For now, FDA held back taking any action against tofacitinib and did not go beyond suggesting that healthcare professionals should "consider the benefits and risks of tofacitinib when deciding whether to prescribe or to continue patients on the medicine," and the patients should not stop taking tofacitinib without first consulting with their physicians. It should be pointed out that the FDA-mandated

"ORAL surveillance" safety study included RA patients aged 50 and over with at least one cardiovascular risk, and it remains to be seen whether the safety profile will be similar in AS patient population who are more likely to be younger and more often males. Although their short half-lives and oral mode of administration carry advantage, the future of tofacitinib and probably other JAKis for the treatment of AS depends on the final conclusions and recommendations of the FDA after completion of their review of all the study data. There are limited or indirect data on the efficacy JAKis in treating the peripheral joint and entheseal manifestations (arthritis, enthesitis, dactylitis) and extra-articular manifestations (uveitis, psoriasis, inflammatory bowel disease) of AS. It needs to be explored in future studies whether JAKis have any effect on the progression of structural damage.

Tofacitinib is approved for the treatment of PsA, both in the USA and European Union, whereas upadacitinib is approved for this indication only in Europe [28]. Both agents significantly improved psoriatic skin lesion, enthesitis, and dactylitis relative to placebo [62–64]. Tofacitinib in phase III trials has been shown to be effective in the treatment of chronic plaque psoriasis [65]. However, it is not licensed for this indication as yet because its manufacturer (Pfizer) has withdrawn its application to expand the indication of tofacitinib to treat psoriasis in 2015 after the FDA asked for additional safety analyses. Tofacitinib has been approved for the treatment of patients with UC [61] but failed to meet the primary endpoint in a phase IIb trial of Crohn's disease [66, 67]. In phase II Crohn's disease trials, filgotinib reached its primary endpoints, but upadacitinib did not [67, 68]. However, upadacitinib met some secondary endpoints. Based on these results, phase III trials have been initiated for each [67]. Few case reports and one case series involving 5 patients of uveitis associated with JIA reported favorable clinical response with tofacitinib and baricitinib [69].

In conclusion the available evidence suggests that JAKis will have a place in the treatment of AS in the very near future. However, head-to-head trials versus biologics or among the JAKis are needed to determine where to position this category of drugs in the treatment pathway of patients with AS.

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Declarations

Conflict of Interest Nurullah Akkoc: Consulting and/or speaking fees from UCB and speaking fees from Amgen. Muhammad A Khan: Receipt of consultation fees from AbbVie, Novartis, and Lilly and from speaker's bureaus of AbbVie and Novartis.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Wilson HM, Barker RN. Cytokines. eLS. 2013. https://doi.org/10.1002/9780470015902.a0000929.pub3.
2. Zhang H, Shi N, Diao Z, Chen Y, Zhang Y. Therapeutic potential of TNFα inhibitors in chronic inflammatory disorders: past and future. Genes & Diseases. 2020. https://doi.org/10.1016/j.gendis.2020.02.004.
3. Goldbach-Mansky R. Blocking interleukin-1 in rheumatic diseases. Ann N Y Acad Sci. 2009;1182:111–23. https://doi.org/10.1111/j.1749-6632.2009.05159.x.
4. Choy EH, De Benedetti F, Takeuchi T, Hashizume M, John MR, Kishimoto T. Translating IL-6 biology into effective treatments. Nat Rev Rheumatol. 2020;16(6):335–45. https://doi.org/10.1038/s41584-020-0419-z.
5. Ruiz de Morales JMG, Puig L, Dauden E, et al. Critical role of interleukin (IL)-17 in inflammatory and immune disorders: an updated review of the evidence focusing in controversies. Autoimmun Rev. 2020;19(1):102429. https://doi.org/10.1016/j.autrev.2019.102429.
6. Lyakh L, Trinchieri G, Provezza L, Carra G, Gerosa F. Regulation of interleukin-12/interleukin-23 production and the T-helper 17 response in humans. Immunol Rev. 2008;226:112–31. https://doi.org/10.1111/j.1600-065X.2008.00700.x.
7. Deodhar A, Gensler LS, Sieper J, et al. Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. Arthritis Rheumatol. 2019;71(2):258–70. https://doi.org/10.1002/art.40728.
8. Baeten D, Ostergaard M, Wei JC, et al. Risankizumab, an IL-23 inhibitor, for ankylosing spondylitis: results of a randomised, double-blind, placebo-controlled, proof-of-concept, dose-finding phase 2 study. Ann Rheum Dis. 2018;77(9):1295–302. https://doi.org/10.1136/annrheumdis-2018-213328.
9. Haibel H, Rudwaleit M, Listing J, Sieper J. Open label trial of anakinra in active ankylosing spondylitis over 24 weeks. Ann Rheum Dis. 2005;64(2):296–8. https://doi.org/10.1136/ard.2004.023176.
10. Sieper J, Braun J, Kay J, et al. Sarilumab for the treatment of ankylosing spondylitis: results of a Phase II, randomised, double-blind, placebo-controlled study (ALIGN). Ann Rheum Dis. 2015;74(6):1051–7. https://doi.org/10.1136/annrheumdis-2013-204963.
11. Sieper J, Porter-Brown B, Thompson L, Harari O, Dougados M. Assessment of short-term symptomatic efficacy of tocilizumab in ankylosing spondylitis: results of randomised, placebo-controlled trials. Ann Rheum Dis. 2014;73(1):95–100. https://doi.org/10.1136/annrheumdis-2013-203559.
12. Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. Drugs. 2017;77(5):521–46. https://doi.org/10.1007/s40265-017-0701-9.
13. Clark JD, Flanagan ME, Telliez JB. Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases. J Med Chem. 2014;57(12):5023–38. https://doi.org/10.1021/jm401490p.
14. Morris R, Kershaw NJ, Babon JJ. The molecular details of cytokine signaling via the JAK/STAT pathway. Protein Sci. 2018;27(12):1984–2009. https://doi.org/10.1002/pro.3519.
15. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. Nat Rev Drug Discov. 2017;16(12):843–62. https://doi.org/10.1038/nrd.2017.201.

16. Ghoreschi K, Laurence A, O'Shea JJ. Janus kinases in immune cell signaling. Immunol Rev. 2009;228(1):273–87. https://doi.org/10.1111/j.1600-065X.2008.00754.x.
17. Baker KF, Isaacs JD. Novel therapies for immune-mediated inflammatory diseases: what can we learn from their use in rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, psoriasis, Crohn's disease and ulcerative colitis? Ann Rheum Dis. 2018;77(2):175–87. https://doi.org/10.1136/annrheumdis-2017-211555.
18. Villarino AV, Kanno Y, O'Shea JJ. Mechanisms and consequences of Jak-STAT signaling in the immune system. Nat Immunol. 2017;18(4):374–84. https://doi.org/10.1038/ni.3691.
19. Reddy V, Cohen S. JAK inhibitors: what is new? Curr Rheumatol Rep. 2020;22(9):50. https://doi.org/10.1007/s11926-020-00931-6.
20. Deodhar A, Yu D. Switching tumor necrosis factor inhibitors in the treatment of axial spondyloarthritis. Semin Arthritis Rheum. 2017;47(3):343–50. https://doi.org/10.1016/j.semarthrit.2017.04.005.
21. Sieper J, Deodhar A, Marzo-Ortega H, et al. Secukinumab efficacy in anti-TNF-naive and anti-TNF-experienced subjects with active ankylosing spondylitis: results from the MEASURE 2 Study. Ann Rheum Dis. 2017;76(3):571–92. https://doi.org/10.1136/annrheumdis-2016-210023.
22. van der Heijde D, Deodhar A, Wei JC, et al. Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomised, placebo-controlled, dose-ranging study. Ann Rheum Dis. 2017;76(8):1340–7. https://doi.org/10.1136/annrheumdis-2016-210322.
23. Deodhar A, Sliwinska-Stanczyk P, Xu H, et al. Tofacitinib for the treatment of adult patients with ankylosing spondylitis: primary analysis of a phase 3, randomized, double-blind, placebo-controlled study [abstract]. Arthritis Rheumatol. 2020;72(suppl 10).
24.•• van der Heijde D, Song IH, Pangan AL, et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. Lancet. 2019;394(10214):2108–17. https://doi.org/10.1016/S0140-6736(19)32534-6 **This multicentre, randomised, double-blind, placebo-controlled, two-period, parallel-group, phase 2/3 study shows that upadacitinib is effective in supressing the signs and symptoms of AS, and also the inflammation in the spine and sacroiliac joints on MRI.**
25.• van der Heijde D, Baraliakos X, Gensler LS, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebo-controlled, phase 2 trial. Lancet. 2018;392(10162):2378–87. https://doi.org/10.1016/S0140-6736(18)32463-2 **This article presents the results of the Phase II TORTUGA trial which investigated the efficacy and safety of filgotinib for the treatment of patients with active ankylosing spondylitis and suggests that filgotinib shows good efficacy across a wide range of parameters relevant for ankylosing spondylitis.**
26. van der Heijde D, Song IH, Pangan A, et al. Efficacy and safety of upadacitinib in a randomized, double-blind, placebo-controlled, multicenter phase 2/3 clinical study of patients with active ankylosing spondylitis. Arthritis & Rheumatology. 2019;71.
27. Abbvie Inc. RINVOQTM (upadacitinib): US prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211675s000lbl.pdf.
28. Abbvie Inc. RINVOQ (upadacitinib). EPAR-Product Information 2021. https://www.ema.europa.eu/en/documents/product-information/rinvoq-epar-product-information_en.pdf. Accessed April 10 2021.
29. Deodhar A, van der Heijde D, Sieper J, et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis: 1-year results from a randomized, double-blind, placebo-controlled study with open-label extension [abstract]. Arthritis Rheumatol. 2020;72(Suppl 10).
30. Gilead and Galapagos Announce New Commercialization and Development Agreement for Jyseleca® (Filgotinib). Press release. December 15, 2020. https://www.gilead.com/news-and-press/press-room/press-releases/2020/12/gilead-and-galapagos-announce-new-commercialization-and-development-agreement-for-jyseleca-filgotinib. Accessed 20 Dec 2020.
31. Cohen SB, Tanaka Y, Mariette X, et al. Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme. RMD Open. 2020;6(3). https://doi.org/10.1136/rmdopen-2020-001395.
32. Cohen SB, Van Vollenhoven R, Curtis JR, et al. Safety profile of upadacitinib up to 3 years of exposure in patients with rheumatoid arthritis [abstract]. Arthritis Rheumatol. 2020;72(Suppl 10).
33. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol. 2017;13(4):234–43. https://doi.org/10.1038/nrrheum.2017.23.
34. 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). https://doi.org/10.3390/biom10071002.
35.• Sunzini F, McInnes I, Siebert S. JAK inhibitors and infections risk: focus on herpes zoster. Ther Adv Musculoskelet Dis. 2020;12:1759720X20936059. https://doi.org/10.1177/1759720X20936059 **A concise review which presents the current evidence on the principal JAK inhibitors and their association with viral infections.**
36. Harigai M, Honda S. Selectivity of Janus kinase inhibitors in rheumatoid arthritis and other immune-mediated inflammatory diseases: is expectation the root of all headache? Drugs. 2020;80(12):1183–201. https://doi.org/10.1007/s40265-020-01349-1.
37. Kay J, Harigai M, Rancourt J, et al. Changes in selected haematological parameters associated with JAK1/JAK2 inhibition observed in patients with rheumatoid arthritis treated with baricitinib. RMD Open. 2020;6(3):e001370. https://doi.org/10.1136/rmdopen-2020-001370.
38. Cohen SB, van Vollenhoven RF, Winthrop KL, et al. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. Ann Rheum Dis. 2020:annrheumdis-2020-218510. https://doi.org/10.1136/annrheumdis-2020-218510.
39. Europen Medicines Agency-Committee for Medicinal Products for Human Use (CHMP). Assessment report. Jyseleca (Filgotinib). 2020. https://www.ema.europa.eu/en/documents/assessment-report/jyseleca-epar-public-assessment-report_en.pdf. Accessed 24 Jan 2020.
40. Alvaro-Gracia JM, Garcia-Llorente JF, Valderrama M, Gomez S, Montoro M. Update on the safety profile of tofacitinib in rheumatoid arthritis from clinical trials to real-world studies: a narrative review. Rheumatol Ther. 2020. https://doi.org/10.1007/s40744-020-00258-9.
41.• Olivera PA, Lasa JS, Bonovas S, Danese S, Peyrin-Biroulet L. Safety of Janus kinase inhibitors in patients with inflammatory bowel diseases or other immune-mediated diseases: a systematic review and meta-analysis. Gastroenterology. 2020;158(6):1554–73 e12. https://doi.org/10.1053/j.gastro.2020.01.001 **A meta-analysis assesing the safety profile of JAK inhibitors in patients with with immune-mediated diseases including ankylosing spondylitis.**
42. Wang F, Sun L, Wang S, et al. Efficacy and safety of tofacitinib, baricitinib, and upadacitinib for rheumatoid arthritis: a systematic review and meta-analysis. Mayo Clin Proc. 2020;95(7):1404–19. https://doi.org/10.1016/j.mayocp.2020.01.039.

43.• Pawar A, Desai RJ, Gautam N, Kim SC. Risk of admission to hospital for serious infection after initiating tofacitinib versus biologic DMARDs in patients with rheumatoid arthritis: a multidatabase cohort study. The Lancet Rheumatology. 2020;2(2):e84–98. https://doi.org/10.1016/s2665-9913(19)30137-7 **This is a multidatabase cohort study which compares the risk of admission to hospital for serious infection and individual seirous infection types including herpes zoster in patients with rheumatoid arthritis initiating tofacitinib versus one of the seven bDMARDs.**

44. Curtis JR, Xie F, Yun H, Bernatsky S, Winthrop KL. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis. 2016;75(10):1843–7. https://doi.org/10.1136/annrheumdis-2016-209131.

45. Bechman K, Subesinghe S, Norton S, et al. A systematic review and meta-analysis of infection risk with small molecule JAK inhibitors in rheumatoid arthritis. Rheumatology (Oxford). 2019;58(10):1755–66. https://doi.org/10.1093/rheumatology/kez087.

46.• Cantini F, Blandizzi C, Niccoli L, Petrone L, Goletti D. Systematic review on tuberculosis risk in patients with rheumatoid arthritis receiving inhibitors of Janus Kinases. Expert Opin Drug Saf. 2020;19(7):861–72. https://doi.org/10.1080/14740338.2020.1774550 **A systematic review on the risk of active tuberculosis occurrence in patients receiving JAK inhibitors.**

47. Scott IC, Hider SL, Scott DL. Thromboembolism with Janus kinase (JAK) inhibitors for rheumatoid arthritis: how real is the risk? Drug Saf. 2018;41(7):645–53. https://doi.org/10.1007/s40264-018-0651-5.

48. Ibrahim F, Scott DL. Thromboembolism and Janus kinase inhibitors. Drug Saf. 2020;43(9):831–3. https://doi.org/10.1007/s40264-020-00973-w.

49. FDA Drug Safety Communication. FDA approves Boxed Warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (Xeljanz, Xeljanz XR). US Food and Drug Administration. www.fda.gov/drugs/drug-safety-and-availability/fda-approves-boxed-warning-about-increased-risk-blood-clots-and-death-higher-dose-arthritis-and. Accessed 29 Dec 2020.

50. Pfizer Inc. XELJANZ (Tofacitinib). EPAR-Product Information. European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf. Accessed 29 Dec 2020.

51. Verden A, Dimbil M, Kyle R, Overstreet B, Hoffman KB. Analysis of spontaneous postmarket case reports submitted to the FDA regarding thromboembolic adverse events and JAK inhibitors. Drug Saf. 2018;41(4):357–61. https://doi.org/10.1007/s40264-017-0622-2.

52. Xie W, Huang Y, Xiao S, Sun X, Fan Y, Zhang Z. Impact of Janus kinase inhibitors on risk of cardiovascular events in patients with rheumatoid arthritis: systematic review and meta-analysis of randomised controlled trials. Ann Rheum Dis. 2019;78(8):1048–54. https://doi.org/10.1136/annrheumdis-2018-214846.

53.•• Yates M, Mootoo A, Adas M, et al. Venous thromboembolism risk with JAK inhibitors: a meta-analysis. Arthritis Rheumatol. 2020. https://doi.org/10.1002/art.41580.

54.• Mease P, Charles-Schoeman C, Cohen S, et al. Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data. Ann Rheum Dis. 2020;79(11):1400–13. https://doi.org/10.1136/annrheumdis-2019-216761 **A detailed analysis assesing the risk of deep vein thrombosis, pulmonary embolism, venous thromboembolism and arterial thromboembolism from the tofacitinib RA, PsA and PsO development programmes and observational studies.**

55.•• Nash P, Kerschbaumer A, Dorner T, et al. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement. Ann Rheum Dis. 2021;80(1):71–87. https://doi.org/10.1136/annrheumdis-2020-218398 **A useful consensus document providing an assessment of evidence for efficacy and safety of an JAKis with guidance on issues of practical management.**

56. Vallejo-Yagüe E, Weiler S, Burden AM. Op0237 thromboembolic safety profile of tofacitinib and baricitinib: an analysis of who vigibase. Annals of the Rheumatic Diseases. 2020;79(Suppl 1):150.1. https://doi.org/10.1136/annrheumdis-2020-eular.2823.

57. Wollenhaupt J, Lee EB, Curtis JR, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. Arthritis Res Ther. 2019;21(1):89. https://doi.org/10.1186/s13075-019-1866-2.

58. Pfizer shares co-primary endpoint results from post-marketing required safety study of XELJANZ® (tofacitinib) in subjects with rheumatoid arthritis (RA). https://www.pfizer.com/news/press-release/press-release-detail/pfizer-shares-co-primary-endpoint-results-post-marketing. Accessed 2 Mar 2021.

59. Initial safety trial results find increased risk of serious heart-related problems and cancer with arthritis and ulcerative colitis medicine Xeljanz, Xeljanz XR (tofacitinib). https://www.fda.gov/drugs/drug-safety-and-availability/initial-safety-trial-results-find-increased-risk-serious-heart-related-problems-and-cancer-arthritis. Accessed 2 Mar 2021.

60. Ward MM, Deodhar A, Gensler LS, et al. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Rheumatol. 2019;71(10):1599–613. https://doi.org/10.1002/art.41042.

61. Pfizer Inc. XELJANZ® (tofacitinib) [package insert]. U.S. Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213082s000lbl.pdf. Accessed 29 Dec 2020.

62. Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. N Engl J Med. 2017;377(16):1537–50. https://doi.org/10.1056/NEJMoa1615975.

63. Gladman D, Rigby W, Azevedo VF, et al. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. N Engl J Med. 2017;377(16):1525–36. https://doi.org/10.1056/NEJMoa1615977.

64. Mease PJ, Lertratanakul A, Anderson JK, et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. Ann Rheum Dis. 2020:annrheumdis-2020-218870. https://doi.org/10.1136/annrheumdis-2020-218870.

65. Papp KA, Menter MA, Abe M, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomized, placebo-controlled, phase III trials. Br J Dermatol. 2015;173(4):949–61. https://doi.org/10.1111/bjd.14018.

66. Panes J, Sandborn WJ, Schreiber S, et al. Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. Gut. 2017;66(6):1049–59. https://doi.org/10.1136/gutjnl-2016-312735.

67. Rogler G. Efficacy of JAK inhibitors in Crohn's disease. J Crohns Colitis. 2020;14(Supplement_2):S746–S54. https://doi.org/10.1093/ecco-jcc/jjz186.

68. Vermeire S, Schreiber S, Petryka R, et al. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial. Lancet. 2017;389(10066):266–75. https://doi.org/10.1016/S0140-6736(16)32537-5.

69. Miserocchi E, Giuffre C, Cornalba M, Pontikaki I, Cimaz R. JAK inhibitors in refractory juvenile idiopathic arthritis-associated uveitis. Clin Rheumatol. 2020;39(3):847–51. https://doi.org/10.1007/s10067-019-04875-w.