Efficacy and safety of Janus kinase inhibitors in axial spondyloarthritis

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Abstract

Skin manifestations are common in axial spondyloarthritis (axSpA) and may precede axial involvement. Multidisciplinary management of patients with spondyloarthritis (SpA) is essential. Combined dermatology–rheumatology clinics are established for early recognition of the disease, comorbidities and a comprehensive treatment approach. Treatment options for axSpA are limited because conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and glucocorticoids are ineffective for axial symptoms. Janus kinase inhibitors (JAKi) are targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) that decrease transduction signalling to the nucleus, resulting in a reduced inflammatory response. Currently, tofacitinib and upadacitinib are approved for treating axSpA in patients with inadequate response to TNF inhibitors (TNFi). Upadacitinib has shown efficacy in non-radiographic axSpA (nr-axSpA), suggesting that JAKi are efficacious across the spectrum of axSpA. The availability of JAKi has opened more options for patients with active axSpA based on the efficacy data and the ease of administration.

Key words: JAK inhibitors, axial spondyloarthritis, multidisciplinary management

Key message

1. JAKi are approved for the treatment of axial spondyloarthritis.
2. Caution needs to be used when prescribing JAKi in patients with cardiovascular risk, smokers and age >65years.
3. All patients should be monitored while taking JAKi.

Introduction

The term spondyloarthritis (SpA) encompasses a group of diseases, including radiographic axial spondyloarthritis (r axSpA) or ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr axSpA), psoriatic arthritis (PsA), reactive arthritis (ReA), inflammatory bowel disease (IBD)-associated SpA and undifferentiated SpA.[1] The presence of axial, peripheral, extra-musculoskeletal manifestations (uveitis, psoriasis and inflammatory bowel disease) and comorbidities impact the choice of pharmacological treatment.[2] Treatment options for axSpA are limited because conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and glucocorticoids are ineffective for axial symptoms.[2,3]

Skin manifestations are common in SpA.[4] Psoriasis is frequent in axSpA and PsA.[5,6] Pyoderma gangrenosum (PG) and hidradenitis suppurativa (HS) are associated with IBD-related SpA.[4] Keratoderma blenorrhagicum or balanitis circinate are skin manifestations of ReA.[4] In many instances, skin manifestations precede axial involvement.[4] Thus, dermatologists play a pivotal role in identifying and treating skin and joint disease.

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Many inflammatory cytokines involved in the pathogenesis of skin disorders signal via the JAK-STAT pathway. Over the past few years, JAKi have shown benefit in many dermatologic disorders and gained FDA approval in some [Table 1]. JAKi have been investigated in many dermatologic diseases like alopecia areata, atopic dermatitis, dermatomyositis, psoriasis and vitiligo.[7] Tofacitinib, baricitinib and ruxolitinib have proven beneficial in patients with cutaneous sarcoidosis.[8] Case reports also show promising results with JAKi in synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome and a tofacitinib pilot study yielded significant remission of nail lesions and palmoplantar psoriasis in patients with SAPHO syndrome.[9,10] JAKi have also shown efficacy in dermatomyositis and juvenile dermatomyositis.[11] Studies indicate that JAKi effectively treat immunobullous diseases such as pemphigoid, pemphigus, dermatitis herpetiformis and epidermolysis bullosa acquisita.[12] A few case reports demonstrate successful therapy with tofacitinib and ruxolitinib in patients with PG.[13,14] A few studies also showed improvement in HS when JAKi were used.[15]

We reviewed published data about JAKi in axSpA, intending to provide an insight into axial involvement and JAKi in this disease entity, which is co-managed by dermatologists and rheumatologists.

Materials and Methods

Our literature search considered papers published in English about using JAKi in SpA, AS, IBD-associated SpA and reactive arthritis. We also searched for relevant papers from the reference list. Papers were identified by searching PubMed using keywords that included 'spondyloarthritis', 'ankylosing spondylitis', 'inflammatory bowel disease and spondyloarthritis', 'arthritis associated with inflammatory bowel disease', 'reactive arthritis', 'Janus Kinase inhibitors', 'JAK inhibitors', 'JAK inhibitors and safety', 'upadacitinib', 'tofacitinib', 'filgotinib' and 'baricitinib'.

Immunopathogenesis and JAK inhibitors

Loss of immune homeostasis resulting in abnormal cytokine production is the cornerstone of inflammation in rheumatoid arthritis (RA), SpA, IBD, psoriasis and other rheumatologic diseases.[16] Anti-cytokine biologics and single cytokine inhibition have fundamentally changed the treatment paradigm of immune-mediated inflammatory diseases (IMID).[16,17] Knowing that more than one cytokine contributes to inflammation in a specific IMID suggests that other mechanistic pathways or a broader approach to counter multiple target molecules by small molecules could be effective and less expensive.[18] Janus kinases (JAKs) are cytoplasmic protein kinases that have the critical function of signal transduction of type 1 and type 2 cytokines.[19]

There are four types of JAKs: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2).[3,16,17,20] Type I and II cytokine receptors selectively associate with particular JAKs.[19,21] Activation of the receptor-bound JAKs phosphorylate signal transducers and activators of transcription (STATs); activated STATs form hetero or homodimers and translocate to the cell nucleus, thereby inducing the transcription of target genes.[22] There are seven STATs (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6) and through

Table 1: JAKi in the treatment of dermatologic diseases

JAKi	FDA approved	Dosage	Potential treatment (no FDA approval yet)
Deucravacitinib	Moderate to severe psoriasis	6 mg once daily	Psoriatic arthritis
Tofacitinib	Psoriatic arthritis	5 mg twice daily or 11 mg once daily	Psoriasis Alopecia areata Refractory pemphigus vulgaris Mucous membrane pemphigoid Dermatitis herpetiformis Epidermolysis bullosa pruriginosa SAPHO syndrome Sarcoidosis Pyoderma gangrenosum Hidradenitis suppurativa
Upadacitinib	Psoriatic arthritis Moderate to severe atopic dermatitis	15 mg once daily 15–30 mg once daily	Hidradenitis suppurativa
Abrocitinib	Moderate to severe atopic dermatitis	100–200 mg once daily	
Topical Ruxolitinib	Mild to moderate atopic dermatitis Non-segmental vitiligo	Apply a thin layer to the affected area twice daily (should not exceed 20% body surface area)	Alopecia areata
Ruxolitinib		Total of 10-30 mg daily	Alopecia areata Sarcoidosis Pyoderma Gangrenosum
Baricitinib	Alopecia areata Moderate to severe atopic dermatitis	2–4 mg once daily	Epidermolysis bullosa pruriginosa Sarcoidosis
Topical delgocitinib	Chronic hand eczema	1, 3, 8, 20 mg g^{-1}	
Topical brepocitinib		1% once daily to twice daily	Atopic dermatitis

multiple combinations with JAKs, they play essential roles in numerous autoimmune pathogenetic processes.[20,22]

JAK1 is directly involved in the signalling of IL-6, IL-10, IL-21, IL-22 and interferon (IFN)α/β; JAK2 directly affects IL-6, IL-12, IL-22, IL-23 and IFNγ signalling; JAK3 directly affects IL-21 signalling; and TKY2 is directly involved in IL-6, IL-10, IL-12, IL-22, IL-23 and IFNα/β/γ signalling.[16] JAKi may indirectly affect tumour necrosis factor (TNF) α and IL-17A cytokines. All the cytokines mentioned above are involved in the pathogenesis of AxSpA.[16] Even though IL-6 and IL-23 play an important role in AS pathogenesis, biologics targeting IL-23 and IL-6 are not efficacious in AS.[17]

JAKi are targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) that decrease transduction signalling to the nucleus, resulting in a reduced inflammatory response.[21] There are several JAKi tested for inflammatory indications including tofacitinib, ruxolitinib, baricitinib, upadacitinib and decernotinib; a few of these have regulatory approvals.[23] The first-generation JAKi, tofacitinib, has shown clinical efficacy in treating multiple autoimmune conditions like RA, PsA and IBD. It is expected that the first-generation non-selective pan-JAKi are likely associated with adverse effects such as leukopenia, neutropenia, and anaemia.[16,23] In principle, next-generation more selective JAKi might treat selected inflammatory disorders at lower doses with fewer adverse effects.[24]

International guideline recommendations

Several guidelines recommend initiating non-steroidal anti-inflammatory drugs (NSAIDs) as first-line treatment for axSpA, titrating up to a maximally tolerated dose if no contraindications or intolerances exist.[2,25] If treatment with NSAIDs is insufficient, biological disease-modifying drugs (bDMARDs), specifically tumour necrosis factor inhibitors (TNFi) or IL 17-A inhibitors, are favoured.[2,25,26] JAKi are recommended in patients with an inadequate response to TNFi.[2,26] TNFi monoclonal antibodies are usually preferred if uveitis or IBD exist.[2,25] IL17-A inhibitors may be desired if there is co-existing and significant psoriasis.[2] If clinical response is insufficient, switching to another TNFi, IL17-A inhibitor, or JAKi is standard practice.[2,3]

Efficacy and safety of JAKi in Axial Spondyloarthritis

Seven major studies have evaluated the efficacy and safety of JAKi in axSpA [Tables 2 and 3].

Filigotnib in axSpA

Filigotnib is a selective JAK1 inhibitor and has been studied in axSpA in the Tortuga trial, a 12-week phase II study investigating the efficacy and safety of filgotinib 200 mg compared with placebo in patients with active AS with inadequate response to at least two NSAIDs.[27] Previous use of one TNFi was allowed.[27] Patients who received previous treatment with more than one TNFi or other bDMARDs were excluded.[27] The primary endpoint was a change in the Ankylosing Spondylitis Disease Activity Score (ΔASDAS) at week 12. Filgotinib 200 mg was superior to placebo and met the primary endpoint (–1.47 in filgotinib group compared to –0.57 in placebo, with a mean difference of –0.85 ; $p < 0.0001$ between groups).[27] Filgotinib 200 mg daily was superior to placebo in terms of ASDAS significant improvement (ASDAS-MI), ASDAS clinically important improvement (ASDAS-CII), Ankylosing Spondylitis Response Criteria (ASAS)20, ASAS40, ASAS5/6 improvement criteria, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI),

Table 2: Concomitant medications and prior bDMARD exposure

Study	Treatment	Concomitant NSAIDs	Concomitant oral glucocorticoids	Concomitant csDMARDs	Prior bDMARDs
Van der Heijde 2017 NCT01786668	Tofacitinib 2 mg, bd	88.5%	11.5%	44.2%	0%
	Tofacitinib 5 mg, bd	90.4%	3.8%	30.8%	0%
	Tofacitinib 10 mg, bd	90.4%	7.7%	30.8%	0%
	Placebo	94.1%	9.8%	27.5%	0%
Van der Heijde 2018 NCT03117270	Filgotinib 200 mg, qd	74%	12%	40%	7%
	Placebo	66%	17%	38%	12%
Van der Heijde 2019 NCT03178487	Upadacitinib 15 mg, qd	76%	6%	14%	0%
	Placebo	86%	13%	18%	0%
Deodhar 2020 NCT03502616	Tofacitinib 5 mg, bd	79.7%	9.8%	21.8%	23.3%
	Placebo	79.4%	5.1%	32.4%	22.8%
Van der Heijde 2022 NCT04169373	Upadacitinib 15 mg, qd	77	13	32	100%
	Placebo	78	9	30	99.5%
Deodhar 2022 NCT04169373	Upadacitinib 15 mg, qd	78%	12%	26%	31%
	Placebo	72%	11%	32%	34%

Table 3: Primary endpoint of AxSpA studies

Study	Primary endpoint	Treatment	N	Results	Adverse events
Van der Heijde 2017 NCT01786668	ASAS20 response rate at week 12	tofacitinib 2 mg, bd	52	51.9%	44.2%
		tofacitinib 5 mg, bd	52	80.8%	53.8%
		tofacitinib 10 mg, bd	52	55.8%	51.9%
		Placebo	51	41.2%	43.1%
Van der Heijde 2018 NCT03117270	△ in ASDAS from baseline to week 12	Filgotinib 200 mg, qd	58	–1.47	31%
		Placebo	58	–0.57	31%
Van der Heijde 2019 NCT03178487	ASAS40 response at week 14	Upadacitinib 15 mg, qd	93	52%	62%
		Placebo	94	26%	55%
Deodhar 2020 NCT03502616	ASAS 20 response at week 16	tofacitinib 5 mg, bid	133	56.40%	54.9%
		placebo	136	29.40%	51.5%
Van der Heijde 2022 NCT04169373	ASAS40 response at week 14	upadacitinib 15 mg, qd	211	45%	41%
		placebo	209	18%	37%
Van der Heijde 2022 Open-label extension	ASAS40 response at week 104	upadacitinib 15 mg, qd	89	NRI 66%, AO 86%	749 events/100 Patient Years
		placebo-to-upadacitinib 15 mg, qd	89	NRI 64%, AO 89%	
Deodhar 2022 NCT04169373	ASAS 40 at week 14	upadacitinib 15 mg	156	45%	48%
		placebo	157	23%	46%

Bath Ankylosing Spondylitis Metrology Index (BASMI), C-reactive protein (CRP), Spondyloarthritis Research Consortium of Canada (SPARCC) spine and sacroiliac (SI) joint scores.[27]

Consistent with the TORTUGA trial, filgotinib also demonstrated positive results in reducing spinal inflammation in the facet joints and posterolateral elements of the vertebral body and improved structural lesions in the SI joints.[28,29]

Tofacitinib in axSpA

Tofacitinib is a non-selective JAKi and has shown efficacy in active AS in two RCTs.[30,31] A tofacitinib phase II 12-week treatment and 4-week washout study evaluated the effectiveness, safety and dose–response (2 mg, 5 mg, 10 mg twice daily) of tofacitinib versus placebo in bDMARD-naïve patients with active AS with inadequate response to at least two NSAIDs.[31] The study's primary endpoint was the ASAS20 response at week 12. Tofacitinib 5 mg twice daily was the only dosage superior to placebo that met the primary endpoint (80.8% in tofacitinib 5 mg twice daily vs. 41.2% in placebo; $p < 0.001$).[31] The difference in the 2 mg and 10 mg twice daily groups versus placebo did not reach statistical significance.[31]

Tofacitinib 5 mg and 10 mg twice daily generally demonstrated significant improvement with ASDAS, ASAS40, ASAS5/6, BASFI and SPARCC SI joint scores compared to placebo.[31] The three tofacitinib groups significantly improved ASAS40, BASDAI50, ASDAS, ASDAS-CII and SPARCC spine scores compared to placebo.[31]

A tofacitinib phase III 16-week placebo-controlled study investigated the efficacy and safety of tofacitinib 5 mg twice daily versus placebo in patients with active AS with inadequate response to at least two NSAIDs. After week 16, all patients received open-label tofacitinib until week 48.[30] Approximately 80% were bDMARD naïve, and 20% were exposed to bDMARDs. About 20% of the patients had a prior inadequate response to one or two TNFi.[30] The study's primary endpoint was the ASAS20 response at week 12. The ASAS20 response was significantly greater with tofacitinib 5 mg twice daily versus placebo at week 16 and met the primary endpoint (56.4% in tofacitinib group vs. 29.4% in placebo, $p < 0.0001$).[30] ASAS20 response was more significant in bDMARD naïve patients than in those exposed to bDMARDs.[30] Significant improvement was seen in ASAS40, ASAS5/6, ASAS partial remission (ASAS-PR), ASDAS, ASDAS-CII, ASDAS-MI, ASDAS low disease activity (ASDAS-LDA), ASDAS inactive disease (ASDAS-IA), BASDAI50, CRP, Ankylosing Spondylitis Quality of Life (ASQoL), Short-Form Health Survey Version-2.0 Physical Component Score (SF-36v2 PCS), BASMI and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) in the tofacitinib group compared to placebo.[30] There was no difference in ΔMaastricht Ankylosing Spondylitis Enthesitis Score (MASES) between the groups.[30] ASAS20/ASAS40 response rates were maintained till week 48 in both groups.[30]

Upadacitinib in AxSpA

Upadacitinib is a selective JAK1 inhibitor. SELECT-AXIS 1 trial was a 14-week Phase II/III trial investigating the efficacy and safety of 15 mg of upadacitinib compared to a placebo in bDMARD-naïve patients with active AS with an inadequate response to at least two NSAIDs.[32] Patients with unstable extra-musculoskeletal manifestations 30 days before study entry were excluded.[32] The primary endpoint of the study was the ASAS40 response. Upadacitinib 15 mg/day met the primary endpoint and had a significant ASAS 40 response compared to placebo (52% in upadacitinib group vs. 26% in placebo group, treatment difference: 26%; $p = 0{\cdot}0003$).[32] More patients improved in ASDAS, ASAS20, ASAS-PR,

BASFI, BASDAI50 and SPARCC MRI spine and SI joint scores at week 14 in the upadacitinib group compared to placebo.[32]

An open-label extension of the SELECT-AXIS 1 trial evaluated the 2-year efficacy and safety of open-label upadacitinib 15 mg in 178 patients with active AS who completed the 14-week SELECT-AXIS 1 study.[33] The primary endpoint of the study was ASAS40. Upadacitinib 15 mg met the primary endpoint and showed significant improvement in ASAS40 after week 14, started to plateau at around 40 weeks and maintained response through week 104. (Non-responder imputation (NRI) response was 66%, as observed (AO) response was 86% with continuous upadacitinib and NRI response of 64%, AO 89% with placebo-to-upadacitinib).[33] With upadacitinib 15 mg, improvement in ASDAS, ASDAS-LDA, ASDAS inactive disease (ASDAS-ID), ASDAS partial remission, BASFI, BASMI, MASES, ASQoL and SPARCC MRI spine and SI joint scores was observed.[33] Most patients had no radiographic progression at week 104 (89.7% in the upadacitinib group and 76.5% in the placebo-to-upadacitinib group).[33] Among the nine patients with the highest modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) progression over two years, four of them were current or former smokers, and the majority had high mSASSS scores at baseline, elevated CRP and were human leucocyte antigen (HLA-B27) positive.[33]

SELECT-AXIS 2 was a 14-week phase III trial investigating the efficacy and safety of upadacitinib 15 mg once daily compared to placebo in active AS patients with inadequate response to at least two NSAIDs and bDMARD.[34] Inadequate response to bDMARD therapy was defined as patients who discontinued bDMARD therapy (TNFi or IL-17 inhibitors) due to lack of efficacy after 12 weeks or more of treatment at an adequate dose.[34] Prior exposure to two bDMARDs (lack of effectiveness to one and intolerance to another) was allowed in up to 30% of patients, but lack of effectiveness to two bDMARDs was not permitted.[34] Seventy four per cent had prior exposure to one TNFi, 13% had previous exposure to one IL-17 inhibitor (IL-17i), 8% had exposure to two TNFi, 5% had exposure to one TNFi and one IL-17i, and 0.5% were exposed to two IL-17i.[34] The primary endpoint of the study was the ASAS40 response. Upadacitinib 15 mg met the primary endpoint and significantly improved ASAS40 at week 14 compared to placebo (45% vs. 18% respectively, $p < 0.0001$).[34] Greater ASAS40 responses were seen in the patients previously exposed to one or two bDMARDs.[34] Better responses were also seen with prior exposure to TNFi or IL-17i compared to placebo.[34] Significant improvement in ASAS20, ASAS-PR, ASDAS, ASDAS-ID, ASDAS-LDA, BASFI, BASMI, BASDAI50, MASES, CRP, SPARCC MRI spine and SI scores, AsQOL and ASAS Health Index (ASAS-HI) was observed in the upadacitinib group compared to placebo.[34]

SELECT-AXIS 2 non-radiographic axial spondyloarthritis study was a 14-week phase III study investigating the efficacy and safety of upadacitinib 15 mg in patients with active nr axSpA with inadequate response to NSAIDs.[35] Previous treatment with one bDMARD (discontinued due to lack of efficacy or intolerance) was permitted for at least 20% and no more than 35% of study participants.[35]

The primary endpoint of the study was the ASAS40 response at week 14. Upadacitinib 15 mg met the primary endpoint and significantly improved ASAS40 response at week 14 compared to placebo (45% vs. 23%, with a treatment difference of 22%; $p < 0.0001$).[35] Upadacitinib 15 mg improved ASAS20, ASAS-PR, ASDAS, BASDAI 50, BASFI and SPARCC MRI SI scores compared to placebo.[35]

Safety of JAKi [Table 4]

In the TORTUGA trial, an equal number of adverse events (AE) emerged in both groups. Infection occurred in 12% of study participants in both groups. Nasopharyngitis was the most reported AE: two patients in the filgotinib group and four in the placebo group. One patient with heterozygous factor V Leiden developed a calf deep vein thrombosis (DVT) and a case of pneumonia was also reported in the filgotinib group. No malignancies, opportunistic infections or deaths were reported in either group.[27]

In the tofacitinib phase II trial, twenty seven, twenty eight and twenty three patients developed AEs in the 10 mg, 5 mg and 2 mg twice daily groups, respectively, versus twenty two patients in the placebo group. The most frequently reported AEs were nasopharyngitis and upper respiratory tract infection (URTI). One patient developed hypertension in the 10 mg twice daily group. Two cases of herpes zoster were reported, one in the 2 mg group and one in the 10 mg group. One case of uveitis was reported as a severe AE, which was thought to be non-related to the study drug in the 5 mg twice daily group. No additional serious infections, malignancy, gastrointestinal perforation or tuberculosis (TB) cases were reported.[31]

In the tofacitinib phase III trial, the number of AEs in the tofacitinib group were 54.9% and 51.1% in the placebo group at week 16. In the 48-week open-label extension, 77.4% AEs were observed in the tofacitinib group and 68.4% in the placebo-to-tofacitinib group. The most common AEs were URTIs and nasopharyngitis. Three patients had non-serious herpes zoster in the tofacitinib group versus two in the placebo-to-tofacitinib group. Uveitis was reported in one patient during the first 16 weeks of the trial and in two patients in the last weeks. In the 48-week study, there were no deaths and no cases of malignancies, major adverse cardiovascular events (MACE), venous thromboembolic events (VTE), gastrointestinal perforation, drug-induced liver injury, opportunistic infections or interstitial lung disease in the upadacitinib group.[30]

Table 4: Adverse events reported in AxSpA studies

Study	Treatment	Serious Infection, n (%)	Herpes Zoster, n (%)	Opportunistic infection, n (%)	TB, n (%)	MACE, n (%)	Malignancies, n (%)	Thromboembolic Events, n(%)
Van der Heijde 2017 NCT01786668 & Deodhar 2020 NCT03502616	***Up to week 16:***					0	0	0
	Tofacitinib 5 mg, bd	1 (0.8)	0	0	NR	0	0	0
	Placebo	0	0	0	NR	0	0	0
	Up to week 48:			0	NR	0	0	0
	tofacitinib 5 mg, bd	1 (0.8)	3 (2.3)					
	Placebo->tofacitinib 5 mg, bd	0	2(1.5)	0	NR	0	0	0
Van der Heijde 2018 NCT03117270	Filgotinib 200 mg, qd	1 (2)	NR	0	0	NR	0	1 (2)
	Placebo	0	NR	0	0	NR	0	0
Van der Heijde 2019 NCT03178487	Upadacitinib 15 mg, qd	0	0	1(1)	0	0	0	0
	Placebo	0	0	0	0	0	0	0
Van der Heijde 2022 NCT04169373	upadacitinib 15 mg, qd	5(2.4)	2(0.9)	0	0	0	0	0
	placebo	0	0	0	0	0	1 (0.5)	0
Van der Heijde 2022 Open-label extension	Any upadacitnib (308.6 PY)	0	5 (1.6 PY)	2 (0.6 PY)	0	0	1 (0.3 PY)	1 (0.3 PY)
Deodhar 2022 NCT04169373	upadacitinib 15 mg	2 (1)	2 (1)	0	0	0	0	0
	placebo	1 (1)	1 (1)	0	0	0	1 (1)	0

NR: Not reported, PY: Patient Years

In the SELECT-AXIS 1 trial, the number of AEs was slightly higher in the upadacitinib group. Nine patients in the upadacitinib group had asymptomatic elevations in creatinine kinase (CK) levels, compared to one symptomatic patient with myalgias and CK elevation >4× upper limit of normal in the placebo group. Other common AEs were diarrhoea and nasopharyngitis in both groups, headache in the upadacitinib group and nausea in the placebo group. Five patients in the upadacitinib group (one receiving concomitant methotrexate) and two in the placebo group developed asymptomatic transaminitis. Twenty per cent had infections in the upadacitinib group compared to 28% in the placebo group. One patient in the upadacitinib group with gastroesophageal reflux disease developed esophageal candidiasis. Elevations in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels were observed only in the upadacitinib group. No changes in LDL to HDL cholesterol ratio were noted in either group. No malignancies, serious infections, renal dysfunctions, VTE, cardiovascular events or deaths were reported in either group.[32]

In the open-label extension of the SELECT-AXIS 1 trial, safety was assessed as the rate of treatment-emergent AE per 100 patient years (PY). The rate of treatment-emergent AE was reported as 242.7 per 100 PY. The most common AEs were nasopharyngitis, CK elevation and URTI. There were five events overall of non-serious herpes zoster that occurred in four patients. Two events of non-serious esophageal candidiasis occurred in the same patient. Otherwise, no opportunistic infections occurred. No serious infections or TB were reported. Thirty five events of CK elevation occurred in twenty nine patients, one being serious. The majority were asymptomatic. One case of pulmonary embolism (PE) was reported in an obese woman who was an active smoker with a history of DVT. One serious colitis event was reported in a man with no history of IBD. The rate of uveitis was reported as 5.2 per 100 PYs and nine out of the ten were HLA-B27 AS patients. Most uveitis events were mild to moderate and resolved with local treatment. Most hepatic disorders were asymptomatic transaminitis at a rate of 10.4 per 100 PY. Squamous cell carcinoma of the tongue was reported in a 60-year-old former smoker and was not thought to be study related. No adjudicated MACE, lymphoma, non-melanoma skin cancer (NMSC), renal dysfunction or gastrointestinal perforation was observed.[33]

In the SELECT-AXIS 2 trial, the rate of AEs was only slightly higher in the upadacitinib group versus placebo, 41% vs. 37%. One patient had acute cholangitis and five had serious infections (four COVID and one uveitis). All four patients with serious COVID had other risk factors for severe disease. The seventeen patients with COVID-19-related AEs in both groups were mostly unvaccinated against COVID-19. Only one patient in the upadacitinib group was vaccinated and had a non-serious asymptomatic COVID-19 AE. Uveitis occurred in four patients: one in the upadacitinib group with a history of uveitis and three in the placebo group (two with a history of uveitis). Two non-serious herpes zoster events (0.9%) occurred in patients on upadacitinib from Japan. One

case of Crohn's disease was reported in a patient without a history of IBD in the upadacitinib group. In the placebo group, psoriasis occurred in one patient with no history of psoriasis. No deaths, opportunistic infections, NMSC, lymphoma, adjudicated gastrointestinal perforation, renal dysfunction, active TB, or adjudicated MACE or VTE were reported. No study drug discontinuation was required.[34]

In the SELECT-AXIS 2 nr axSpA study, seventy five patients in the upadacitinib group had AEs compared to seventy two patients in the placebo group. One percent of each group had serious infections. One percent of patients had herpes zoster in each group not requiring treatment discontinuation. Four patients in the upadacitinib and four in the placebo group had non-serious transaminitis. Uveitis occurred in one patient on upadacitinib who had a history of uveitis. No malignancies, deaths, opportunistic infections, TB, adjudicated MACE, renal dysfunction or gastrointestinal perforation were reported in the upadacitinib group.[35]

Discussion

Currently, two JAKi, tofacitinib and upadacitinib are approved for treating axSpA in patients with inadequate response to TNFi, based on the data from multiple studies.[30–35] Upadacitinib was the first JAKi that has shown efficacy even in nr-axSpA, suggesting that JAKi are efficacious across the spectrum of axSpA.[27,30–35] Both tofacitinib and upadacitinib improved pain, disease activity, physical function and quality of life in patients with axSpA.[30–35] The response improved and was sustained over 48 weeks and 104 weeks, respectively.

In this review, we have provided details about the efficacy of JAKi in axSpA. AxSpA-associated dermatologic manifestations like psoriasis, PG, erythema nodosum, cutaneous Crohn's disease, HS, keratoderma blenorrhagicum or balanitis circinate were not evaluated as outcomes in these studies. Cutaneous manifestations in SpA add additional morbidity and impose a psychosocial burden on affected patients. Individuals with complex inflammatory diseases need to be screened for these comorbidities in daily practice to achieve optimal patient care. In the future, these cutaneous manifestations are expected to be studied as secondary outcomes. Available reports demonstrated that several JAKi, including tofacitinib/upadacitinib, approved for axSpA are also effective for psoriasis[20], enthesitis[20], pyoderma gangrenosum[14], and hidradenitis suppurativa[15]. Thus, in appropriate clinical scenarios, JAKi may also provide adequate relief for the associated inflammatory cutaneous manifestations of axSpA.

The longest safety study that has been studied in AS is the 2-year open-label SELECT-AXIS 1 study.[33] The remaining AS trials have followed patients for shorter periods, and a longer-term safety profile is still pending study. Nevertheless, no new safety concerns were seen and the studies were consistent with the safety profile of JAKi in other immunomodulatory diseases. Familiar serious AEs from RA JAKi studies include herpes zoster, TB, MACE, VTEs and malignancies.[17]

JAKi use is mainly associated with a higher infection risk than placebo. Most infections were nasopharyngitis, URTIs and herpes zoster. Transaminitis and CK elevation were also observed. It is still unclear whether JAK inhibition influences flares of uveitis.

The ORAL Surveillance study was performed on patients with RA who were 50 years or older and had at least one cardiovascular risk factor. The results suggested that tofacitinib was associated with a higher risk of MACE, NMSC and opportunistic infections than TNFi.[36] The incidence of MACE was higher in patients aged 65 and above.[36]

One patient in the TORTUGA trial developed DVT but was heterozygous for factor V Leiden.[27] In the 2-year open-label extension of the SELECT-AXIS 1 trial, one case of PE was reported in the upadacitinib group in an obese, active smoker with a history of DVT before initiating the study drug.[33] One case of squamous cell carcinoma of the tongue was also reported in the 2-year open-label SELECT-AXIS 1 trial thought not to be related to the study drug (the patient was an active smoker).[33] International guidelines recommend caution with starting JAKi in patients above 65 and those above 50 with at least one cardiovascular risk factor.[2] Although MACE and malignancy were not commonly observed in the axSpA studies, it is still unclear if the cardiovascular risk and malignancy risk will apply to axSpA. Nevertheless, we suggest following EULAR/ASAS recommendations for the treatment of axSpA when prescribing JAKi.[2]

Phase III studies assessing the efficacy and safety of filigotinib were terminated due to concerns about testicular toxicity.

Monitoring while patients are taking JAKi

All patients should have testing for active and latent TB before initiating JAKi and patients with positive latent TB tests should be treated accordingly before initiating therapy. Routine TB monitoring while on treatment is also recommended. A baseline CBC should be done before starting the medicine and repeated in 1–2 months and, after that, every 12 weeks. Subjects with Hb levels < 9 g/dL, an absolute lymphocyte count < 500/mm^3 and an absolute neutrophil count < 1000/mm^3 should not be started on the therapy. Baseline lipid levels should be obtained and monitored eight weeks after starting treatment. Liver function should be monitored and JAKi are not recommended for severe hepatic impairment. Females who are lactating and receiving treatment are advised not to breastfeed 18–36 hours following the last dosage.

Conclusion

Skin manifestations in SpA add another dimension and complexity to the successful management of SpA. Knowledge of associated disorders and their therapeutic approaches is

vital to an interdisciplinary approach and optimal patient care. Here, we present an update on the regulatory role of JAK in axSpA and its clinical relevance. This information will be helpful to dermatologists who are involved with the multispecialty care of patients with autoimmune diseases. The availability of JAKi has opened more options for patients with active axSpA based on the efficacy data and the ease of administration.

Further long-term studies are required to evaluate the safety of JAKi in our younger patients with SpA to evaluate whether the same safety concerns demonstrated in RA studies apply to patients with SpA. Comparative studies are needed comparing TNFi, IL-17A inhibitors and JAKi in axSpA. Studies guiding treatment switches in insufficient response and treatment failures to these three biologics in axSpA are still required.

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