Upadacitinib (RINVOQ) in Axial Spondyloarthritis National Drug Monograph Addendum June 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description / Mechanism of Action

- Upadacitinib is the second Janus kinase inhibitor (JAKI) approved for ankylosing spondylitis (AS; aka radiographic axial spondyloarthritis [r-axSpA]) and the first JAKI and targeted synthetic immunomodulator approved for nonradiographic axial spondyloarthritis (nr-axSpA).

Indications Under Review in This Document

- Treatment of adults with **active AS** who have had an inadequate response or intolerance to one or more tumor necrosis factor inhibitors (TNFIs).[1]
- Treatment of adults with **active nr-axSpA** with objective signs of inflammation who have had an inadequate response or intolerance to TNFIs.
- *Limitations of Use*: Upadacitinib is not recommended for use in combination with other JAKIs, biologic immunomodulators, or with potent immunosuppressants such as azathioprine and cyclosporine.

Pretreatment Tests and Evaluations

- Similar to those for previously approved indications.

Dosage Regimen and Dosage Form Under Review

- *AS and nr-axSpA*: 15 mg once daily.
- Extended-release tablets: 15 mg

Dosage Modifications and Interruptions

- *Renal impairment*: No dosage adjustment for mild, moderate or severe renal impairment in patients treated with upadacitinib for AS or nr-axSpA.
    - Dosage modification is recommended in patients treated with upadacitinib for atopic dermatitis or ulcerative colitis who have severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2) or end stage renal disease (eGFR < 15 mL/min/1.73 m^2).
- *Hepatic impairment*: Use is not recommended in severe hepatic impairment. No dosage adjustment is needed for mild or moderate hepatic impairment (Child-Pugh A or B) in patients treated with upadacitinib for AS or nr-axSpA.
    - Dosage modification is recommended in patients treated with upadacitinib for ulcerative colitis who have mild to moderate hepatic impairment (Child-Pugh A or B).
    - No dosage modification is needed in patients treated with upadacitinib for atopic dermatitis who have mild to moderate hepatic impairment.

- *Strong CYP3A4 inducers*: Use is not recommended.
- *Strong CYP3A4 inhibitors*: Unlike in atopic dermatitis and ulcerative colitis, there is no recommendation to modify dosage of upadacitinib for AS or nr-axSpA.
- *Infections*: Interrupt treatment; may restart when infection is controlled.
- Absolute neutrophil count < 1000 cells/mm^3, absolute lymphocyte count < 500 cells/mm^3, hemoglobin < 8 g/dL: Interrupt treatment; may restart once values return to above these thresholds.
- Elevated hepatic transaminases / suspected drug-induced liver injury: Interrupt treatment until diagnosis is excluded.

Efficacy Considerations

- No active-controlled trials with upadacitinib have been performed in patients with either AS or nr-axSpA.
- Two phase 3 placebo-controlled randomized clinical trials (RCTs) showed efficacy of upadacitinib in patients with active AS.
    - The SELECT-AXIS 1 AS biologic disease-modifying antirheumatic drug (bDMARD)-naïve study involved AS patients with inadequate response or intolerance to nonsteroidal antiinflammatory agents (NSAIDs).[2,3,4 5] This study is referred to as the SELECT-AXIS 1 AS study in this review from here on.
    - The SELECT-AXIS 2 AS bDMARD inadequate response (IR) study evaluated upadacitinib in patients refractory to biologic therapy (TNFIs or interleukin-17 inhibitors [IL-17Is).[6,7] This study is referred to as the SELECT-AXIS 2 AS study in this review.
- A phase 3 placebo-controlled RCT, the SELECT-AXIS 2 nr-axSpA study, showed efficacy in patients with active nr-axSpA who had an inadequate response to NSAIDs with or without prior inadequate response to biologics.[8]
- There has been a dilemma related to whether AS / r-axSpA (presence of definite radiographic sacroiliitis / sacroiliac joint damage with or without structural changes in the spine) and nr-axSpA (without definite radiographic sacroiliitis), represent two different disease processes or different phenotypes in the spectrum of axial spondyloarthritis (axSpA) disease, with nr-axSpA believed to be an early stage of axSpA.[9] Efforts to treat axSpA at an earlier stage (when it is nr-axSpA) aim to prevent the irreversible post-inflammatory structural damage. The FDA approved upadacitinib for both AS and nr-axSpA; however, the distinction between the two types of axSpA may be more conceptual in a contemporary diagnostic framework. The International Classification of Diseases version 10 (ICD-10) included separate codes for AS / r-axSpA and nr-axSpA. The ICD-11 only includes the general term “axial spondyloarthritis.”

Phase 3 Randomized Clinical Trials

- Table 1 summarizes the methods of the phase 3 RCTs.

Table 1 Methods of Phase 3 RCTs

Topic	SELECT-AXIS 1 AS[2,4] (biologic-naïve)	SELECT-AXIS 2 AS[6] (biologic-exposed)	SELECT-AXIS 2 nr-axSpA[8] (NSAID ± biologic exposure)
Study Design	14-wk, phase 2/3 MN DB PC RCT	14-wk, phase 3 MN DB PC RCT	14-wk MN DB PC RCT
Major Entry Criteria	*Inclusion Criteria:* Age ≥ 18 y, Modified NY criteria for AS, Active disease (BASDAI ≥ 4), inadequate response to ≥ 2 NSAIDs or intolerance or CI to NSAIDs *Exclusion Criteria*: Previous exposure to JAKI or BIO with potential effect on SpA; unstable extra-articular manifestations; total spinal ankylosis	*Inclusion Criteria:* Age ≥ 18 y, Modified NY criteria for AS, active disease (BASDAI and patient's assessment of total back pain score of ≥ 4 on a 0–10 scale), inadequate response to ≥ 2 NSAIDs or intolerance or CI to NSAIDs, and inadequate response or intolerance to biologic (TNFI or IL-17I). *Exclusion Criteria:* Lack of efficacy to two biologics (but prior exposure to two biologics was allowed); prior JAKI use; total spinal ankylosis.	*Inclusion Criteria*: Age ≥ 18 y, clinical diagnosis of nr-axSpA (2009 ASAS criteria), active disease (BASDAI and patient's assessment of total back pain score ≥ 4 on a 0–10 scale, ≥ 1 objective sign of active inflammation (on MRI of SIJs, hsCRP > 2.87 mg/l, or both); inadequate response to ≥ 2 NSAIDs or intolerance or CI to NSAIDs. Not more than one previous biologic (TNFI or IL-17I) was allowed for 20%–35% of patients who discontinued biologic because of either nonresponse or intolerance. *Exclusion Criteria*: Met radiographic criteria for AS; nonresponse to both a TNFI and IL-17I; other inflammatory arthritis; previous use of JAKI.
Interventions	For 14 wks: • Upadacitinib 15 mg QD • Placebo Stable doses of csDMARDs or oral GCs, NSAIDs, analgesics	For 14 wks: • Upadacitinib 15 mg QD • Placebo Stable doses of NSAIDs, oral GCs, or cIMMs.	For 14 wks: • Upadacitinib 15 mg QD • Placebo Stable doses of background medications including cIMMs, oral GCs, and NSAIDs
Maintenance Phase or Long-term Extension	OL extension, treat-straight-through design For 90 wks (to Wk 104): • Upadacitinib 15 mg QD (continuous) • Placebo-to-Upadacitinib 15 mg QD (switched after Wk 14)	—	52-wk OL extension
Primary Efficacy Measure	ASAS40 response at Wk 14	ASAS40 response at Week 14	ASAS40 response at Wk 14

ASAS40, ≥ 40% improvement on the Assessment of SpondyloArthritis international Society score and an absolute improvement of at least 2 units on a numerical rating scale of 0–10 from baseline in at least 3 of 4 domains with no worsening in the remaining domain (Patient Global Assessment of disease activity, patient assessment of back pain, Bath Ankylosing Spondylitis Functional Index, and inflammation defined as the mean of the BASDAI questions on severity and duration of morning stiffness); **ASDAS**, ASDAS, Ankylosing Spondylitis Disease Activity Score; **BASDAI**, Bath Ankylosing Spondylitis Disease Activity Index (scale, 0–10); **hsCRP**, High sensitivity C-reactive protein; **SIJ**, Sacroiliac joint; **mSASSS**, Modified Stoke Ankylosing Spondylitis Spine Score (range, 0–72)

Table 2 Baseline Patient Characteristics

Characteristic	SELECT-AXIS 1 AS[2,4]	SELECT-AXIS 2 AS[6]	SELECT-AXIS 2 nr-axSpA[8]
N	187	420	314
Male, %	70	74	59
Age, y	46	42	42
White, %	83	80	84
Asian, %	16	19	15
US and CN / N. American region, %	10	12	14
HLA B27-positive, %	76	83	60
Time since diagnosis, y	6.9	7.7	4.5
Symptom duration, y	14.4	12.8	9.1
Concomitant NSAIDs, %	81	78	75
Concomitant oral GCs, %	10	11	12
Concomitant cIMMs, %	16	31	29
Previous biologic therapy, %	—	99.8‡	32
Enthesitis (MASES > 0), %	—	74	80
MRI-positive at screening†	—	—	44

† *MRI-positive* was defined as active sacroiliitis according to the ASAS/Outcome Measures in Rheumatology Clinical Trials definition

‡ One TNFI 74%; two TNFIs 8%; one IL-17I 12%, two IL-17Is 0.5%; one TNFI and one IL-17I 4.5%. One placebo patient did not receive prior biologic.

Results

- Selected efficacy data are summarized in Table 3 and Table 4.

Table 3 Efficacy results from clinical trials

Outcome	Study	Upadacitinib	PBO	Relative Risk (95% CI)	Difference (95% CI)
ASAS40 at Wk 14, n/N (%)	SELECT-AXIS 1 AS[2]	**48/93 (52)**	**24/94 (26)**	**2.0 (1.36, 3.00)**	**26 (13, 40)**
	SELECT-AXIS 2 AS[6]	**95/211 (45)**	**38/209 (18)**	**2.5 (1.79, 3.42)**	**26 (18, 35)**
	SELECT-AXIS 2 nr-axSpA[8]	**70/156 (45)**	**35/157 (23)**	**2.0 (1.43, 2.83)**	**22 (12, 32)**

Bold blue: Statistically significant ($p < 0.05$), multiplicity controlled.

ASAS40, At least 40% improvement from baseline on the Assessment of Spondyloarthritis International Society response criteria; **CFB**, Change from baseline; **NR**, Not reported; **SIJ**, Sacroiliac joint; **SPARCC**, Spondyloarthritis Research Consortium of Canada

† Nominal $p \leq 0.021$ (not multiplicity controlled).

Table 4 Absolute Effects for Achieving ASAS40 for Upadacitinib vs Placebo at Week 14

Trial	AAE, per 1000 pts (95% CI)	NNT (95% CI)	Q
SELECT-AXIS 1 AS[2]	260 (126, 395)	4 (3, 8)	M[α]
SELECT-AXIS 2 AS[6]	268 (183, 354)	4 (3, 6)	M[α]
SELECT-AXIS 2 nr-axSpA[8]	226 (124, 327)	5 (4, 9)	M[α]

AAE, Anticipated absolute effect for achieving the outcome; **NNT**, Number needed to treat for one additional patient to benefit; **Q**, GRADE quality of evidence (M = Moderate)

[α] Downgraded for imprecision (optimal information size not met; wide CIs)

- **Radiographic Progression**: In the SELECT-AXIS 1 AS open-label extension, the mean (95% CI) change from baseline to Week 104 (2 years) in the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS; range 0–72) was 0.7 (0.3, 1.1) for the total group (upadacitinib continuous [n = 69] and placebo-to-upadacitinib switchers [n = 67]. The mean change in mSASSS met the definition of no radiographic progression (mSASSS score of either < 2 units in 2 years or ≤ 0 units, which indicates no new syndesmophyte formation).[4,10]
- **Secondary Efficacy Outcomes**: See Table 5.

Table 5 Secondary Efficacy Outcomes from Placebo-controlled Treatment Periods, Week 14

Trial	Disease Activity	Pain	Inflammation	Function / Disability	Quality of Life
SELECT-AXIS 1 AS[2]	ASAS20† ASAS PR ASDAS ASDAS CII† ASDAS ID† ASDAS LDA† ASDAS MI† BASDAI50 MASES†	—	SPARCC MRI SIJ† SPARCC MRI Spine	ASAS HI† BASFI BASMI† WPAI (NSD)	ASQoL†
SELECT-AXIS 2 AS[6]	ASAS20 ASAS PR ASDAS ASDAS CII† ASDAS ID ASDAS LDA ASDAS MI† BASDAI50 MASES	Total BP Nocturnal BP	hsCRP SPARCC MRI SIJ† SPARCC MRI Spine	ASAS HI BASFI BASMI	ASQoL
SELECT-AXIS 2 nr-axSpA[8]	ASAS20 ASAS PR ASDAS ID ASDAS LDA ASDAS MI† ASDAS CII† BASDAI50 MASES (NSD) PtGA†	PtGA BP† Total BP	hsCRP† SPARCC MRI SIJ SPARCC MRI Spine†	BASFI BASMI (NSD)	ASQoL

Blue unmarked text denotes results with significant p-values in multiplicity-controlled analyses.
ASAS, Assessment of SpondyloArthritis international Society; **ASDAS**, Ankylosing Spondylitis Disease Activity Score, **BASDAI50**, ≥ 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index; **BASFI**, Bath Ankylosing Spondylitis Functional Index; **BASMI**, Bath Ankylosing Spondylitis Metrology Index (spinal mobility); **BP**, Back pain; **CII**, Clinically important improvement (≥ 1.1-point decrease from baseline in ASDAS); **HI**, Health index; **ID**, Inactive disease (ASDAS-CRP < 1.3); **LDA**, Low disease activity (ASDAS-CRP < 2.1); **MASES**, Maastricht Ankylosing Spondylitis Enthesitis Score **MI**, Major improvement (≥ 2-point decrease from baseline in ASDAS); **NSD**, No statistically significant difference; **PR**, Partial remission (absolute score of ≤ 2 units for each of the four ASAS40 domains); **PtGA**, Patient's Global Assessment; **SIJ**, Sacroiliac joint; **SPARCC**, Spondyloarthritis Research Consortium of Canada
† Nominal $p < 0.05$ (not multiplicity controlled).

- Subgroup Analyses
    - SELECT-AXIS 1 AS: Not reported.
    - *SELECT-AXIS 2 AS*: No ASAS40 response predictors were identified in subgroup analyses including by prior TNFI exposure or prior IL-17I exposure.[6]
    - *SELECT-AXIS 2 nr-axSpA*: No ASAS40 response predictors were identified in subgroup analyses by biologic-naïve, biologic inadequate responders, TNFI inadequate responders, and IL-17I inadequate responders, MRI sacroiliitis and hsCRP status.

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

- Onset of effects (earliest significant treatment difference) and duration of an adequate therapeutic trial (time of maximal or near-maximal response rate) are summarized by outcome measure in Table 6.

Table 6 Onset of Benefit and Adequate Therapeutic Trial Based on ASAS40 Response

Trial	Onset of Significant Treatment Benefit (Wks)	Duration of an Adequate Therapeutic Trial (Wks)
SELECT-AXIS 1 AS[2,4] (biologic-naïve)	2	32†
SELECT-AXIS 2 AS[6] (biologic IRs)	4	NE
SELECT-AXIS 2 nr-axSpA8	2	12

NE, Not evaluable

† Additional gain of 18 percentage points from 52% at Week 14 to 70% at Weeks 32–40 in the continuous upadacitinib group.

Durability of Response

- Not assessed. There was no re-randomization and therefore no upadacitinib-to-placebo group to assess durability of response and no placebo-controlled assessment of maintenance of response with upadacitinib in the extension study of SELECT-AXIS 1 AS.[4]

Safety Considerations

Safety Profile from US Prescribing Information

- **Boxed Warnings, Contraindications, and Other Warnings / Precautions** are the same as for the other approved indications for upadacitinib.
- **Overall Safety Profile**: The safety profile of upadacitinib in AS and nr-axSpA was similar to that seen in rheumatoid arthritis and psoriatic arthritis.
- **Common Adverse Events in Patients with AS or Nr-axSpA (≥ 1%)**: Upper respiratory tract infections, acne, herpes simplex, headache, blood creatine phosphokinase increased, cough, hypersensitivity, folliculitis, nausea, abdominal pain, pyrexia, increased weight, herpes zoster, influenza, fatigue, neutropenia, myalgia, and influenza-like illness.

Safety Results from Clinical Trials

- There were no deaths in SELECT-AXIS 1 AS,[2] its open-label extension,[4] SELECT-AXIS 2 AS,[6] and SELECT-AXIS 2 nr-axSpA.[8]
- Table 7 summarizes selected safety data from the clinical trials.

Table 7 Selected Adverse Events to Week 14

Study	Upadacitinib	Placebo
Serious Adverse Events		
SELECT-AXIS 1 AS,[2]	1/93 (1)	1/94 (1)
SELECT-AXIS 2 AS[6]	6/211 (2.8)	1/209 (0.5)
SELECT-AXIS 2 nr-axSpA[8]	4/156 (3)	2/157 (1)
Serious Infections		
SELECT-AXIS 1 AS[2]	0/93 (0)	0/94 (0)
SELECT-AXIS 2 AS[6]	5/211 (2.4)	0/209 (0)
SELECT-AXIS 2 nr-axSpA[8]	2/156 (1)	1/157 (1)
Discontinuations Due to Adverse Events		
SELECT-AXIS 1 AS[2]	2/93 (2)	3/94 (3)
SELECT-AXIS 2 AS[6]	0/211 (0)	3/209 (1.4)
SELECT-AXIS 2 nr-axSpA[8]	4/156 (3)	2/157 (1)

Results are shown as n/N (%)

Evidence Gaps

- Patient Satisfaction
- Radiographic progression in biologic inadequate responders treated with upadacitinib

Network Meta-analyses

- One NMA assessed JAKIs as a class (upadacitinib, filgotinib, and tofacitinib; 3 RCTs) in the treatment of patients with AS but did not compare drugs[11] and is therefore not reviewed here.
- Likewise, a systematic literature review informing the 2022 Assessment of SpondyloArthritis international Society-European Alliance of Associations for Rheumatology (ASAS-EULAR) recommendations for the management of axial spondyloarthritis (axSpA)[12] did not provide drug comparisons and is not summarized.
- A network meta-analysis (NMA) evaluated 6 RCTs including one upadacitinib trial (SELECT-AXIS 1 AS[2]) that met the following criteria: Compared a JAKI or secukinumab with placebo for patients with active AS who had an inadequate response or intolerance to NSAIDs and were TNFI-naïve, and clinical efficacy and safety outcomes were reported at 12 to 16 weeks.[13] This NMA (Lee, et al. [2022]) is summarized in Table 8.

Table 8 Comparative Efficacy and Safety of AS Treatments in TNFI-naïve Patients with Inadequate Response or Intolerance to NSAIDs (Weeks 12–16): Network Meta-analysis

Drug Ranked Best (Worst)†	UPA Superior to	UPA Similar to	UPA Inferior to
Achievement of ASAS40			
Tofacitinib 5 mg (Secukinumab 150 mg)	—	Tofacitinib 5 mg Secukinumab 150 mg	—
Serious Adverse Events			
Tofacitinib 5 mg (**Upadacitinib** 15 mg)	—	Tofacitinib 5 mg Secukinumab 150 mg	—

† Rankings were based on the surface under the cumulative ranking curve (SUCRA). Filgotinib was excluded in this monograph because it is not approved in the US.

- Another NMA (by Cao, et al. [2022]) included 39 trials (7383 patients) in ASAS40 outcome analyses and 38 trials (6496 patients) in ASAS20 analyses.[14] SELECT-AXIS 1 AS (assessed as low risk of bias) was the only upadacitinib RCT included. The league plots for individual agents is summarized in Table 9.

Table 9 Summary of League Plots for ASAS40 Response and Serious Adverse Events

Drug Ranked Best (Worst)	UPA Superior to	UPA Similar to	UPA Inferior to
Achievement of ASAS40			
Infliximab (Tocilizumab, ineffective)	Ustekinumab, tocilizumab (both agents ineffective)	Certolizumab, infliximab, golimumab, ixekizumab, adalimumab, etanercept, secukinumab, tofacitinib, risankizumab	—
Serious Adverse Events			
Ustekinumab (Tocilizumab, ineffective)	—	Certolizumab, infliximab, golimumab, ixekizumab, adalimumab, etanercept, secukinumab, tofacitinib, risankizumab, ustekinumab, tocilizumab	—

ASAS40, At least 40% improvement from baseline on the Assessment of Spondyloarthritis International Society response criteria; **UPA**, Upadacitinib

  - Serious adverse events were the only safety outcome evaluated in simultaneous comparisons of multiple-outcome indicators (cluster-rank plots). Table 10 summarizes the cluster rank plots of ASAS40 efficacy and safety for individual agents. Agents within a cluster are considered to be similar in effects.

Table 10 Efficacy–Safety Cluster Ranks for Individual Agents

Drugs With Best Efficacy and Safety by Cluster	Drugs with Better Efficacy and Worse Safety by Cluster	Drugs With Worse Efficacy and Better Safety by Cluster	Drugs with Worse Efficacy and Safety by Cluster
ASAS40 SUCRA ≥ 50 SAE SUCRA ≥ 50	ASAS40 SUCRA ≥ 50 SAE SUCRA < 50	ASAS40 SUCRA < 50 SAE SUCRA ≥ 50	ASAS40 SUCRA < 50 SAE SUCRA < 50
Infliximab	Ixekizumab, **upadacitinib**, golimumab, etanercept, adalimumab	Secukinumab, tofacitinib, risankizumab	Tocilizumab (ineffective)
	Certolizumab	Ustekinumab (ineffective)	

Only FDA-approved drugs are shown. The cluster-rank plots were arbitrarily divided by SUCRA < or ≥ 50 for ease of presentation.
SAE, Serious adverse event; **SUCRA**, Surface under the cumulative ranking analysis; indicates the probability of the drug ranking best in efficacy or safety (ranking range, 100 = best, 0 = worst)

  - The drug class most likely to be the most effective and safest is an unapproved IL-17A/F inhibitor (bimekizumab).
  - The TNFI monoclonal antibodies had the highest probability of being most effective and best tolerated (lowest withdrawals due to adverse events).
- Limitations and other considerations about the two NMAs are provided in Table 11.

Table 11 Other Considerations About the Network Meta-analyses

Consideration	Lee, et al. (2022)		Cao, et al. (2022)
Limitations	Single author Databases searched and language restrictions not reported (potentially missed RCTs) No quality of evidence ratings	Heterogeneity = 0.61 Short time period Limited scope of outcomes Small number of RCTs	Excluded low-quality studies (potential missed RCTs) No assessment of overall certainty of evidence per outcome Median follow-up < 4 mos Lack of RCTs with direct treatment comparisons
Funding	None		National Key R&D Program of China, National Natural Science Foundation of China, and the Natural Science Foundation of Hunan Province, and the Fundamental Research Funds for the Central Universities of Central South University
Author COI with AbbVie	No		No

- The literature search found no NMAs of nr-axSpA treatments.

Other Therapeutic Options

- Treatment alternatives for AS and nr-axSpA are limited.
- Therapeutic trials of two NSAIDs each given for 2 to 4 weeks are generally the first step in therapy for symptomatic AS or nr-axSpA.[16] It is uncertain whether NSAIDs prevent radiographic progression in axSpA[10] and their long-term use is associated with risks of significant gastrointestinal, renal, and cardiovascular harms. In patients with stable AS receiving TNFI with concomitant NSAIDs, continuation with TNFI monotherapy is conditionally recommended over continuing both treatments.[16]
- Conventional immunomodulators (sulfasalazine and methotrexate) are conditionally recommended for active AS or active nr-axSpA despite treatment with NSAIDs. For AS, the conventional immunomodulators are conditionally recommended only in patients with prominent peripheral arthritis[16,17] or when TNFIs are medically inadvisable or not available.[16] If TNFIs are medically inadvisable because of infection or TB risk, sulfasalazine is preferred over either IL-17AIs or tofacitinib.[16] There is little to no evidence that

sulfasalazine and methotrexate improve axial symptoms and they seem to be ineffective for radiographic progression.[15] Sulfasalazine has more evidence than methotrexate in AS.

- TNFIs, IL-17AIs, or JAKIs should be considered in patients with active AS or active nr-axSpA despite NSAIDs.[16,17] TNFIs are conditionally recommended over IL-17AIs or tofacitinib[16] and TNFIs and IL-17AIs are each preferred over JAKIs.[16,17] TNFIs except etanercept may be preferred in patients with comorbid recurrent uveitis or active inflammatory bowel disease.[17]
- In patients who fail the first biologic or targeted synthetic immunomodulator, switching to an alternate biologic or targeted synthetic immunomodulator should be considered.[17] In patients with loss of response to the first TNFI, a different TNFI is conditionally recommended over switching to a non-TNFI agent.[16] However, given a paucity of data on the efficacy of drugs in patients previously exposed to within-class or out-of-class drugs, switching to another class of agents can also be considered.[17]
- JAKIs and other therapies used for active AS or active nr-axSpA despite TNFIs are summarized in Table 12.

Table 12 Treatment Alternatives for Active AS or Active Nr-axSpA Despite TNFI Therapy

Drug	On VANF	CFU Place in Therapy	FDA Place in Therapy	Guideline Place in Therapy	Safety Considerations	Other Considerations
JAK Inhibitors						
Upadacitinib	No	*AS and Nr-axSpA*: TBD CFU in RA, PsA, AD, and UC	*AS and Nr-axSpA*: TNFI IR or INT	*Active AS or nr-axSpA despite NSAIDs:* JAKIs should be considered but current practice is to start with a TNFI or IL-17AI.[17]	Similar to those for tofacitinib except pregnancy should be avoided during upadacitinib therapy and for 4 weeks after therapy ends. *In AS and nr-axSpA*: No dosage modifications needed for renal impairment, mild or moderate hepatic impairment, or strong CYP3A4 inhibitors. There may be confusion about dosage modifications needed with other indications.	Prevents radiographic progression in AS.[4] Orally administered. Lacks antidrug antibodies. Potential use for comorbid RA, PsA, AD, or UC
Tofacitinib	No	*AS*: TNFI IR, INT, or MIA CFU in RA, PsA, UC, and AS	*AS*: TNFI IR or INT	*Active AS or nr-axSpA despite NSAIDs:* Conditionally recommended below TNFI (QE: Very low) and secukinumab and ixekizumab (QE: Very low)[16] *Active AS or nr-axSpA despite NSAIDs and CI to TNFIs:* Conditionally recommended below secukinumab and ixekizumab (QE: Low for AS, very low for nr-axSpA).[16] Alternative at the same level as tofacitinib: SSZ or MTX.[16]	*Boxed Warnings*: Serious infections, mortality, malignancies, MACE, thrombosis. Risks of boxed warnings in axSpA are uncertain.[17] As a precaution, the ASAS/EULAR guideline recommends restricted use in patients with risk factors (patients > 50 years with ≥ 1 cardiovascular risk factor and patients ≥ 65years). Myelosuppressive Herpes zoster infection Routine lab monitoring required (Hg, neutrophils, lymphocytes, liver enzymes, lipids). *DDIs*[†]: Live vaccines, CYP3A4 inducers / inhibitors, potent cIMMs (e.g., AZP, CSA).	Uncertain ability to prevent radiographic progression.[‡] *Nr-axSpA:* No studies found. Not approved for nr-axSpA. Orally administered. Lacks antidrug antibodies. Potential use for comorbid RA, PsA, or PJIA.

Drug	On VANF	CFU Place in Therapy	FDA Place in Therapy	Guideline Place in Therapy	Safety Considerations	Other Considerations
					Dosage modifications needed for moderate or severe renal impairment, moderate hepatic impairment, strong CYP3A4 inhibitors (e.g., ketoconazole), and moderate CYP3A4 inhibitors with strong CYP2C19 inhibitors (e.g., fluconazole). *Pregnancy*: Consider pregnancy prevention in patients with reproductive potential.	
IL-17A Inhibitors						
Ixekizumab	No	*AS and Nr-axSpA*: TNFI IR, INT, or MIA CFU in PsO, PsA, AS, and nr-axSpA	*AS and Nr-axSpA*: Potential 1st line	*Active AS or nr-axSpA despite NSAIDs:* Conditionally recommended below TNFI and over tofacitinib (QE: Very low[16]).[17] *Active AS or nr-axSpA despite NSAIDs and CI to TNFIs:* Conditionally recommended over SSZ, MTX, or tofacitinib (QE: Low for AS, very low for nr-axSpA.[16] *Active AS or nr-axSpA and primary nonresponse to first TNFI:* Conditionally recommended over switching to a different TNFI (QE: Very low).[16] *Active AS with loss of response to 1st TNFI:* Recommended below switching to a different TNFI (QE: Very low).[16]	Serious infections, TB, hypersensitivity, new or worsening IBD, avoid live vaccines. Fungal infections	Was similar to adalimumab in efficacy in biologic-naïve patients in active AS.[18] Prevents radiographic progression in AS.[19] Potential use for comorbid PsO or PsA. IL-17AIs may be preferred over TNFIs in patients with significant comorbid PsO.[17]
Secukinumab	No	*AS and Nr-axSpA*: TNFI IR, INT, or MIA CFU in PsO, PsA, AS, and nr-axSpA	*AS and Nr-axSpA*: Potential 1st line	Same as for ixekizumab	Serious infections, TB, hypersensitivity, new or worsening IBD, avoid live vaccines. Fungal infections	Prevents radiographic progression in AS.[20] Potential use for comorbid PsO, PsA, or ERA IL-17AIs may be preferred in patients with significant comorbid PsO.[17]

Guideline Sources: 17. Note that this guideline only included one phase 2 trial of tofacitinib in AS.

AD, Atopic dermatitis; **AS**, Ankylosing spondylitis; **AZP**, Azathioprine; **CFU**, Criteria for Use; **ERA**, Enthesitis-related arthritis; **INT**, Intolerance; **IR**, Inadequate response; **MIA**, Medical inadvisability; **MTX**, Methotrexate; **nr-axSpA**, Nonradiographic axial spondyloarthritis; **OLE**, Open-label extension without control group; **PJIA**, Polyarticular Course Juvenile Idiopathic Arthritis; **PsA**, Psoriatic arthritis; **PsO**, Plaque psoriasis; RA, Rheumatoid arthritis; **SSZ**, Sulfasalazine. † DDIs for which concomitant use is not recommended.

‡ Preliminary, post hoc data from a phase 2 RCT suggested that tofacitinib improved spinal inflammation on MRI in biologic-naïve patients with AS.[21] A 32-week open-label extension study[22] was short of the minimum of 2 years required to assess radiographic progression.[23]

Projected Place in Therapy

- **Potential Place in Therapy Based on the Evidence**. No head-to-head trials were available to inform upadacitinib's place in therapy in axSpA. Moderate-quality evidence from two placebo-controlled trials supports the use of upadacitinib in patients with active AS who have an inadequate response or intolerance to NSAIDs or biologics (TNFIs or IL-17AIs) or for whom those therapies are medically inadvisable. Moderate-quality evidence from one RCT supports the use of upadacitinib in patients with active nr-axSpA who mainly had an inadequate response or intolerance to prior trials of NSAIDs or for whom NSAIDs were medically inadvisable. Overall, upadacitinib therapy reduced disease activity, met mSASSS cutoff values for prevention of radiographic progression in AS, reduced axial (spinal or sacroiliac) MRI inflammation, and improved function, and the benefits were clinically meaningful (improved quality of life). A low-quality network meta-analysis suggested that upadacitinib is similar to tofacitinib and secukinumab in ASAS40 efficacy and rates of serious adverse events. A better quality network meta-analysis suggested that upadacitinib was similar to other agents approved for AS in terms of ASAS40 efficacy and serious adverse events. The main issue to consider when comparing cost-benefits and choosing between the two JAKIs in the treatment of patients with active AS / r-axSpA is that in an uncontrolled, open-label extension study, upadacitinib seemed to prevent or slow radiographic progression while there is no radiographic progression data with tofacitinib.
  For nr-axSpA, the important issue is that the SELECT-AXIS 2 nr-axSpA trial[8] provided evidence of efficacy and safety of upadacitinib in only patients with objective signs of inflammation, and the US prescribing information for upadacitinib requires the presence of objective signs of inflammation; i.e., nr-axSpA should be "active." Structural damage is believed to result from chronic inflammatory activity. Signs of inflammation may include elevated high-sensitivity CRP (above upper limit of normal at local laboratory) and/or sacroiliitis on MRI. It is possible for a patient with correctly diagnosed nr-axSpA to have no signs of inflammation, implying that back pain and any other symptoms are not related to inflammatory activity. The evidence does not support use of targeted biologic or synthetic immunomodulators for treatment of patients without inflammatory disease.
- **Potential Place in Therapy in VHA**. Upadacitinib may be used for the treatment of patients with active AS / r-axSpA or active nr-axSpA with objective signs of inflammation who have an inadequate response or intolerance to TNFIs or for whom TNFIs are medically inadvisable. For treatment of patients with active nr-axSpA who are candidates for JAKI therapy, upadacitinib may be preferred because tofacitinib lacks evidence to support its off-label use for nr-axSpA. For active AS or active nr-axSpA, JAKIs may be used as alternatives to IL-17AIs (ixekizumab or secukinumab) when TNFI therapy is inadequate, not tolerated, or medically inadvisable.

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