Tofacitinib (XELJANZ) in Ankylosing Spondylitis National Drug Monograph Addendum May 2022

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

- First Janus kinase inhibitor (JAKI) FDA-approved for ankylosing spondylitis.[1]

Indication(s) Under Review in This Document

- Treatment of adult patients with active ankylosing spondylitis who have had an inadequate response or intolerance to one or more tumor necrosis factor inhibitors (TNFIs).
- *Limitations of use*: Use of tofacitinib in combination with biologic disease modifying antirheumatic drugs (DMARDs) or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Dosage Regimen Under Review

- *Adult dose*: Tofacitinib immediate release 5 mg twice daily or tofacitinib extended release 11 mg once daily.
- *Dosage in patients receiving strong CYP3A4 inhibitors (e.g., ketoconazole) or moderate CYP3A4 inhibitors with a strong CYP2C19 inhibitor (e.g., fluconazole)*: tofacitinib immediate release 5 mg once daily.
- *Dosage in patients with moderate and severe renal impairment or moderate hepatic impairment*: tofacitinib immediate-release 5 mg once daily.

Clinical Evidence Summary

Efficacy Considerations

- The efficacy and safety of tofacitinib in the treatment of AS was mainly supported by a 48-week, phase 3, randomized clinical trial (RCT)[2] and a 16-week, phase 2, dose-ranging, placebo-controlled RCT (TORTUGA)[3,4].
- Both RCTs involved patients with AS who had inadequate responses or intolerance to at least 2 nonsteroidal antiinflammatory drugs (NSAIDs).
- A post hoc analysis of phase 2 RCT data showed that tofacitinib was better than placebo in achieving minimally important changes in SPondyloArthritis Research Consortium of Canada (SPARCC) magnetic resonance imaging (MRI) inflammation scores for the sacroiliac joint and the spine.[4] The changes in MRI inflammation scores correlated with ASAS20 clinical responses.

Phase 3 Randomized Clinical Trial

Study Design

- The phase 3 RCT consisted of a 16-week double-blind, placebo-controlled phase then a 32-week noncontrolled, open-label phase. In both phases, the dose of tofacitinib was 5 mg twice daily.[2]
- Randomization was stratified by (1) biologic DMARD-naïve and (2) TNFI-inadequate responder or [any] prior biologic DMARD [including TNFIs] without inadequate response.

Primary Efficacy Measure

- Percentage of patients who achieved at least a 20 percent improvement on the Assessment in Ankylosing Spondylitis response criteria (ASAS20) at Week 16.

Patient Characteristics

- Patients had active AS defined by both the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and BASDAI back pain score of ≥ 4 despite ≥ 2 NSAIDs, or were intolerant to NSAIDs. Patients already on oral glucocorticoids or disease modifying antirheumatic drug (DMARD) therapy could enter the trial if doses were stable.
- Of 270 randomized patients, 91% were male, 79% White, about 10% were from North America, 39% from the EU, 23% from Asia, and 31% from other countries. The mean age of patients was about 41 years.
- Nearly all patients (99.7%) had previously used NSAIDs, 77% were biologic DMARD-naïve, and 1.1% had prior biologic DMARD use without inadequate response. Sixty-two patients (23%) had an inadequate response to not more than two TNFIs or had prior experience with biologic DMARD therapy (including TNFIs) without inadequate response, including 43 patients (16%) and 16 patients (6%) who had inadequate response to one and two TNFIs, respectively).
- Patients with current or prior treatment with targeted synthetic DMARDs (including JAKIs) and current biologic DMARD therapy were excluded.
- Stable doses of NSAIDs, methotrexate (≤ 25 mg/week), sulfasalazine (≤ 3 g/day) and oral glucocorticoids (≤ 10 mg/day prednisone equivalent) could be continued as background therapies. On Day 1, about 80% of patients used NSAIDs, 8% used oral glucocorticoids, and 27% of patients used concomitant conventional synthetic immunomodulators (methotrexate or sulfasalazine).

Results

- Efficacy data are summarized in Table 1.

Table 1 Efficacy results from the phase 3 RCT at Week 16

Outcome	Tofacitinib	PBO	Relative Risk (95% CI)	Difference vs PBO (95% CI)	Q
ASAS20 response, n/N (%)	75/133 (56.4)	40/136 (29.4)	1.9 (1.4, 2.6)	27 (16, 38)	M[α]
ASAS40 response, n/N (%)	54/133 (40.6)	17/136 (12.5)	3.2 (2.0, 5.3)	28 (18, 38)	M[α]
CFB in BASFI, LSM (SE) (N)	–2.05 (0.17) (129)	–0.82 (0.17) (131)	—	–1.2 (–1.64, –0.79)	M[β]
CFB in ASQoL, LSM (SE) (N)	–4.03 (0.40) (129)	–2.01 (0.41) (130)	—	–2.0 (–0.9, –3.1)	M[β]
ASDAS LDA (< 2.1), n/N (%)	51/131 (38.9)	11/136 (8.1)	4.8 (2.6, 8.8)	30.8 (21.0, 40.0)	L[γ]
ASDAS Inactive Disease (< 1.3), n/N (%)	9/133 (6.8)	0/136 (0.0)	19.4 (1.1, 330.5)	6.8 (2.6, 12.4)	L[γ]

ASDAS, Ankylosing Spondylitis Disease Activity Score using high-sensitivity C-reactive protein; ASQoL, Ankylosing spondylitis quality of life; BASFI, Bath Ankylosing Spondylitis Functional Index (scale 0 / Easy to 10 / Impossible); CFB, Change from baseline; LDA, Low disease activity; LSM, Least square mean; Q, GRADE quality of evidence (L = Low; M = Moderate)

[α] Downgraded for imprecision because optimal information size not met. Relative risk reduction CI close to 1.0.

[β] Downgraded for imprecision; CI close to 0.

[γ] Downgraded for imprecision because optimal information size not met; relative risk reduction CI close to 1.0 or wide CI. Downgraded for risk of bias because there was no statistical control for multiplicity.

- Tofacitinib showed small to moderate benefits in achieving ASAS20 and ASAS40 responses.
- The anticipated absolute effect for achieving ASAS20 in 16 weeks was 265 (95% CI, 118 to 471) more per 1000 patients and for achieving ASAS40 in the same time frame was 275 (125 to 538) more per 1000 patients.
- The numbers-needed-to-treat for benefit were 4 (95% CI 3–7) and 4 (3–6) for ASAS20 and ASAS40 response rates, respectively.
- Secondary efficacy results with type I error control:
    - Tofacitinib showed efficacy in terms of the ASAS40 response rate (41% vs 13% for tofacitinib vs placebo, respectively).
    - Functional ability / Disability, as assessed with the Bath Ankylosing Spondylitis Functional Index (BASFI) component of the ASAS (where a score of 0 corresponded to *Easy* and 10 corresponded to *Impossible*), also showed a significant treatment benefit (–2.05 vs –0.82 for tofacitinib vs placebo, respectively) although the upper limit of the 95% CI for the treatment difference included a value close to zero (–0.79) (Table 1).
    - The Ankylosing Spondylitis Quality of Life (ASQoL) score showed greater improvement from baseline on tofacitinib vs placebo (–4.03 vs –2.01, respectively) at Week 16.
- Secondary efficacy results without type I error control
    - There was no significant treatment difference in the change from baseline in the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES).
- *Durability*: In the open-label phase, ASAS20 and ASAS40 response rates in the tofacitinib / tofacitinib group remained stable up to Week 48.
- *Onset of Significant Treatment Difference*: Week 2 for ASAS20 and Week 4 for ASAS40.
- *Duration of an Adequate Trial*: A near-peak ASAS20 response rate of 63.9% was reached by Week 12. The peak response of 68.4% occurred at Week 32. A similar pattern was seen with ASAS40 response.

Descriptive Subgroup Analyses

- Tofacitinib showed higher ASAS20 and ASAS40 response rates than placebo in the subgroup of TNFI inadequate responders. Results for tofacitinib vs placebo, respectively, were as follows (no statistical analyses were performed):
    - ASAS20 response: 12/29 (41%) vs 5/30 (17%); difference (95% CI) 25 (2, 47).
    - ASAS40 response: 8/29 (28%) vs 2/30 (7%); difference 21 (2, 39).

Evidence gaps

- Radiographic progression
- Patient Satisfaction

Network Meta-analyses (Indirect Comparative Efficacy)

- A network meta-analysis of 30 studies (N = 6711) evaluating treatments for active AS showed that tofacitinib (5 mg; based on the phase 2 study and investigational at the time of the report) was indirectly better than tofacitinib 10 mg and 2 mg, risankizumab 90 mg and 180 mg, secukinumab 75 mg SC, ustekinumab 45 mg and 90 mg, and apremilast 30 mg in achieving ASAS20 at Weeks 12 to 16.[5]
    - Tofacitinib (5 mg), golimumab (2 mg/kg IV), etanercept (50 mg and 25 mg), and infliximab (5 mg/kg) were significantly better than placebo using the adjusted odds ratio for achieving ASAS20 response.
    - Agents nonsignificantly different from placebo based on 95% credible intervals (CrIs) (i.e., CrIs included the value 1) were golimumab 50 and 100 mg, certolizumab 200 mg and 400 mg, adalimumab 40 mg, secukinumab 75, 150, and 300 mg IV, ixekizumab 80 mg every 2 weeks and every 4 weeks, secukinumab 75 mg SC and 150 mg SC with or without a loading dose,

risankizumab 18 mg, 90 mg, and 180 mg, tofacitinib 2 mg and 10 mg, ustekinumab 45 mg and 90 mg, and apremilast 30 mg.
  - Tofacitinib was not significantly different in ASAS20 response from golimumab 2 mg/kg IV and 100 and 50 mg SC, etanercept 50 and 25 mg, infliximab 5 mg/kg, certolizumab 400 or 200 mg, adalimumab 40 mg, secukinumab 75, 150, and 300 mg IV and 150 mg SC (with or without a loading dose), ixekizumab 80 mg every 2 or 4 weeks, and risankizumab 18 mg.
  - Using changes from baseline in BASFI and C-reactive protein as the outcome measures, tofacitinib was not significantly different from the other treatments.
  - By Surface Under the Cumulative Ranking curve (SUCRA) values, tofacitinib 5 mg, golimumab 2 mg/kg IV, and infliximab 5 mg/kg were ranked the most likely to achieve ASAS20. There were no significant indirect treatment differences among these three agents.
  - This network meta-analysis was funded by Janssen Scientific Affairs (manufacturer of golimumab).

Safety Considerations

- The adverse events observed in AS clinical trials were consistent with the known safety profile of tofacitinib in patients with rheumatoid arthritis and psoriatic arthritis.
- By Week 16 in the phase 3 RCT, the percentage of patients that reported serious adverse events was 1.5% (2/133) with tofacitinib and 0.7% (1/136) with placebo.
- By Week 48, 3 (2.3%) of 133 tofacitinib / tofacitinib patients had adjudicated hepatic events, 3 (2.3%) had nonserious herpes zoster (HZ), and 1 (0.8%) had a serious infection. Of 133 placebo / tofacitinib patients, 2 (1.5%) had nonserious herpes zoster.
- In the phase 3 RCT, there were no thromboembolic events, major adverse cardiovascular events, deaths, malignancies, or opportunistic infections. However, in a long-term safety RCT (median follow-up 4 years) involving patients ≥ 50 years old who had rheumatoid arthritis and at least one other cardiovascular risk factor, tofacitinib was shown to increase the risks of mortality, malignancy, major adverse cardiovascular events, and thrombosis compared with TNF inhibitors.[1,6]
- HZ is a safety issue of concern with tofacitinib. HZ during tofacitinib therapy was common in patients with psoriatic arthritis (4%–4.6%)[7,8] with an incidence rate of 1.8 (95% CI 1.2, 2.4) per 100 PY.[8] Recurrence of HZ occurred in 2.8% of 36 patients with psoriatic arthritis who had a first episode of HZ (in contrast to 0.4% in the general population).[8]

Other Therapeutic Options

- NSAIDs are strongly recommended (over no treatment with NSAIDs) for adults with active AS[9] and are considered the first-line drug therapy of symptomatic AS. NSAIDs reduce back pain and stiffness and may reduce symptoms of peripheral arthritis. Whether NSAIDs reduce radiographic progression is uncertain. Therapeutic trials of two NSAIDs, each for 2 to 4 weeks, is recommended.
- The conventional synthetic immunomodulators (csIMMs) sulfasalazine and methotrexate are mainly used for peripheral symptoms in patients who inadequately respond to NSAIDs.

  - Both agents are conditionally recommended and should be considered only in patients with prominent peripheral arthritis or when TNFIs are not available.[9]
  - They show little or no evidence of benefit for axial symptoms and seem to be ineffective for reducing radiographic progression.[10]
  - Sulfasalazine is preferable over IL-17AIs and tofacitinib if TNFI is contraindicated because of infection or TB risk.[9]
  - Methotrexate has less evidence than sulfasalazine.[10]
- Table 2 summarizes the alternative targeted treatments for patients with active AS not responding to NSAIDs. Except for tofacitinib, all of the targeted agents are indicated for the treatment of adults with active AS without a trial of any previous agents.

Table 2 Targeted Therapies for Active AS Despite NSAID Therapy

Drug	Formulary Status	Place in Therapy in AS	Safety Considerations	Other Considerations
JAKI Tofacitinib	NonF w/CFU	For active AS despite NSAIDs: Conditionally recommended 2nd line after TNFI and after IL-17AI. For active AS in primary nonresponder to TNFI: Conditionally recommended 3rd-line after SEC or IXE. For active AS in secondary nonresponder to TNFI: Conditionally recommended against.	Hematocytopenias, GI perforation, hepatotoxicity, thrombosis, MACE, death, malignancy, infections including TB. Multiple drug interactions; avoid strong CYP3A4 inducers, other immunosuppressives and myelosuppressives.	Convenience of oral dosing. Lacks data on radiographic progression but achieves clinically important reductions in spinal MRI inflammation.[4]
TNFIs	On VANF (except golimumab) w/PA-F (restricted to providers appropriate for prescribing TNFIs)	For active AS despite NSAIDs: Considered 1st-line targeted therapy. Conditionally recommended over IL-17AIs and tofacitinib. For loss of response to a TNFI: A 2nd TNFI is conditionally recommended over switching to a non-TNFI / non-IL-17AI.	Demyelinating disease; heart failure; rare pancytopenia and aplastic anemia; hepatitis B; infections, TB, malignancy.	Co-use with csIMM does not add benefit in AS. Considered effective for reducing radiographic progression.[11] No TNFI is clinically preferred over the others. Certolizumab is also approved for nrAxSp.

Drug	Formulary Status	Place in Therapy in AS	Safety Considerations	Other Considerations
IL-17AIs Ixekizumab Secukinumab	NonF with CFU. Ixekizumab preferred. CFU Place in Therapy in AS: After TNFI.	For active AS despite NSAIDs: Conditionally recommended 2nd line after TNFI. For primary nonresponse to first TNFI: Conditionally recommended over a second TNFI. Conditionally recommended over tofacitinib. For active AS in secondary nonresponder to TNFI: Conditionally recommended against. If TNFIs are contraindicated: Conditionally recommended over SSZ, MTX or tofacitinib.	Infections including candidiasis and tinea; TB IBD onset or worsening	Less experience than TNFIs. Also approved for nrAxSpA. Uncertain benefits in reducing radiographic progression (very low to low quality evidence).[12,13] IL-17AI is preferred over SSZ or MTX if TNFI is contraindicated because of heart failure or demyelinating disease.

IL-17AI, Interleukin-17A inhibitor (IL-17AIs approved for AS: ixekizumab, secukinumab); **nrAxSpA**, Nonradiographic axial spondyloarthritis; **TB**, Tuberculosis; **TNFI**, Tumor necrosis factor inhibitor (TNFIs approved for AS: adalimumab, certolizumab, etanercept, golimumab, infliximab)

Projected Place in Therapy

- **Epidemiology and Prevalence of AS**. AS is the predominant type of chronic inflammatory arthritis of the axial (spinal) skeleton, with a mean prevalence of 31.9 per 10,000 in North America.[14]
- **Place in Therapy Based on Medical Society Guidelines**. The 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 placed tofacitinib as a second-line therapy conditionally recommended after TNFIs or IL-17AIs for patients with active AS with an inadequate response or intolerance to NSAID therapy, or third-line therapy conditionally recommended after IL-17AIs for active AS after primary nonresponse to TNFI.[9] However, these guidelines reviewed only the phase 2 RCT of tofacitinib in active AS and preceded its FDA approval for AS.
- **Potential Place in Therapy Based on the Evidence**. There were no head-to-head trials to inform place in therapy. Low- to moderate-quality evidence from the phase 3 placebo-controlled RCT suggested that tofacitinib, with or without co-use of NSAIDs, conventional synthetic immunomodulators (sulfasalazine or methotrexate), or low-dose glucocorticoids (≤ 10 mg/day prednisone equivalent), may be beneficial as a first-line targeted therapy in patients with active AS. Tofacitinib was shown to be safe and effective for up to 48 weeks in patients who had inadequate responses or intolerance to at least two NSAIDs and who were primarily TNFI-naïve and were JAKI-naïve. Results of descriptive subgroup analyses suggested that tofacitinib might have benefit in TNFI inadequate responders; however, these findings are inconclusive. Despite the uncertainty of efficacy in TNFI inadequate responders, the FDA approved tofacitinib for patients with active AS who had an inadequate response or intolerance to at least one TNFI. Tofacitinib offers the convenience of oral administration and lack of infusion reactions or injection site reactions as potential advantages over other targeted therapies that require in-clinic intravenous infusions or patient self-administered subcutaneous injections. Disadvantages of tofacitinib include major safety concerns (e.g., mortality, major adverse cardiovascular events, malignancy, and thrombosis[1]) and lack of evidence for radiographic benefit.

- **Potential Place in Therapy in VHA**. In keeping with the prescribing information, tofacitinib may be used in patients with active AS despite TNFI therapy unless a TNFI is medically inadvisable. Live vaccines should be administered at least 2 weeks prior to initiation of tofacitinib therapy.
    - When possible, all patients, regardless of prior herpes zoster history, should complete the two-dose series of recombinant zoster vaccine (SHINGRIX) before becoming immunosuppressed, as recommended by the Centers for Disease Control and Prevention (CDC). If tofacitinib is initiated before HZ vaccination, the vaccine series should preferably be given when immune response is likely to be strong (e.g., when tofacitinib doses are low or disease is stable) and at least be in process by the end of the first year of treatment with tofacitinib (VHA Rheumatology Field Advisory Board, e-mail communication, January 2022).

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