Substance: Tofacitinib

General information

Full title:	Tofacitinib Citrate
Chemical name:	(3R,4R)-4-Methyl-3-(methyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-β-oxo-1-piperidinepropanenitrile 2-hydroxy-1,2,3-propanetricarboxylate (1:1)
CAS number:	540737-29-9
INV Number:	CP-690550-10

Substance classifications

- 92:36 Disease-modifying Antirheumatic Drugs
- 92:20 Immunomodulatory Agents
- 56:92 GI Drugs, Miscellaneous
- 84:92 Skin and Mucous Membrane Agents, Miscellaneous
- JAK Inhibitor JAK Inhibitor
- Janus Kinase Inhibitor Janus Kinase Inhibitor

Contents

General information
Introduction
> Uses
> Dosage and Administration
> Cautions
> Drug Interactions
Advice to Patients
Preparations
References
Copyright

Introduction

Tofacitinib citrate, a Janus kinase (JAK) inhibitor, is an immunomodulating agent and a disease-modifying antirheumatic drug (DMARD). [1,3,4,5,6,7,11]

Uses

Rheumatoid Arthritis

Tofacitinib citrate (as conventional or extended-release tablets) is used for the management of moderately to severely active rheumatoid arthritis in adults who have had an inadequate response or intolerance to one or more tumor necrosis factor (TNF) blocking agents. [1,3,4,5,11,34] Tofacitinib has been shown to induce clinical responses, improve physical function, and inhibit progression of structural damage in patients with rheumatoid arthritis. [1,3,4,5,6,14,17,34] Safety and efficacy of tofacitinib in the treatment of rheumatoid arthritis in adults is principally based on results from 5 randomized controlled trials. [1,3,4,5,6,14,17,34] Guidelines generally support use of Janus kinase (JAK) inhibitors, including tofacitinib, as add on therapy to methotrexate in patients who do not meet treatment goals with methotrexate alone. [2003]

Tofacitinib can be used alone or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs; examples include hydroxychloroquine, leflunomide, and sulfasalazine). [1] Concomitant use of tofacitinib with biologic DMARDs, such as TNF blocking agents (e.g., adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), interleukin-1 (IL-1) receptor antagonists (e.g., anakinra), anti-CD20 monoclonal antibodies (e.g., rituximab), selective costimulation modulators (e.g., abatacept), and anti-interleukin-6-receptor monoclonal antibodies (e.g., sarilumab, tocilizumab), is not recommended. [1] Concomitant use of tofacitinib with potent immunosuppressive agents (e.g., azathioprine, cyclosporine) also is not recommended. [1]

Clinical Experience

Safety and efficacy of tofacitinib have been evaluated in 6 randomized, double-blind, controlled studies of 6–24 months' duration in adults (18 years of age or older) with moderate to severe active rheumatoid arthritis. [1,3,4,5,6,14] In these studies, tofacitinib was administered as monotherapy in patients with an inadequate response to at least one biologic or nonbiologic DMARD, [3,14] in combination with methotrexate in patients with an inadequate response to methotrexate [4,5,14] or at least one TNF blocking agent, [6,14] or in combination with nonbiologic DMARD(s) in patients with an inadequate response to at least one biologic or nonbiologic DMARD. [15] Patients in these studies generally had 6 or more tender joints and 6 or more swollen joints. [3,4,5,6] Those receiving low stable dosages of corticosteroids (equivalent to 10 mg or less of prednisone daily) and/or stable dosages of nonsteroidal anti-inflammatory agents (NSAIAs) generally could continue such agents. [3,5,6] In some studies, patients also were allowed to continue stable dosages of DMARD antimalarial agents. [3,6] Tofacitinib was administered orally at a dosage of 5 or 10 mg twice daily (as conventional tablets). [1,3,4,5,6] In all 5 studies, patients randomized to receive placebo were subsequently advanced in a blinded manner to a second predetermined treatment of tofacitinib 5 or 10 mg twice daily. [1,3,4,5,6,14] Advancement to tofacitinib therapy occurred at 3 months in clinical studies of 6 months' duration. [1,3,6,14] In studies of at least 12 months' duration, treatment was advanced at 3 months in placebo recipients who were nonresponders and at 6 months in all other placebo recipients. [1,4,5,14]

The principal measures of clinical response in studies evaluating the efficacy of tofacitinib were the American College of Rheumatology criteria for improvement (ACR response) in measures of disease activity, changes in the Health Assessment Questionnaire–Disability Index (HAQ-DI, a measure of physical function and disability), and achievement of a Disease Activity Score (DAS28 [ESR]) of less than 2.6 (i.e., DAS-defined remission) at 3 or 6 months. [1,3,4,5,6] DAS28 (ESR) is a composite index of 4 weighted variables: swollen and tender counts for 28 joints, patient global assessment, and erythrocyte sedimentation rate (ESR). [3,4] An ACR 20 response is achieved if the patient experiences a 20% or greater improvement in tender and swollen joint count and a 20% or greater improvement in at least 3 of the following criteria: patient pain assessment, patient global assessment, physician global assessment, patient self-assessed disability, or laboratory measures of disease activity (i.e., ESR or C-reactive protein [CRP] concentrations). [1,3,12,16] An ACR 50 or ACR 70 response is defined using the same criteria but with a level of improvement of 50 or 70%, respectively. [1,12] Structural damage, as measured by changes in the total modified Sharp/van der Heijde score, a composite measure of radiographically assessed structural damage (i.e., joint erosion and joint space narrowing), also was assessed in the 2-year study. [5,14]

Clinical evaluations of tofacitinib indicate that, in adults with active rheumatoid arthritis despite therapy with methotrexate or other DMARD(s), administration of tofacitinib (alone or in combination with methotrexate or other nonbiologic DMARDs) at a dosage of 5 or 10 mg twice daily (as conventional tablets) results in higher ACR 20, ACR 50, and ACR 70 response rates at 3 and 6 months compared with placebo. [1,3,4,5,6,28] In clinical trials, higher ACR 20 response rates compared with placebo were observed within 2 weeks. [1,3,6,28] In clinical trials with a duration of at least 12 months, ACR response rates and HAQ-DI results were consistent at 6 and 12 months in patients receiving tofacitinib. [1,4,5,28] Across the 5 clinical trials, improvements in HAQ-DI scores for tofacitinib versus placebo were similar. [1,3,5,6,28]

In a 6-month study evaluating tofacitinib as monotherapy, 610 patients who had an inadequate response to prior DMARD therapy (biologic or nonbiologic) received tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, or placebo. [1,3] An ACR 20 response at 3 months was achieved in 59, 65, or 26% of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, or placebo, respectively. [1,3,28] The ACR 20 response rate following 6 months of therapy with tofacitinib 5 or 10 mg twice daily was 69 or 70%, respectively. [1,3,28] Patients receiving tofacitinib experienced greater improvements in physical functioning (as measured by change in HAQ-DI score) from baseline to 3 months, but were not substantially more likely to achieve DAS-defined remission at 3 months, compared with patients receiving placebo. [3]

In a 12-month clinical study evaluating concomitant therapy with tofacitinib and methotrexate, 717 patients with an inadequate response to prior methotrexate therapy were randomized to receive tofacitinib 5 or 10 mg twice daily, adalimumab 40 mg subcutaneously every other week, or placebo, each given in conjunction with a stable dosage of methotrexate. [1,4] Patients receiving tofacitinib 5 or 10 mg twice daily demonstrated greater improvement from baseline in physical functioning at 3 months compared with patients receiving placebo. [1,4,28] The mean difference from placebo in HAQ-DI improvement from baseline was −0.22 or −0.32 in patients receiving tofacitinib 5 or 10 mg twice daily, respectively. [1,28] At 6 months, an ACR 20 response was achieved in 52, 53, 47, or 28% and DAS-defined remission was achieved in 6, 13, 7, or 1% of patients assigned to receive tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab, or placebo, respectively; [4,14] in these analyses, in order to account for patients who switched from placebo to tofacitinib at 3 months, patients who did not respond by 3 months were considered nonresponders even if they responded after 3 months. [4]

In a 24-month clinical study evaluating concomitant therapy with tofacitinib and methotrexate, 797 patients with an inadequate response to prior methotrexate therapy were randomized to receive tofacitinib 5 or 10 mg twice daily or placebo, each given in conjunction with a stable dosage of methotrexate. [1,5] Patients receiving tofacitinib 10 mg twice daily, but not those receiving tofacitinib 5 mg twice daily, demonstrated greater improvement from baseline in HAQ-DI scores at 3 months compared with patients receiving placebo. [5] An ACR 20 response at 3 months was achieved in 55, 67, or 27% of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, or placebo, respectively; [1,28] at 6 months, ACR 20 response rates were 50, 62, and 25%, respectively. [1,5,28] DAS-defined remission at 6 months was reported in 6, 13, or 1% of patients assigned to receive tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, or placebo, respectively. [1,28] In these analyses, patients who did not achieve a response by month 3 were considered nonresponders even if they achieved a response after month 3. [5] At 6 months, tofacitinib 10 mg twice daily inhibited progression of structural damage, as measured by mean change in the total modified Sharp/van der Heijde score, compared with placebo; the difference between tofacitinib 5 mg twice daily and placebo did not reach statistical significance. [1,28] At 6 months, 84 or 79% of patients receiving tofacitinib 5 or 10 mg twice daily, respectively, had no progression of structural damage compared with 74% of those receiving placebo. [1,28] Although radiographic findings from this study suggested that tofacitinib slows progression of joint damage, [5,14] interpretation of the results is complicated because the proportion of study patients with radiographic progression of structural damage during this time period was small, approximately one-half of placebo recipients were considered nonresponders at 3 months and were advanced to a tofacitinib regimen, and missing data created problems with analysis. [14] Analysis of outcomes at study completion revealed that among 539 patients who completed 24 months of treatment, the proportion of patients who achieved disease remission or low disease activity was maintained from month 12 to month 24 and were similar between tofacitinib 5 or 10 mg twice daily. [34] Similarly, disease progression as measured by changes in Sharp/van der Heijde score, Erosion score, and Joint Space Narrowing score indicated that progression was minimal between month 12 and month 24 and was similar between tofacitinib dosages. [34]

Another 6-month clinical study evaluated concomitant therapy with tofacitinib and methotrexate in 399 patients with an inadequate response to prior therapy with at least one TNF blocking agent; patients were randomized to receive tofacitinib 5 or 10 mg twice daily or placebo, each given in conjunction with a stable dosage of methotrexate.[1][6] An ACR 20 response at 3 months was achieved in 41, 48, or 24% of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, or placebo, respectively.[1][6][28] The ACR 20 response rate following 6 months of therapy with tofacitinib 5 or 10 mg twice daily was 51 or 54%, respectively.[1][6][28] Patients receiving tofacitinib experienced greater improvements in physical functioning (as measured by change in HAQ-DI score) from baseline to 3 months and were substantially more likely to achieve DAS-defined remission at 3 months compared with patients receiving placebo.[6] DAS-defined remission was reported at 3 months in 7, 9, or 2% of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, or placebo, respectively.[6] The DAS-defined remission rate following 6 months of therapy with tofacitinib 5 or 10 mg twice daily was 8 or 15%, respectively.[6]

In a 12-month study in 792 patients with an inadequate response to at least one biologic or nonbiologic DMARD, tofacitinib 5 or 10 mg twice daily or placebo was added to a stable dosage of a nonbiologic DMARD (excluding potent immunosuppressive agents such as azathioprine or cyclosporine).[1][15] ACR responses and improvements in physical functioning generally were similar to those observed in other clinical studies evaluating tofacitinib for management of rheumatoid arthritis.[1][14][28]

A sixth clinical study, which was conducted in 952 adults with moderately to severely active rheumatoid arthritis who had never received methotrexate therapy, provided additional evidence that tofacitinib inhibits progression of joint damage.[1][17] In this 2-year study, patients were randomized to receive tofacitinib 5 or 10 mg twice daily (as conventional tablets) or methotrexate (initiated at a dosage of 10 mg weekly and increased to 20 mg weekly, if tolerated, by week 8).[1][17] At 6 and 12 months, tofacitinib 5 or 10 mg twice daily inhibited progression of structural damage, as measured by the mean change from baseline in the total modified Sharp/van der Heijde score, compared with methotrexate.[1][17][28] At 6 months, 73 or 77% of patients receiving tofacitinib 5 or 10 mg twice daily, respectively, had no progression of structural damage compared with 55% of patients receiving methotrexate.[1][28]

Although other dosages of tofacitinib have been studied, the recommended dosage of tofacitinib for the management of rheumatoid arthritis in adults is 5 mg twice daily (as conventional tablets) or 11 mg once daily (as extended-release tablets).[1] A dosage of 10 mg twice daily (as conventional tablets) or 22 mg once daily (as extended-release tablets) is *not* recommended for the management of rheumatoid arthritis.[1]

For further information on the treatment of rheumatoid arthritis, see Uses: Rheumatoid Arthritis, in Methotrexate 10:00.

Clinical Perspective

The American College of Rheumatology issued guidelines for the treatment of rheumatoid arthritis in 2021.[2003] Disease-modifying treatments for rheumatoid arthritis include nonbiologic DMARDs (e.g., hydroxychloroquine, leflunomide, methotrexate, sulfasalazine), biologic DMARDs (e.g., TNF blocking agents, abatacept, tocilizumab, sarilumab, rituximab), and/or targeted synthetic DMARDs (e.g., Janus kinase [JAK] inhibitors).[2003] Specific agents for rheumatoid arthritis treatment are selected according to current disease activity, prior therapies used, and the presence of comorbidities.[2003] A "treat-to-target" approach is typically employed, with the goal of achieving a predefined target of low disease activity or remission.[2003]

Targeted synthetic DMARDs used in the treatment of rheumatoid arthritis include the JAK inhibitors baricitinib, tofacitinib, and upadacitinib.[2003] Methotrexate monotherapy is strongly recommended over biologic or targeted synthetic DMARD monotherapy in DMARD-naive patients with moderate to high disease activity.[2003] Methotrexate monotherapy also is strongly preferred over combined therapy with a non-TNF blocking agent biologic DMARD or targeted synthetic DMARD because of the lack of proven benefit and additional risks and costs associated with combined therapy.[2003] Randomized controlled trials evaluating add-on therapy with a biologic or targeted synthetic DMARD or triple therapy (methotrexate, sulfasalazine, and hydroxychloroquine) demonstrated equivalent long-term outcomes in patients with receiving add-on therapy with a biologic or targeted synthetic DMARD and those receiving triple therapy; therefore, targeted synthetic DMARDs and biologic DMARDs (including TNF blocking agents) are conditionally recommended as add-on therapy for patients with an inadequate response to maximally tolerated doses of methotrexate.[2003][2053][2054][2055] Recommendations for the use and selection of targeted synthetic DMARDs in rheumatoid arthritis vary based on the presence of certain comorbidities (e.g., heart failure, previous serious infection, nontuberculous mycobacterial lung disease).[2003] Consult the American College of Rheumatology guidelines for additional details.[2003]

Juvenile Idiopathic Arthritis

Tofacitinib (as oral solution or conventional tablets) is used for the management of active polyarticular-course juvenile idiopathic arthritis (JIA) in pediatric patients 2 years of age and older who have had an inadequate response or intolerance to one or more TNF blocking agents.[1][29] Tofacitinib has been shown to reduce disease flares in such patients.[1][29] Concomitant use of tofacitinib with biologic DMARDs or with potent immunosuppressive agents (e.g., azathioprine, cyclosporine) is not recommended.[1] Safety and efficacy of tofacitinib in polyarticular-course JIA is based principally on the results of a randomized controlled trial.[1][29][35]

Clinical Experience

Efficacy and safety of tofacitinib for the management of polyarticular-course JIA has been evaluated in a double-blind, placebo-controlled, randomized-withdrawal study (NCT02592434) in pediatric patients 2–17 years of age with active polyarthritis.[1][29][35] The study included patients with rheumatoid factor (RF)-negative polyarthritis (46%), RF-positive polyarthritis (17%), extended oligoarthritis (12%), or systemic JIA with active arthritis but without systemic manifestations (6%) who had an inadequate response or intolerance to one or more DMARDs (methotrexate or biologic agents), as well as pediatric patients with juvenile psoriatic arthritis (9%) or enthesitis-related arthritis (9%) who had an inadequate response to nonsteroidal anti-inflammatory agents (NSAIAs).[1][29] The principal measures of clinical response were the ACR core criteria for juvenile idiopathic arthritis (JIA ACR criteria).[1] A JIA ACR 30 response is achieved if the patient experiences a 30% or greater improvement in at least 3 of the following 6 criteria, with no more than 1 criterion worsening by more than 30%: number of active joints, number of joints with limited range of motion, physician's global assessment of disease activity, parent's or patient's global assessment of overall well-being, physical function, and ESR.[30][31]

Following an 18-week, run-in period during which 225 patients received open-label treatment with tofacitinib (5 mg twice daily or an equivalent, weight-based, twice-daily dosage), those who achieved a JIA ACR 30 response were randomized to receive tofacitinib (5 mg twice daily or an equivalent, weight-based, twice-daily dosage) or placebo for 26 weeks; tofacitinib was administered as oral solution or conventional tablets.[1] During both treatment periods, approximately one-third of patients received oral corticosteroids and approximately two-thirds received methotrexate concomitantly; concomitant use of biologic agents or DMARDs other than methotrexate was not permitted.[1] A total of 173 patients were entered into the 26-week randomized-withdrawal period.[1] Over this period, a smaller proportion of tofacitinib-treated patients compared with placebo recipients (31 versus 55%) experienced disease flares (defined as worsening of at least 30% from baseline in at least 3 of the 6 JIA ACR core criteria and improvement of at least 30% in no more than 1 of the core criteria).[1]

Clinical Perspective

Polyarticular JIA is characterized by involvement of more than 5 joints.[2013] Because of the prolonged course of active disease, children with polyarticular-course JIA are often refractory to treatment compared with children without polyarticular disease, and are at greater risk for joint damage, poor functional outcome, and decreased quality of life.[2050]

The American College of Rheumatology and the Arthritis Foundation issued a joint guideline for the treatment of juvenile idiopathic arthritis manifesting as nonsystemic polyarthritis (including polyarticular disease), sacroiliitis, or enthesitis in 2019.[2013] Several drug classes are used to treat juvenile idiopathic arthritis, including NSAIAs, systemic and intra-articular corticosteroids, nonbiologic DMARDs (e.g., methotrexate, sulfasalazine, hydroxychloroquine, leflunomide), and biologic DMARDs (e.g., TNF blocking agents, abatacept, tocilizumab, rituximab).[2013] Specific agents for juvenile idiopathic arthritis treatment are selected according to the presence of certain risk factors (e.g., positive anti-cyclic citrullinated peptide antibodies, positive rheumatoid factor, joint damage), level of disease activity, involvement of specific joints, presence of certain comorbidities (e.g., uveitis), and prior therapies used.[2013] An individualized "treat-to-target" approach is typically employed, with the goal of achieving remission or minimal/low disease activity.[2014]

Psoriatic Arthritis

Tofacitinib citrate (as conventional or extended-release tablets) is used for the management of active psoriatic arthritis in adults who have had an inadequate response or intolerance to one or more TNF blocking agents.[1][18][19] Tofacitinib has been shown to induce clinical responses and improve physical functioning in patients with psoriatic arthritis.[1][18][19] Concomitant use of tofacitinib with biologic DMARDs or with potent immunosuppressive agents (e.g., azathioprine, cyclosporine) is not recommended.[1] Safety and efficacy of tofacitinib in treatment of psoriatic arthritis is based principally on the results of 2 randomized controlled trials.[1][18][19] Guidelines for the treatment of psoriatic arthritis generally recommend that patients with active disease despite treatment with an oral small molecule or with a TNF blocking agent be switched to a TNF blocking agent, an IL-17 inhibitor, or an IL-12/23 inhibitor instead of switching to tofacitinib.[2005] Tofacitinib may also be used if oral administration is preferred by the patient or if the patient has a history of recurrent or severe Candida infection.[2005]

Clinical Experience

Efficacy and safety of tofacitinib for the management of psoriatic arthritis in adults have been established in 2 randomized, double-blind studies.[1][18][19] OPAL Broaden was a 12-month active-and placebo-controlled study in 422 patients who had not responded adequately to at least one nonbiologic DMARD and had not received prior therapy with a TNF blocking agent.[1][18] OPAL Beyond was a 6-month placebo-controlled study in 394 patients with a history of inadequate response or intolerance to at least one TNF blocking agent.[1][19] Patients in both studies had active psoriatic arthritis (with at least 3 tender/painful joints and at least 3 swollen joints) and active plaque psoriasis.[1][18][19] In OPAL Broaden, patients were randomized in a 2:2:2:1:1 ratio to receive tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab 40 mg every 2 weeks, placebo for 3 months followed by tofacitinib 5 mg twice daily, or placebo for 3 months followed by tofacitinib 10 mg twice daily.[1][18] In OPAL Beyond, patients were randomized in 2:2:1:1 ratio to receive tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo for 3 months followed by tofacitinib 5 mg twice daily, or placebo for 3 months followed by tofacitinib 10 mg twice daily.[1][19] Patients in these studies received tofacitinib as conventional tablets.[1] Patients in both studies received concomitant therapy with a stable dosage of a single nonbiologic DMARD, most commonly methotrexate, throughout the study.[1][18][19] The primary measures of efficacy were the proportion of patients achieving an ACR 20 response at 3 months and the change from baseline in HAQ-DI score at 3 months; ACR 50 and ACR 70 responses also were assessed.[1][18][19] OPAL Broaden was not designed to evaluate noninferiority or superiority of tofacitinib compared with adalimumab.[1][18]

Patients enrolled in the 2 studies had various manifestations of psoriatic arthritis: involvement of more than 5 joints (90%), distal interphalangeal joint involvement (61%), involvement of fewer than 5 joints or asymmetric involvement (21%), spondylitis (19%), and arthritis mutilans (8%).[1] Enthesitis or dactylitis was present in 80 or 53% of patients, respectively.[1] The mean duration of the disease prior to enrollment in OPAL Broaden or OPAL Beyond was 6 or 9.4 years, respectively.[18][19][22] In OPAL Beyond, 66, 19, or 15% of patients had experienced treatment failure following use of 1, 2, or at least 3 TNF blocking agents, respectively.[1]

A greater proportion of patients receiving tofacitinib (5 or 10 mg twice daily) compared with those receiving placebo achieved ACR 20, ACR 50, and ACR 70 responses at 3 months in OPAL Broaden and ACR 20 and ACR 50 responses in OPAL Beyond.[1] [18] [19] [28] In these 2 studies, ACR 20, ACR 50, and ACR 70 responses were achieved at 3 months in 50, 28–30, and 17%, respectively, of patients receiving tofacitinib 5 mg twice daily; 47–61, 28–40, and 14%, respectively, of patients receiving tofacitinib 10 mg twice daily; 52, 33, and 19%, respectively, of those receiving adalimumab 40 mg every 2 weeks (in OPAL Broaden); and 24–33, 10–15, and 5–10%, respectively, of those receiving placebo.[1] [18] [19] [28] Improvement in ACR 20 response was observed within 2 weeks following initiation of tofacitinib therapy.[1] [18] [19] [28] ACR responses were maintained through the end of the studies (6 or 12 months), but could not be compared with placebo because of the advancement from placebo to tofacitinib at 3 months.[18] [19] Improvements in dactylitis and enthesitis also were observed in tofacitinib-treated patients.[1] [18] [28]

Improvements in physical function, as measured by change in HAQ-DI score from baseline to 3 months, were greater in both studies for patients receiving tofacitinib 5 or 10 mg twice daily compared with those receiving placebo.[1] [18] [19] [28] In the 2 studies, 50–53 of patients receiving tofacitinib 5 mg twice daily and 41–55% of those receiving tofacitinib 10 mg twice daily achieved a HAQ-DI response (defined as improvement from baseline to 3 months of 0.35 or greater) compared with 28–31% of those receiving placebo.[1] [22] [28]

Although radiographic evaluations were performed at baseline and 12 months in OPAL Broaden, all placebo recipients were advanced to tofacitinib therapy at 3 months and mean change in total modified Sharp/van der Heijde score from baseline to 12 months was minimal in all treatment groups in this study.[1] [18] [22] [28] Comparisons between the tofacitinib groups and the placebo or adalimumab groups were insufficient to establish an effect of tofacitinib on progression of structural damage in patients with psoriatic arthritis.[1] [22] [28]

Although other dosages of tofacitinib have been studied, the recommended dosage of tofacitinib for the management of psoriatic arthritis in adults is 5 mg twice daily (as conventional tablets) or 11 mg once daily (as extended-release tablets).[1] A dosage of 10 mg twice daily (as conventional tablets) or 22 mg once daily (as extended-release tablets) is *not* recommended for the management of psoriatic arthritis.[1]

Clinical Perspective

The American College of Rheumatology and the National Psoriasis Foundation issued a joint guideline for the treatment of psoriatic arthritis in 2018.[2005] Nonpharmacologic (e.g., physical therapy, occupational therapy, smoking cessation, weight loss, exercise, massage therapy) and pharmacologic therapy can ameliorate psoriatic arthritis symptoms and can occasionally result in disease remission.[2005] Disease-modifying treatments for psoriatic arthritis include nonbiologic DMARDs (e.g., methotrexate, sulfasalazine, cyclosporine, leflunomide, apremilast), biologic DMARDs (e.g., TNF blocking agents, secukinumab, ixekizumab, ustekinumab, brodalumab, abatacept), and/or targeted synthetic DMARDs (e.g., Janus kinase [JAK] inhibitors).[2005] Specific agents for psoriatic arthritis treatment are selected according to disease characteristics, including disease severity, as well as patient preferences and comorbidities.[2005] A "treat-to-target" approach is typically employed, with the goal of achieving low/minimal disease activity or remission.[2005] [2006]

Tofacitinib is a targeted synthetic DMARD that is used in the treatment of psoriatic arthritis, generally in patients with disease activity despite treatment.[2005] ACR and NPF conditionally recommend switching to a TNF blocking agent, IL-17 inhibitor, or IL-12/23 inhibitor over switching to tofacitinib therapy in adults with active disease despite treatment with nonbiologic DMARDs; however, clinicians should consider patient preferences and characteristics (e.g., administration route, comorbidities, risk of bacterial or fungal infection).[2005] Consult the American College of Rheumatology/National Psoriasis Foundation guideline for additional details.[2005]

Ankylosing Spondylitis

Tofacitinib citrate (as conventional or extended-release tablets) is used for the treatment of adults with active ankylosing spondylitis who have had an inadequate response or intolerance to one or more TNF blocking agents.[1] Concomitant use of tofacitinib with biologic DMARDs or with potent immunosuppressive agents (e.g., azathioprine, cyclosporine) is not recommended.[1] Safety and efficacy of tofacitinib for this use is based principally on the results of a placebo-controlled, randomized trial.[1] [36] Guidelines for the treatment of ankylosing spondylitis generally recommend other agents, including conventional synthetic DMARDs, TNF blocking agents, secukinumab, and ixekizumab over treatment with tofacitinib in patients with active disease.[2004]

Clinical Experience

Efficacy and safety of tofacitinib in ankylosing spondylitis have been assessed in one placebo-controlled, randomized, double-blind trial.[1] In this study, 269 adults with active ankylosing spondylitis (defined by both Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] and back pain score of 4 or greater despite therapy with an NSAIA, corticosteroid, or DMARD) were randomized to receive tofacitinib 5 mg twice daily for 16 weeks followed by tofacitinib 5 mg twice daily for 32 weeks, or placebo for 16 weeks followed by tofacitinib 5 mg twice daily for 32 weeks.[1] Approximately 7 or 21% of enrolled patients received concomitant methotrexate or sulfasalazine, respectively, from baseline to week 16.[1] The primary endpoint was the proportion of patients who achieved a response (defined as an Assessment of SpondyloArthritis International Society score of at least 20% improvement [ASAS20]) at 16 weeks.[1] The mean age of enrolled patients was approximately 40–42 years; 80–87% of patients were male, 78–81% were white, and 22% did not achieve an adequate response to 1 or 2 TNF blocking agents.[36]

At week 16, patients treated with tofacitinib 5 mg twice daily achieved substantially greater improvements in ASAS20 (56 versus 29%) and ASAS40 (41 versus 13%) responses compared to placebo.[1] In the subgroup of patients who had an inadequate response to TNF blocking agents, ASAS20 and ASAS40 response rates were 41 or 28%, respectively, in patients receiving tofacitinib 5 mg twice daily and 17 or 7%, respectively, in placebo recipients.[1]

Clinical Perspective

The American College of Rheumatology (ACR), the Spondylitis Association of America (SAA), and the Spondyloarthritis Research and Treatment Network (SPARTAN) issued a joint guideline for the treatment of ankylosing spondylitis in 2019.[2004] Treatments for ankylosing spondylitis include NSAIAs, nonbiologic DMARDs (e.g., methotrexate, sulfasalazine), biologic DMARDs (e.g., TNF blocking agents, secukinumab, ixekizumab), and/or targeted synthetic DMARDs (e.g., tofacitinib).[2004] Specific agents for ankylosing spondylitis treatment are selected according to current disease activity, prior therapies, and the presence of comorbidities.[2004] Treatment goals in ankylosing spondylitis include amelioration of symptoms, improved functioning, maintained ability to work, decreased complications, and prevention or slowing of skeletal damage.[2004]

Tofacitinib is a targeted synthetic DMARD used in the treatment of ankylosing spondylitis.[2004] For adults with active ankylosing spondylitis despite treatment with NSAIAs, ACR/SAA/SPARTAN conditionally recommend secukinumab or ixekizumab over treatment with tofacitinib, and in those who have contraindications to TNF blocking agents, secukinumab or ixekizumab are conditionally recommended over treatment with methotrexate, sulfasalazine, or tofacitinib.[2004] Clinicians should consider patients preferences and comorbidities (e.g., iritis, inflammatory bowel disease) when selecting therapy.[2004] Consult the joint guideline issued by the American College of Rheumatology, the Spondylitis Association of America, and the Spondyloarthritis Research and Treatment Network for additional details.[2004]

Ulcerative Colitis

Tofacitinib citrate (as conventional or extended-release tablets) is used for the management of moderately to severely active ulcerative colitis in adults who have had an inadequate response to or have not tolerated therapy with one or more TNF blocking agents.[1] [20] [27] Tofacitinib has been shown to induce clinical remission, improve endoscopic appearance of the mucosa, and produce sustained corticosteroid-free remission during maintenance therapy in patients with ulcerative colitis.[1] Concomitant use of tofacitinib with biologic therapies for ulcerative colitis or with potent immunosuppressive agents (e.g., azathioprine, cyclosporine) is not recommended.[1] Safety and efficacy of tofacitinib in the management of ulcerative colitis are based principally on the results of 3 randomized controlled trials.[1] [20] [21] Guidelines generally support the use of tofacitinib as an option for induction of remission in patients with moderate to severe ulcerative colitis; continuation of tofacitinib is recommended in patients with previously moderate to severe active disease who are in remission after induction with tofacitinib.[2019] [2020]

Clinical Experience

Efficacy and safety of tofacitinib for the management of ulcerative colitis in adults have been established in 3 randomized, double-blind, placebo-controlled studies, including 2 identically designed studies (OCTAVE Induction studies 1 and 2) evaluating tofacitinib (as conventional tablets) as induction therapy in a total of 1139 patients and one study (OCTAVE Sustain) evaluating tofacitinib (as conventional tablets) as maintenance therapy in 593 patients who achieved a clinical response upon completion of an OCTAVE Induction study.[1] [20] [21]

Patients enrolled in the induction studies had moderately to severely active ulcerative colitis (as defined by a Mayo score of 6–12 with an endoscopy subscore of at least 2 and rectal bleeding subscore of at least 1) and had a history of inadequate response or intolerance (i.e., treatment failure) to at least 1 of the following drugs: oral or IV corticosteroids, azathioprine, mercaptopurine, or a TNF blocking agent.[1] [20] The Mayo score ranges from 0–12 and includes 4 subscales (i.e., stool frequency, rectal bleeding, findings on endoscopy, and physician global assessment), each scored from 0–3 (normal to most severe, respectively).[1] [20] An endoscopy subscore of 2 is defined by marked erythema, lack of vascular pattern, friability, and erosions, whereas an endoscopy subscore of 3 is defined by spontaneous bleeding and ulceration.[21] The median baseline Mayo score for the induction studies was 9.[20] Patients were randomized in a 4:1 ratio to receive tofacitinib (10 mg twice daily) or placebo for 8 weeks.[1] [20] Stable dosages of oral aminosalicylates and corticosteroids (up to 25 mg daily of prednisone or equivalent) were permitted during the induction studies, but concomitant therapy with immunosuppressive agents (oral immunomodulators or biologic therapies) was not allowed.[1] [20] In the 2 induction studies combined, 52, 73, or 72% of patients had a history of treatment failure with TNF blocking agents, corticosteroids, or immunosuppressive agents, respectively.[1] [20] During the induction studies, 47% of patients received concomitant therapy with oral corticosteroids and 71% received aminosalicylates.[1]

In the induction studies, the primary measure of efficacy was the proportion of patients achieving clinical remission at 8 weeks; other outcome measures included clinical response and improved or normalized mucosal appearance at 8 weeks.[1] [20] Clinical remission was defined as a Mayo score of 0–2 with no individual subscore exceeding 1 and a rectal bleeding subscore of 0.[1] [20] Clinical response was defined as a decrease in Mayo score of at least 3 points and at least 30% from baseline score, with a reduction in rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 (no blood seen) or 1 (streaks of blood with stool less than half the time).[1] [20] [21] Improved mucosal appearance was defined as a Mayo endoscopy subscore of 0 (normal mucosa or inactive disease) or 1 (erythema, decreased vascular pattern), and normalized mucosal appearance was defined as a Mayo endoscopy subscore of 0.[1]

In both induction studies, clinical remission rates and rates of improved mucosal appearance were higher in patients receiving tofacitinib compared with those receiving placebo.[1] [20] Clinical remission was achieved in 17–18 or 4–8% of patients receiving tofacitinib or placebo, respectively, and improved mucosal appearance was observed in 28–31 or 12–16% of those receiving tofacitinib or placebo, respectively.[1] [20] In addition, clinical response was achieved in 55–60 or 29–33% of patients receiving tofacitinib or placebo, respectively, and mucosal appearance was normalized in 7% of patients receiving tofacitinib and 2% of those receiving placebo in both studies.[1] [20] Decreases in subscores for rectal bleeding and stool frequency were observed as early as 2 weeks in patients receiving tofacitinib.[1]

In OCTAVE Sustain, patients who achieved a clinical response at 8 weeks in OCTAVE Induction study 1 or 2 were re-randomized in a 1:1:1 ratio to receive tofacitinib (5 or 10 mg twice daily) or placebo for 52 weeks. [1] [20] [21] Approximately 30% of patients were in clinical remission at the start of the maintenance study; 49% were receiving oral corticosteroids; and 45, 75, or 70% had a history of treatment failure with TNF blocking agents, corticosteroids, or immunosuppressive agents, respectively. [1] [20] In patients receiving corticosteroids, a corticosteroid-tapering regimen was initiated at the start of the maintenance trial. [1] [20] As in the induction studies, concomitant therapy with oral aminosalicylates was permitted, but concomitant therapy with immunosuppressive agents (oral immunomodulators or biologic therapies) was not allowed. [1] [20] The primary measure of efficacy was the proportion of patients in clinical remission at 52 weeks. [1] [20] Other outcome measures included improved or normalized mucosal appearance at 52 weeks, maintenance of clinical response (i.e., clinical response at both baseline and 52 weeks), maintenance of clinical remission (i.e., clinical remission at both baseline and 52 weeks), and sustained corticosteroid-free remission (i.e., corticosteroid-free remission at baseline, 24 weeks, and 52 weeks). [1] [20]

In the maintenance study, both dosages of tofacitinib were more effective than placebo for achieving remission at 52 weeks, improved mucosal appearance at 52 weeks, and sustained corticosteroid-free remission. [1] [20] Clinical remission was achieved at 52 weeks in 34 or 41% of patients receiving tofacitinib 5 or 10 mg twice daily, respectively, compared with 11% of those receiving placebo. [1] [20] Improved mucosal appearance was observed at 52 weeks in 37 or 46% of patients receiving tofacitinib 5 or 10 mg twice daily, respectively, compared with 13% of those receiving placebo. [1] [20] Sustained corticosteroid-free remission was achieved in 35 or 47% of patients receiving tofacitinib 5 or 10 mg twice daily, respectively, compared with 5% of those receiving placebo. [1] [20] In addition, maintenance of clinical remission or clinical response was observed in 46 or 52%, respectively, of patients receiving tofacitinib 5 mg twice daily; 56 or 62%, respectively, of those receiving tofacitinib 10 mg twice daily, and 10 or 20%, respectively, of those receiving placebo. [1] [20] Mucosal appearance was normalized at 52 weeks in 15, 17, or 4% of patients receiving these respective treatments. [1]

Exploratory subgroup analysis demonstrated treatment effects regardless of prior failure of TNF blocking agent therapy, but suggested that response and remission rates tended to be higher in patients without a history of failed therapy with TNF blocking agents. [1] [21]

Data are available from an open-label extension study for a subset of 291 patients who did not achieve a clinical response upon completion of an OCTAVE Induction study but continued to receive tofacitinib at a dosage of 10 mg twice daily; after a total of 16 weeks of tofacitinib therapy, 149 of these patients (51%) achieved a clinical response and 25 patients (8.6%) achieved clinical remission. [1] [21] Data available at 52 weeks (for 144 of these patients) indicated that 65 patients were in clinical remission following 52 weeks of treatment with tofacitinib 10 mg twice daily. [1]

Clinical Perspective

The American College of Gastroenterology (ACG) and the American Gastroenterological Association (AGA) issued guidelines for the medical treatment of ulcerative colitis in adults in 2019 and 2020. [2018] [2019] [2020] Goals of therapy in ulcerative colitis include achieving and maintaining corticosteroid-free remission and promoting mucosal healing. [2020] Specific treatments for ulcerative colitis are selected according to the disease severity, as well as disease location/extent, disease prognosis, and previous therapies used. [2018] [2019] [2020] Drug classes used to treat ulcerative colitis include oral and rectal 5-aminosalicylates, oral and rectal corticosteroids, immunomodulators (e.g., thiopurines, methotrexate), tofacitinib, and biologic agents, including TNF blocking agents, vedolizumab, and ustekinumab. [2018] [2019] In most cases, if a drug used for induction therapy is effective, it is continued as maintenance of remission. [2019]

For adult outpatients with moderate to severe ulcerative colitis, AGA recommends TNF blocking therapies, vedolizumab, tofacitinib, or ustekinumab over no treatment. [2019] ACG recommends the use of oral corticosteroids, TNF blocking agents, vedolizumab, or tofacitinib for induction of remission in patients with moderately to severely active ulcerative colitis. [2020] Early use of biologic agents with or without immunomodulator therapy is conditionally recommended over gradual step up therapy after failure of 5-aminosalicylates. [2019] Patients with mildly active ulcerative colitis and multiple prognostic factors associated with an increased risk of hospitalization or surgery should be treated with therapies for moderately to severely active disease. [2020] Consult the American College of Gastroenterology guideline for additional details. [2020]

Other Uses

Psoriasis

Tofacitinib has been investigated for the treatment of plaque psoriasis†in several phase 3 randomized controlled trials. [39] [40] In two similarly designed 16-week trials, patients with moderate to severe chronic plaque psoriasis were randomized to receive tofacitinib 5 or 10 mg twice daily (as conventional tablets) or placebo twice daily. [39] Primary efficacy end points included the proportion of patients achieving Physician's Global Assessment (PGA) score of "clear" or "almost clear" (also referred to as PGA response) and the proportion of patients achieving a 75% or greater reduction in Psoriasis Area and Severity Index (PASI 75) score. [39] In these trials, substantially higher proportions of patients receiving tofacitinib 5 mg (41.9–46%) or 10 mg twice daily (approximately 59%) achieved PGA responses compared with placebo recipients (9–10.9%) at 16 weeks. [39] Similarly, substantially higher PASI 75 rates was observed in patients receiving tofacitinib 5 mg (39.9–46%) or 10 mg twice daily (59.2–59.6%) compared with placebo recipients (6.2–11.4%,). [39]

An additional 12-week phase 3 noninferiority trial randomized adult patients with chronic stable plaque psoriasis to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, etanercept 50 mg twice weekly, or placebo. [40] Primary efficacy end points included the proportion of patients achieving PGA response and the proportion achieving PASI 75. [40] Tofacitinib 10 mg twice daily demonstrated noninferiority compared with etanercept for PGA response and PASI 75 response; however, tofacitinib 5 mg twice daily did not meet the prespecified criteria for noninferiority. [40]

Dosage and Administration

General

Pretreatment Screening

Evaluate for latent or active tuberculosis infection prior to initiation of therapy; initiate antimycobacterial therapy if indicated. [1]

Evaluate for risk of thrombosis prior to initiation of therapy. [1]
Measure absolute lymphocyte count, absolute neutrophil count (ANC), and hemoglobin prior to initiation of therapy. [1] Do not initiate therapy in patients with an absolute lymphocyte count of <500/mm^3, ANC <1000/mm^3, or hemoglobin concentration <9 g/dL. [1]
Screen for viral hepatitis infection before initiating therapy. [1]

Patient Monitoring

Evaluate for latent or active tuberculosis infection during therapy according to applicable guidelines. [1]

Monitor closely for signs or symptoms of infection, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis prior to initiating therapy, during and after treatment with tofacitinib. [1]
Monitor lymphocyte count every 3 months during therapy. [1]
Monitor ANC and hemoglobin concentrations 4–8 weeks after initial of therapy and then every 3 months. [1]
Monitor liver enzymes periodically during therapy. [1]
Perform dermatologic examinations periodically throughout therapy in patients at increased risk for skin cancer. [1]
Monitor lipids 4–8 weeks after therapy initiation. [1]

Other General Considerations

Do not use concomitantly with biologic disease-modifying antirheumatic drugs (DMARDs), or potent immunosuppressive agents. [1]

Concomitant use with potent inducers of cytochrome P-450 (CYP) isoenzyme 3A4 (e.g., rifampin) may result in loss of or reduced clinical response to tofacitinib. [1]
Update immunizations according to current immunization guidelines prior to initiating therapy. [1]

Administration

Tofacitinib citrate conventional tablets, oral solution, or extended-release tablets are administered orally without regard to meals. [1] The extended-release tablets should be swallowed intact and should not be crushed, split, or chewed. [1] The oral solution should be administered using the press-in bottle adapter and oral dosing syringe provided by the manufacturer. [1]

Changes between conventional and extended-release tablets should be made by a clinician. [1] Pediatric patients receiving 5 mg as oral solution may be switched to the equivalent dose as conventional tablets. [1] The extended-release tablets and the oral solution are not interchangeable and should not be substituted for each other. [1]

Store tofacitinib (conventional tablets, extended-release tablets, and oral solution) at 20–25°C; excursions permitted between 15–30°C for tofacitinib oral solution . [1] Protect from light. [1] Tofacitinib oral solution must be used within 60 days of opening; discard any remaining oral solution after 60 days. [1]

Dosage

Dosage of tofacitinib citrate is expressed in terms of tofacitinib. [1]

Dosage recommendations specific to the condition being treated should be followed. [1] [25] [27]

Rheumatoid Arthritis, Psoriatic Arthritis, or Ankylosing Spondylitis in Adults

For the management of rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis in adults who have had an inadequate response or intolerance to methotrexate or for the management of psoriatic arthritis in adults who have had an inadequate response or intolerance to one or more tumor necrosis factor (TNF) blocking agents, the recommended dosage of tofacitinib is 5 mg twice daily (as conventional tablets) or 11 mg once daily (as extended-release tablets). [1] Patients receiving tofacitinib 5 mg twice daily (as conventional tablets) may be switched to tofacitinib 11 mg once daily (as extended-release tablets) the day following the last dose of the conventional tablets. [1]

In patients receiving concomitant therapy with potent inhibitors of CYP3A4 (e.g., ketoconazole) and in patients receiving concomitant therapy with a moderate inhibitor of CYP3A4 and potent inhibitor of CYP2C19 (e.g., fluconazole), dosage of tofacitinib (as conventional or extended-release tablets) should be reduced to 5 mg once daily (as conventional tablets). [1]

Dosage Modifications for Toxicity

If a serious infection develops, tofacitinib therapy should be interrupted until the infection has been controlled. [1]

Tofacitinib therapy also should be interrupted or discontinued in patients with lymphopenia, neutropenia, or anemia. [1]

In patients who develop a lymphocyte count of less than 500/mm^3(confirmed by repeat testing), tofacitinib should be discontinued. [1]

In patients with a persistent decrease in ANC to 500–1000/mm^3, tofacitinib therapy should be interrupted until the ANC exceeds 1000/mm^3; tofacitinib therapy then may be resumed at the usual dosage of 5 mg twice daily (as conventional tablets) or 11 mg once daily (as extended-release tablets). [1] Tofacitinib therapy should be discontinued in patients with an ANC of less than 500/mm^3. [1]

In patients with a decrease in hemoglobin concentration of more than 2 g/dL or with a hemoglobin concentration of less than 8 g/dL, tofacitinib therapy should be interrupted until the hemoglobin concentration has normalized. [1]

Juvenile Idiopathic Arthritis

For the management of active polyarticular-course juvenile idiopathic arthritis (JIA) in pediatric patients 2 years of age and older who have had an inadequate response or intolerance to one or more TNF blocking agents, dosage of tofacitinib (as conventional tablets or oral solution) is based on body weight; pediatric patients weighing 10 to less than 20 kg should receive 3.2 mg twice daily (as oral solution), those weighing 20 to less than 40 kg should receive 4 mg twice daily (as oral solution), and those weighing 40 kg or more should receive 5 mg twice daily (as conventional tablets or oral solution). [1]

In pediatric patients receiving concomitant therapy with potent inhibitors of CYP3A4 (e.g., ketoconazole) and in patients receiving concomitant therapy with one or more drugs that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole), dosage of tofacitinib should be reduced from 3.2 mg twice daily to 3.2 mg once daily, from 4 mg twice daily to 4 mg once daily, or from 5 mg twice daily to 5 mg once daily. [1]

Dosage Modifications for Toxicity

If a serious infection develops, tofacitinib therapy should be interrupted until the infection has been controlled. [1]

Tofacitinib therapy also should be interrupted or discontinued in patients with lymphopenia, neutropenia, or anemia. [1]

In patients who develop a lymphocyte count of less than 500/mm^3(confirmed by repeat testing), tofacitinib should be discontinued. [1]

In patients with a persistent decrease in ANC to 500–1000/mm^3, tofacitinib therapy should be interrupted until the ANC exceeds 1000/mm^3. [1] Tofacitinib therapy should be discontinued in patients with an ANC of less than 500/mm^3. [1]

In patients with a decrease in hemoglobin concentration of more than 2 g/dL or with a hemoglobin concentration of less than 8 g/dL, tofacitinib therapy should be interrupted until the hemoglobin concentration has normalized. [1]

Ulcerative Colitis

For the management of ulcerative colitis in adults who have had an inadequate response or intolerance to TNF blocking agents, the recommended induction dosage of tofacitinib is 10 mg twice daily (as conventional tablets) or 22 mg once daily (as extended-release tablets) for at least 8 weeks; patients should then be evaluated and, depending on therapeutic response, may begin maintenance therapy with the drug. [1] If necessary, the induction dosage of 10 mg twice daily (as conventional tablets) or 22 mg once daily (as extended-release tablets) may be administered for a maximum of 16 weeks. [1] If adequate therapeutic benefit is not achieved after 16 weeks of treatment at this dosage, this dosage should be discontinued. [1]

The recommended adult maintenance dosage is 5 mg twice daily (as conventional tablets) or 11 mg once daily (as extended-release tablets). [1] For patients with loss of response during maintenance therapy, a dosage of 10 mg twice daily (as conventional tablets) or 22 mg once daily (as extended-release tablets) may be considered and should be limited to the shortest duration needed, with careful consideration of potential benefits and risks for the individual patient. [1] The lowest effective dosage that maintains response should be used. [1]

Patients may be switched from therapy with tofacitinib conventional tablets to therapy with the extended-release tablets (i.e., from 5 mg twice daily [as conventional tablets] to 11 mg once daily [as extended-release tablets] or from 10 mg twice daily [as conventional tablets] to 22 mg once daily [as extended-release tablets]) the day following the last dose of the conventional tablets. [1]

In patients receiving concomitant therapy with potent inhibitors of CYP3A4 (e.g., ketoconazole) and in patients receiving concomitant therapy with a moderate inhibitor of CYP3A4 and potent inhibitor of CYP2C19 (e.g., fluconazole), dosage of tofacitinib (as conventional tablets) should be reduced from 10 mg twice daily to 5 mg twice daily or from 5 mg twice daily to 5 mg once daily and dosage of tofacitinib (as extended-release tablets) should be reduced from 22 mg once daily to 11 mg once daily or from 11 mg once daily (as extended-release tablets) to 5 mg once daily (as conventional tablets). [1]

Dosage Modifications for Toxicity

If a serious infection develops, tofacitinib therapy should be interrupted until the infection has been controlled. [1]

Tofacitinib therapy also should be interrupted or discontinued in patients with lymphopenia, neutropenia, or anemia. [1]

In patients who develop a lymphocyte count of less than 500/mm^3(confirmed by repeat testing), tofacitinib (as conventional tablets or extended-release tablets) should be discontinued. [1]

In patients receiving tofacitinib (as conventional tablets) who have a persistent decrease in ANC to 500–1000/mm^{3}on a dosage of 10 mg twice daily, dosage of the drug should be reduced to 5 mg twice daily; when the ANC exceeds 1000/mm^3, dosage may be returned to 10 mg twice daily based on clinical response. [1] In patients with a persistent decrease in ANC to 500–1000/mm^{3}on a dosage of 5 mg twice daily, tofacitinib therapy should be interrupted until the ANC exceeds 1000/mm^3; therapy with tofacitinib conventional tablets then may be resumed at a dosage of 5 mg twice daily. [1] Tofacitinib therapy should be discontinued in patients with an ANC of less than 500/mm^3. [1]

In patients receiving tofacitinib (as extended-release tablets) who have a persistent decrease in ANC to 500–1000/mm^{3}on a dosage of 22 mg once daily, dosage of the drug should be reduced to 11 mg once daily; when the ANC exceeds 1000/mm^3, dosage may be returned to 22 mg once daily based on clinical response. [1] In patients with a decrease in ANC to 500–1000/mm^{3}on a dosage of 11 mg once daily, tofacitinib therapy should be interrupted until the ANC exceeds 1000/mm^3; therapy with tofacitinib extended-release tablets then may be resumed at a dosage of 11 mg once daily. [1] Tofacitinib therapy should be discontinued in patients with an ANC of less than 500/mm^3. [1]

In patients with a decrease in hemoglobin concentration of more than 2 g/dL or with a hemoglobin concentration of less than 8 g/dL, tofacitinib therapy should be interrupted until the hemoglobin concentration has normalized. [1]

Psoriasis†

For the treatment of plaque psoriasis†in adults, tofacitinib 5 or 10 mg twice daily (as conventional tablets) has been used. [39] [40]

Special Populations

Hepatic Impairment

Dosage reduction may be necessary in patients with hepatic impairment(see Table 1). [1]

Table 1. Recommended Dosage Modification for Tofacitinib in Patients with Hepatic Impairment [1]

Severity	Rheumatoid Arthritis, Psoriatic Arthritis, or Ankylosing Spondylitis	Juvenile Idiopathic Arthritis	Ulcerative Colitis
Mild hepatic impairment	No dosage adjustment necessary	No dosage adjustment necessary	No dosage adjustment necessary
Moderate hepatic impairment	*Conventional tablet* : Reduce dosage to 5 mg once daily	*Oral solution* : If current dosage is 3.2 mg twice daily, reduce dosage to 3.2 mg *once* dailyIf current dosage is 4 mg twice daily, reduce dosage to 4 mg *once* dailyIf current dosage is 5 mg twice daily, reduce dosage to 5 mg *once* daily	*Conventional tablet* : If current dosage is 10 mg twice daily, reduce dosage to 5 mg twice dailyIf current dosage is 5 mg twice daily, reduce dosage to 5 mg *once* daily
	Extended-release tablet : Reduce dosage to 5 mg once daily (as conventional tablets)		*Extended-release tablet* : If current dosage is 22 mg once daily, reduce dosage to 11 mg once daily; if current dosage is 11 mg once daily, reduce dosage to 5 mg once daily (as conventional tablets)
Severe hepatic impairment	Do not use	Do not use	Do not use

Renal Impairment

Dosage reduction may be necessary in patients with renal impairment(see Table 2). [1]

Table 2. Recommended Dosage Modification for Tofacitinib in Patients with Renal Impairment [1]

Severity	Rheumatoid Arthritis, Psoriatic Arthritis, or Ankylosing Spondylitis	Juvenile Idiopathic Arthritis	Ulcerative Colitis
Mild renal impairment	No dosage adjustment necessary	No dosage adjustment necessary	No dosage adjustment necessary

Moderate or severe renal impairment	*Conventional tablet* : Reduce dosage to 5 mg once daily	*Oral solution* : If current dosage is 3.2 mg twice daily, reduce dosage to 3.2 mg *once* dailyIf current dosage is 4 mg twice daily, reduce dosage to 4 mg *once* dailyIf current dosage is 5 mg twice daily, reduce dosage to 5 mg *once* daily	*Conventional tablet* : If current dosage is 10 mg twice daily, reduce dosage to 5 mg twice dailyIf current dosage is 5 mg twice daily, reduce dosage to 5 mg *once* daily
	Extended-release tablet : Reduce dosage to 5 mg once daily (as conventional tablets)		*Extended-release tablet* If current dosage is 22 mg once daily, reduce dosage to 11 mg once daily; if current dosage is 11 mg once daily, reduce dosage to 5 mg once daily (as conventional tablets)
Hemodialysis	Administer after dialysis session; if a dose is taken before the dialysis procedure, administering a supplemental dose after dialysis is not necessary	Administer after dialysis session; if a dose is taken before the dialysis procedure, administering a supplemental dose after dialysis is not necessary	Administer after dialysis session; if a dose is taken before the dialysis procedure, administering a supplemental dose after dialysis is not necessary

Geriatric Patients

The manufacturer makes no specific dosage recommendations for geriatric patients. [1]

Cautions

Contraindications

The manufacturer states that there are no known contraindications to the use of tofacitinib. [1]

Warnings/Precautions

Warnings

Infectious Complications

A boxed warning regarding the risk of infectious complications is included in the prescribing information for tofacitinib. [1] Patients receiving tofacitinib are at increased risk of developing serious infections that may require hospitalization or result in death. [1] [3] [4] Serious and sometimes fatal infections caused by bacterial, mycobacterial, invasive fungal, viral, or other opportunistic organisms—including cryptococcosis, pneumocystosis, histoplasmosis, tuberculosis and other mycobacterial infections, esophageal candidiasis, multidermatomal herpes zoster, cytomegalovirus infection, listeriosis, and BK virus infection—have been reported in patients receiving tofacitinib. [1] [3] [4] [5] The most common serious infections reported in patients receiving tofacitinib included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. [1] Other serious infections (e.g., coccidioidomycosis) also may occur. [1] Patients may present with disseminated rather than localized disease. [1] Most patients who developed serious infections were receiving concomitant therapy with immunosuppressive agents such as methotrexate or corticosteroids. [1]

In controlled clinical trials in patients with rheumatoid arthritis, the overall frequency of infections during the first 3 months of treatment was 20, 22, or 18% in patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, or placebo, respectively. [1] Serious infections were reported at a rate of 1.7 events per 100 patient-years in tofacitinib-treated patients and 0.5 events per 100 patient-years in placebo-treated patients during the first 3 months of therapy. [1] The rate of serious infections during the first 12 months of tofacitinib therapy was 2.7 events per 100 patient-years. [1]

In patients with ulcerative colitis, the risk of serious infections and herpes zoster (including meningoencephalitis and ophthalmologic and disseminated cutaneous infections) was dose dependent, occurring more frequently in patients receiving tofacitinib 10 mg twice daily compared with those receiving tofacitinib 5 mg twice daily. [1]

The risk of infection may be higher with increasing degrees of lymphopenia. [1] Lymphocyte counts should be considered when assessing an individual patient's risk of infection. [1]

Because of the higher incidence of infections generally observed in patients with diabetes mellitus, tofacitinib should be used with caution in diabetic patients. [1] In addition, because patients with a history of chronic lung disease and those who develop interstitial lung disease may be more susceptible to infections, caution is advised in these patients. [1]

Patients should be closely monitored during and after treatment with tofacitinib for the development of signs or symptoms of infection (e.g., fever, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates, serious systemic illness including shock). [1]

Tofacitinib therapy should not be initiated in patients with serious active infections, including localized infections. [1] Tofacitinib should be interrupted in patients who develop a serious infection, opportunistic infection, or sepsis and should not be resumed until the infection is controlled. [1] Clinicians should consider potential risks and benefits of tofacitinib prior to initiating therapy in patients with a history of chronic, recurring, serious, or opportunistic infections; patients with underlying conditions that may predispose them to infections; and patients who have been exposed to tuberculosis or who reside or have traveled in regions where tuberculosis or mycoses are endemic. [1] Any patient who develops a new infection while receiving tofacitinib should undergo a thorough diagnostic evaluation (appropriate for an immunocompromised patient), appropriate anti-infective therapy should be initiated, and the patient should be closely monitored. [1]

Because tuberculosis has been reported in patients receiving tofacitinib, all patients should be evaluated for active or latent tuberculosis and for the presence of risk factors for tuberculosis prior to and periodically during therapy with the drug. [1] When indicated, an appropriate antimycobacterial regimen for the treatment of latent tuberculosis infection should be initiated prior to tofacitinib therapy. [1] Antimycobacterial therapy also should be considered prior to initiation of tofacitinib in individuals with a history of latent or active tuberculosis in whom an adequate course of antimycobacterial therapy cannot be confirmed and in individuals with a negative test for latent tuberculosis who have risk factors for tuberculosis. [1] Consultation with a tuberculosis specialist is recommended when deciding whether antimycobacterial therapy should be initiated. [1] Patients receiving tofacitinib, including individuals with a negative test for latent tuberculosis, should be monitored for signs and symptoms of active tuberculosis, which may present with pulmonary or extrapulmonary disease. [1]

Viral reactivation can occur in patients receiving tofacitinib. [1] Herpes zoster reactivation has been reported in patients receiving the drug. [1] The risk of herpes zoster is increased in patients receiving tofacitinib and appears to be increased in patients treated in Japan or Korea. [1]

Reactivation of hepatitis B virus (HBV) infection also has been reported during postmarketing experience. [1] The effect of tofacitinib on the risk of reactivation of chronic viral hepatitis is not known; patients with serologic evidence of HBV or hepatitis C virus (HCV) infection were excluded from clinical trials of the drug. [1] All patients should be screened for viral hepatitis in accordance with clinical guidelines before initiation of tofacitinib therapy. [1]

Mortality

A boxed warning regarding the increased risk of mortality is included in the prescribing information for tofacitinib. [1] In a postmarketing study (NCT02092467; RA Safety Study 1) evaluating safety of tofacitinib in patients with rheumatoid arthritis, a higher overall mortality rate, including sudden cardiovascular death, in patients receiving tofacitinib 5 or 10 mg twice daily compared with those receiving a tumor necrosis factor (TNF) blocking agent (0.88 and 1.23, respectively, versus 0.69 cases of all-cause mortality per 100 patient-years) was observed. [1] [27] Because the study was designed to assess cardiovascular risks as well as risks of cancer and opportunistic infections, enrolled patients were 50 years of age or older and had at least one cardiovascular risk factor. [25] [26] [27]

The 10-mg twice-daily (as conventional tablets) or 22-mg once-daily (as extended-release tablets) dosage of tofacitinib is FDA-labeled only for the management of ulcerative colitis for use as induction therapy and in limited situations during maintenance therapy. [1] [27] Tofacitinib at a dosage of 10 mg twice daily or an equivalent weight-based, twice-daily dosage (as conventional tablets or oral solution) or at a dosage of 22 mg once daily (as extended-release tablets) is *not* recommended for the management of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or polyarticular-course JIA. [1] In patients with ulcerative colitis, tofacitinib should be used at the lowest effective dosage and for the shortest duration needed to achieve and maintain therapeutic response. [1] [27]

Malignancies and Lymphoproliferative Disorders

A boxed warning regarding the risk of malignancies and lymphoproliferative disorders is included in the prescribing information for tofacitinib. [1] Lymphoma and other malignancies (e.g., lung cancer, breast cancer, melanoma, prostate cancer, pancreatic cancer) have been observed in patients receiving tofacitinib. [1] [4] [5] In addition, an increased incidence of Epstein Barr virus (EBV)-associated posttransplant lymphoproliferative disorder has been observed in renal allograft recipients receiving tofacitinib concomitantly with immunosuppressive agents. [1]

Among 3328 patients with rheumatoid arthritis receiving tofacitinib with or without other disease-modifying antirheumatic drugs (DMARDs) in clinical trials, 11 solid tumors and one lymphoma were diagnosed during the first 12 months of treatment compared with no cases of solid tumors or lymphoma in 809 patients receiving placebo with or without other DMARDs. [1] Lymphomas and solid tumors also have been observed in long-term extension studies in patients with rheumatoid arthritis receiving tofacitinib. [1] [4]

In controlled clinical trials in patients with rheumatoid arthritis, malignancies (excluding nonmelanoma skin cancer) were reported at a rate of 0.3 events per 100 patient-years in tofacitinib-treated patients and 0 events per 100 patient-years in placebo-treated patients during the first 3 months of treatment. [1] The rate of malignancies (excluding nonmelanoma skin cancer) during the first 12 months of treatment in patients receiving tofacitinib in clinical trials was 0.6 events per 100 patient-years in patients receiving 10 mg twice daily and 0.4 events per 100 patient-years in patients receiving 5 mg twice daily. [1] The most common malignancies reported, including those reported during long-term extension studies, were lung and breast cancer, followed by gastric, colorectal, renal cell, and prostate cancer, lymphoma, and malignant melanoma. [1]

Initial results from a postmarketing safety study (NCT02092467) in patients with rheumatoid arthritis have suggested a higher incidence of malignancies (excluding nonmelanoma skin cancer) in patients receiving tofacitinib (either 5 or 10 mg twice daily) compared with those receiving a TNF blocking agent. [32] The manufacturer released results indicating that the trial failed to establish noninferiority of tofacitinib for this outcome compared with a TNF blocking agent; the incidence of malignancies (excluding nonmelanoma skin cancer) in patients receiving tofacitinib (both dosages combined) or a TNF blocking agent was 1.13 or 0.77 events per 100 patient-years, respectively. [33] The manufacturer stated that the most frequently reported malignancy (excluding nonmelanoma skin cancer) in patients receiving tofacitinib was lung cancer. [33] FDA is awaiting additional results from the study. [32]

In controlled clinical trials in patients with psoriatic arthritis, 3 malignancies (excluding nonmelanoma skin cancer) were diagnosed in 474 patients receiving tofacitinib with nonbiologic DMARDs for 6–12 months compared with no malignancies in 236 patients receiving placebo with nonbiologic DMARDs for 3 months and no malignancies in 106 patients receiving adalimumab with nonbiologic DMARDs for 12 months. [1] Malignancies also have been observed in a long-term extension study in patients with psoriatic arthritis receiving tofacitinib. [1]

In controlled clinical trials in 1220 patients with ulcerative colitis (including both 8-week induction and 52-week maintenance trials), no cases of solid tumors or lymphoma were diagnosed in tofacitinib-treated patients. [1] In a long-term extension study, malignancies (including solid tumors and lymphoma) were observed more frequently in patients receiving a tofacitinib dosage of 10 mg twice daily. [1] The occurrence of nonmelanoma skin cancer in tofacitinib-treated patients with ulcerative colitis was dose dependent; a tofacitinib dosage of 10 mg twice daily was associated with increased risk. [1]

In the RA Safety Study 1 (NCT02092467), malignancies occurred more frequently in patients with rheumatoid arthritis treated with tofacitinib 5 or 10 mg twice daily compared with those who received a TNF blocking agent. [1] The incidence rate of malignancies (excluding nonmelanoma skin cancer) per 100 patient-years was 1.13 with tofacitinib 5 mg twice daily, 1.13 with tofacitinib 10 mg twice daily, and 0.77 with TNF blocking agents. [1] Lymphomas and lung cancers were observed at a higher rate in patients treated with tofacitinib 5 mg twice a day and tofacitinib 10 mg twice a day compared to those treated with TNF blocking agents. [1] The incidence rate of lymphomas per 100 patient-years was 0.07 for tofacitinib 5 mg twice daily, 0.11 for tofacitinib 10 mg twice daily, and 0.02 for TNF blocking agents. [1] The incidence rate of lung cancers per 100 patient-years among current and past smokers was 0.48 for tofacitinib 5 mg twice a day, 0.59 for tofacitinib 10 mg twice a day, and 0.27 for TNF blocking agents. [1] Based