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Formulary Drug Reviews

Tofacitinib

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Generic Name:	Tofacitinib
Proprietary Name:	*Xeljanz* (Pfizer, Inc.)
Approval Rating:	1S
Therapeutic Class:	Immunomodulators, Jak Inhibitors
Similar Drugs:	None
Sound- or Look-Alike Names:	Tositumomab

INDICATIONS

Tofacitinib is a novel, small-molecule Janus-associated kinase (Jak) inhibitor approved for the treatment of adult patients with moderate to severe rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate therapy. It can be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs). Combination therapy with biologic DMARDs or potent immunosuppressants, such as azathioprine and cyclosporine, should not be used with tofacitinib.[1] See **Table 1** for a comparison of the approved indications for selected biological agents used in the treatment of RA.

The 4 members of the Jak family, Jak1, Jak2, Jak3, and tyrosine kinase 2 (Tyk2), serve a critical function in immune cell activation, proinflammatory cytokine production, and cytokine signaling.[2-5] Jak1, Jak2, and Tyk2 are universally expressed; however, Jak3 is primarily expressed in hematopoietic cells.[6,7] Jak3 interacts with the interleukin (IL)–2 receptor common gamma chain shared by the receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21.[3,7,8] These cytokines bind to type I and II cytokine receptors and signal via the Jak-signal transducers, resulting in the activation of transcription of genes for lymphopoiesis and homeostasis.[4] The function of Jak signaling illustrates the vital role it plays in mediation of inflammatory immune responses and presents a novel approach to influence the pathophysiology of inflammatory autoimmune diseases, such as RA.

RA is a chronic inflammatory autoimmune disease that affects more than 1.3 million Americans and 1% of the world population.[9] The presentation of RA is the gradual development of joint pain and stiffness and swelling of joints lined by synovial membrane.

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Table 1. FDA-approved indications for selected biological agents used in the treatment of rheumatoid arthritis[1,11,12]

				Indications							
Generic	Brand	Major mechanism	Mode of administration	Ankylosing spondylitis	Crohn disease	Ulcerative colitis	Plaque psoriasis	Psoriatic arthritis	Juvenile idiopathic arthritis	Rheumatoid arthritis	Renal transplant
Abatacept	*Orencia*	T-cell costimulation modulator	IV/ subcutaneous injection						X	X	
Adalimumab	*Humira*	TNF- alpha inhibitor	Subcutaneous injection	X	X		X	X	X	X	
Anakinra	*Kineret*	IL-1 receptor antagonist	Subcutaneous injection							X	
Certolizumab pegol	*Cimzia*	TNF-alpha inhibitor	Subcutaneous injection		X					X	
Etanercept	*Enbrel*	TNF-alpha inhibitor	Subcutaneous injection	X	X[a]		X	X	X	X	
Golimumab	*Simponi*	TNF-alpha inhibitor	Subcutaneous injection	X				X		X	
Infliximab	*Remicade*	TNF-alpha inhibitor	IV injection	X	X	X	X	X	X	X	
Tocilizumab	*Actemra*	IL-6 receptor antagonist	IV injection							X	
Tofacitinib	*Xeljanz*	Jak1/2/3 inhibitor	Oral		X[b]		X[b]			X	X[b]

Note: FDA = US Food and Drug Administration; IV = intravenous; TNF = tumor necrosis factor.
[a]Off-label use.
[b]Investigational uses.

The elicited autoimmune inflammatory response inevitably results in irreversible damage to bones, cartilage, and other joint structures. Despite advances in RA treatments in the past decade, with DMARDs providing the foundation of therapy, it is estimated that 30% to 40% of patients are not adequately controlled by the available treatments, resulting in significant health and socioeconomic burden.[8,10]

CLINICAL PHARMACOLOGY

Tofacitinib is an orally bioavailable, small-molecule inhibitor of the Jak family, Jak1, Jak2, Jak3, and Tyk2, that competitively binds the active site of the adenosine triphosphate kinase domain, resulting in the prevention of phosphorylation and subsequent activation of the signal transducers and activators of transcription (STATs).[1,3,13] In vivo kinase assays have demonstrated the greatest potency of inhibition of Jak3, followed by Jak1, Jak2, and Tyk2.[3,13]

PHARMACOKINETICS

Tofacitinib has a linear pharmacokinetic profile, with dose-dependent decreases in clinical scores in collagen-induced arthritis and adjuvant-induced arthritis rodent models.[8] The tofacitinib pharmacokinetic profile is best characterized by a 1-compartment open model with first-order absorption.[3,14]

Tofacitinib is well absorbed following oral administration, with an absolute bioavailability of 74% in healthy subjects.[1,15] Coadministration with a high-fat meal reduces peak plasma concentrations (C_{max}) by 32%; however, the manufacturer states the drug can be administered without regard to meals.[1] Following oral administration, tofacitinib time to C_{max} is 30 minutes to 1 hour and elimination half-life is approximately 3 hours.[1,3,16,17] Steady-state concentrations are reached within 24 to 48 hours following administration, with insignificant accumulation observed with twice-daily administration.[1] The volume of distribution of tofacitinib is 87 L following intravenous (IV) administration.[1] Protein binding of tofacitinib is approximately 40%, predominantly to albumin, and demonstrates equal partitioning between red blood cells and the plasma.[1,3]

Elimination of tofacitinib includes hepatic and renal excretion of the parent drug, approximately 70% and 30%, respectively.[1,3,18,19] Tofacitinib is primarily metabolized by the enzymatic hepatic pathway cytochrome

P450 (CYP-450) 3A4, with minor metabolism using the CYP2C19 pathway.[1] In a human radiolabeled study, administration of a single oral dose of tofacitinib 50 mg resulted in more than 65% of the total circulating radioactivity recovered as unchanged tofacitinib; the remainder included 8 metabolites, each of which accounted for less than 8% of the total radioactivity. The parent molecule of tofacitinib is responsible for the pharmacologic activity.[1,3,16,19]

No clinically significant changes in the pharmacokinetics of tofacitinib are directly related to RA; instead, any variation would be a result of variations in the patient's renal function and/or hepatic function. A clinically insignificant linear relationship between body weight and volume of distribution was observed in lighter patients, with higher C_{max} and lower trough concentrations observed following administration. Variability between patients in total drug exposure is approximately 27%.[1,18,19]

COMPARATIVE EFFICACY

Indication: Treatment of Rheumatoid Arthritis With Tofacitinib Monotherapy

Studies

Drug: Tofacitinib vs Placebo

Reference: Kremer JM, et al, 2009[8]

Study Design: Dose-ranging, randomized, double-blind, placebo-controlled, parallel-group, multicenter, international, proof-of-concept study

Study Funding: Pfizer, Inc.

Patients: 264 adult patients with clinical diagnosis of active RA who demonstrated an inadequate or toxic response to methotrexate, etanercept, infliximab, or adalimumab.

Intervention: Patients were equally randomized to receive placebo or tofacitinib 5, 15, or 30 mg twice daily for 6 weeks and then subsequently followed for 6 weeks. All previous DMARDs and immunosuppressive/immunomodulatory drugs were discontinued at least 4 weeks prior to the first dose of the study medication. Patients were permitted to continue stable background therapy of nonsteroidal anti-inflammatory drugs (NSAIDs), selective cyclooxygenase-2 (COX-2) inhibitors, opioids, acetaminophen, and/or oral corticosteroids (daily dose of 10 mg or less of prednisone or equivalent).

Results:

Primary Endpoint(s):

- Dose-dependent improvements of the American College of Rheumatology 20% improvement criteria (ACR20) response rate after 6 weeks of therapy was 29.2%, 70.5%, 81.2%, and 76.8% in the placebo and 5, 15, and 30 mg treatment groups, respectively ($P < .001$ compared with placebo).

Secondary Endpoint(s):

- Improvements of ACR20 response rates compared with placebo were detected after 1 week of therapy.
- Increases to ACR50 and ACR70 response rates were also observed at all time points; however, they reached significance compared with placebo at week 2 in the tofacitinib 30 mg twice-daily treatment group and at week 4 in all other treatment groups.
- An exploratory endpoint of mean Disease Activity Scores in 28 joints, based on measurements of C-reactive protein levels (DAS28-CRP), demonstrated dose-dependent improvements compared with baseline values in all tofacitinib treatment groups compared with placebo.

Reference: Fleischmann R, et al, 2012 (ORAL Solo)[1,20,21]

Study Design: Randomized, double-blind, placebo-controlled, parallel-group, international, multicenter study

Study Funding: Pfizer, Inc.

Patients: 610 adult patients clinically diagnosed with active RA with an inadequate response to at least 1 DMARD (nonbiologic or biologic) due to lack of efficacy or toxicity.

Intervention: Patients were randomized in a 4:4:1:1 ratio to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo for 3 months followed by tofacitinib twice daily, or placebo for 3 months followed by tofacitinib 10 mg twice daily. Patients who did not achieve a 20% or greater reduction of swollen and painful joints from baseline at 12 or 24 weeks were blindly reassigned to tofacitinib 5 or 10 mg twice daily. Patients were required to have discontinued all DMARDs with a predetermined adequate washout period. Continuation of stable background therapy, which may include antimalarial agents, NSAIDs, and/or low-dose corticosteroids (daily dose of 10 mg or less of prednisone or equivalent), was permitted throughout the trial. The mean age of the patients ranged from 49.7 to 52.4 years, mean duration of RA ranged from 7.7 to 8.6 years, 67% were White, and 86.6% were women. Antimalarial agents were used by 12.3% of the placebo group, 18.5% of the tofacitinib 5 mg group, and 16.7% of the tofacitinib 10 mg group. Glucocorticoids were used by 63.1%, 57.4%, and 60.4%, respectively.

Results:
Primary Endpoint(s):
- The ACR20 response rates after 12 weeks of therapy were observed in 59.8%, 65.7%, and 26.7% for tofacitinib 5 mg, tofacitinib 10 mg, and placebo treatment groups, respectively ($P < .001$, for all comparisons).
- The mean change from baseline to week 12 in physical function status, as assessed with the use of the Health Assessment Questionnaire Disability Index (HAQ DI), was improved in all active treatments compared with placebo ($P < .001$, for all comparisons).
- The DAS28- erythrocyte sedimentation rate (ESR) of less than 2.6 at 12 weeks was 5.6% in the tofacitinib 5 mg treatment group, 8.7% in the tofacitinib 10 mg treatment group, and 4.4% in the placebo treatment group ($P = .62$ and .1, respectively).

Secondary Endpoint(s):
- The ACR50 response rates after 12 weeks of therapy were 31.1%, 36.8%, and 12.5% for tofacitinib 5 mg, tofacitinib 10 mg, and placebo treatment groups, respectively ($P < .001$, for all comparisons).
- The ACR70 response rates after 12 weeks of therapy were 15.4% ($P < .003$), 20.3% ($P < .001$), and 5.8% for tofacitinib 5 mg, tofacitinib 10 mg, and placebo treatment groups, respectively.
- Significant improvements in physical functioning were observed by week 2 with continued improvement to the end of the trial.
- Improvements of ACR20, ACR50, and ACR70 were sustained throughout the 6 months of therapy in both treatment groups.
- The difference in ACR20 and ACR50 responses in each tofacitinib treatment group compared with placebo ($P < .001$, for all comparisons) was observed within 4 weeks of therapy.

Comments: Post hoc subgroup analysis showed that the ACR20 response rate in patients who had previously had an inadequate response to a TNF inhibitor or other biologic agent was less compared with overall response rates at week 12: 42.9% in the tofacitinib 5 mg group, 62.5% in the tofacitinib 10 mg group, and 17.7% in the placebo group ($P = .06$ and $P < .001$, respectively).

Drug: Tofacitinib or Adalimumab vs Placebo
Reference: Fleischmann R, et al, 2012[22]
Study Design: Randomized, double-blind, placebo-controlled, active-comparator, parallel-group, international, multicenter study
Study Funding: Pfizer, Inc.
Patients: 384 patients with active RA with an inadequate response to at least 1 DMARD due to lack of efficacy or toxicity.
Intervention: Patients were randomized to receive placebo; tofacitinib 1, 3, 5, 10, or 15 mg orally twice daily for 24 weeks; or adalimumab 40 mg subcutaneously every 2 weeks for a total of 10 weeks followed by tofacitinib 5 mg twice daily for 12 weeks. Continuation of stable background therapy of antimalarial agents, NSAIDs, opiates, acetaminophen, and/or corticosteroids (daily dose of 10 mg or less of prednisone or equivalent) was permitted throughout the study. Patients who did not achieve a 20% or greater reduction of swollen and painful joints from baseline at 12 weeks were blindly reassigned to 5 mg twice daily.
Results:
Primary Endpoint(s):
- The ACR20 response rates after 12 weeks of therapy were observed in 31.5% (1 mg, $P = .256$), 39.2% (3 mg, $P \leq .05$), 59.2% (5 mg, $P < .001$), 70.5% (10 mg, $P < .001$), 71.9% (15 mg, $P < .001$), 35.9% (adalimumab, $P = .105$), and 22% (placebo).

Secondary Endpoint(s):
- Improvements of ACR20, ACR50, ACR70, and DAS28-CRP were sustained throughout the 24 weeks of therapy in tofacitinib treatment groups.
- The response rate in patients initially treated with adalimumab at week 12 for ACR20 was 4.8%, ACR50 was 0%, and ACR70 was 0%; following reassignment to tofacitinib 5 mg twice daily for the remainder of the study, their response rates at 24 weeks were 52.6% for ACR20, 21.1% for ACR50, and 10.5% for ACR70.

Indication: Treatment of Rheumatoid Arthritis With Tofacitinib With Stable Background Therapy

Studies

Drug: Tofacitinib vs Placebo With Background Methotrexate Therapy
Reference: Kremer JM, et al, 2012[21,23]
Study Design: Randomized, double-blind, placebo-controlled, parallel-group, dose-escalation, international, multicenter study
Study Funding: Pfizer, Inc.
Patients: 507 adult patients with a clinical diagnosis of active RA on stable methotrexate therapy who had not achieved an adequate response.

Intervention: Patients were equally randomized to treatment with tofacitinib 1, 3, 5, 10, or 15 mg twice daily; tofacitinib 20 mg once daily; or placebo for 12 weeks. An additional 12 weeks of treatment was administered to determine the durability of efficacy with tofacitinib. All patients were required to be on stable methotrexate background therapy with folic acid supplementation, oral or IV methotrexate for at least 4 months, and a stable dosage of 7.5 to 25 mg/week for at least 6 weeks prior to the administration of the first dose of study drug. All other biologic or nonbiologic DMARDs and immunosuppressive therapies were discontinued for at least 4 weeks prior to the first dose of the study medication. Stable background therapy of NSAIDs, selective COX-2 inhibitors, opioids, acetaminophen, and/or oral corticosteroids (daily dose of 10 mg or less of prednisone or equivalent) was also permitted. Patients who were randomized to tofacitinib 1 or 3 mg twice daily, tofacitinib 20 mg daily, or placebo and did not achieve at least a 20% reduction of swollen and painful joints by the 12th week were classified as nonresponders and subsequently reassigned to receive tofacitinib 5 mg twice daily for the remainder of the study (12 weeks).

Results:

Primary Endpoint(s):

- The ACR20 response rates observed at 12 weeks were 33.3% (placebo), 45.7% (1 mg twice daily), 52.9% (3 mg twice daily), 50.7% (5 mg twice daily), 58.1% (10 mg twice daily), 56% (15 mg twice daily), and 53.8% (20 mg daily) ($P \leq .05$, for all tofacitinib doses 3 mg or more).
- All tofacitinib 3 mg or greater treatment groups achieved ACR20 response rates greater than placebo after 2 weeks of therapy ($P \leq .05$).
- ACR20 response rates were sustained after 24 weeks of therapy in dosages of tofacitinib 3, 10, or 15 mg twice daily and 20 mg daily compared with placebo ($P \leq .05$).

Secondary Endpoint(s):

- The ACR50 response rate at weeks 12 and 24 was significantly greater in patients receiving tofacitinib at dosages of 15 mg twice daily and 20 mg daily compared with placebo ($P \leq .05$).
- The ACR50 response rate at week 12 was significantly greater in patients receiving tofacitinib 5 mg twice daily compared with placebo ($P \leq .05$).
- Improvement in physical functioning and health-related quality of life was demonstrated in patients treated with tofacitinib.

Comments: Another phase 2, dose-ranging study conducted in Japan demonstrated similar results.[24]

Reference: The Oral Rheumatoid Arthritis Phase 3 Trials Step (ORAL Step)[1,21]
Study Design: Randomized, placebo-controlled study
Study Funding: Pfizer, Inc.
Patients: 399 adult patients clinically diagnosed with moderate to severe RA with an inadequate response to 1 approved TNF inhibitor biologic agent.
Intervention: Patients were randomized to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and placebo advanced to tofacitinib 5 mg or 10 mg at week 12 added to background methotrexate. After 3 months of therapy, patients determined to be nonresponders to placebo therapy (less than 20% reduction of swollen and painful joints from baseline) were switched (advanced) to either tofacitinib 5 or 10 mg twice daily. Patients were required to continue stable background nonbiologic DMARD therapy, including methotrexate, throughout the trial.
Results:
Primary Endpoint(s):

- The ACR20 response rates after 3 months of therapy were 41.7%, 48.1%, and 24.4% in the tofacitinib 5 mg, tofacitinib 10 mg, and placebo treatment groups, respectively ($P < .001$, for both comparisons).

Secondary Endpoint(s):

- ACR50, ACR70, physical function (HAQ DI), patient global assessment of disease activity, health-related quality of life, fatigue, and sleep improved compared with placebo after 3 and 6 months of therapy ($P < .05$).

Comments: Results have only been presented in abstracts, press releases, and the US Food and Drug Administration (FDA) Advisory Committee briefing documents.

Reference: The Oral Rheumatoid Arthritis Phase 3 Trials Scan (ORAL Scan)[1,21]
Study Design: Randomized, placebo-controlled study
Study Funding: Pfizer, Inc.
Patients: 797 adult patients clinically diagnosed with moderate to severe RA with an inadequate response to methotrexate.
Intervention: Patients were randomized to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, or placebo. At week 12, nonresponders to placebo therapy (less than 20% reduction of swollen and painful joints from baseline) were advanced in a blind fashion to a second predetermined treatment of

tofacitinib 5 or 10 mg twice daily. At week 24, all patients in the placebo treatment group were advanced to their second predetermined treatment in a blind fashion. Patients were required to continue stable background methotrexate throughout the trial.
Results:
Primary Endpoint(s):
- The ACR20 response rates after 6 months of therapy were 51.5%, 61.8%, and 25.3% in the tofacitinib 5 mg, tofacitinib 10 mg, and placebo treatment groups, respectively ($P < .001$, for both comparisons).
- The mean change from baseline in modified total sharp score after 6 months of therapy was −0.34 ($P = .0792$) in the tofacitinib 5 mg treatment group and −0.4 in the tofacitinib 10 mg treatment group ($P = .0376$).

Secondary Endpoint(s):
- ACR50, ACR70, physical function (HAQ DI), patient global assessment of disease activity, health-related quality of life, pain, CRP, and tender and swollen joints improved compared with placebo after 3 and 6 months of therapy ($P < .001$).
- The modified total sharp score after 12 months of tofacitinib 10 mg twice daily continued to improve compared with placebo ($P = .008$), with the 5 mg treatment group failing to reach significance.

Comments: Study is currently ongoing, with preliminary results presented in the FDA Advisory Committee briefing documents.

Drug: Tofacitinib, Adalimumab, or Placebo With Background Methotrexate Therapy
Reference: van Vollenhoven RF, et al, 2012 (ORAL Standard)[1,21,25]
Study Design: Randomized, double-blind, placebo-controlled, active-comparator, parallel-group, international, multicenter study
Study Funding: Pfizer, Inc.
Patients: 717 adult patients clinically diagnosed with active RA on stable methotrexate background therapy. The average age ranged from 51.9 to 55.5 years; 75% to 85.3% were women; 67.3% to 74% were White; and the mean duration of RA ranged from 6.9 to 9 years.
Intervention: Patients were randomized in a 4:4:4:1:1 ratio to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab 40 mg subcutaneously every 2 weeks, placebo for 3 or 6 months followed by tofacitinib twice daily, or placebo for 3 or 6 months followed by tofacitinib 10 mg twice daily. All patients received both self-administered injections of adalimumab or placebo once every 2 weeks and took a placebo or tofacitinib-containing pill twice daily. Continuation of stable background therapy, which included methotrexate supplemented with folic acid and could include NSAIDs, opiates, acetaminophen, and/or low-dose corticosteroids (daily dose of 10 mg or less of prednisone or equivalent) was permitted throughout the trial. Patients who did not achieve a 20% or greater reduction of swollen and painful joints from baseline at 12 or 24 weeks with placebo were randomly switched to tofacitinib 5 or 10 mg twice daily. Patients originally randomly assigned to tofacitinib or adalimumab continued on the same regimen throughout the study regardless of their level of response.
Results:
Primary Endpoint(s):
- The ACR20 response rates after 12 weeks of therapy were observed in 51.5%, 52.6%, 47.2%, and 28.3% for tofacitinib 5 mg, tofacitinib 10 mg, adalimumab, and placebo treatment groups, respectively ($P < .001$, for all comparisons).
- The mean change from baseline to week 12 in physical function status, as assessed with the use of the HAQ DI, was improved in all active treatments compared with placebo ($P < .001$).
- The DAS28-ESR of less than 2.6 at month 6 was greater in all active treatments compared with placebo ($P < .05$, for the comparison of the tofacitinib 5 mg group, and $P < .001$, for the comparison of the tofacitinib 10 mg group).

Secondary Endpoint(s):
- Improvements of ACR20, ACR50, ACR70, and DAS28-ESR were sustained throughout the 12 months of therapy in all active treatment groups and were numerically similar as well.
- A difference in ACR20 and ACR50 responses in each tofacitinib treatment group compared with placebo ($P < .001$, for all comparisons) was observed after 4 weeks of therapy.

Comments: Glucocorticoids were used by 73.2% of the patients assigned to treatment with placebo followed by tofacitinib 5 mg, 59.6% assigned to placebo therapy followed by tofacitinib 10 mg, 61.8% assigned to tofacitinib 5 mg, 64.2% assigned to tofacitinib 10 mg, and 61.3% assigned to adalimumab. Patients were permitted to continue taking tofacitinib following the end of the trial as part of a long-term extension trial (ORAL Sequel) to evaluate pooled safety data.[21]

Drug: Tofacitinib vs Placebo With Nonbiologic DMARD Background Therapy
Reference: Strand V, et al, 2011 (ORAL Sync)[1,21,26-28]
Study Design: Randomized, double-blind, placebo-controlled, parallel group, international, multicenter study
Study Funding: Pfizer, Inc.
Patients: 792 adult patients clinically diagnosed with moderate to severe RA with an inadequate response to 1 or more nonbiologic or biologic DMARDs.
Intervention: Patients were randomized in a 4:4:1:1 ratio to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo advanced to 5 mg twice daily, or placebo advanced to 10 mg twice daily, respectively, for a total of 12 months of treatment. Patients were permitted to continue stable background nonbiologic DMARD therapy, including methotrexate and excluding azathioprine and cyclosporine, throughout the trial. After 3 months of therapy, patients determined to be nonresponders to placebo therapy (less than 20% reduction of swollen and painful joints from baseline) were switched (advanced) to either tofacitinib 5 or 10 mg twice daily.
Results:
Primary Endpoint(s):
- The ACR20 response rates after 6 months of therapy were 52.7%, 58.3%, and 31.2% in the tofacitinib 5 mg, tofacitinib 10 mg, and placebo treatment groups, respectively ($P < .001$, for both comparisons).

Secondary Endpoint(s):
- ACR50, ACR70, physical function (HAQ DI), patient global assessment of disease activity, health-related quality of life, fatigue, and sleep improved compared with placebo after 3 and 6 months of therapy ($P < .05$). There were patient-reported improvements and clinically important differences in patient global assessment of disease activity and quality of life.

Comments: Results have only been presented in abstracts, press releases, and the FDA Advisory Committee briefing documents.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

The product labeling has no contraindications for tofacitinib use.[1] However, general considerations for administration outline that tofacitinib should not be used in patients with severe hepatic impairment, and patients with a lymphocyte count less than 500 cells/mm^3, an absolute neutrophil count less than 1,000 cells/mm,^{3} or who have a hemoglobin level less than 9 g/dL should not initiate therapy. Additionally, concomitant therapy with potent inducers of CYP3A4 may result in a loss of or reduction of clinical response to tofacitinib.[1]

Warnings and Precautions

Reports of serious and sometimes fatal infections have been documented in patients with RA receiving tofacitinib due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens. The most common serious infections reported include pneumonia, cellulitis, herpes zoster, and urinary tract infection. Reported opportunistic infections include tuberculosis and other mycobacterial infections, *Cryptococcus*, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus, and BK virus. Patients taking concomitant immunomodulating agents, such as methotrexate or corticosteroids, more frequently presented with disseminated rather than localized disease. Tofacitinib therapy should not be initiated in patients with an active infection, including localized infection. Initiating tofacitinib therapy should be carefully considered in patients with chronic or recurrent infections, those exposed to tuberculosis, and those who have a history of serious or opportunistic infections, have resided or traveled in areas with endemic tuberculosis or endemic mycoses, or have underlying conditions that may predispose them to infection. It is recommended that patients be closely monitored for the development of signs and symptoms of infection during and following the discontinuation of therapy. Immediate discontinuation of tofacitinib therapy is warranted if a patient develops a serious infection, an opportunistic infection, or sepsis. Standard of care procedures, including complete diagnostic testing, appropriate selection of antimicrobial therapy, and close monitoring for an immunocompromised patient, should be followed.[1]

Prior to the initiation of tofacitinib, patients should be evaluated and tested for latent or active tuberculosis. Patients with active or latent tuberculosis should be treated with standard antimycobacterial therapy prior to initiation of tofacitinib therapy. In patients with a history of active or latent tuberculosis without confirmation of receiving adequate treatment or patients with a negative test for latent tuberculosis but who have risk factors for tuberculosis infection, a consultation with a health care provider with expertise in the treatment of tuberculosis is recommended to determine whether antituberculosis therapy is appropriate.[1]

Cases of viral reactivation, including cases of herpes virus reactivation, were observed in clinical trials. Patients positive for hepatitis B or C were excluded from participation in tofacitinib trials; thus, the clinical significance and impact on chronic viral hepatitis reactivation is currently unknown.[1]

Cases of malignancy and lymphoproliferative disorder have been reported in clinical studies of tofacitinib. The pattern, types, incidence rates, and incidence ratios of malignancies and lymphomas observed with tofacitinib therapy in RA patients continue to be evaluated. It is recommended that patients with known malignancy, other than a successfully treated nonmelanoma skin cancer, or who develop a malignancy during treatment carefully consider the risks and benefits of therapy before initiation or continuation of tofacitinib therapy. Epstein-Barr virus–associated posttransplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with tofacitinib and concomitant immunosuppressive medications.[1]

There have been reports of gastrointestinal (GI) perforation with tofacitinib therapy. Patients with increased risk of GI perforation should use caution. A new onset of abdominal symptoms indicative of GI perforation should be promptly evaluated for early identification and treatment.[1]

Tofacitinib therapy is associated with initial lymphocytosis at 1 month of exposure followed by a gradual decrease in mean lymphocyte counts below baseline of approximately 10% during 12 months of therapy. It is recommended that lymphocyte counts be monitored at baseline and every 3 months throughout the duration of tofacitinib therapy. In clinical studies, lymphocyte counts less than 500 cells/mm^3 were associated with increased incidence of serious infection. Initiation of therapy in patients with lymphocyte counts less than 500 cells/mm^3 is not recommended. Dose modifications based on lymphocyte counts are outlined in detail in the product labeling, with recommended discontinuation of therapy in confirmed lymphocyte counts less than 500 cells/mm^3.[1]

An increased risk of neutropenia is associated with tofacitinib therapy in comparison with placebo. It is recommended that neutrophil counts be monitored at baseline, after 4 to 8 weeks of treatment, and every 3 months throughout the duration of tofacitinib therapy. Dose modifications and recommendations based on neutrophil counts are outlined in detail in the product labeling.[1]

The initiation of tofacitinib therapy should be avoided in patients with a hemoglobin level less than 9 g/dL. Dose interruption is recommended in patients who develop hemoglobin levels less than 8 g/dL or experience a drop in hemoglobin greater than 2 g/dL during therapy. It is recommended that hemoglobin levels be monitored at baseline, after 4 to 8 weeks of treatment, and every 3 months throughout the duration of therapy. Dose modifications based on hemoglobin levels are outlined in the product labeling.[1]

An increased incidence of liver enzyme elevation was observed with tofacitinib therapy in comparison with placebo, with the majority of cases reported in studies with background DMARD therapy, primarily methotrexate. It is recommended that routine liver enzyme tests be conducted throughout therapy. Prompt investigation of the causes of liver enzyme elevations is recommended to effectively identify potential cases of drug-induced liver injury. Discontinuation of therapy is recommended in all cases of suspected drug-induced liver injury.[1]

Tofacitinib therapy is associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein cholesterol. Increases to lipid parameters are generally observed within 6 weeks of therapy. Patients that present with elevated lipid parameters should be managed according to the clinical treatment guidelines for hyperlipidemia. It is recommended that assessment of lipid parameters should be performed approximately 4 to 8 weeks following the initiation of tofacitinib therapy. The effect of elevations in lipid parameters on cardiovascular morbidity and mortality is currently unknown and continues to be evaluated.[1] Reductions in total and LDL cholesterol are possible with statin therapy.[21,28]

All immunizations should be current with immunization guidelines prior to initiating treatment. No data are available regarding the response to vaccination or on the secondary transmission of infection by live vaccines in patients administered tofacitinib; however, due to the immunosuppressive effects of therapy, it is recommended that no live vaccines be administered to patients taking tofacitinib therapy.[1]

Treatment with tofacitinib is not recommended in patients with severe hepatic impairment. Dose modification to 5 mg once daily for patients with moderate hepatic impairment is recommended.[1]

Tofacitinib therapy is classified in Pregnancy Category C. No adequate and well-controlled studies have been conducted in pregnant women. Feticidal and teratogenic effects have been observed in rats and rabbits with exposures 146 and 13 times, respectively, the maximum recommended human dose for tofacitinib. It is unknown

whether tofacitinib is secreted in human breast milk. Due to the potential risk of serious adverse reactions to breastfeeding infants, careful consideration of the risk and benefits to both mother and infant should be considered.[1]

The safety and effectiveness of tofacitinib in pediatric patients have not been established.[1]

No dosage adjustment for patients 65 years or older is required with tofacitinib therapy; however, an increased risk and incidence of infection was observed in clinical trials in this population. Caution should be used when treating elderly patients.[1,28]

ADVERSE REACTIONS

The most common adverse event reported in patients in the 7 phase 2 and 3 clinical studies with tofacitinib therapy was the overall frequency of infection. In the first 3 months of tofacitinib exposure, approximately 20% of patients in the 5 mg twice-daily treatment group and 22% in the 10 mg twice-daily treatment group experienced an infection compared with 18% of patients in the placebo treatment group and 16% of patients in the adalimumab treatment group. The most commonly reported infections included upper respiratory tract infection, nasopharyngitis, and urinary tract infection at an incidence of 4%, 3%, and 2% of patients, respectively. Infection remained the most common adverse event reported over time in all 5 phase 3 studies with increasing exposure to tofacitinib.[1,20-23,25]

GI disorders, including diarrhea, dyspepsia, and nausea, were also reported with tofacitinib therapy. Approximately 16% to 17% of patients treated with tofacitinib compared with 14% of patients treated with placebo and 10% of patients treated with adalimumab reported an adverse GI event.[28]

DRUG INTERACTIONS

Administration of a single dose of fluconazole, a moderate CYP3A4 inhibitor and potent CYP2C19 inhibitor, produced a 27% increase in tofacitinib C_{max} and a 79% increase in area under the curve (AUC).[28,29,30]

Coadministration with ketoconazole, a strong CYP3A4 inhibitor, increased the mean AUC by 103% and C_{max} by 16%.[1,28]

Administration of rifampin, a potent CYP3A4 inducer, substantially decreased the mean AUC by 84% and decreased C_{max} by 74%.[1,28]

Concomitant potent immunosuppressive drugs, such as azathioprine, tacrolimus, and cyclosporine, increase the risk of immunosuppression when taken with tofacitinib. Although the combined use of multiple-dosed tofacitinib with immunosuppressive agents has not been studied in RA, the theoretical risk exists.[1]

Coadministration of tofacitinib with stable methotrexate therapy produces a 10% decrease in methotrexate AUC and a 13% decrease in methotrexate C_{max}. However, this is not considered to be clinically significant.[28,31]

RECOMMENDED MONITORING

Patients should be monitored for the development of signs and symptoms of infection prior to, during, and following tofacitinib therapy. Tofacitinib therapy should be promptly discontinued if a patient develops a serious infection, an opportunistic infection, or sepsis, and appropriate treatment of the infection should be initiated.[1]

Prior to the initiation of therapy, patients should be carefully evaluated and tested for latent or active tuberculosis infection. Patients with a history of latent or active tuberculosis will require conformation of receiving adequate treatment and/or require expertise consultation to determine whether initiation of antituberculosis therapy is necessary. Continual monitoring of all patients for active tuberculosis is recommended throughout tofacitinib therapy.[1]

It is recommended that lymphocyte counts be evaluated at baseline and every 3 months throughout tofacitinib therapy. Additionally, neutrophil counts and hemoglobin laboratory values should be evaluated at baseline, after 4 to 8 weeks of treatment, and every 3 months throughout therapy.[1]

Routine monitoring of liver function is recommended to identify liver enzyme elevations indicative of tofacitinib-induced liver injury.[1]

A complete lipid panel should be taken at baseline and after approximately 4 to 8 weeks of tofacitinib therapy.[1]

Additional monitoring parameters may include clinical markers and symptoms of disease progression.

DOSING

The approved dosage of tofacitinib is 5 mg orally twice daily with or without food.[1]

No dosage adjustments are necessary for patients with mild hepatic or renal impairment.[1] Patients with moderate or severe renal insufficiency, with moderate hepatic impairment, receiving potent inhibitors of CYP3A4, or receiving 1 or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 require a reduction in administration frequency to 5 mg once daily.[1] Supplemental administration of tofacitinib is not required in patients following dialysis.[1]

Additional dose modifications may be necessary if the patient presents with lymphopenia, neutropenia,

or anemia. These adjustments are outlined in detail in the product labeling.[1]

PRODUCT AVAILABILITY

A new drug application was accepted for review by the FDA in December 2011, with an anticipated Prescription Drug User Fee Act action date of August 2012.[9] Tofacitinib was approved by the FDA on November 6, 2012.[32]

Tofacitinib is available in 5 mg immediate-release film-coated tablets in bottles of 28, 60, and 180. Each 5 mg tablet is equivalent to tofacitinib citrate 8 mg and contains microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, HPMC 2910/hypromellose 6cP, titanium dioxide, macrogol/PEG3350, and triacetin.[1]

Tablets should be stored at controlled room temperature (68° to 77°F [20° to 25°C]) and dispensed in the original container.[1]

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Due to the risk of serious and opportunistic infections, tuberculosis, malignancy, increase in cholesterol panel, and decrease in hematologic counts, the FDA required the development of a REMS.[32] The approved REMS includes a medication guide for patients, a communication plan for health care providers and pharmacists, and periodic submissions of assessments regarding patients', pharmacists', and prescribers' knowledge and understanding of the serious risks of tofacitinib therapy.[32,33]

The manufacturer is required to complete 2 postmarketing studies to determine the pharmacokinetics of multiple-dose tofacitinib in children diagnosed with juvenile idiopathic arthritis and a randomized withdrawal, double-blind, placebo-controlled trial to evaluate the safety and efficacy of tofacitinib in pediatric patients diagnosed with polyarticular-course juvenile idiopathic arthritis.[32]

In addition, the FDA is requiring the completion of a controlled clinical trial to evaluate the long-term safety of tofacitinib in patients with rheumatoid arthritis. The trial is expected to include an active comparator and be of sufficient enrollment and duration to effectively evaluate the risk of cardiovascular events, opportunistic and serious infections, and malignancy.[32]

CONCLUSION

The advent of biologic therapies for RA has revolutionized treatment and has allowed symptom relief and reduction in disease progression. Tofacitinib targets a distinct biochemical pathway that is unique in comparison with available biologic treatments for RA. Because many patients may require multiple therapies or have an inadequate response to existing agents when used alone or in combination, there is still a need for more therapeutic options. Tofacitinib may be a useful agent for the treatment of some patients with RA who are receiving background methotrexate, as demonstrated in short-term studies. The majority of the published studies are short-term, dose-ranging studies that compared tofacitinib plus methotrexate with placebo plus methotrexate in the treatment of RA. Tofacitinib was able to produce a significant change in the ACR20 response rates and other surrogate markers of decreased disease progression within 3 months, with sustained improvements through the duration of the trials. One 24-week study compared tofacitinib, adalimumab, and placebo in the treatment of RA and found tofacitinib was better than placebo; adalimumab also produced an improvement in the ACR20 response rates but was not better than placebo. Preliminary results from the ongoing ORAL Scan trial have demonstrated that tofacitinib 10 mg twice daily impacts disease progression (eg, improved Sharp scores), but this dose is not the approved dose in the United States. Additional studies will be required to evaluate the efficacy and safety of tofacitinib therapy with long-term use in monotherapy and with concomitant nonbiologic DMARD therapy.

REFERENCES

1. *Xeljanz* [package insert]. New York: Pfizer Inc; November 2012.

2. Garber K. Pfizer's JAK inhibitor sails through phase 3 in rheumatoid arthritis. *Nat Biotechnol.* 2011;29(6):467-468.

3. Riese RJ, Krishnaswami S, Kremer J. Inhibition of JAK kinases in patients with rheumatoid arthritis: scientific rationale and clinical outcomes. *Best Pract Res Clin Rheumatol.* 2010;24(4):513-526.

4. Walker JG, Smith MD. The Jak-STAT pathway in rheumatoid arthritis. *J Rheumatol.* 2005;32(9):1650-1653.

5. Ghoreschi K, Laurence A, O'Shea JJ. Janus kinases in immune cell signaling. *Immunol Rev.* 2009;228(1):273-287.

6. Vijayakrishnan L, Venkataramanan R, Gulati P. Treating inflammation with the Janus kinase inhibitor CP-690,550. *Trends Pharmacol Sci.* 2011;32(1):25-34.

7. Ghoreschi K, Jesson MI, Li X, et al. Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). *J Immunol.* 2011;186(7):4234-4243.

8. Kremer JM, Bloom BJ, Breedveld FC, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo

[published correction appears in *Arthritis Rheum*. 2012;64(5):1487]. *Arthritis Rheum*. 2009;60(7):1895-1905.

9. Pfizer announces FDA acceptance for review of new drug application for tofacitinib for adult patients with moderately to severely active rheumatoid arthritis. Business Wire Web Site. http://www.businesswire.com/news/home/20111220005356/en/Pfizer-Announces-FDA-Acceptance-Review-Drug-Application. Published December 20, 2011. Accessed December 21, 2011.

10. Yazici Y, Regens AL. Promising new treatments for rheumatoid arthritis – the kinase inhibitors. *Bull NYU Hosp Jt Dis*. 2011;69(3):233-237.

11. Tofacitinib. *Drug Facts and Comparisons*. Facts & Comparisons [database online]. St. Louis, MO: Wolters Kluwer Health; 2012. Accessed December 7, 2012.

12. Tofacitinib. ClinicalTrials.gov website. http://www.clinicaltrials.gov. Accessed December 11, 2012.

13. Meyer DM, Jesson MI, Li X, et al. Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. *J Inflamm (Lond)*. 2010;7:41.

14. Hutmacher MM, Krishnaswami S, Kowalski KG. Exposure-response modeling using latent variables for the efficacy of a JAK3 inhibitor administered to rheumatoid arthritis patients. *J Pharmacokinet Pharmacodyn*. 2008;35(2):139-157.

15. Gupta P, Stock TC, Wang R, et al. A phase 1 study to estimate the absolute bioavailability of tofacitinib (CP-650,550) in healthy subjects [abstract 122902]. *J Clin Pharmacol*. 2011;51(9):1348.

16. Prakash C, Lin J, Chan G, Boy M. Metabolism, pharmacokinetics and excretion of a Janus kinase-3 inhibitor, CP-690,550, in healthy male volunteers [abstract]. *AAPS J*. 2008;10:2492.

17. Lawendy N, Krishnaswami S, Wang R, et al. Effect of CP-690,550, an orally active Janus kinase inhibitor, on renal function in healthy adult volunteers. *J Clin Pharmacol*. 2009;49(4):423-429.

18. Chow V, Krishnaswami S, Chan G. Pharmacokinetics of CP-690,550, a Janus kinase inhibitor, in subjects with impaired renal function and end-stage renal disease [abstract PII-86]. *Clin Pharmacol Ther*. 2009;85:S63.

19. Lawendy N, Chan G, Wang R, Lamba M, Krishnaswami S. The effect of mild to moderate hepatic impairment on the pharmacokinetic of tasocitinib (CP-650,550) [abstract]. *Clin Pharmacol Ther*. 2011;89:S93.

20. Fleischmann R, Kremer J, Cush J, et al; ORAL Solo Investigators. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *New Engl J Med*. 2012;367(6):495-507.

21. US Food and Drug Administration Advisory Committee Meeting. Tofacitinib for the treatment of rheumatoid arthritis: NDA 203214 briefing document. Food and Drug Administration Web site. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM302960.pdf. Published May 9, 2012. Accessed November 9, 2012.

22. Fleischmann R, Cutolo M, Genovese MC, et al. Phase IIB dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. *Arthritis Rheum*. 2012;64(3):617-629.

23. Kremer JM, Cohen S, Wilkinson BE, et al. A phase IIB dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and methotrexate alone. *Arthritis Rheum*. 2012;64(4):970-981.

24. Tanaka Y, Suzuki M, Nakamura H, et al. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Care Res (Hoboken)*. 2011;63(8):1150-1158.

25. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *New Engl J Med*. 2012;367(6):508-519.

26. Strand V, Kremer JM, Li S, et al. Tofacitinib (CP-690,550) in combination with traditional disease-modifying anti-rheumatic drugs: phase 3 study patient-reported outcomes in patients with active rheumatoid arthritis and an inadequate response to disease-modifying anti-rheumatic drugs [abstract]. *Arthritis Rheum*. 2011;63(11):S1032.

27. Pfizer announces detailed results of ORAL Sync showing investigational compound tofacitinib reduces signs and symptoms and improves physical function in patients with moderate-to-severe active rheumatoid arthritis, with results seen as early as two weeks [news release] New York: Pfizer Inc; May 24, 2011. http://www.evaluatepharma.com/Universal/View.aspx?type=Story&id=245880. Accessed January 4, 2012.

28. Arthritis Advisory Committee Meeting. NDA 20314: tofacitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had inadequate response to one or more disease-modifying anti-rheumatic drugs. US Food and Drug Administration Web site. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM302958.pdf. Published May 9, 2012. Accessed November 9, 2012.

29. Chow V, Ni G, LaBadie R, Chan G. Open label study to estimate the effect of fluconazole on the pharmacokinetics of a JAK3 antagonist (CP-650,550) [abstract]. *Clin Pharmacol Ther*. 2008;83:S36.

30. Krishnaswami S, Kudlacz E, Yocum S, et al. Effect of CYP2C19 polymorphism on the pharmacokinetics of CP-690,550, a Janus kinase inhibitor [abstract]. *AAPS J*. 2009;11:36.

31. Chow V, Wilkinson B, LaBadie R, et al. Open label study of the pharmacokinetics of a JAK3 antagonist (CP-690,550) and single doses of oral methotrexate in rheumatoid arthritis subjects [abstract]. *Clin Pharmacol Ther*. 2008;83:S36.

32. Rosebraugh CJ. NDA approval letter: *Xeljanz* (tofacitinib NDA 203214). US Food and Drug Administration Web site. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/203214Orig1s000ltr.pdf. Published November 6, 2012. Accessed December 12, 2012.

33. Multimedia: US Food and Drug Administration approves Pfizer's *Xeljanz* (tofacitinib citrate) for adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate [news release]. New York: Pfizer Inc; November 7, 2012. http://press.pfizer.com/press-release/multimedia-us-food-and-drug-administration-approves-pfizers-xeljanz-tofacitinib-citrat. Accessed November 20, 2012. ■

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Continuing Education Case Study Quiz

Goal— The goal of this program is to educate pharmacists about the use of tofacitinib for the treatment of rheumatoid arthritis (RA).

Objectives—At the completion of this program, the reader will be able to:
1. Describe the pharmacology and pharmacokinetics of tofacitinib.
2. Discuss the risks associated with the use of tofacitinib.
3. Discuss the potential benefit of tofacitinib for an individual patient.
4. Apply the information on the use of tofacitinib to a case study.

Key Words—Janus kinase inhibitors, new drugs, rheumatoid arthritis

1. The US Food and Drug Administration (FDA)–approved indication for tofacitinib is:
   a. Adjunctive treatment of adult patients with moderately to severely active RA who have responded to methotrexate therapy.
   b. Treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate.
   c. Treatment of adult patients with mild active RA who have had an inadequate response or intolerance to methotrexate.
   d. Adjunct treatment of adult patients with mild active RA who have tolerated methotrexate.

2. Tofacitinib is administered:
   a. As a subcutaneous injection.
   b. As an intravenous injection.
   c. Topically via a patch.
   d. Orally.

3. Tofacitinib has the greatest potency of inhibition on which of the following cytokines?
   a. JAK1
   b. JAK2
   c. JAK3
   d. Tyk2

4. Tofacitinib is primarily metabolized hepatically?
   a. True
   b. False

5. The usual dose of tofacitinib is:
   a. 5 mg once a day.
   b. 5 mg twice a day.
   c. 10 mg once a day.
   d. 10 mg twice a day.

6. The tofacitinib dosage should be reduced in a patient:
   a. With moderate to severe renal insufficiency.
   b. With moderate hepatic impairment.
   c. Receiving potent inhibitors of cytochrome P450 3A4.
   d. All of the above.

7. Tofacitinib therapy should not be interrupted if the patient develops a serious infection.
   a. True
   b. False

8. The most common adverse side effect observed with tofacitinib was:
   a. Infection.
   b. Headache.
   c. Nausea.
   d. Liver enzyme elevation.

9. In the 12-month, phase 3 study, what percentage of patients receiving tofacitinib 5 mg achieved ACR20 after 6 months of therapy?
   a. 31.2%
   b. 40.3%
   c. 52.7%
   d. 58.3%

10. Tofacitinib is classified as Pregnancy Category:
    a. C.
    b. X.
    c. B.
    d. A.

Case History

PT is a 48-year-old male with a history of alcohol and cigarette abuse who has RA, moderate hepatic impairment, hypertension, and hyperlipidemia. He is currently taking adalimumab 40 mg every other week, lisinopril 12.5 mg once a day, and simvastatin 40 mg once a day. PT has been experiencing injection site reactions with the adalimumab and has asked about changing therapy. His doctor would like PT to initiate therapy with tofacitinib.

11. Initiation of tofacitinib therapy should be avoided in this patient if he has a:
    a. Positive tuberculosis test.
    b. Lymphocyte count less than 500 cells/mm^3.
    c. Hemoglobin level less than 9 g/dL.
    d. All of the above.

12. What is the recommended dose of tofacitinib for PT?
    a. 5 mg once daily
    b. 5 mg twice daily
    c. 10 mg once daily
    d. 10 mg twice daily

13. PT should be instructed to take tofacitinib on an empty stomach 1 hour before or 2 hours after a meal.
    a. True
    b. False

14. After being on tofacitinib for 6 months, PT comes to your pharmacy to get his annual flu vaccine. Which of the following products would be most appropriate for PT?
    a. High-dose influenza virus vaccine intramuscular injection
    b. Influenza virus vaccine subcutaneous injection
    c. Influenza virus vaccine intramuscular injection
    d. Influenza virus vaccine intranasal spray

15. Temporary dose interruption is recommended if PT develops which of the following conditions?
    a. Moderate renal insufficiency
    b. Anemia
    b. Lymphopenia
    b. Diarrhea

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