Review Article

Oral Tofacitinib: Contemporary Appraisal of Its Role in Dermatology

Abstract

Tofacitinib, an oral Janus kinase inhibitor (Jakinib), is an emerging treatment modality whose well-established efficacy in systemic inflammatory diseases is now being actively explored for cutaneous disorders (arising due to the patient's dysimmune responses) that are not responding to and/or sustaining intolerable adverse effects with the classical immunosuppressives and other targeted therapies such as the biologics. The most common dermatoses for which oral as well as topical Jakinibs such as tofacitinib have been evaluated and are being used albeit as an off-label indication include psoriasis, psoriatic arthritis, alopecia areata, vitiligo, and atopic dermatitis. This article provides a succinct review on the current status of oral tofacitinib in dermatology through literature search of PubMed database and stresses on the need for further evidence generation to define the drug's place in the therapeutic arsenal of dysimmune cutaneous disorders.

Keywords: *Alopecia areata, atopic dermatitis, Jakinib, Janus kinase inhibitors, psoriasis, psoriatic arthritis, tofacitinib, vitiligo*

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Introduction

Tofacitinib, an immunomodulator of Janus kinase inhibitor (Jakinib) family, blocks tyrosine kinases of the Janus family.[1] Janus kinase-signal transducer and activator of transcription (JAK/STAT) is an intracellular pathway that drives downstream signaling of several pro-inflammatory pathways. The well-established efficacy of Jakinibs in inflammatory disorders, particularly rheumatoid arthritis (RA) and ulcerative colitis (UC), suggests the potential of their positive effects in a myriad of inflammatory dermatoses as well.[2]

Jakinibs constitute an attractive and preferable option as a targeted therapy over biologics, owing to inhibition of signaling from multiple cytokines, unreported potential of generating neutralizing antibodies, and the ease of administration by oral and topical routes.[3] The aim of this paper is to provide a review of studies exploring their use (tofacitinib as the prototype) in dermatology.

Methods

A literature search was performed without the use of filters on PubMed with the following set of keywords: tofacitinib dermatology, tofacitinib skin disorders, JAK inhibitors dermatology, JAK inhibitors skin, tofacitinib psoriasis, tofacitinib psoriatic arthritis, tofacitinib alopecia, tofacitinib vitiligo, and tofacitinib atopic dermatitis. Articles from year 2001 to 2018 were reviewed, and 149 search results and their references were obtained. Criteria for consideration of search articles for inclusion purpose in the review were based on mutual decision of both the authors as per their relevance to the journal. After data extraction, information pertaining to the different subsections were processed and reorganized in the form of this narrative review. An attempt was made to objectivize the article by summarizing the content in tables.

Mechanism of action of tofacitinib: The JAK/STAT pathway

JAKs are intracellular enzymes that bind to the cytoplasmic domains of many cytokine receptors. The JAK/STAT signaling pathway is involved in many inflammatory skin diseases [Figure 1], particularly those resulting from type I/II cytokine receptors-associated cytokines.[2]

The major cutaneous and associated disorders that have shown the most promising results with tofacitinib and other Jakinibs include psoriasis and

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psoriatic arthritis (PsA), alopecia areata (AA) and variants including AA totalis (AT) and AA universalis (AU), atopic dermatitis (AD), and vitiligo.[4] Anecdotal reports have also suggested their efficacy in cutaneous lupus erythematosus, dermatomyositis, chronic actinic dermatitis, erythema multiforme, hypereosinophilic syndrome, cutaneous graft-versus-host disease, pyoderma gangrenosum (PG), lichen planus, and Sjogren's syndrome, amongst others.[5]

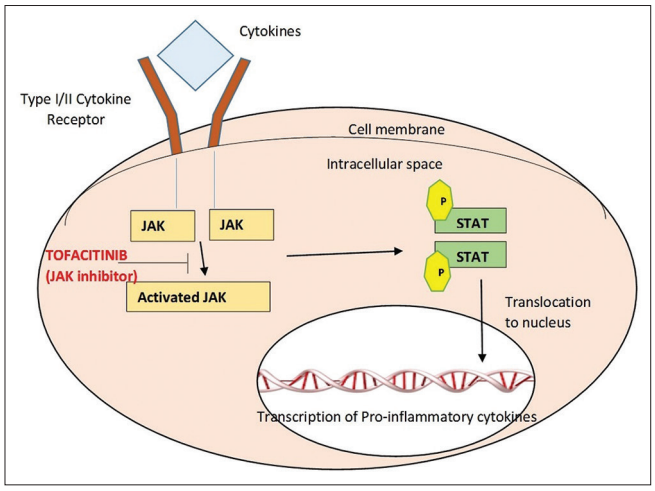

Figure 1: Type I/II cytokine receptors lack intrinsic kinase activity and signal through the cytoplasmic Janus kinases (JAK1, JAK2, JAK3, and TYK2) along with the DNA-binding proteins called signal transducers and activators of transcription (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6). Upon engagement of extracellular ligands with the receptors, intracellular JAK proteins become activated and phosphorylate STAT proteins which dimerize and translocate to the nucleus to regulate gene expression. Jakinibs interfere with the cytokine signal transduction to bring about their antiinflammatory effects

Types of Jakinibs

Four JAK isoforms are known: JAK1, JAK2, JAK3, and TYK2. While JAK1, JAK2, and TYK2 bind to many cytokine receptors, JAK3 only binds one subunit, the common gamma chain. This shared receptor subunit is used by a small family of cytokines that includes interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21. While first-generation Jakinibs (tofacitinib, ruxolitinib, baricitinib) block multiple JAKs, the second generation (decernotinib, experimental agents such as VX-509, GLPG0634) target a particular JAK.[6] Specific Jakinibs are associated with less adverse events (AEs), particularly serious infections and cytopenias. Table 1 summarizes the current US Food and Drug Administration (FDA) approved indications of first-generation Jakinibs, with psoriatic arthritis representing the only skin-associated disorder for which oral tofacitinib is currently approved.[4] Second-generation Jakinibs are currently being evaluated in phase II studies. Tofacitinib, a JAK 1/3 inhibitor, is the most studied Jakinib in cutaneous diseases. As it blocks JAK2 only weakly, the JAK2-blockade associated hematological AEs are much lesser with this drug.[4] The key pharmacological concepts of tofacitinib[7] are detailed in Table 2.

Clinical Use of Oral Tofacitinib in Skin Disorders: An Appraisal

Psoriasis

JAK/STAT-dependent cytokines IL-12 and IL-23 are principle mediators of psoriasis, the first cutaneous disease evaluated for treatment with tofacitinib. Their upstream blockade by tofacitinib indirectly decreases IL-17 levels.[5]

Table 1: List of first-generation oral Jakinibs currently US FDA-approved for human use[4]

Drug	Inhibits	Brand name (Manufacturer)	FDA-approved indication (s) (year of approval)	FDA-approved dosing
Tofacitinib	JAK 1/3>2	XELJANZ®-(Pfizer)	Rheumatoid arthritis (2012)	Standard: 5mg BD XR: 11 mg OD
			Psoriatic arthritis (2017)	Standard: 5 mg BD XR: 11 mg OD
			Ulcerative colitis (2018)	Standard: 10 mg BD
Ruxolitinib	JAK 1/2	Jakafi®-Incyte/Novartis	Myelofibrosis (2011)	5-25 mg BD
			Polycythemia vera (2014)	5-25 mg BD
Baricitinib	JAK 1/2	Olumiant®-Incyte/Eli Lilly	Rheumatoid arthritis (2018)	2 mg OD

US FDA=United States Food and Drug Administration, JAK=Janus kinase, OD=once-a-day, BD=twice-a-day, XR=Extended release

Table 2: Oral tofacitinib: Key pharmacological concepts[7]

Absorption and bioavailability			Elimination			Coefficient of variance (based on age, weight, gender, and race)
Peak levels	Bioavailability	Plasma protein binding	Half-life	Metabolism	Excretion	
30 min	74%	~40%	~3 h	70% Hepatic metabolism. Primarily mediated by CYP3A4 with minor contribution from CYP2C19	30% renal excretion	27% No clinically relevant change in tofacitinib exposure, after accounting for differences in renal function between patients, based on age, weight, gender, and race

Results from multiple placebo-controlled and comparative randomized controlled trials (RCT) have established good efficacy of tofacitinib in psoriasis.[8-14] The therapeutic outcome with 5 or 10 mg tofacitinib was significantly better than placebo and comparable or superior to etanercept.[8-10] Results of a long-term extension study involving 2867 psoriatic patients who were administered tofacitinib 5–10 mg twice daily as per a specific protocol of more than three months showed that 52–62% patients achieved 75% improvement in Psoriasis Area and Severity Index (PASI75) through month 54. General and serious AEs were reported in 82.5% and 13.7% patients, respectively; 13.9% discontinued the drug owing to AEs. Twenty-nine deaths occurred during the study, of which nine were considered potentially related to tofacitinib, malignancy being the most common cause.[12] In an aggregate data model-based meta-analysis that quantitatively evaluated the time-course and treatment effects of systemic agents for psoriasis, tofacitinib 10 mg twice daily showed PASI75 and PASI90 response rates comparable to cyclosporine, noninferior or better than methotrexate and better than acitretin and apremilast.[14]

Psoriatic arthritis

PsA is a US FDA-approved indication of oral tofacitinib with evidence of efficacy of tofacitinib being better than placebo and comparable to adalimumab.[15] The drug also showed improvement in patients not responding despite 6 months treatment with at least one TNF-α inhibitor.[16] Although results were better with the higher dose (10 mg twice-a-day), 5 mg twice daily is currently the preferred dose for PsA owing to better safety.[17]

Alopecia areata

The serendipitous discovery of tofacitinib as a treatment for AA led to further exploration.[18] JAK-STAT-dependent cytokines interferon (IFN)-γ and IL-15 drive activation of autoreactive CD8 T cells that are crucial in the pathogenesis of AA.[5] Improvement of >50% in Severity of Alopecia Tool (SALT) score has been reported in 32–66% patients treated with tofacitinib.[19-21] The efficacy varies with disease severity, drug dosage, and adjuvant treatments. Better overall outcomes were reported in patchy AA (versus AT/AU), with 10 mg twice daily (instead of 5 mg twice daily), and with concomitant oral steroids.[20,21] Relapses were frequent but responded to higher doses and/or corticosteroid addition.[20] The well-known waxing-and-waning and relapsing course of severe variants of AA such as AT and AU (despite the use of tofacitinib) mandates thorough pretreatment counseling of the patient and/or guardians about the possibility of waning treatment response, possible need for dosage increment, and unpredictability of relapse following cessation of therapy.[22] Tofacitinib has been reported to provide similar efficacy as oral ruxolitinib, higher efficacy than contact immunotherapy, and better tolerability than conventional immunosuppressive treatments (corticosteroids ± cyclosporine) in AA.[23,24] In addition, the drug has demonstrated improvement in nail symptoms of AA.[25] The longest reported duration of treatment with tofacitinib in AA/AT/AU is 18 months.[20,21]

Vitiligo

Tofacitinib inhibits IFN-γ signaling, which drives the CD8 T cell-mediated melanocyte destruction.[5] Satisfactory re-pigmentation has been reported with 5–10 mg twice daily,[26] with better outcome seen in sun-exposed areas and concomitant narrowband ultraviolet B (NB-UVB) therapy.[27,28]

Atopic dermatitis

Tofacitinib decreases IL-4, IL-5, and IL-13 signaling involved in the pathogenesis of AD.[5,29,30] It additionally reduces AD-associated pruritus, because JAK signaling in nerves critically regulates AD-associated itch.[31]

Other dermatoses

Recent anecdotal reports and short case series have demonstrated efficacy of tofacitinib in certain other cutaneous disorders as well. Oral tofacitinib 5–10 mg twice daily given to three patients with Crohn's disease (primarily for associated severe inflammatory arthritis) and PG refractory to biologics, resulted in resolution of all PG lesions in 12 weeks.[32] Oral tofacitinib 5 mg two to three times daily given for 2–19 months in combination with other immunomodulatory therapies such as low-dose methotrexate reportedly produced significant improvement in patients with generalized deep morphea and eosinophilic fasciitis nonresponsive to corticosteroids, and in patients with treatment-recalcitrant lichen planopilaris.[33,34]

A review of major studies evaluating the efficacy and safety of oral tofacitinib in specific dermatoses is detailed in Table 3.

Oral versus Topical Tofacitinib

The AEs associated with oral Jakinibs may be offset with their topical formulations. Topical tofacitinib (TT), most commonly used as a 2% ointment with/without penetration enhancers, demonstrated modest improvement in psoriasis and AD.[35] In psoriasis, lower concentrations (0.02, 0.2, and 1%) showed efficacy comparable to 2% formulation.[36] In a 24-week, open-label pilot study of 10 patients with AA treated with tofacitinib 2% ointment applied twice daily, 3 patients experienced hair regrowth with a mean decrease of 34.6% in SALT score. The response was less than oral tofacitinib but similar to that reported with clobetasol 0.05% ointment under occlusion.[37] Although results in AA/AT/AU have been modest and conflicting,[35] TT may be a favorable treatment option to induce hair regrowth in locations such as eyebrows and eyelashes. A near complete regrowth of eyelashes was reported with tofacitinib 2% solution by 4 months in a patient who had used multiple ineffective prior modalities.[38] At the time of authoring this review,

Table 3: Review of the efficacy and safety profile of oral tofacitinib reported in major clinical studies for Jakinib-responsive dermatological disorders

Author(s)	Indication	Methodology	Results	Adverse events (AEs)
Psoriasis				
Bissonnette *et al*. 2015[8]	Moderate-to-severe chronic plaque psoriasis	Phase 3 placebo-controlled RCT 666 patients Randomization and intervention details and duration of therapy: Patients randomly divided into two groups: Tofacitinib 5 mg or 10 mg BD given for 24 weeks → Patients who achieved both PASI75 and PGA response, randomized into two groups: Tofacitinib at same dosage or placebo (withdrawal) until relapse (>50% reduction in the PASI improvement during initial treatment) or week 40 → Tofacitinib given at initial dose for 16 weeks Outcome measures Proportion of patients attaining PASI75 Proportion of patients achieving a PGA score of "clear" or "almost clear" (PGA response)	Initial treatment: Patients who achieved both PASI75 and PGA responses Tofacitinib 5 mg BD-33.5% Tofacitinib 10 mg BD-55.2% Treatment withdrawal: Patients who maintained PASI75 and PGA responses and did not relapse Tofacitinib 5 mg-56.2, 49.9, and 92.3% Tofacitinib 10 mg-62.3, 63.9, and 93.0% Placebo 5 mg-23.3, 22.9, and 32.8% Placebo 10 mg-26.1, 18.0, and 42.9% Retreatment: Relapsed patients who regained PASI75 and PGA responses Tofacitinib 5 mg-36.8 and 44.8% Tofacitinib 10 mg-61.0 and 57.1% Patients who received continuous treatment with tofacitinib, maintained the median PASI scores, more effectively as compared to placebo recipients	Overall rate of AEs-comparable in continuous and retreatment groups Most common AEs-infections and infestations, especially nasopharyngitis Other AEs-gastrointestinal complaints Elevations noted in LDL cholesterol levels after initial treatment, reversed upon withdrawal
Bachelez *et al*. 2015[9]	Moderate-to-severe chronic plaque psoriasis	Phase 3 placebo-controlled noninferiority RCT 1101 patients Randomization and intervention details: Patients randomly divided in a 3:3:3:1 ratio into four groups: Tofacitinib 5 mg BD Tofacitinib 10 mg BD Etanercept twice-a-week (subcutaneous) Placebo Duration of therapy 12 weeks Outcome measures Proportion of patients attaining PASI75 Proportion of patients achieving a PGA score of "clear" or "almost clear" (PGA response)	PASI75 and PGA responses Tofacitinib 5 mg BD-39.5 and 47.1% Tofacitinib 10 mg BD-63.6 and 68.2% Etanercept twice weekly-58.8 and 66.3% Placebo-5.6% and 15%	Overall rate of AEs including serious issues-similar across the four groups (2%) Rate of discontinuation due to AEs: Tofacitinib 5 mg-1% Tofacitinib 10 mg-3% Etanercept-3% Placebo-4% Specific AEs observed in patients on tofacitinib: Herpes zoster-5 patients Other specific AEs reported in patients on tofacitinib-dose-dependent elevations in HDL and LDL cholesterol, elevation in CPK levels, and decrease in hemoglobin levels

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Table 3: Contd...

Author(s)	Indication	Methodology	Results	Adverse events (AEs)
Valenzuela *et al*. 2016[10]	Moderate to severe plaque psoriasis	Phase 3, placebo-controlled RCT 1092 patients. Randomization and intervention details: Patients randomly divided in a 3:3:3:1 ratio into four groups: Tofacitinib 5 mg BD Tofacitinib 10 mg BD Etanercept twice-a-week (subcutaneous) Placebo Duration of therapy: 12 weeks Outcome measures: Patient-reported outcomes (PROs) including DLQI, Itch Severity Item Score (ISIS) and Patient Global Assessment of psoriasis (PtGA)	Improvement of DLQI scores Tofacitinib 5 mg BD-30.9% Tofacitinib 10 mg BD-47.3% Etanercept twice weekly-43.6% Placebo-7.8% Itch was significantly reduced by tofacitinib compared with etanercept and placebo within 1 day of starting treatment. Frequency of ITIS of "little or no itch" Tofacitinib 10 mg-68.6% Etanercept-57.4% Placebo-12.2% PtGA response rate significantly greater with tofacitinib 10 mg versus placebo	
Lloyd-Lavery 2018[11] (Linked artice: Valenzuela *et al*.)[12]	Moderate to severe chronic plaque psoriasis	Multiple phase 2 and global phase 3 trials with open-label long-term extension (LTE) study 2867 patients Intervention details and duration of therapy: Patients received tofacitinib 10 mg BD for 3 months followed by 5-10 mg BD for a median duration of 35.6 months Longest efficacy and safety data reported up to month 66 Outcome measures: PASI75 and PGA response	PGA response and PASI75 Achieved by 52-62% and 56-74% of patients at each study visit through Month 54 15·8% patients discontinued treatment due to inadequate clinical response	AEs and severe AEs-82.5 and 13.7% Treatment discontinuation due to AEs-13.9% Most frequent AEs-nasopharyngitis (20.9%), elevations in creatine kinase (13.5%), URTI (11%) and hypertension (7.4%) of which 2.3% hypertensive cases were potentially related to tofacitinib. No increased risk of herpes zoster infection noted with longer exposure Incidence rates (patients with event/100 patient-years)-serious infections (1.16), malignancies (0.67) and MACEs (0.26) Laboratory parameters-generally stable over 54 months

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Author(s)	Indication	Methodology	Results	Adverse events (AEs)
Strober *et al*. 2019[13]	Moderate to severe chronic plaque psoriasis	Pooled data from one phase 2, four phase 3 trials, and one long-term extension (LTE) study Intervention details and duration of therapy: For efficacy analyses, 745, 741, and 373 patients were included who received tofacitinib 5 mg BD, tofacitinib 10 mg BD, and placebo, respectively For analyses of safety across all tofacitinib-treated patients up to 3 years, 3623 patients were included (5204 patient-years of exposure) Outcome measures: PASI75 and PGA response, PASI90, DLQI, ISIS	Tofacitinib 5 and 10 mg BD showed superiority over placebo for all efficacy end points at week 16, with response maintained for 52 weeks of continued treatment Clinical response was maintained in many patients for up to 2 years Tofacitinib improved patients' quality of life and was well tolerated Tofacitinib 10 mg BD demonstrated greater efficacy than 5 mg BD	Rates of safety events of interest (except herpes zoster) were similar to those in the published literature and healthcare databases for other systemic psoriasis therapies The majority of cases of herpes zoster were nonserious, were of mild or moderate severity and resolved on treatment. Serious infections and herpes zoster were numerically higher with tofacitinib 10 mg BD than with 5 mg BD; but were below that reported in some studies for tumor necrosis factor antagonists
Checchio *et al*. 2017[14]	Moderate to severe psoriasis	Aggregate data model-based meta-analysis Evaluation of the magnitude and onset of the drug effect by two mathematical models: (1) Longitudinal model to quantify the time course of PASI75. 2) Landmark model to quantify the dose-response relationship for PASI responders (PASI50, PASI75, PASI90, PASI100) at week 12	Tofacitinib 5 mg BD showed similar efficacy to methotrexate and etanercept 25 mg twice weekly, and numerically higher than acitretin and apremilast Tofacitinib 10 mg BD showed efficacy in the range of injectable tumor necrosis factor (TNF) antagonists, similar to ciclosporin, and greater than other oral treatments (apremilast, acitretin, methotrexate, and fumarates)	
Psoriatic arthritis				
Mease *et al*. 2017[15]	Psoriatic arthritis (PsA) not responding to synthetic DMARDs and TNF-α inhibitor naïve Patients received a stable background dose of a single conventional synthetic DMARD-methotrexate, sulfasalazine, or leflunomide	Double-blind, active, and placebo-controlled, phase 3 RCT-OPAL BROADEN study (Oral Psoriatic Arthritis trial) 422 patients Randomization and intervention details: Patients randomized in a 2:2:2:1:1 ratio into five groups: Tofacitinib 5 mg BD Tofacitinib 10 mg BD Adalimumab 40 mg once every 2 weeks (subcutaneous) Placebo with a blinded switch to either 5 or 10 mg tofacitinib at 3 months Duration of therapy: 12-months Outcome measures: Proportion of patients with ACR20 response at month 3 Change from baseline in HAQ-DI score at month 3	ACR20 responses and HAQ-DI scores at 3 months Tofacitinib 5 mg BD: 50% and−0.35 Tofacitinib 10 mg BD: 61% and−0.40 Adalimumab once every 2 weeks: 52% and−0.38 Placebo: 33% and−0.18 Improvements observed as early as week 2 At month 12, 91-98% of patients across all trial groups met radiographic criteria for nonprogression Tofacitinib 10 mg BD was better than 5 mg BD only in change from baseline in Leeds Enthesitis Index and dactylitis severity score at month 3 but without differences at month 12	Overall rate of AEs at month 3 and 12-tofacitinib 10 mg: 45 and 71% Tofacitinib 5 mg: 39 and 66% Adalimumab: 46 and 72% Placebo: 35 and 69% Most common AEs: nasopharyngitis, URTI and headache Specific AEs observed in patients on tofacitinib: Cancer-4 cases Serious infections-3 cases Herpes zoster-4 cases

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Table 3: Contd...

Author(s)	Indication	Methodology	Results	Adverse events (AEs)
Gladman *et al*. 2017[16]	PsA with an inadequate response to at least one TNF-α inhibitor for 6 months	Double-blind, active, and placebo-controlled, phase 3 RCT-OPAL BROADEN study (Oral Psoriatic Arthritis trial) 422 patients Randomization and intervention details: Patients randomized in a 2:2:2:1:1 ratio into five groups: Tofacitinib 5 mg BD Tofacitinib 10 mg BD Adalimumab 40 mg once every 2 weeks (subcutaneous) Placebo with a blinded switch to either 5 or 10 mg tofacitinib at 3 months Duration of therapy: 12 months Outcome measures: Proportion of patients with ACR20 response at month 3 Change from baseline in HAQ-DI score at month 3	ACR20 responses and HAQ-DI scores at 3 months Tofacitinib 5 mg BD: 50% and−0.39 Tofacitinib 10 mg BD: 47% and−0.35 Placebo: 24% and−0.14	Serious AEs-low and similar across treatment groups Tofacitinib 10 mg: 6% Tofacitinib 5 mg: 4% Specific AEs observed in patients on tofacitinib: Serious infections-4 cases Herpes zoster-3 Myocardial infarction-1 Ischemic stroke-1 Overall rates of laboratory changes were consistent with expected tofacitinib effects.
Alopecia Areata				
Crispin *et al*. 2016[19]	AA with>50% scalp hair loss, AT and AU	Phase IIa open-label, single-arm trial 66 patients Intervention and duration of therapy: Tofacitinib 5 mg BD for 3 months Outcome measures: Proportion of patients attaining>50% improvement in SALT score	Improvement of>50% in SALT score in 32% of patients Relapse occurred after an average of 8.5 weeks following treatment discontinuation	Most common AEs: URTIs
Liu *et al*. 2017[20]	AA with >40% scalp hair loss, AT, and AU	Retrospective study 90 patients. (>18 years) Intervention details: Patients received: Tofacitinib 5 mg BD (43%) or more (29%) alone or with prednisolone (28%) Duration of therapy: 4-18 months Outcome measures: Proportion of patients attaining>50% improvement in SALT score	Improvement of>50% in SALT score in 58% of patients Improvement rates were higher in patients with AA vs AT and AU Relapse occurred in five responders with subsequent hair regrowth using increased tofacitinib, 20 mg/day, or adjuvant prednisone, 300 mg/month for 3 months	Most common AEs-URTIs in 29% of patients

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Table 3: Contd...

Author(s)	Indication	Methodology	Results	Adverse events (AEs)
Jabbari *et al*. 2018[21]	Moderate to severe AA, AT, and AU	Phase II open-label trial 12 patients Intervention details: Patients received tofacitinib 5 mg BD escalated to 10 mg BD in nonresponders Duration of therapy: 6-18 months Outcome measures: Proportion of patients attaining>50% improvement in SALT score	Improvement of>50% in SALT score in 66% of patients 1 subject showed no response after 36 weeks. Variable hair shedding occurred after treatment completion, but three of the eight responders, maintained lower SALT scores compared to baseline at nearly 24 weeks off tofacitinib	Most common AEs-URTI AE leading to treatment discontinuation-Hypertensive urgency in 1 patient with prior history of hypertension, at 12 weeks of treatment No major laboratory abnormalities. Treatment discontinuation in 1 patient-persistent 1 + blood on urinalysis
Almutairi *et al*. 2018[23]	AA with>30% scalp hair loss, AT and AU	Open-label comparative study 75 patients Intervention details: Patients randomized into two groups: Oral ruxolitinib 20 mg BD Oral tofacitinib 5 mg BD Duration of therapy: 6-months followed by 3 months of follow-up off therapy. Outcome measures: Change in SALT score	Mean change in SALT score: 93.8+3.25 in ruxolitinib group 95.2+2.69 in tofacitinib group Duration for initial hair regrowth-shorter in ruxolitinib group Overall hair regrowth-remarkable and statistically similar in both groups at the end of 6 months treatment Relapse rate at the end of the 3-month follow-up-around two-thirds of cases experienced relapse in both groups	Both drugs were well tolerated, with no reported serious adverse effects Most common AEs noted (both groups)-leukopenia, acute infections, mild raise in liver enzymes, dyslipidemia
Shin *et al*. 2019[24]	AT and AU	Retrospective comparative study 74 patients Intervention details: 18 patients treated with tofacitinib 5-10 mg BD, 26 treated with conventional oral treatment (steroid±cyclosporine), and 30 treated with DPCP Duration of therapy: 6 months Outcome measures 50% improvement in SALT score	Improvement of 50% in SALT score in: 44.4% of patients in tofacitinib group, 37.5% in conventional oral treatment group, and 11.1% in DPCP group Oral tofacitinib was more effective than DPCP immunotherapy and more tolerable than conventional oral treatment	AEs and treatment discontinuation observed in: Tofacitinib-10%: None Conventional oral treatment group-73, 23.1% DPCP group-10, 10%
Lee *et al*. 2018[25]	Moderate-to-severe AA with >30% hair loss and associated with nail involvement	Retrospective study 33 patients Intervention details and duration of therapy Patients divided into two subgroups-with or without nail involvement, group with nail involvement divided into-patients with or without nail deformity improvement after tofacitinib administration-10 mg BD decreased or increased to 5mg or 11 mg OD according to response Outcome measures: Improvement in SALT score for scalp hair Nail involvement and body hair assessed at follow-up visits	Of 15 patients with nail involvement, 73.3% showed improvement regardless of type of nail change Nail involvement is not a poor prognosis factor in hair regrowth with tofacitinib treatment Among patients with nail improvement, the median response time to tofacitinib treatment was 5 months (range, 1-11), 2.5 months (range, 1-10), and 2 months (range, 1-6) for nail, scalp hair, and body hair, respectively Nail improvement tended to occur later than scalp and body hair regrowth	

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Table 3: Contd...

Author(s)	Indication	Methodology	Results	Adverse events (AEs)
Vitiligo				
Craiglow *et al*. 2015[26]	Progressive vitiligo involving 10% BSA Continued progression with NB-UVB phototherapy	Case report 1 patient (50 years/F) Intervention and duration of therapy Tofacitinib 5 mg every other day/3 weeks →5 mg once daily/5 months	Clinical response at 2 months and almost complete repigmentation of the forehead and hands and partial repigmentation of other areas at 5 months Depigmentation recurred after discontinuing treatment	No AEs or laboratory abnormalities
Liu *et al*. 2017[27]	Generalized vitiligo/acral vitiligo of 4--33 years duration	Retrospective case series 10 patients (28-73 years) Intervention details: Tofacitinib 5-10 mg daily/twice daily Duration of therapy: 3-15 months Outcome measures: Decrease in BSA of depigmentation	A mean decrease of 5.4% BSA involvement with vitiligo in 5 of 10 patients, only in sun-exposed or NB-UVB phototherapy treated areas	Most common AEs-URTI, weight gain, arthralgia, mild elevations of lipid levels. No serious AEs
Kim *et al*. 2018[28]	Longstanding vitiligo with significant facial involvement	Case report 2 patients Intervention and duration of therapy: Tofacitinib 5 mg BD and low-dose NB-UVB 2-3 times weekly for 3-6 months	Rapid and nearly complete repigmentation of face after 3-6 months	No AEs or laboratory abnormalities
Atopic dermatitis				
Levy *et al*. 2015[29]	Moderate-to-severe AD that had failed all common treatments, including systemic agents	Case series 6 patients (18-55 years) Intervention: Tofacitinib 5 mg daily/twice daily Duration of therapy: given for 8-29 weeks Outcome measures Reduction in Severity Scoring of AD Index (SCORAD), pruritus, and sleep loss scores	Reduction in SCORAD-66.6% Reduction in pruritus and sleep loss scores-69.9%	No AEs or laboratory abnormalities
Vu *et al*. 2017[30]	Lifelong history of AD, 4-year history of alopecia areata (AA), with previous alopecia totalis (AT) and a 3-year history of nonsegmental multifocal vitiligo	Case report 1 patient (44 years) Intervention: Tofacitinib 5 mg BD Duration of therapy: 6 months Outcome measures: Decline in Eczema Area and Severity Index (EASI)	EASI-decline within 2 weeks and complete remission of AD in 3 months Continuous improvement in AA Marginal improvement in vitiligo	URTI, diarrhea, not requiring treatment interruption

Contd...

Table 3: Contd...

Author(s)	Indication	Methodology	Results	Adverse events (AEs)
Morris *et al*. 2018[31]	Moderately severe AD with AU not responding to multiple treatments	Case report 1 patient (22 years) Intervention: Tofacitinib 5 mg BD Duration of therapy: 10 months Outcome measure: Reduction in numerical rating scale itch score	Improvement in AD. Reduction in numerical rating scale itch score from 8 to 3. Hair regrowth on all of the affected body parts	No AEs or laboratory abnormalities

RCT=Randomized controlled trial, OD=Once-a-day, BD=Twice-a-day, PASI75: >75% reduction in Psoriasis Area and Severity Index, PGA=Physician's Global Assessment, AEs=Adverse effects, LDL=Low-density lipoprotein, HDL=High-density lipoprotein, CPK=Creatinine phosphokinase, PROs=Patient reported outcomes, DLQI=Dermatology Life Quality Index, ISIS=Itch severity item score, PtGA=Patient's Global Assessment, LTE=Long-term extension, URTI=Upper respiratory tract infection, MACEs=Major adverse cardiovascular events, TNF-α=Tumor necrosis factor-α, ACR20=American College of Rheumatology 20 response (≥20% improvement from baseline in the number of tender and swollen joints and at least three of five other important domains), HAQ-DI=Health Assessment Questionnaire-Disability Index score (ranging from 0 to 3, with higher scores indicating greater disability), PsA=Psoriatic arthritis, DMARD=Disease modifying antirheumatic drugs, AA=Alopecia areata, AT=Alopecia totalis, AU=Alopecia universalis, SALT score=Severity of Alopecia Tool, DPCP=Diphenylcyclopropenone, BSA=Body surface area, NB-UVB=Narrow band ultraviolet B, AD=Atopic dermatitis, SCORAD=Scoring of Atopic Dermatitis, EASI=Eczema Area and Severity Index

there was no report published in indexed literature of TT in vitiligo, although topical ruxolitinib demonstrated decent efficacy in facial lesions of vitiligo.[39] The vehicle of the topical formulation impacts the efficacy; better results were reported with liposomal-based TT.[40] The most common AEs seen with TT were erythema, hyperpigmentation, transient acne, and minor and reversible laboratory abnormalities.[35] A succinct review on the current status of topical Jakinibs for inflammatory dermatoses is advised for further reading for interested readers.[35]

Use in Specific Populations

The use of oral tofacitinib in special populations[2,7,41-43] has been summarized in Table 4.

AEs reported with oral tofacitinib

The six major groups of AEs[1] associated with tofacitinib that dermatologists should be aware and vigilant about have been summarized in Table 5 and include:

1. Infections: Cutaneous/Systemic; new onset/reactivation of latent infections; nasopharyngitis/severe infections; opportunistic infections (OIs)
2. Malignancies: Solid organ cancers, lymphoproliferative malignancies including lymphomas, cutaneous including nonmelanoma skin cancers (NMSC) and melanoma[17]
3. Gastrointestinal: Gastrointestinal perforations and obstruction[7]
4. Laboratory abnormalities: Hematological, liver derangement with enzyme elevations, dyslipidemia
5. Hypersensitivity reactions and miscellaneous: Urticaria, angioedema, headache,[44] hypertension,[12] distal symmetric polyneuropathy, and musculoskeletal complaints such as arthralgia, back pain, and pain in extremities[17]
6. Drug interactions: As such tofacitinib does not cause any significant inhibition or induction of the major human drug-metabolizing Cytochrome P450s (CYPs), but its pharmacokinetics and effects/adverse effects may be altered by drugs affecting CYP isoforms. The important drug interactions[7] that must be known to a dermatologist prescribing oral tofacitinib have been mentioned in Table 6.

Inhibition of multiple JAKs by tofacitinib suggests a high risk for *infections* and malignancies.[5] Interestingly, clinically observed toxicity is limited, probably attributable to rapid kinetics of action.[3] The most common AEs reported with oral tofacitinib include upper respiratory tract infections, headache, diarrhea, and reactivation of viral infections (particularly herpes zoster). Risk of disseminated disease and serious infections is more with higher dose (10 mg BD) and with concomitant immunomodulators (methotrexate or corticosteroids) necessitating more cautious monitoring.[4]

Reactivation of latent tuberculosis (TB) infection (LTBI) has been reported in patients with systemic inflammatory disorders such as RA.[7,45] India is endemic for TB and one of the high background TB incidence rate (IR) countries (TB IR >0.05/100 patient-years). As per a review of phases II and III and long-term extension clinical trial data from the tofacitinib RA program, 26 out of 5675 RA patients (0.45%) on tofacitinib (phase II studies) developed active TB as an OI. Of these 26 patients, 21 (81%) belonged to TB-endemic countries like India.[46] Majority of cases developed in patients treated with high doses (10 mg BD). Secondly, of the phase III study cohort, 263 patients were diagnosed with LTBI by one of the following LTBI screening tests—QuantiFERON-TB Gold In-Tube (QFT-IT; Quest Diagnostics) or tuberculin

Table 4: Use of oral tofacitinib in special populations/situations

Special population/situation	Experience and/or evidence of use of oral tofacitinib	Additional remarks
Pregnancy	Pregnancy outcomes analyzed in patients with rheumatoid arthritis or psoriasis treated with oral tofacitinib were similar to those in the general population and patients treated with biologic therapies[41]	Oral tofacitinib is a pregnancy category C drug-safety in pregnancy is not well established and should be used only if benefits outweigh the potential risks[7]
Lactation	The drug is secreted in breast milk. To avoid exposure to the feeding infant, breastfeeding should be avoided during and for a duration of six elimination half-lives of the drug and its formulation	Breastfeeding is best avoided during treatment and for at least 18 h after the last dose (36 h after the last dose of the extended release formulation)[7]
Pediatric population	Evidence is not robust. A study conducted for AA in 13 adolescents (aged 12-17 years), treated with tofacitinib 5 mg twice daily for 2-16 months showed good efficacy and no serious AEs.[42] In a case series of four preadolescent children with AA, treated with oral tofacitinib 5 mg twice daily, good response was seen, and no AEs were noted over 6-15 months[43]	Benefit-risk should be discussed with the child's parents/guardians before starting therapy since safety in individuals less than 18 years of age is not confirmed[2]
Geriatric population	Evidence is not robust Higher incidence of infectious events reported in the elderly patients treated with oral tofacitinib[7]	Benefit-risk should be discussed with the patient and caregivers before starting therapy since safety remains to be established

Table 5: Oral tofacitinib: Reported AEs (from studies done in dermatologic indication plus other indications)

Cutaneous	Others
Infections (including activation/ re-activation of latent/remitted infections)[1]	
Herpes zoster	Upper respiratory tract infections, nasopharyngitis
Reactivation of herpes simplex	Urinary tract infections
	Opportunistic infections
	Activation of latent tuberculosis
	Pulmonary cryptococcosis
	Histoplasmosis
	Reactivation of a past hepatitis B infection
Malignancy[17]	
NMSC	Cancers of prostate, lungs, breast, pancreas
Melanoma	Lymphomas and EBV-induced lymphoproliferative disorders
Gastrointestinal[7]	
	Gastrointestinal perforations-especially in patients with diverticulitis, on concomitant NSAIDs or corticosteroids
	With preexisting severe gastrointestinal narrowing (pathologic or iatrogenic)
	Gastrointestinal obstruction-rare, but risk with XR preparation in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic)
Laboratory abnormalities[1]	
Hematological-reversible dose-dependent decrease in hemoglobin levels, RBC count, absolute neutrophil counts, and absolute lymphocyte count	
Enzyme elevations-dose-dependent increase in SGPT, SGOT, CPK	
Dyslipidemia-dose-dependent elevation in HDL, LDL, and total cholesterol levels, TG levels	
Hypersensitivity and miscellaneous	
Urticaria[44]	Headache
Angioedema	Distal symmetric polyneuropathy[1]
Rash	Hypertension[12]
	Musculoskeletal issues such as arthralgia, back pain, pain in extremities[17]

EBV=Epstein Barr virus, NSAIDs=Nonsteroidal antiinflammatory drugs, XR=Extended release, RBC=Red blood cell, SGPT=Serum glutamic pyruvic transaminase, SGOT=Serum glutamic oxaloacetic transaminase, CPK=Creatinine phosphokinase, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, TG=Triglyceride

skin test (TST; positive if induration ≥5 mm), and all of them received concomitant Isoniazid (INH) prophylaxis that guarded them from developing active TB. Also, while tofacitinib-treated patients using INH were slightly more

Table 6: Important drug interactions of oral tofacitinib[7]

As such tofacitinib does not cause any significant inhibition or induction of the major human drug-metabolizing CYPs, but its pharmacokinetics and effects/adverse effects may be altered by other drugs affecting CYP isoforms as detailed below	
Strong CYP3A4 inhibitor(s) (e.g., ketoconazole) OR moderate CYP3A4 inhibitor (s) with strong CYP2C19 inhibitor(s) (e.g., fluconazole)	
Pharmacological effect	Reduced metabolism leading to increased serum levels of tofacitinib
Intervention	Dosage reduction, e.g., from 5 mg BD or 11 mg XR OD to 5 mg OD
Strong CYP3A4 inducers (e.g., rifampin)	
Pharmacological effect	Increased metabolism leading to increased serum levels of tofacitinib Additive hepatotoxicity
Intervention	Co-administration is not recommended by the innovator. Also, risk of hepatic dysfunction will be more
Immunosuppressive Drugs (e.g., azathioprine, tacrolimus, cyclosporine)	
Pharmacological effect	Co-administration to be avoided owing to increased risk of immunosuppression
Intervention	Co-administration is not recommended
Coadministration with biologics, DMARDs or other potent immunosuppressants	
Pharmacological effect	Not well-studied. Theoretical risk of added immunosuppression
Intervention	Co-administration not recommended

DMARD=Disease-modifying anti-rheumatic drugs (such as hydroxychloroquine, sulfones)

likely to develop small elevations in liver enzymes during therapy, they were no more likely to develop significant liver transaminases elevation (>3× upper limit of normal) during therapy than tofacitinib-treated patients not using INH.[46] However, it is important to note that active TB with/without prior LTBI has till now not been reported as an AE of tofacitinib treatment for any dermatoses from India or the globe.[2] Although speculative, this dichotomy may result from many factors—overall less pool of patients treated till now (compared to RA), lack of screening for LTBI, lack of active surveillance for active TB during and after treatment, reporting bias, lower doses and treatment duration used relative to RA, lesser incidence of the use of concomitant immunomodulatory therapies, higher doses, and the fact that majority of the published studies on tofacitinib use for skin disorders hail from TB-nonendemic and low TB IR countries. Thus, it may be premature to comment on this risk any further as of now. Till then, the recommended guidelines of pretreatment evaluation for latent and active TB and administration of INH treatment (if required) with annual screening for TB should be followed in all patients planned for oral tofacitinib treatment for any skin disorder.[12] Table 7 summarizes the current recommendations regarding the risk of latent/active TB and use of oral tofacitinib.

Malignancies, most commonly cancers involving the prostate, lungs, breast, and NMSC have been reported in tofacitinib studies, with the risk being comparable to that observed with other targeted immunosuppressive therapies.[11,47] Lymphomas and Epstein Barr virus-associated posttransplant lymphoproliferative disorders have been observed at an increased rate in renal transplant patients treated with tofacitinib and concomitant immunosuppressive medications.[4] Targeted screening with personal and family history of malignancy, including NMSC and other risk factors such as past treatment with UVB, merits consideration in high-risk patients before tofacitinib administration.[17] Long-term studies are warranted to evaluate the specific risk of malignancy induction with oral tofacitinib in cutaneous disorders.

Gastrointestinal perforation has been reported; risk factors being history of diverticulitis, concomitant intake of nonsteroidal antiinflammatory drugs, oral corticosteroids. Although rare, there is a possibility of gastrointestinal obstruction due to the nondeformable XR preparation in patients with preexisting severe pathologic or iatrogenic gastrointestinal narrowing.[7]

Laboratory derangements may occur. Cytopenias are generally not common with tofacitinib (due to weak JAK2 inhibition), particularly in patients with healthy bone marrow reserves.[4] However, anemia, and fall in red blood cells, neutrophil and lymphocyte counts have been reported in studies of tofacitinib given for RA and UC. Elevations in creatine phosphokinase enzyme and liver enzymes (transaminases) greater than three times the upper limit of normal have been observed in patients treated with tofacitinib. Dyslipidemia with minor elevations in low-density lipoprotein, high-density lipoprotein, and total cholesterol and serum triglyceride levels are well known with this drug. Despite an increased risk of hypertension and dyslipidemia, an increased risk of major adverse cardiovascular events has not been reported.[12] Tofacitinib-induced hyperlipidemia may last for up to 12 weeks followed by stabilization. Persistent hyperlipidemia should be treated as per standard clinical guidelines, e.g., National Cholesterol Educational Program

Table 7: Guidelines for oral tofacitinib treatment and risk of tuberculosis (TB)

Patients should be evaluated and tested for latent or active infection prior to drug initiation and then annually.
Tests that may be used for LTBI screening-QuantiFERON-TB Gold In-Tube (QFT-IT), Mantoux tuberculin skin test (TST)*, chest X-ray.
Additional tests that may be considered if the above are negative and/or there is suspicion of active TB (individualized for each case)-clinical review to look for a source of EPTB such as enlarged lymph nodes, sputum analysis with AFB staining and mycobacterial culture, ultrasonography and/or CT-scan of abdomen and pelvis, endometrial brushing in women, etc.
Anti-tuberculosis therapy should be strongly considered prior to drug administration in patients:[7]
With past history of latent or active TB in whom an adequate course of treatment cannot be confirmed
With a negative test for latent TB but who have risk factors for TB infection.
Patients confirmed with active TB should not be treated with tofacitinib; rather first treated with multidrug ATT as per the nation's recommended protocol.
Isoniazid therapy should be concomitantly given to any patient who is diagnosed with LTBI with preferably 1 month of isoniazid prior to starting tofacitinib and complete 9 months regime thereafter. In view of modest risk of transaminitis, more frequent liver enzyme monitoring may be considered in these patients.[46]
Consider consultation with a TB specialist regarding decision about initiating anti-tuberculosis therapy in an individual patient.
Close monitoring for development of signs and symptoms of TB is warranted, even in patients who tested negative for latent TB prior to initiating therapy.

LTBI=Latent tuberculosis infection, TB=Tuberculosis, EPTB=Extra-pulmonary tuberculosis, AFB=Acid-fast bacilli, ATT=Antitubercular therapy. *TST should be conducted as per the national health program recommendation, e.g., in India, as per the latest guidelines of the Revised National TB Control Programme (RNTCP, 2016). 0.1 ml of 2TU/5TU given intradermally over the volar aspect of the forearm, induration ≥10 mm at 48-72 h considered POSITIVE

(NCEP). Use of lipid lowering agents such as statins improves the dyslipidemia, although regular monitoring of hepatic enzymes becomes mandatory in such cases.[17]

Drug hypersensitivity presenting as angioedema and urticaria have been observed in post marketing experience.[44]

Dose-dependent adverse reactions (seen more in patients treated with 10 mg twice daily than 5 mg twice daily) include herpes zoster infections, serious infections, and malignancy induction, particularly NMSC.[17]

Contraindications and Precautions

While there are no contraindications for tofacitinib *per se*, in Table 8 we have listed conditions in which treatment should not be initiated (may be construed as "absolute contraindications"), conditions in which tofacitinib should preferably be started if the required benefit outweighs the risk (may be construed as "relative contraindications"—treatment may be given but only after discussion about possible adverse issues with the patient and with extra cautious and close clinical and/or laboratory monitoring), and situations that warrant temporary or permanent interruption of the treatment.[7]

Table 9 summarizes the recommended guidelines for monitoring treatment with oral tofacitinib, independent of therapeutic indication.[4,7,44] Table 10 describes the Child-Pugh Score, to be applied for monitoring patients with hepatic impairment.

Availability in India

While topical formulations are not available in India, oral tablets of the innovator brand XELJANZ®/XELJANZ XR® manufactured by Pfizer have become recently available. Tablets of three doses and types (instant release versus XR-extended release) that are internationally available include:

XELJANZ® Tablets:
- 5 mg tofacitinib
- 10 mg tofacitinib.

XELJANZ XR® Tablets:
- 11 mg tofacitinib.

Patients treated with XELJANZ 5 mg twice daily may be switched to XELJANZ XR 11 mg once daily, the day following the last dose of XELJANZ 5 mg.[7]

Conclusion

Based on current literature, tofacitinib holds a significant potential to broaden the treatment options for many chronic inflammatory dermatoses with unmet medical needs. Although the absence of data on long-term efficacy, frequent post-cessation relapses, inadequately evaluated safety issues, and high cost limit its use, the drug's ability to induce rapid improvement and the reported clinical toxicity being much lesser than the predicted potential have added tofacitinib and its congeners to the ever-expanding therapeutic armamentarium of inflammatory dermatoses. Multicentric well-designed controlled studies are needed to address the gaps regarding the ideal dosing, treatment duration, and safety profile of tofacitinib. Innovative research in development of better topical formulations and more selective Jakinibs offer the potential of harnessing better efficacy with lesser AEs.

Table 8: Conditions in which oral tofacitinib should not be started, may be given with caution and close monitoring, and situations warranting interruption of treatment[7,17]

Do not start tofacitinib therapy in the following conditions:
Active infections: Presence of active tuberculosis (TB), serious localized infections such as cellulitis, sepsis, or opportunistic infections
Infectious seropositivity: Positive serology for hepatitis B, hepatitis C, HIV*
Hematological abnormalities: Absolute lymphocyte count <500/mm^3 or absolute neutrophil count (ANC) <1000/mm^3 or hemoglobin <9 g/dL
Severe hepatic impairment†
Hypersensitivity to the active substance or to any of the excipients
Indications for treatment interruption include development of a serious infection, opportunistic infection, sepsis, serious hypersensitivity reaction, confirmed absolute lymphocyte count <500 cells/mm^3, for patients who develop a persistent ANC of 500-1000 cells/mm^3, interrupt XELJANZ/XELJANZ XR dosing until ANC is greater than or equal to 1000 cells/mm^3. In patients who develop an ANC <500 cells/mm^3, treatment with XELJANZ/XELJANZ XR is not recommended. Treatment with XELJANZ/XELJANZ XR should be interrupted in patients who develop hemoglobin levels <8 g/dL or whose hemoglobin level drops >2 g/dL on treatment. If drug-induced liver injury is suspected, the administration of XELJANZ/XELJANZ XR should be interrupted.
Administer tofacitinib only if necessary and monitor closely‡
Patients with chronic or recurrent infections with a history of a serious or an opportunistic infection who have been exposed to TB§ who have resided or traveled in areas of endemic TB§ or endemic mycoses with underlying conditions that may predispose them to infection with a history of chronic lung disease, or in those who develop interstitial lung disease, as they may be more prone to infections with past history of hepatitis-B (re-activation has been reported) who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis, concomitant intake of NSAIDs, oral corticosteroids) with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic)-relevant for the nondeformable XR preparation with a known malignancy other than a successfully treated nonmelanoma skin cancer (NMSC)-periodic skin examination is recommended for patients who are at increased risk for skin cancer with pregnancy who are lactating and breastfeeding the baby

*Because these patients were excluded from tofacitinib trials and the drug is well known to flare up viral infections, they should ideally not be given tofacitinib till clear recommendations and precautions are suggested. †Grade C impairment by Child-Pugh scoring (10-15 points). ‡All these patients warrant close monitoring for the development of signs and symptoms of infection or other mentioned potential complication both during and after treatment with tofacitinib. If a patient develops a new infection during treatment, prompt and thorough diagnostic evaluation appropriate for an immunocompromised patient should be conducted and appropriate antimicrobial therapy should be initiated while continuing close monitoring. §India is endemic for TB and one of the high background TB incidence rate (IR) counties, i.e., a TB IR >0.05/100 patient-years

Table 9: Oral tofacitinib-general monitoring guidelines[4,7]

Baseline screening:
CBC*
Serum creatinine
LFT
Serum CPK levels
Fasting lipid panel
Serology for HIV, hepatitis B and hepatitis C
Screening for TB-Mantoux test or IFN-γ release assay such as Quantiferon -TB Gold test
Follow-up:
At 1 month posttreatment initiation and then every 3 months:
CBC
Serum creatinine
LFT
Fasting lipid panel
Annually
Screening for TB
As and when required
Diagnostic evaluation appropriate for the infection suspected to have developed/re-activated during or after treatment
Dosage reduction to 5 mg OD is recommended in patients with moderate or severe renal insufficiency† and with moderate hepatic impairment‡
Active infection: Treatment not initiated or should be interrupted, even with localized infection
Immunizations done prior to initiating therapy (impaired response to vaccination). Use of live vaccines concurrently with tofacitinib not recommended. They should be administered at least 2 weeks, preferably 4 weeks prior to drug initiation[44]

CBC=Complete blood count, LFT=Liver function test, CPK=Creatinine phosphokinase, HIV=Human immunodeficiency virus, TB=Tuberculosis, IFN-γ=Interferon-γ, OD=Once-a-day, XR=extended release. *Treatment not initiated if: Absolute lymphocyte count <500/mm^3 or absolute neutrophil count (ANC) <1000/mm^3 or hemoglobin <9 g/dL. †Moderate and severe renal insufficiency-creatinine clearance 30-49 mL/min and <30 mL/min, respectively. ‡Moderate hepatic impairment-Child-Pugh score Grade B (7-9 points)

Table 10: The Child-Pugh score

Points	1	2	3
Encephalopathy	None	Minimal	Advanced (coma)
Ascites	Absent	Controlled	Refractory
Bilirubin (μmol/L)	<34	34-51	>51
Albumin (g/L)	>35	28-35	<28
Prothrombin (s)*	<4	4-6	>6

*Prothrombin time values of 4 and 6 s correspond approximately to 50 and 40% of normal, respectively. (Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. J Hepatol 2005;42 Suppl 1:100-7)

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Conflicts of interest

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