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Tofacitinib for the treatment of psoriasis and psoriatic arthritis

Abstract

Introduction: Psoriasis and psoriatic arthritis (PsA) are inflammatory immune mediated conditions which can cause considerable disability and reduced quality of life. Management can be complex as clinical heterogeneity may lead to different treatment pathways. Tofacitinib is a novel, oral janus kinase (JAK) inhibitor with proven efficacy in rheumatoid arthritis.

Areas covered: This review analyses recent studies of tofacitinib in psoriatic disease treatment. The relevant literature was identified using clinicaltrials.gov, PubMed and Google Scholar. Tofacitinib efficacy was demonstrated in PsA by the OPAL Broaden and OPAL Beyond phase III studies, and received FDA and EMA approval. Tofacitinib was superior to placebo for the treatment of moderate to severe plaque psoriasis in the OPT Pivotal 1 and 2, OPT Retreatment studies, but FDA approval was declined for this indication based on issues of clinical efficacy and long term safety.

Expert Commentary: Tofacitinib is an important oral drug for the treatment of PsA. However, the long term safety data requires further evaluation. Tofacitinib and other JAK inhibitors show potential to broaden the treatment options in PsA and other inflammatory conditions.

Keywords: Tofacitinib, JAK inhibitors, plaque psoriasis, psoriatic arthritis

1 Introduction

Psoriasis and psoriatic arthritis are the main clinical manifestations of psoriatic disease (PsD). Both have complex and heterogeneous phenotypic expression which may represent fundamentally diverse sub-types of disease. Although thought initially to be relatively benign disorders, more recent work has demonstrated the destructive and progressive nature of the arthritis and significant associated cardiovascular co-morbidities with increased mortality. At the same time advances in treatment, and in particular with biological drugs, have provided effective tools with which to control the many facets of the disease. This review examines the role of a new class of drug, the Janus Kinase (JAK) inhibitors, in the treatment of psoriatic disease and the likely place of such a drug in the treatment hierarchy.

2 Methods

The relevant literature was identified using the clinicaltrials.gov database combined with PubMed and Google Scholar search. Our search was focused on phase III clinical trials of tofacitinib in psoriasis and psoriatic arthritis and on existing long term safety data. Only English language publications were reviewed. Approval information was obtained from drugs.com, reuters.com, emc.com in addition to the official Pfizer website and European medicines agency. The accuracy of the data presented was reviewed independently by the manufacturer before publication in order to ensure that all relevant up-to-date information has been cited.

3 Overview of the market

Little research has been done on different treatment algorithms for PsD and, given the complexities of presentation, it seems likely that different algorithms will be required for different phenotypic expressions [1]. The most common approach is a ‘step-up’ model where treatment is escalated gradually and sequentially according to response. International treatment recommendations have been published and are based on available evidence and expert opinion [2]. Such recommendations outline the different treatments that are considered efficacious for the six main domains of PsD. Currently there is good evidence available for biologics, however there is poor evidence for traditional “conventional” therapeutics. However, cost is important - so conventional treatments, including topical treatments, are placed early in the treatment algorithm. Another aspect is that biologics need to be injected – with implicated logistic difficulties - whereas conventional drugs as well as JAK inhibitors can be given orally, an option preferred by many patients. It is beyond the scope of this article to go into detailed analysis of the current treatments for PsD and the reader is directed to the latest GRAPPA recommendations published in 2016 [3] and those of the American Academy of Dermatologists [4].

4 Tofacitinib

4.1 Chemistry

Tofacitinib is an orally available inhibitor of Janus kinases (JAK) with a molecular weight of 312.377 g/mol , water solubility of 155.1 mg/L at 25 deg C (est), pKa1 = 8.46 (cyano); pKa2 = 13.56 (secondary amine). Its molecular formula is $C_{16}H_{20}N_6O$ and the chemical name is 3-[(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile.

4.2 Pharmacokinetics and pharmacodynamics

Pharmacokinetics and –dynamics have been described in detail by Dowty et al [5]. In brief, about 70% of the drug is cleared via the hepatic and 30% via the renal pathway. Tofacitinib seems to be mainly metabolised by CYP3A4, with a smaller contribution from CYP2C19.

4.3 Biology of JAK inhibitors / Tofacitinib

Immune responses are coordinated and regulated by soluble mediators, the most prominent of which are cytokines. A large proportion of these cytokines translate their impact on immune and tissue cell behavior by using a JAK / signal transducer and activator of transcription (STAT) signaling pathway. JAKs are enzymes which provide an “on / off” switch function for the “message” provided by the cytokine. Due to this function JAKs have been identified as therapeutic targets for the control of overactive immune responses. When referring to cell behavior of immune cells this includes: proliferation /expansion, cytotoxic attack against pathogens or other cells, coordinated forms of cell death such as apoptosis or production of a special pattern of cytokines. Tofacitinib is predominantly a JAK1/3 inhibitor but can have some functions on JAK2 as well at higher doses. JAK2 signaling plays an important role in hematopoietic cells - having low activity on JAK2 signaling is the reason for tofacitinib showing less side effects with regard to cytopenias as comparedto some other JAK inhibitors. However, both JAK1 and JAK3 are also essential signaling molecules as evidenced by the fact that loss-of-function mutations in JAK3 lead to severe combined immunodeficiency syndrome. Thus the therapeutic aim of JAK inhibitors is to dampen but not to abrogate JAK signaling. This can be achieved with a reversible, competitive inhibitor to a binding site in the catalytic region of the JAK1/3 kinases such as tofacitinib [6, 7].

The most important effects of inhibiting JAK1/JAK3 regarding the cytokine network is reduction in signaling of interferons (IFNs), IL-10 family members including IL-22 and of all “Common Cytokine Receptor gamma-Chain Family Cytokines” also referred to as common ɣ-chain cytokines. This family includes IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. Among those IL-2, IL-4, IL-15, IL-7 contribute to growth and survival for T cells. Human T cells depend on IL-2 and / or IL-15 to stay alive and for expansion. While CD4 T cells produce their own IL-2, CD8 T cells are dependent on the IL-2 provided by CD4 T cells. Interestingly, regulatory T cells also depend on exogenous IL-2 for their function. While IL-2 is mainly produced by Th cell, skin cells (keratinocytes) can produce IL-15. The good therapeutic effect of tofacitinib on alopecia areata (AA) is believed to be mainly delivered through its inhibition of hair follicle attacking CD8 T cells, IL-15 and IFNγ [8]. In this context, IL-21 is also of importance as it is mainly produced by CD4 T cells and seems to be required for sustained CD8 T cell effector activity. Of interest for the side effect profile of tofacitinib with regard to endogenous

varicella zoster re-activation, IL-21 may be a critical factor in the control of persistent viral infections. The effect on all IFN subtypes has a broad effect on immune cells including antiviral and cytotoxic activity but also T cell polarisation for IFNγ producing cells. It also effects the production of a broad range of tissue derived chemokines such as CXCL10 and CCL2 which in turn reduces the influx of macrophages or lymphocytes into the tissue. Another reported effect of tofacitinib is reduction in osteoclast mediated bone resorption. This seems to be mediated by reduced T cell activity and RANKL expression. A wide range of other molecules important in the pathology of the psoriatic disease continuum are affected directly or indirectly by tofacintinib. For example, the drug can affect IL-23R expression impacting on Th17 polarisation and IL-22/IL-24/IL-19 both of which are key for some of the features of psoriasis lesion development and of psoriatic arthritis initiation [9] (Table 1). A wide range of studies have investigated human tissue samples, ex-vivo or cultured cells from psoriasis skin and synovial/joint tissue, which have shown JAK1 and JAK3 dependent pathway activation in tissue resident cells, including synovial fibroblasts and infiltrating leukocytes, higher than in healthy controls or blood derived samples [9, 10, 11, 12].

Taken together tofacitinib resembles the conventional immunosuppressive drugs used in psoriasis such as cyclosporine A (CsA) or methotrexate in that it has a broad range of action on immune cells (such as neutrophils, lymphocytes, macrophages), tissue resident cells (such as synoviocytes, keratinocytes and osteoclasts), and their mediators. However, its activity on immune and tissue cells is different from existing medications and importantly it has – beyond actions on lymphocytes - properties to directly affect molecules driving skin morphology changes (IL-22, IL-19, IL-24) and bone biology.

4.4 Tofacitinib in the treatment of psoriatic arthritis

Two phase 3 studies have published results evaluating the use of tofacitinib in patients with psoriatic arthritis. The OPAL Broaden study [13] was a 12-month, double-blind, active and placebo controlled, phase 3 trial which randomly assigned patients to receive either tofacitinib 5mg or 10 mg twice daily (BID), adalimumab 40mg subcutaneously fortnightly, or placebo with a blinded switch to either 5mg or 10mg tofacitinib at 3 months. In this study patients were selected having had a previously unsatisfactory response to synthetic DMARDs and had to be TNF-I naïve. Patients

had to be on a synthetic DMARD (methotrexate, sulfasalazine, leflunomide, hydroxychloroquine) at a stable dose throughout the trial.

The primary endpoint was the percentage of patients who achieved at least 20% improvement according to the American College of Rheumatology criteria (ACR20) at month 3. This is defined as at least 20% improvement from baseline in number of tender (68) or swollen (66) joints, as well as 20% improvement in three of the following additional measures: global assessment of arthritis according to both patient and physician as measured on a visual analogue scale (VAS), c-reactive protein level, disability as measured by the HAQ-DI tool, and patient's measurement of arthritis pain according to a VAS measurement.

Secondary endpoints included measurement of the ACR50 and ACR70 responses and the psoriasis area-and-severity index (PASI) of 75% improvement from baseline. Also included in secondary endpoints were measurements of the Leeds Enthesitis Index, Spondyloarthritis Research Consortium of Canada enthesitis index score, minimal disease activity score, Chronic Illness Therapy-Fatigue (FACIT-F) scores, Medical Outcomes Study 36-Item Short-Form Health Survey version 2 (SF-36) and the Dactylitis Severity Score, as well as the Psoriatic Arthritis Response Criteria. DAS-28 CRP score was also measured. Plain films of the hands and feet were taken at baseline and at month 12. Progression in radiographic images was assessed using the modified total Sharp score for psoriatic arthritis.

Patients treated with tofacitinib had better ACR20 responses for both 5mg and 10mg doses (50% & 61% respectively) when compared with placebo (33%) at 3 months (table 2(a)). The adalimumab group achieved 52% ACR20. HAQ-DI scores also improved in the 5mg (-0.35), 10mg (-0.40) doses when compared with placebo (-0.18). PASI75 response was higher in the tofacitinib group ($P<0.001$ for both comparisons) than the placebo group. All secondary endpoints showed improvement compared to placebo but with the hierarchical statistical faltering on the Leeds Enthesitis Index for tofacitinib 5mg bid, significance testing was not performed for other secondary endpoints lower in the testing hierarchy. At month 12 of the study a range of 91-98% of patients across all the trial groups met radiographic criteria for non-progression. Month 12 ACR response is shown in table 2(b).

The OPAL Beyond study [14] was a 6-month, phase 3, placebo-controlled and double-blinded study which randomly assigned 395 patients in a 2:2:1:1 ratio to four regimes. One hundred and thirty-two patients received tofacitinib 5mg BID, 132 patients received tofacitinib 10mg BID, 66 patients received placebo for 3 months and then switched to 5mg tofacitinib BID and another group of 65 patients who received placebo for 3 months switched to 10mg tofacitinib BID. Patients had to have a diagnosis of PsA for at least 6 months, fulfilled the CASPAR criteria, had active plaque psoriasis and joint inflammation at screening, and an inadequate response to at least one TNF inhibitor. Patients were on a variety of DMARDS at a stable background dose throughout the trial.

The primary endpoint for both the 5mg and 10mg doses was met (ACR20 response 50% and 47% response respectively compared with placebo 24 %) at 3 months (table 3(a)). In the continuous tofacitinib groups at 6 months the changes were similar numerically to the changes observed at 3 months. ACR50 response rates were better with both the 5mg (P=0.003) and 10mg (P=0.007) tofacitinib doses when compared with placebo but not the ACR70. PSAI75 response was seen with the 10mg Tofacitinib dose (P<0.001, 43%) but not the 5mg dose when compared with placebo at 3 months. Improvements in ACR20 response were noted in the tofacitinib groups by week 2 (5mg P=0.005, 10mg P=0.001). The ACR response at 6 months is shown in table 3(b).

In terms of secondary endpoints the mean changes at 3 months could not be tested for statistical significance due to failure of the hierarchical testing scheme, but the changes were trending in a positive direction comparable to the changes for the primary endpoints. Minimal disease activity at 3 months was achieved in 21% of the 10mg group, 23% of the 5mg group and 15% in the pooled placebo group.

This study demonstrated that tofacitinib at both 5mg and 10mg doses were superior to placebo over 3 months in improving patients' disease activity. This was certainly true for the ACR20 and ACR50 responses but not the ACR70 response. The ACR20 response rate was lower in the 10mg group when compared with the 5mg group at 3 months, although this group did have a higher mean number of tender and painful joints at baseline, thus possibly explaining the lower response rate.

4.5 Tofacitinib in the treatment of psoriasis

Two large similarly designed, multi-center, randomized, placebo-controlled, double-blind phase III studies (NCT01276639, Oral-treatment Psoriasis Trial - OPT Pivotal 1, n=901 and NCT01309737, OPT Pivotal 2, n=960) demonstrated the efficacy of tofacitinib, both 5 and 10 mg BID at week 16 in comparison to placebo for the treatment of moderate-to-severe plaque-type psoriasis. Patients included were ≥18 years, with a reported disease activity of at least 12 months, PASI ≥12, Physician Global Assessment (PGA) of moderate/severe and involvement of ≥10% body surface area (BSA) at baseline. Subjects with other types of psoriasis; recent infections; current or previous malignancies (except for adequately treated or excised basal/squamous cell carcinoma (BCC/SCC) or cervical carcinoma in situ); latent, active or inadequately treated Mycobacterium tuberculosis (TB) infection were excluded.

Patients were randomized 2:2:1 to receive tofacitinib 5 or 10 mg or placebo, BID until week 16 when the placebo group was re-randomised to continue on either tofacitinib 5 or 10 mg, BID. Participants were followed up to 52 weeks, except for patients who didn't achieve at least a 75% reduction in their PASI score relative to baseline (PASI 75) or a clear or almost clear PGA score (PGA response) at week 28 and therefore were withdrawn from the study.

The two primary end points consisted of the PASI 75 and PGA response rates at week 16. Secondary end points included PASI 75 and PGA response rates at week 4; PASI 90 (at least a 90% reduction in the PASI score relative to baseline) response rate at week 16; the percentage change in psoriasis BSA involvement and in Nail Psoriasis Severity Index (NAPSI); time to PASI 75 or PGA response to week 16; change in baseline Dermatology Life Quality Index (DLQI) total score; the effect of tofacitinib on pruritus, assessed by the Itch Severity Item (ISI); patient reported disease severity by using the Patient Global Assessment (PtGA).

The PGA response was significantly greater in both tofacitinib groups compared to placebo at week 16 (OPT Pivotal 1: 5 mg, 41.9%; 10mg, 59.2%; placebo, 9.0%; OPT Pivotal 2: 5 mg, 46.0%; 10 mg, 59.1%; placebo, 10.9%) ($p < 0.001$), with similar PASI 75 response (OPT Pivotal 1: 5 mg, 39.9%; 10mg, 59.2%; placebo, 6.2%; OPT Pivotal 2: 5 mg, 46.0%; 10 mg, 59.6%; placebo, 11.4%) ($p < 0.001$). A dose-dependent improvement was also observed as a significantly higher percentage of patients

achieved PASI 75 and PGA response, and in a shorter median time, on tofacitinib 10 mg than on 5 mg, BID. The secondary end point results also supported the higher efficacy of the two tofacitinib doses vs. placebo at week 16 in BSA, DLQI, PtGA and NAPSI improvement and PASI 90 response in a dose dependent manner.

The proportion of PASI 75 responders further increased from week 16 to 28 in both tofacitinib groups, however it was significantly higher with tofacitinib 10 mg (68.8%) vs. 5 mg (55.6%), BID at week 28. PASI 75 responders at week 16 maintained response through week 52 in both tofacitinib arms of the pivotal studies.

Both doses of tofacitinib improved pruritus as early as study day 2 compared to placebo. [15, 16]

Another phase III, randomized, double-blind, multicenter, parallel-group study (NCT01186744, OPT Retreatment) assessed the effects of tofacitinib withdrawal and re-treatment. Their inclusion and exclusion criteria were similar as for the OPT Pivotal studies. The study was divided into three phases: initial treatment (24 weeks), treatment withdrawal (16 weeks) and re-treatment (up to week 56). Initially patients were randomized 1:1 to receive either tofacitinib 5 or 10 mg, BID for 24 weeks, when non-responders were discontinued, while patients achieving both a PASI 75 and PGA response entered the treatment withdrawal phase and were re-randomized 3:1 to either continue on their initial tofacitinib dose or to receive placebo, BID for 16 weeks. Patients with psoriasis relapse (>50% reduction in the PASI improvement from baseline to week 24) immediately entered the re-treatment period. During re-treatment, tofacitinib treated patients continued on the same dose regime, while those randomized to placebo were switched back to their initially randomised tofacitinib doses.

The primary efficacy endpoints of the OPT Retreatment study were in the treatment withdrawal period (the proportion of patients maintaining a PASI 75 response; the proportion of patients maintaining a PGA response) and retreatment period (the proportion of patients achieving a PASI 75 response during the retreatment period following relapse during the treatment withdrawal period; the proportion of patients achieving a PGA response during the retreatment period following loss of PGA response during the treatment withdrawal period). Secondary endpoints examined treatment related changes in patients-reported outcomes (PROs).

At the end of the initial treatment period (week 24), a dose dependent response was observed as 43.8% compared to 67.6% of patients achieved a PASI 75 while 41.6% compared to 62.8% achieved a PGA response with tofacitinib 5 and 10 mg, BID, respectively. 33.5% and 55.2% of participants in the tofacitinib 5 and 10 mg, BID group, respectively, achieved both a PASI 75 and PGA response and were eligible to continue in the treatment withdrawal phase. Similarly, a greater proportion of patients achieved PASI 90 response on tofacitinib 10 mg (42.0%) than on 5 mg (22.5%), BID, at the end of the initial treatment period. By the end of the treatment withdrawal period , 92.3% and 93.0% of patients receiving tofacitinib 5 and 10 mg twice daily had not relapse and maintain a PASI score similar to the score at the end of the initial treatment phase. In contrast, there was a significant increase in the median PASI score of patients in the placebo group, while only 32.8% and 42.9% of patients switched to placebo from tofacitinib 5 and 10 mg, BID had not relapse by week 16. By the end of the re-treatment period, 63.0% and 73.8% of patients continuously receiving either tofacitinib 5 or 10 mg, BID from the beginning of the study, regained or maintained a PASI 75 and 66.7% and 64.3% a PGA response, respectively. Of all patients switched to placebo during the treatment withdrawal period, 48.0% and 72.5% were able to regain or maintain a PASI 75 response, while 52.0% and 64.2% a PGA response, after 16 weeks of retreatment with tofacitinib 5 and 10 mg, BID daily, respectively. Of patients on placebo who relapsed during the treatment withdrawal phase, 36.8% and 61.0% regained a PASI 75 response and 44.8% and 57.1% a PGA response upon 16 weeks retreatment. Both tofacitinib doses demonstrated an important reduction in mean ISI scores and improvement in other PROs (DLQI, PtGA, Short Form-36). [17, 18].

A 52 week, phase III, randomized, double blind study (NCT01519089) investigated the efficacy of tofacitinib 5 and 10 mg BID in Japanese patients with moderate to severe plaque psoriasis and/or psoriatic arthritis.

Study results at week 16 showed that, the efficacy of tofacitinib 10 mg BID (72.7% and 68.2%) was only slightly better compared to tofacitinib 5 mg BID (62.8% and 67.4%) in achieving a PASI 75 and PGA response, respectively. However, a significantly greater proportion of patients achieved PASI 75 response at week 4 with the higher tofacitinib dose. ACR20 response was achieved in all PsA patients by week 16, with

ACR50 or ACR70 response rates in more than half of patients. Both tofacitinib doses produced improvement in psoriatic nail disease, itch and DLQI scores [19].

So far there has been a single major study which directly compared the efficacy of tofacitinib to another systemic psoriasis treatment, etanercept. In this phase III, multicenter, double-blinded, placebo-controlled, 12 week non-inferiority trial (NCT01241591, OPT Compare Study) patients with moderate to severe plaque type psoriasis (n=1101) were randomized 3:3:3:1 and received oral tofacitinib 5 (n=329) or 10 mg (n=330) BID, etanercept 50 mg (n=335) subcutaneously twice weekly or placebo (n=107). The inclusion and exclusion criteria was similar to the previously described studies, but in addition they excluded patients who had previously been treated with or had contraindication to etanercept and had previously failed to respond to treatment with any tumor necrosis factor inhibitors.

The co-primary efficacy endpoints were the proportion of patients achieving a PASI 75 and a PGA response at week 12. Secondary endpoints included the PASI 90 response rates and PRO.

At week 12, a greater proportion of patients achieved PASI 75 response with tofacitinib 10mg BID (63.6%) compared to etanercept 50 mg twice weekly (58.8%), while the lower tofacitinib dose, 5 mg BID (39.5%) proved inferior to etanercept. All 3 groups met the superiority criteria versus placebo (5.6%). A similar trend was valid for the PGA response rate (47.1%, 68.2%, 66.3% and 15% in the tofacitinib 5, 10 mg, BID, etanercept 50 mg twice weekly and placebo, respectively). Furthermore, tofacitinib 10 mg BID achieved in a shorter median time PASI 75 response compared to both the lower dosage (as previously showed in the Pivotal studies) and to etanercept. There was a substantial improvement in patients DLQI scores in all three active treatment groups compared to placebo. Both tofacitinib 5 and 10 mg BID lead to more rapid amelioration of pruritus (within 1 day) compared to etanercept, reflected in the ISI score [20]. A summary of the plaque psoriasis studies is included in Table 4.

4.6 Safety and Tolerability

4.6.1 Common Adverse Events

In OPAL Broaden adverse events (AE) were higher in the tofacitinib 10mg (45%), 5mg (39%) and adalimumab (46%) group when compared with the placebo (35%) group

over 3 months. The most common AEreported were nasopharyngitis, upper respiratory tract infection and headache, similarly to OPAL Beyond, where patients taking the 10mg dose had higher rates of AE and discontinuation. The most frequent AE reported in the cutaneous psoriasis studies were also nasopharingitis, upper respiratory tract infections, headaches and gastrointestinal disorders (diarrhea, nausea, vomiting, constipation), however the short term safety data were similar for both tofacitinib doses. The most common AEs are presented in Table 5.

4.6.2 Herpes infection

Herpes zoster (HZ) infection occurred in 3 patients in OPAL Beyond (n=1,on 5mg, n=2 on 10mg), and in 4 patients in OPAL Broaden (n=2 on 5mg, n= 2 on 10mg), all of whom had received tofacitinib.

Among plaque psoriasis patients HZ infection occurred more frequently on the higher tofacitinib dose (10 mg BID, n=5, n=1, n=7; 5 mg BID n=3, n=3, n=1 in OPT Pivotal 1, Pivotal 2 and OPT Retreatment, respectively). The same dose dependent pattern was also valid in Japanese patients with an overall increased incidence of HZ infection (16 patients out of 94; tofacitinib 5 mg BID n=2; tofacitinib 10 mg BID n=13; follow up after tofacitinib 10 mg BID n=1). There was one severe case, but no cases with multidermatomal, disseminated, systemic or ophthalmic HZ.

4.6.3 Serious Infection

Over the course of six months in OPAL Beyond there were four serious infections in the tofacitinib groups (n=1 pneumonia, n=1 oral candidiasis on 5mg, n=1 bilateral pyelonephritis, n=1 parotitis on 10mg), and in OPAL Broaden there were three serious infections in patients receiving the drug reported over 12 months (n=1 influenza, n=1 appendicitis and n=1 pneumonia), compared with 1 serious infection in the adalimumab group (herpes simplex and streptococcal pyoderma). There were no serious infections reported in the placebo groups in both trials.

A few cases of serious infections occurred in the cutaneous psoriasis studies: OPT Pivotal 1 (tofacitinib 10 mg BID, n=1 appendicitis, n=1 pneumonia and n=1 pyelonephritis; placebo, n=1 burn infection, n=1 aseptic meningitis); OPT Pivotal 2 (tofacitinib 5 mg BID, n=1 pneumonia, n=1 HZ, n=1 erysipelas); OPT Retreatment (tofacitinib 10 mg BID, n=1 HZ, n=1 peritonsillar abcess, n=1 bronchitis). Only one case with diverticular perforation was reported across studies (OPT Retreatment) in a

patient with extensive diverticular disease on tofacitinib 5 mg, BID. None of the patients developed tuberculosis.

4.6.4 Malignancy

Although no cancers were reported in OPAL Beyond, four cancers (n=1 bladder transitional cell carcinoma day 1, n=1 SCC of the vulva day 11, n=1 invasive ductal breast cancer day 232 and n=1 BCC day 103) were observed in OPAL Broaden over a 12-month period in patients who had received tofacitinib from baseline compared to zero patients in the placebo group.

Malignancies other than nonmelanoma skin cancer (NMSC) were also reported in the plaque psoriasis studies, as follows: OPT Pivotal 1 (tofacitinib 5 mg BID, n=2 malignant melanoma, n=1 oesophageal carcinoma, n=1 prostate cancer; date of onset <16 weeks); OPT Retreatment (tofacitinib 10 mg BID, n=1 colon cancer day 59, n=1 prostate cancer day 84, n=1 pancreatic cancer day 138). The rates of NMSC were low, in OPT Pivotal 2 (tofacitinib 10 mg BID, n=1 SSC, n=1 BCC; date of onset <16 weeks) and OPT Pivotal Retreatment (initial treatment period: tofacitinib 5 mg BID, n=2 BCC; tofacitinib 10 mg BID, n=1 BCC, n=1 SCC; treatment-withdrawal period: placebo following tofacitinib 5mg BID, n=1 BCC; re-treatment period: tofacitinib 10 mg BID following placebo, n=1 BCC). No malignancies were reported in the Japanese study.

4.6.5 Cardiovascular Events

In OPAL Beyond there were two major adverse cardiovascular effects (myocardial infarction in the 5mg tofacitinib group and ischaemic stroke in the 10mg group) and in OPAL Broaden one patient who had switched from placebo to 5mg tofacitinib at month 3 died of a cardiac arrest during month 4.

Major adverse cardiovascular events were considered unrelated to the study treatment in the OPT Pivotal and Retreatment studies (tofacitinib 10 mg BID n=1, n=0; tofacitinib 5mg BID, n=2; n=1 in, respectively). No cardiovascular events or deaths were reported in the Japanese study.

4.6.6 Abnormal Laboratory Parameters

Blood abnormalities that were observed in the tofacitinib groups in the OPAL studies were elevations in lipid profile, although these levels did not rise further beyond 3 months. One patient in the continuous 10mg tofacitinib group developed a neutrophil

count of <1.0x10^9 cells per litre and had to be withdrawn from the OPAL Beyond study after month 3. In OPAL Broaden greater reductions in neutrophil count were observed with all active treatments at month 3 than with placebo. There were no reported cases of lymphopenia (<0.5x10^9 cells per litre) or neutropenia (<1.0x10^9 cells per litre).

In OPAL Beyond elevations in liver enzymes (ALT & AST) greater than the upper limit of the normal range were seen in 30% and 32% respectively of patients in the continuous tofacitinib groups. Elevations of 3 or more times the upper limit of normal range were seen in 6 patients during the trial. There were no cases of drug-induced liver injury. Elevations in liver enzymes were also observed in the OPAL Broaden study.

Across the cutaneous psoriasis trials an early, dose dependent increase in mean concentrations of creatinine phosphokinase (CPK), low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels, and a moderate decrease in median haemoglobin and neutrophil levels were observed. Rhabdomyolysis or severe anemia was not reported.

4.6.7 Long term safety data

An open label long-term extension study (LTE) enrolled patients who participated for a minimum of 12 weeks in the Pivotal studies, including withdrawn patients due to insufficient PASI 75 or PGA response at week 28. Following an initial 3 months, when each participant received 10 mg tofacitinib, BID, dose was adjusted to either 5 or 10 mg, BID, based on safety and efficacy. Patients were followed up to 2 years. Authors used pooled data from the two Pivotal studies and additional long-term data for these patients (33 months) from the LTE study (interim data cut-off) to report on the incidence of AEs over the longest exposure period. They reported data on 1807 patients (all tofacitinib doses), 502 patients receiving tofacitinib for more than 2 years. Serious Adverse Events (SAE) occurred in 10.1% of study subjects, while 10.7% discontinued treatment because of AEs. The most common AEs remained nasopharingitis and upper respiratory tract infections. Except for HZ infection, the data analysis showed no increased risk of AEs over time. In total 10 deaths occurred during the total tofacitinib exposure (causes included esophageal carcinoma, malignant lung neoplasm, pancreatic carcinoma, myocardial infarction, cardiac arrest, acute respiratory death syndrome and road traffic accident) [21].

5 Regulatory affairs

- Tofacitinib (Xeljanz®, Pfizer) 5 mg BID oral tablet was first approved for the treatment of moderate-to-severe active RA in November 2012 by the U.S. Food and Drug Administration (FDA) [22];
- In March 2013, the Japanese Ministry of Health, Labor and Welfare (MHLW) has also approved Xeljanz® 5 mg BID for the treatment of RA in patients who have had an inadequate response to existing therapies [23];
- In October 2015 FDA **declined** authorisation of tofacitinib for the use in moderate-to-severe plaque type psoriasis based on safety concerns [24];
- In February 2016, FDA authorised Xeljanz® XR (tofacitinib) extended-release 11 mg tablets for the once-daily (OD) treatment of moderate-to-severe RA in patients who have had an inadequate response or intolerance to MTX. Xeljanz® XR is the first and only once-daily oral RA treatment in its class [25];
- In March 2017, marketing authorisation from the European Commission (EC) had been obtained for tofacitinib 5 mg BID oral tablets in combination with MTX for the treatment of moderate-to-severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. Tofacitinib was approved as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate [26];
- In December 2017, Pfizer announces approval of Xeljanz® 5 mg BID and Xeljanz® XR extended release 11 mg OD for the treatment of adult patients with active PsA who have had an inadequate response or intolerance to MTX or other DMARDs [27].

In summary, Xeljanz® 5mg BID and Xeljanz® XR extended release 11 mg OD oral tablet have been approved for the treatment of moderate-to-severe active RA and PsA by the FDA in the U.S. Only Xeljanz® 5mg BID, in monotherapy or in combination with MTX, is approved by EC in the European Union and Xeljanz® 5mg BID is approved by the Japanese MHLW for the treatment of moderate-to-severe active RA. Tofacitinib is currently not approved for the treatment of moderate-to-severe plaque type psoriasis by the major regulators (FDA, EMA, PMDA) but has been approved in Russia for this indication.

6 Expert-commentary/Discussion

In recent years several new treatment options have become available for the treatment of psoriatic arthritis (PsA), with biological therapies revolutionising the market. However, parenteral administration potentially restricts the use of biologics, highlighting the need for new, effective and safe oral therapies. Although tofacitinib (5 mg BID or once daily 11 mg extended release tablets) has been recently approved by FDA for the treatment of PsA approval has been denied for use in moderate-to-severe plaque psoriasis. The range of new oral treatments in skin psoriasis is currently limited to the small molecule phosphodiesterase-4 inhibitor, apremilast. However, with JAK inhibitors including tofacitinib proving successful in dermatology phase II trials for alopecia areata (AA) and vitiligo, it is likely to become available for those indications due to lack of efficient alternative therapies.

All of the above mentioned dermatology trials demonstrated the superiority of both tofacitinib 5 and 10 mg BID versus placebo in the treatment of moderate-to-severe plaque type psoriasis. Nevertheless, tofacitinib 10 mg BID was more effective compared to the 5mg BID dosage, producing results in a shorter time period and having a greater proportion of patients achieve PASI75, PASI90 and PGA responses, albeit at the cost of more adverse events. However, rapid regression of the disease occurs upon cessation of treatment [15, 17, 19]. Yet, the OPT Retreatment study indicates that the majority of patients effectively regain response to tofacitinib following a single interruption, results which are reassuring as treatment interruption (due to poor compliance, pregnancy, infections, surgery) is not unusual in clinical practice. Having said that, the study also proved continuous treatment to be better than interrupted treatment in optimal disease control [17]. This is in line with previous observations in the treatment of psoriasis [28], however, it has not yet been established whether the long-term continuous use of tofacitinib is safe (33 months being the longest treatment period examined within the Pivotal and LTE studies). The combination of tofacitinib 5 mg, BID with MTX, as approved for the treatment of RA, could also be a future option in the management of plaque psoriasis, especially if associated with PsA. In the Pivotal Retreatment study no rebound phenomena have been experienced [18], however it is not fully clear if tofacitninib can produce rebound phenomena upon withdrawal as reported for CsA. Similar to CsA the effect on T cell suppression is strong but rapidly reversible.

Both rheumatology studies have shown significantly higher ACR20 responses for each dose of tofacitinib compared to placebo at month 3. Improvements in both trials were observed with tofacitinib as early as week 2. Patients in OPAL Beyond had failed one or more TNF inhibitors, implying that they had disease which was resistant to treatment, and yet 50-60% had an ACR20 response to treatment with tofacitinib by the end of the study. Both studies used the ACR composite measure, which is validated for rheumatoid arthritis but not PsA. It could also be argued that ACR20 as a primary endpoint is a relatively low target to assess for efficacy. The higher targets of ACR50 and ACR70 were achieved apart from ACR70 in the OPAL Beyond study. When composite endpoint measures of disease specific for PsA (such as the Psoriatic Arthritis Disease Activity Score and Composite Psoriatic Disease Activity Score) are applied to the results of the OPAL trials both doses of tofacitinib showed improvements compared with placebo at 3 months [29]. This demonstrates that tofacitinib improves measures that assess across all domains of PsA.

The safety of tofacitinib has a number of issues. Altogether the rate of malignancies was low across studies. Data taken from RA patients treated with tofacitinib (first approved indication for the drug) showed that the overall malignancy rate and type remain stable over time with increased tofacitinib exposure [30] and the risk is similar to that of available non-biological and biological DMARDs. However, in the LTE studies the numerical incidence rate of specific malignancies (especially NMSC) was higher for tofacitinib 10 mg than with biologics used in RA (etanercept, certolizumab, tocilizumab) [31]. Targeted screening based on the personal and family history of patients, and on use of previous therapies such as UVB, should be considered in high risk patients before tofacitinib administration. Long term data from registries would be needed to examine the malignancy risk with tofacitinib.

The high incidence of HZ infection in both PsA and psoriasis patients treated with tofacitinib, especially in Japanese population, is also of some concern. The identified risk factors for HZ in tofacitinib treated patients include: asian race, increased age, higher dose and prior biologic exposure [32]. Vaccination against HZ prior to starting the drug may be considered. Patients should at least be counselled about the risk of HZ when being initiated on treatment. The current vaccine available is a live vaccine, although an inactivated vaccine has recently been developed and approved for use by the CDC. According to the summary product characteristics for tofacitinib it is not

recommended that live vaccines be given concurrently with the drug, but should be administered preferably at 4 weeks prior to drug initiation or in accordance with vaccination guidelines in reference to immunosuppressive medications [33]. Downregulated molecules are believed to have an impact on persistent viral infection control (i.e. IL-21) raising slight concerns regarding the risk of slow viral diseases of the central nervous system – although there is no current data supporting this concern.

No cases of tuberculosis were observed in either study, although all patients would have been screened for TB prior to entering the study and those positive would have been filtered out. It would be prudent to screen patients for TB prior to starting the drug until further safety data becomes available.

The increased cardiovascular morbidity in psoriasis and psoriatic arthritis is well recognised. For this reason, the cardiovascular risk profile is an important consideration for tofacitinib use as studies have shown elevations in lipid values. However, values increased up to month 3, and then apparently stabilised. The use of tofacitinib in high risk patient groups needs further evaluation. The association of tofacitinib with lipid lowering agents, such as statins, may increase the safety of JAKs but additional attention to the hepatic enzymes would be recommended. The modest rise in CK levels seen with this drug may also be worth noting both in the context of statin use and if acute cardiovascular events do occur. Monitoring patients on tofacitinib with regular blood tests, including full blood count, liver enzymes, CPK, and lipid profile would be recommended.

Many immunosuppressive drugs have adverse effects on the neutrophil count. It would be prudent for clinicians to monitor neutrophil counts whilst patients are taking JAK inhibitors as tofacitinib can cause neutropenia. Haemoglobin levels can be also reduced although severe anaemia was not reported in the pivotal studies.

The oral formulation of tofacitinib improves patients' convenience, independence and compliance to treatment and reduces health care costs associated with parenteral administration. Clinicians and patients prefer a drug for psoriatic arthritis to treat all the different clinical domains of the disease. It would seem that this is true with tofacitinib for skin, dactylitis and enthesitis, recognising the methodological and statistical difficulties that were encountered. For rheumatologists treating psoriatic arthritis a key question with regards to tofacitinib use would be where would its use fall in a treatment

algorithm? At what stage during the treatment pathway should tofacitinib be used for maximal benefit? Currently clinicians move from conventional synthetic disease modifying drugs to TNFi inhibitors, possibly switching to an alternative biologic or apremilast if there are contraindications to TNFi. The choice of an alternative to TNFi will depend on a number of factors, including patient preference, the presence of co-morbidities and predominant domain involved. For example, if a patient has psoriasis as the predominant domain an IL17 inhibitor may be the drug of choice, or an IL12/23 inhibitor if there are safety issues. Tofacitinib will be an important drug for those who prefer oral therapies and it may be positioned alongside apremilast in the hierarchy, although it appears to have slightly better efficacy on the articular manifestations than apremilast. OPAL Beyond showed that tofacitinib was effective in patients who had failed one or more biologic DMARD previously (both TNF-I & other biologic agent), suggesting that it was an effective treatment in patients with difficult to treat disease. OPAL Broaden examined the use of tofacitinib in patients who had failed to respond to synthetic DMARD, using adalimumab as an active comparator. However, although the authors state that there was no apparent difference between drug performance, the study was not powered as a head-to-head study. Long term use in practice, strategy and head to head trials will prove informative.

Unique bone changes occur in psoriatic arthritis, including both bone loss (erosions and osteolysis) and bone formation (particularly juxta-articularly but also as periostitis). These changes can develop in the same patient, even in the same digit, consisting a paradox of this disease. The effect of tofacitinib on RANKL and IL22 may have an important role in this respect, particularly with regard to bone loss, but larger and longer studies with appropriate imaging will be required to demonstrate these changes.

Tofacitinib is unlikely to be licensed for treating psoriasis alone but it may be used in circumstances where there in concomitant musculoskeletal disease, as indicated above. Tofacitinib is also of potential use in other skin disorders such as alopecia areata so may be available in the dermatology area for that condition. However, the lower dose regime of 5mg bid has less impressive efficacy on psoriasis compared to conventional drugs such as methotrexate and certainly compared to biologic drugs. Given the likely pricing of tofacitinib this makes the lower dose less attractive for treating psoriasis. It is worth noting the beneficial results of tofacitinib on nail psoriasis

especially as this clinical feature is refractory to conventional treatments and can impact significantly on quality of life [34, 35, 36]. Tofacitinib is greatly efficient in the reduction of itching, with ameliorations seen as soon as following the first day of treatment.

In summary, tofacitinib is an interesting new drug for the treatment of psoriatic disease. It may be of particular interest for those patients refusing injection therapies and in those with multiple molecular pathways affected by their genetic background and maintaining disease activity. Different from CsA and MTX the effect of tofacitinib on tissue cells relevant for psoriatic disease manifestations may be stronger and more direct.

7 Five-year view

What place will tofacitinib take in the treatment of psoriasis and psoriatic arthritis over the next 5 years? It is difficult to see tofacitinib achieving approval for treating psoriasis at the 5mg bid dose and there are safety concerns, as noted by the FDA, of the more effective 10mg bid dose. In due course other JAK inhibitors may come to market for treating psoriasis. From the point of view of psoriatic arthritis many patients prefer an oral drug and a drug that can improve all aspects of their disease while having minimal side effects (particularly nausea) will be a welcome addition to the therapeutic array. However, experience with the drug in practice and emerging data on persistence and safety from registries will be required before the drug can be fully recommended. Dosing is important – 5mg bid is associated with less adverse effects and will be the dose of choice for psoriatic arthritis. The order in which the drug will be used in practice will need further investigation, both in practice and clinical trials. Combination therapy will also require consideration in certain, difficult to treat, patients and the safety of such combinations will require careful monitoring. Head to head studies will emerge so that the rheumatology community can assess the comparative efficacy and safety of tofacitinib. Such studies will also inform the cost benefit issues which are of particular importance where limited resources exist. With the eventual introduction of cheaper generic forms of this drug then cost benefit issues will change and it is possible to envisage a time when generic tofacitinib is the first disease modifying drug to be used in psoriatic arthritis. There is no doubt that this class of drugs is here to stay and we can expect other members of this drug class to appear for treating both psoriasis and psoriatic arthritis.

Key issues

- The JAK/STAT signaling pathway plays a fundamental role in cytokine messaging, therefore it has become an interesting therapeutic target in several immune mediated, inflammatory diseases;
- Tofacitinib is an oral JAK inhibitor, first approved for the treatment of RA, which is now investigated for the treatment of moderate-to-severe plaque psoriasis and PsA;
- The OPAL Broaden and OPAL Beyond phase III studies demonstrated the clinical efficacy of tofacitinib in the treatment of PsA;
- Tofacitinb has recently received FDA approval (December 2017) for the treatment of PsA, administered p.o. 5 mg BID or as an extended release tablet 11 mg OD.
- Tofacitinib approval has previously been rejected (October 2015) by the FDA for the treatment of moderate-to-severe plaque psoriasis;
- Multiple dermatology phase III trials (OPT Pivotal 1 and 2; OPT Retreatment) have demonstrated the efficacy and short term safety of tofacitinib treatment in plaque psoriasis, with tofacitinib 10 mg BID administration proven to be the most effective dosage.
- As more phase III study data becomes available regarding the efficacy and short term safety of tofacitinib in the treatment of plaque psoriasis, there is a higher chance that tofacitinib will receive FDA approval upon resubmission for this indication.
- Long term safety concerns regarding malignancy, serious infection and viral reactivation still exist, especially with the 10 mg BID dosage, therefore there is a need for drug registries to evaluate the long term safety profile.

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