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Attenuating Janus Kinases (JAK) by Tofacitinib Effectively Prevented Psoriasis Pathology in Various Mouse Skin Inflammation Models

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Abstract

Background: Tofacitinib is a Janus kinase (JAK) inhibitor that preferentially inhibits signaling by JAK1 and JAK3 that blocks the signaling of type I interferons, IL-6 as well as IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. Together these cytokines are important to lymphocyte function and therefore regulate multiple aspects of the immune response. Tofacitinib has demonstrated efficacy in clinical trials of various autoimmune diseases including psoriasis.

Objectives: To understand the mechanisms of action of tofacitinib in improving psoriasis.

Methods: Tofacitinib was evaluated in several IL-23/Th17 pathway-dependent, psoriasis-like skin inflammation models.

Results: We demonstrate that similar to mice that received mouse IL-12/23 p40 antibody (anti-p40), treatment with tofacitinib also reduced clinical signs of skin inflammation. Histologic analysis confirmed the clinical data: skin inflammation, the number of cells expressing pSTAT3 were significantly decreased in affected skin of mice treated with tofacitinib and with anti-p40 Ab relative to vehicle/isotype-treated mice. Gene expression analysis of the affected skin revealed that tofacitinib also significantly down-modulated various pro-inflammatory mediators including CXCL10, IL-1β, IL-6, IL-7, IL-17A, IL-22 and S100A8.

Conclusion: These results suggest the mechanism of action of tofacitinib is likely due to its ability to block multiple cytokines and attenuate immune response that contribute to the positive clinical efficacy in psoriasis.

Introduction

The Janus kinase (JAK) family (JAK1, JAK2, JAK3 and TYK2) plays a pivotal role in cytokine signaling and immune function [1-4]. The definitive role of JAK signaling in immune modulation is illustrated in circumstances where these kinases are mutated or deleted and from studying patients with primary immunodeficiencies [5,6]. In mice, deletion of JAK1 or JAK2 is lethal, whereas disruption of JAK1 gene results in non-responsiveness to type I and II IFNs, as well as cytokines that signal through the common γ chain (IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21) and gp130 subunit (IL-6 family, granulocyte colony stimulating factor) [7], while deficiency of JAK2 leads to failure in signaling of hormone-like cytokines including GM-CSF, erythropoietin and thrombopoietin [8]. In humans, mutations of JAK3 that affect common γ chain signaling or TYK2 that influences type I IFNs, IL-6 and IL-12/23 result in clinical immunodeficiencies named severe combined immune-deficiency syndrome (Scid) and autosomal recessive hyperimmuno-globulin E syndrome (hyper IgE syndrome), respectively. These phenotypes are also implicated in mouse models [9,10]. Because of the importance of cytokines in various autoimmune diseases, targeting of JAKs appeared to be a promising strategy to interfere with autoimmune disorders. Indeed, a number of JAK inhibitors are in various stages of pre-clinical/clinical development for inflammatory disorders, including psoriasis [11-15].

Psoriasis is a common debilitating chronic systemic inflammatory disease involving primarily the skin, which affects approximately 2-3% of the general population [16]. Although the exact cause of psoriasis is unknown, mounting evidence suggests that a dysregulated interplay between keratinocytes and inflammatory cell infiltrates results in the production of inflammatory cytokines and chemokines which contribute to disease pathology [17]. Recent studies have highlighted a role for the IL-23 and Th17 cytokine network in mediating cutaneous skin inflammation [18,19]. IL-23, a cytokine produced by macrophages and DCs, drives the expansion of Th17 cells that have differentiated from naïve T cells in the presence of IL-6 and TGFβ [20-23]. Ustekinumab, an antibody against the p40 common subunit shared by IL-12 and IL-23, demonstrated efficacy in treating psoriatic lesions which further underscores the importance of the IL-23/Th17 pathway in psoriasis.

In addition to targeting the prominent IL-23/IL-17 pathway, beneficial effects of inhibiting JAKs in alleviating the pathogenesis of psoriasis is first implicated in a mouse model of psoriasis, where R348, a JAK1/3 and Syk inhibitor had demonstrated efficacy [11]. Tofacitinib is a novel selective inhibitor of the JAK family with nanomolar potency and a high degree of kinome selectivity has achieved positive clinical outcome in psoriasis clinical trials [24]. Results from cell based assays have shown that tofacitinib prevents Th1 and Th2 cell differentiation [25]. Tofacitinib is expected to have limited inhibition of IL-12 and IL-23, however, depending on the cytokine milieu present during the differentiation of Th17 cells, tofacitinib can either enhance or prevent Th17 cytokine production [25].

Although there is no good mouse model that accurately reproduces all facets of psoriasis, there are models available to provide mechanistic insight into the pathogenesis of psoriasis [26]. We evaluated the effect of

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tofacitinib and anti-p40 in several skin inflammation models induced by IL-23, imiquimod and $CD4^+CD45^{Rb}$ high T cell transfer to gain a mechanistic understanding of tofacitinib in psoriasis.

Materials and Methods

Mice

Female BALB/c, BALB/cBy, and C.B-17/prkdc *scid/scid* (recipient mice) were purchased from The Jackson Laboratory (Bar Harbor, ME). All mice were housed in a specific pathogen-free environment at a Pfizer animal facility, and were used between 6 and 8 weeks of age. All protocols were approved by Pfizer Animal Care and Use Committee.

Reagents

Recombinant mouse IL-23 was purchased from eBiosciences. Anti-mouse IL-12/23 p40 (clone C17.8), and isotype control antibody (rat IgG2a), were purchased from BioLegend (San Diego, CA). Tofacitinib, was generated at Pfizer and re-suspended in 0.5% methylcellulose/0.025% Tween 20 (Sigma-Aldrich, St. Louis, MO).

Mouse skin inflammation models and treatments

In the IL-23 injection model, ears from BALB/c mice (n=8-10 for each group) were each injected intra-dermally every other day with 150 ng of mouse recombinant IL-23 (eBiosciences) or PBS in a total volume of 25 µl. Ear swelling was measured in triplicate using a micrometer (Mitutoyo) right before each IL-23 challenge. On Day 12, mice were euthanized and ears were collected for H&E staining, pSTAT3 immunohistochemical staining, and evaluated for cytokine gene expression.

In the imiquimod model, mice received a daily topical dose of 31.25 mg of commercially available imiquimod cream (5%) (Aldara; 3M Pharmaceuticals, St. Paul, MN) on the shaved back and the right ear for 3 consecutive days followed by one additional application on Day 5. This translates into a daily dose of 1.56 mg of the active compound. This dosing regimen was optimized in our facility to achieve robust skin inflammation in mice. Control mice were treated similarly with a control vehicle cream (Vaseline Lanette cream; Fagron). At the days indicated, the ear thickness was measured in triplicate using a micrometer (Mitutoyo).

$CD4^+CD45^{Rb}$ high T cell transfer studies, cells for adoptive transfer were prepared as previously described with slight modification [27]. $CD4^+$ T cells were enriched from BALB/cBy splenocytes using a mouse CD4 enrichment kit (R&D Systems). The cells were then labeled with PE-conjugated anti-CD4, FITC conjugated anti-CD45RB, and APC conjugated anti-CD25 antibodies. Cells were subsequently sorted using a Moflo (Dako, Fort Collins, CO) cell sorter. $CD4^+CD45RB^{hi}CD25^-$ cells were collected and >95% pure. Cells were re-suspended in saline, and 4×10^5 cells/mouse were injected intraperitoneally (i.p.) into C.B-17/Prkdc *scid/scid* mice.

In vivo treatment

Mice were administered 16 mg/kg of either anti-p40 Ab twice per week i.p. or 3-30 mg/kg of tofacitinib/vehicle twice daily (BID) orally for the duration of the study as indicated in the figure legends. Mice were monitored for external signs of skin lesions twice per week. At termination of the study, mouse ear, back skin, lymph nodes, and spleen were collected for further *ex-vivo* studies.

Macroscopic evaluation: Mouse ear thickness was monitored daily in the IL-23 intra-dermal injection and imiquimod models using a micrometer (Mitutoyo). In the T cell transfer model, mice were evaluated twice per week starting 10 days post adoptive transfer. To record disease progression, semiquantitative disease severity scores from 0 to 6 were given to each mouse based on their external physical appearance: 0=no skin or ear abnormalities; 0.5=slight erythema on either the ears or eyelids, 1=mild to moderate erythema on the ears or eyelids, with mild thickening of the ear (<2% of the body surface); 2=moderate to severe erythema on 2-10% of the body surface, mild scaling; 3=severe erythema and scaling on 10-20% of the body surface; 4=very severe and extensive erythema, and scaling on 20-40% of the body surface. 5=very severe and extensive erythema, and scaling on 40-60% of the body surface. 6=very severe and extensive erythema, and scaling on greater than 60% of the body surface. Specific observations were noted based on fur condition, ear manifestations, eyelid appearance, and presence of abnormalities on the limbs and tail.

Histopathological analysis: Tissues were processed into paraffin tissue blocks using routine methods, sectioned, or serially sectioned to obtain consecutive levels. The sections were stained with hematoxylin and eosin (H&E). For immunohistochemistry, paraffin tissue sections were stained with antibodies specific for pSTAT3 or isotype control as described previously [19].

Histopathological evaluation of the severity of findings was performed in a blinded fashion by a board-certified veterinary pathologist using a semiquantitative scale in which 1=minimal infiltrates observed within the dermis; 2=mild infiltrates observed within the dermis, rare foci of "3"; 3=moderate infiltrates within the dermis, multifocal to coalescing foci; 4=marked, diffuse infiltrates within the dermis (>66%); and 5=severe, diffuse infiltrates, with tissue damage.

Cytokine detection

Skin cytokines were extracted from pulverized frozen mouse ears with T-Per tissue extraction buffer supplemented with protease inhibitors (Thermo Scientific, Waltham, MA). Specific immunoassays were used to determine tissue levels of IL-6 (MSD, Rockville, MD), IL-17A (Millipore, Billerica, MA), IL-22 and IL-23 (R&D Systems, Minneapolis, MN). Data were expressed as picograms of cytokine per milligram of total protein in the extract.

Quantification of cytokine transcripts

RNA was isolated from the mouse ears using the Qiagen RNeasy kit (Qiagen, Valencia, CA). Quantitative RT-PCR for various transcripts was performed using pre qualified primers and probes to IL-1α, IL-1β, IL-7, IL-22, IL-17A, IL-17F, IL-6, IL-23p19, IFNγ, CXCL-10, S100A8, IL-21R, IL-22R, IL-12Rα, IL-12Rβ (Applied Biosystems, Foster City, CA). The ΔCt method was used to normalize transcripts to GAPDH.

Statistical analysis

The student's t test was used to calculate statistical significance

for difference between groups. A p value of ≤0.05 was considered statistically significant.

Results

Tofacitinib attenuated IL-23 induced skin inflammation

One of the hallmark gene signature in psoriatic lesional skin is the up-regulation of IL-23p19, the level correlates directly with the pathogenesis of psoriasis [28,29]. Intra-dermal injection of IL-23 into mouse skin has provided insights into the mechanism involved in IL-23-induced psoriasiform inflammation in skin [18,19,30]. We first evaluated the efficacy of tofacitinib and anti-p40 antibody in this model; mice were dosed orally with either 30 mg/kg, 10 mg/kg, 3 mg/kg of tofacitinib or anti- p40 Ab (16 mg/kg) as described in the methods. In Figure 1A, mice treated with tofacitinib and anti-p40 Ab experienced significant reduction in ear thickness when compared to vehicle treated control. Additionally, mice received tofacitinib exhibited a dose dependent inhibition of ear swelling. Tofacitinib at 30 mg/kg almost completely prevented skin inflammation (68.8%) and 10 mg/kg behaved similarly to the anti-p40 treatment (45.6%), while 3 mg/kg was not efficacious (<0%).

Consistent with the clinical readout, histological analysis revealed that tofacitinib decreased inflammatory infiltrates in mouse skin in a dose dependent manner with 30 mg/kg of tofacitinib being most effective and effects of 10 mg/kg were similar to that of anti-p40 treatment (Figure 1B). To understand the impact of tofacitinib and anti-p40 Ab on the downstream transcriptional factors, we analyzed the expression of several activated phospho-STATs (pSTATs, data not shown) in the skin. Among them, pSTAT3 staining provided the most robust and reproducible signal. pSTAT3 is elevated in psoriatic skin and is one of the markers for keratinocyte/immune cell proliferation [31]. As depicted in Figure 1C, more intense pSTAT3 signal was detected in the epidermal layer (keratinocytes) and dermal inflammatory infiltrates indicating these cells were activated and proliferating. Tofacitinib (30 mg/kg) dramatically decreased the number of pSTAT3+ cells. Although reduced, residual pSTAT3+ cells were observed in the skin of mice treated with either 10 mg/kg tofacitinib or anti-p40 Ab. Consistent with

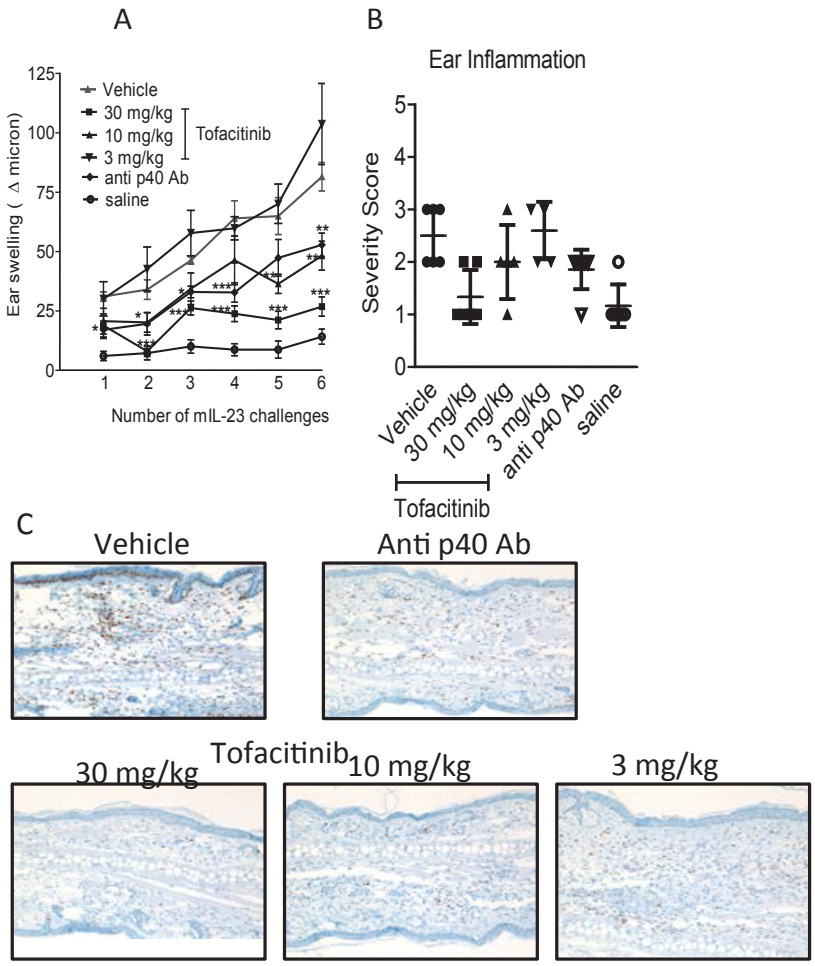

Figure 1: Tofacitinib prevented IL-23 induced skin inflammation. (A) Ear thickness was measured before and at multiple time points after injection; results are reported as mean ± SEM following 7 intra-dermal injections of 150 ng of IL-23 or saline in a total volume of 25 µl every other day. Mice (6 mice per treatment group) were dosed prophylactically with twice daily treatment of various quantities tofacitinib, twice weekly anti-p40 Ab or negative control vehicle starting on Day 0. (B) At study termination, mice were sacrificed and ears were harvested for H&E stain. Graph represents semi-quantitative inflammatory infiltrate scores on H&E sections. Each symbol denotes a single specimen, and horizontal bars indicate the mean of scatter plots. (C) Representative immunohistochemistry images of pSTAT3 staining of the ear sections from (B). H&E and pSTAT3 sections were evaluated by board certified pathologist blinded to the treatment conditions.

the clinical/histology findings, mice treated with 3 mg/kg tofacitinib had noticeable amounts of the pSTAT3 signal in the dermal layer. Overall, tofacitinib at 30 mg/kg and 10 mg/kg demonstrated comparable efficacy as anti-p40 Ab in reducing skin inflammation driven by IL-23.

Optimization of imiquimod induced skin inflammation model

We have optimized the imiquimod induced skin inflammation model by reducing the amount of imiquimod and the frequency of applications as described in Figure 2A and the methods. We found that a lesser amount of imiquimod applied on Days 1, 2 and 3 resulted in continuous increase in the ear thickness during the 5-day period, a more dramatic increase in ear swelling was detected on Day 4 (Figure 2A). Histological analysis of the ear skin indicated that mice treated with imiquimod had intense epidermal hyperplasia and inflammatory infiltrates when compared to mice treated with vehicle cream alone (Figure 2B). Gene expression analysis confirmed the previous findings that IL-17/IL-23 axis of cytokine genes including IL-17, IL-22 and IL-23α (p19) were expressed in addition to the IL-12α gene, 48-72 hours post imiquimod application.

Tofacitinib reduced ear thickening and proinflammatory cytokine expression in the imiquimod induced skin inflammation model

To examine tofacitinib and anti-p40 antibody in the imiquimod model, mice were treated with either tofacitinib 30 mg/kg (BID), anti-p40 Ab (16mg/kg) or vehicle control immediately before the first imiquimod application and throughout the study. As shown in Figure 3, compared with vehicle-treated mice, mice receiving tofacitinib or anti-p40 antibody experienced a significant reduction in ear thickness of 35% and 83% respectively. The clinical observation was further confirmed by the histological readout, vehicle-treated

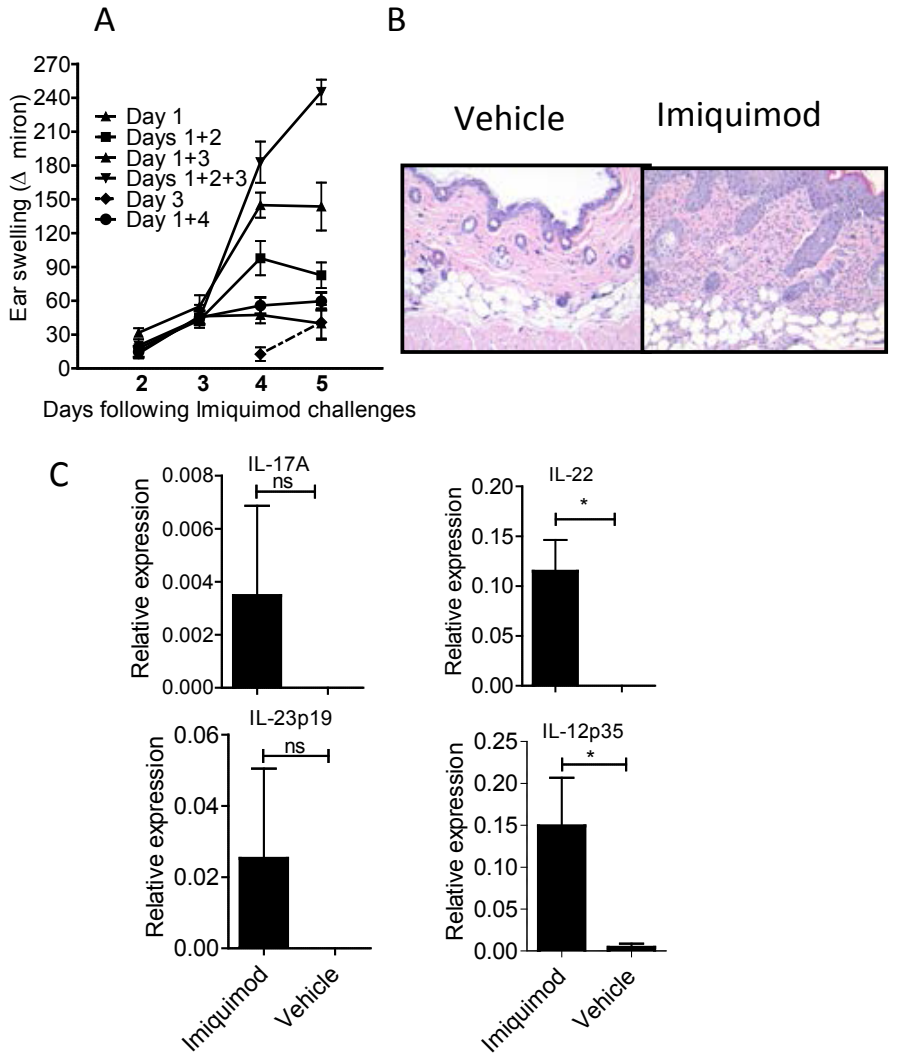

Figure 2: Optimization of imiquimod induced skin inflammation. Imiquimod or vehicle cream was applied to the shaved back and one ear of the BALB/c mice with different frequencies as depicted in the figure. (A) Ear thickness was measured before imiquimod application and at multiple time points during the 5 day study. (B) At the study termination, mice were sacrificed and ears were harvested for H&E stain. Representative images are shown. (C) Two to three days post imiquimod application, mice were sacrificed and ears were harvested. Real time RT-PCR on RNA isolated from individual mouse ears from each group for indicated cytokines was determined. Results reported as mean ± SEM. All data represent the mean of at least two independent experiments n=6 for each group.

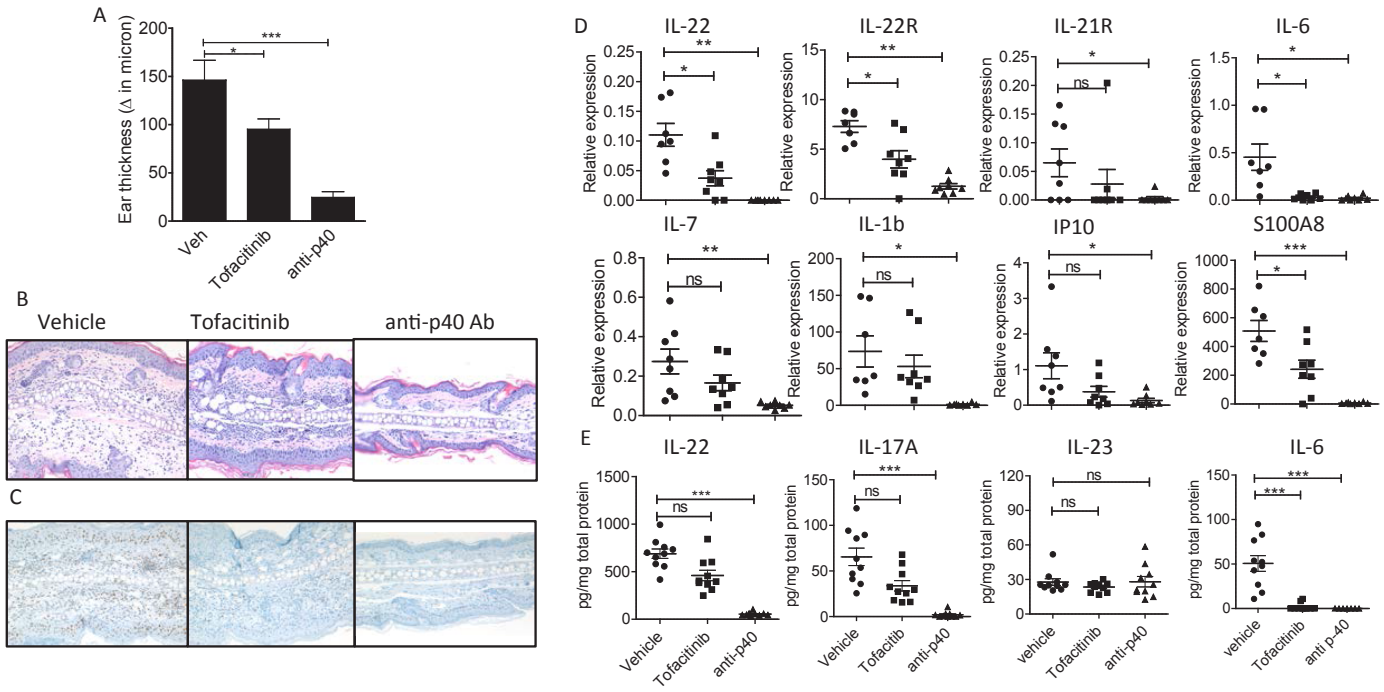

Figure 3: Tofacitinib suppressed imiquimod induced skin inflammation. (A) Imiquimod was applied to the shaved back and one ear of each BALB/c mouse as described in Figure 2. These mice also received prophylactic treatment of either twice daily 30 mg/kg tofacitinib orally, twice weekly anti-p40 Ab or vehicle control starting on Day 0. Ear thickness was measured on Day 5; results are reported as mean ± SEM with n=10 for each treatment group. (B and C) Representative images of H&E and pSTAT3 stained ear sections from mice treated with tofacitinib and anti-p40 Ab. (D) At study termination, real time RT-PCR on RNA isolated from individual mouse ears from each group for indicated cytokines. Results reported as means ± SEM. All data represent the mean of at least two independent experiments n=10 for each group. E) Cytokine ELISA on protein isolated from individual mouse ears from each group for each indicated cytokine. Results reported as means ± SEM.

mice displayed extensive epidermal hyperplasia and inflammatory infiltrates. In contrast, mice treated with tofacitinib had slightly reduced inflammatory infiltrates with similar changes in the epidermal thickness. Remarkably, anti-p40 antibody almost completely prevented the infiltration of inflammatory immune cells in the mouse skin along with considerably reduced epidermal thickness. Relative to vehicle treated mice, fewer pSTAT3 positive immune cells were detected in the epidermis and dermis of the tofacitinib treated group, whereas the anti-p40 antibody almost completely prevented epidermal and dermal pSTAT3 staining.

To further examine the effect of tofacitinib and anti-p40 Ab on cytokine responses, we performed quantitative RT-PCR on the mRNA from mouse-ears of each group. Anti-p40 antibody treatment significantly decreased IL-6, IL-1β, IL-22, IL-7, IP10, S100A8, IL-21R and IL-22R transcripts while tofacitinib either significantly or demonstrated a trend of reducing these above cytokine transcripts. We were unable to detect some of the Th17 cytokine transcripts at the end of the study; however, some cytokine transcripts like IL-23p19, IL-17A usually peak at 2-3 days post imiquimod application and return back to the baseline levels after 5 days which would explain this observation [32]. Nevertheless, Th17 cytokines including IL-22 and IL-17A proteins were detected in the affected mouse ears (Figure 3E). While anti-p40 antibody completely attenuated IL-17A, IL-22 and IL-6 protein secretion in the ear, tofacitinib partially inhibited these cytokines. The attenuated efficacy of tofacitinib in reducing skin inflammation in this model could suggest that IL-23 pathway is critical in this acute skin inflammation model and a thorough coverage of IL-23/Th17 pathway is essential to demonstrate efficacy.

Tofacitinib reduced skin inflammation in the CD4^{+}CD45Rb^{hi} transfer GVHD model

We also examined the impact of tofacitinib in the CD4^{+}CD45Rb^{hi} T cell mediated GVHD skin inflammation model. We have shown previously that transfer of BALB/c CD4^{+}CD45RB^{hi} T cells alone into CB17 *scid/scid* mice leads to the development of psoriaform lesions. The pathology is driven by adaptive immunity where Th17/IL-23 pathway is critically involved in the disease progression and mice treated with anti-p40 Ab did not develop disease [33,34]. As demonstrated in Figure 4A, tofacitinib significantly attenuated skin inflammation starting from Day 42 and onwards. In contrast to mice treated with p40 antibody previously [33,34], tofacitinib-treated mice also maintained some residual skin inflammation that did not resolve completely to baseline (Figure 4A). H&E and pSTAT3 staining results revealed that mice received tofacitinib had a reduction in the epidermal thickness and inflammatory infiltrating cells as well as pSTAT3+ cells in the epidermal and dermal layer (Figure 4B). Gene expression analysis of mouse ears treated with tofacitinib displayed that IL-6, IL-23p19 and IL-12α and S100A8 were significantly inhibited, whereas IL-23/Th17 pathway cytokines (IL-17A, IL-22, IL-23) were partially suppressed (Figure 4C). These results suggest that inhibition of JAK1/JAK3 by tofacitinib led to inhibition of the IL-23/Th17 pathway.

Discussion

Tofacitinib has demonstrated efficacy in a variety of autoimmune

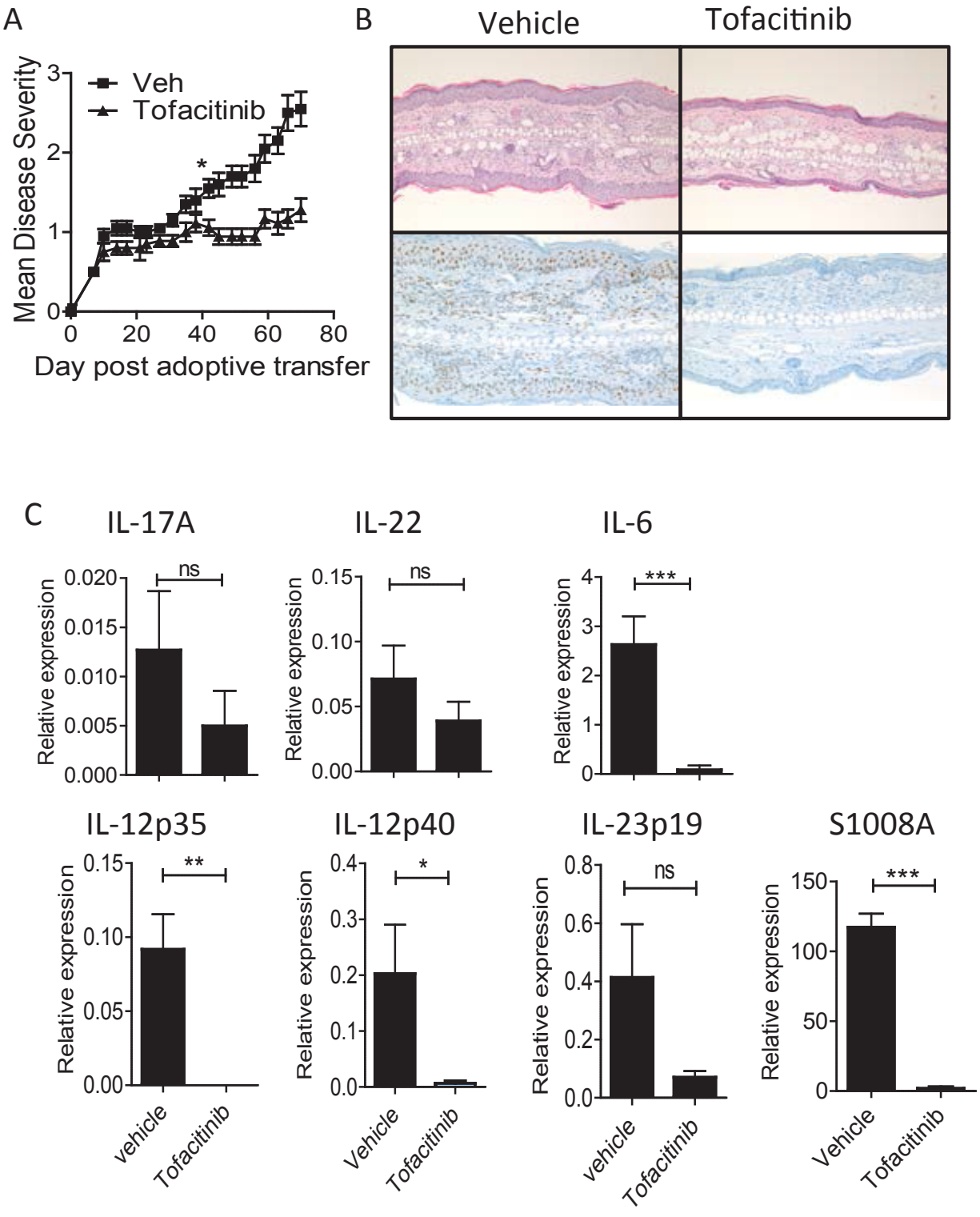

Figure 4: Tofacitinib is efficacious in CD45Rb^{hi} adoptive transfer skin inflammation model. (A) Disease severity in CB17 *scid/scid* mice receiving CD4^{+}CD45RB^{hi}CD25- cells and twice per day of 30 mg/kg tofacitinib starting immediately before the adoptive transfer. The mean disease severity scores are reported for 10 mice from each group ± SEM *p<0.05 starting on Day 24, comparing the two groups. (B) Representative images of H&E and pSTAT3 stained ear sections from mice treated with tofacitinib. (C) At study termination, real time RT-PCR on RNA isolated from individual mouse ears from each group for each indicated cytokine. Results reported as mean ± SEM. All data represent the mean of at least two independent experiments n=10 for each treatment group.

diseases including rheumatoid arthritis, ulcerative colitis, transplantation and psoriasis [13-15,35,36]. In Phase 2 psoriasis clinical trials, efficacy of tofacitinib at 15 mg twice a day is comparable to Stelara and Enbrel [15,37], however, the mode of action by which tofacitinib exerts efficacy in treating psoriasis remains unresolved. Owing to the lack of a fully human translation model for psoriasis, we evaluated tofacitinib and Stelara in several IL-23/IL-12 dependent mouse skin inflammation models. We found that similar to anti-p40 antibody blockade, tofacitinib effectively prevented skin inflammation via attenuating inflammatory infiltrates, decreased inflammatory cytokine expression, reduced epidermal hyperplasia, and inhibited STAT3 phosphorylation in these models.

Common to all three models, the IL-23/Th17 axis of inflammation is key to the pathogenesis of disease. IL-17A and IL-22 are the critical downstream players in the IL-23 injection induced skin inflammation where IL-23 induced epidermal hyperplasia are being reduced by blocking either IL-17A or IL-22 pathways [18,19,30]. In the acute imiquimod model, the TLR 7/8 agonist primarily activates cutaneous dendritic cells to release IL-23, and support the IL-17 production from innate immune cells including resident γδ T cells and innate lymphoid cells (ILCs) that drives skin inflammation [38-40]. In the $CD4^{+}45Rb^{hi}$ T cell transfer model, Th17 and Th1 cells are the major contributors in disease progression [33,34]. We and others have demonstrated that the anti-p40 Ab, which directly neutralizes IL-23 and subsequently blocks the Th17 pathway, is effective in reducing skin inflammation and downstream pSTAT3 signaling [32,38,41]. Interestingly, tofacitinib, which mainly acts on JAK1/3 that blocks the common gamma chain cytokines, IL-6 and type I IFNs with relative lesser coverage on the IL-12/IL-23 pathway, is also efficacious in these models.

Recent evidence in *ex-vivo* studies have indicated that tofacitinib attenuates the generation of IL-23 dependent Th17 cells, likely through blocking the up-regulation of IL-23R and eventually abrogated STAT3-mediated IL-22 and IL-21 expression in Th17 cells [25]. Additionally, it is likely that cytokines other than IL-17A and IL-22 are also highly upregulated in psoriatic skins and participate in lesional skin development. Indeed, current and previous data support the presence of a complex cytokine network in psoriatic lesions that consists of elevated levels of proinflammatory cytokines (IFN-γ, TNF-α, IL-1, IL-2, IL-6, IL-8, IL-12p40 IL-17, IL-19 and IL-21), and multiple chemokines (including MIG/CXCL9, IP-10/CXCL10, I-TAC/CXCL11, and MIP3α) in addition to Th17 cytokines [28,33,42]. IL-6 together with TGFβ could facilitate the differentiation of Th17 cells that may be blocked by tofacitinib. Although IL-21mRNA was not detected in the affected skin in these skin inflammation models (data not shown), IL-21 is known to be produced by activated T cells (Th1, Th17), NKT cells and T follicular helper cells [43-46]. The IL-21 receptor (IL-21R) is expressed on both immune and non-immune cells [47]. IL-21 not only controls the differentiation and function of T cells in an autocrine manner [47], but also leads to epidermal hyperplasia that eventually drives the skin inflammation as demonstrated in the psoriatic skin xenograft transplantation model [48,49]. Although the effect of tofacitinib on IL-23/Th17 pathway is less potent, its ability to attenuate other cytokine signals (i.e. IL-6, IL-21 and type I IFNs) which directly or indirectly contribute to the network of inflammation could explain the efficacy in these models. Furthermore, tofacitinib is not as efficacious in reducing ear inflammation in the imiquimod and T cells transfer induced skin inflammation models suggesting that IL-23 pathway may be predominantly important these settings.

Clinical findings in psoriatic patients support the concept that IL-23/Th17 pathway is critical in psoriasis pathogenesis. Monoclonal antibodies, Stelara and briakinumab, directed against IL-12/23p40 have shown remarkable clinical efficacy in patients with moderate to severe psoriasis [50-52]. Several inhibitors that block IL-23 (IL-23p19) or IL-17A pathway alone have demonstrated promising results [24,53]. The inhibition of the JAK1 and JAK3 pathways by tofacitinib is not very strong in suppressing the IL-23 pathway and yet demonstrates efficacy in psoriasis. Our results suggest that the mechanism of action of tofacitinib is likely due to its ability to block multiple inflammatory cytokines and attenuate the signaling cascades that underlie psoriasis.

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Conflict of Interest

All the authors are employees at Pfizer Inc and hold Pfizer stock/option.

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