Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial

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Summary

Background Despite unmet need, 15 years have passed since a topical therapy with a new mechanism of action for atopic dermatitis (AD) has been approved. Janus kinase (JAK) inhibitor treatment effect via topical application in patients with AD is unknown.

Objectives Tofacitinib, a small-molecule JAK inhibitor, was investigated for the topical treatment of AD.

Methods In this 4-week, phase IIa, randomized, double-blind, vehicle-controlled study (NCT02001181), 69 adults with mild-to-moderate AD were randomized 1:1 to 2% tofacitinib or vehicle ointment twice daily. Percentage change from baseline (CFB) in Eczema Area and Severity Index (EASI) score at week 4 was the primary end point. Secondary efficacy end points included percentage CFB in body surface area (BSA), CFB in EASI Clinical Signs Severity Sum Score, proportion of patients with Physician’s Global Assessment (PGA) response and CFB in patient-reported pruritus. Safety, local tolerability and pharmacokinetics were monitored.

Results The mean percentage CFB at week 4 in EASI score was significantly greater (P < 0.001) for tofacitinib (−81.7%) vs. vehicle (−29.9%). Patients treated with tofacitinib showed significant (P < 0.001) improvements vs. vehicle across all pre-specified efficacy end points and for pruritus at week 4. Significant improvements in EASI, PGA and BSA were observed by week 1 and improvements in pruritus were observed by day 2. Safety/local tolerability were generally similar for both treatments, although more adverse events were observed for vehicle vs. tofacitinib.

Conclusions Tofacitinib ointment showed significantly greater efficacy vs. vehicle across end points, with early onset of effect and comparable safety/local tolerability to vehicle. JAK inhibition through topical delivery is potentially a promising therapeutic target for AD.

What's already known about this topic?

- Atopic dermatitis (AD) is a common, inflammatory skin condition affecting adults and children worldwide with prevalence rates of up to 20% and increasing.
- Despite unmet medical need, it has been 15 years since a new AD drug with a novel mechanism of action has been approved, highlighting the need for other effective agents.
- Recent clinical and nonclinical data support the potential therapeutic benefit of Janus kinase (JAK) inhibition in treating AD.
Atopic dermatitis (AD) is a common, inflammatory skin condition affecting adults and children worldwide with prevalence rates of up to 20% and increasing. Onset typically occurs during childhood. Diagnosis is based on clinical signs, morphology and distribution of skin lesions and historical features. AD is associated with a high socioeconomic burden, with an impact on the use of healthcare resources and patient health-related quality of life (HRQoL). Pruritus is a cardinal symptom of AD and negatively affects patient HRQoL, particularly mental health and sleep quality.

Topical agents including emollients, corticosteroids and calcineurin inhibitors (CNIs) are the mainstay of AD therapy. Other treatments include refined coal tar, topical and oral antibiotics, phototherapy and systemic immunosuppressants. The limitations of current therapies include inadequate efficacy of nonsteroidal topical treatments, restrictions on application to particular body regions, ‘steroid and CNI phobia’ and application site reactions. Long-term safety concerns include systemic side-effects and skin atrophy (for striae and other atrophic changes) with topical corticosteroids and increased risk of infections with CNIs. Despite the ongoing unmet medical need, it has been 15 years since a new AD drug with a novel mechanism of action has been approved, highlighting the need for other effective agents for the treatment of AD.

The pathogenesis and aetiology of AD is not fully elucidated, as AD is a multifactorial disease arising from a complex interaction between genetic, environmental and immunological factors. In particular, T-helper cell (Th)2 cytokines interleukin (IL)-4, IL-5, IL-13 and IL-31 have been implicated in the pathogenesis of AD. Dupilumab, an investigational, injectable monoclonal antibody that inhibits IL-4/IL-13 signalling, has recently demonstrated marked improvements in adults with moderate-to-severe AD in early-phase clinical trials.

The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway is utilized by numerous cytokines and growth factors for signal transduction. Tofacitinib is a small-molecule JAK inhibitor. Tofacitinib has been shown to inhibit cytokines such as IL-4 directly and leads to rapid attenuation of JAK–STAT signalling in keratinocytes. Tofacitinib ointment was efficacious in a phase II study in patients with mild-to-moderate chronic plaque psoriasis, and oral tofacitinib has demonstrated efficacy in phase IIb and phase III studies in moderate-to-severe chronic plaque psoriasis.

This is the first reported randomized clinical trial of a topical, small-molecule JAK inhibitor in patients with AD. The objectives of this study were to characterize the efficacy, patient-reported outcomes (PROs), safety, local tolerability and pharmacokinetics (PK) of 2% tofacitinib ointment vs. vehicle ointment over 4 weeks in adults with mild-to-moderate AD.

### Patients and methods

#### Study design and treatment

The study was performed in compliance with the International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients provided written informed consent and ethics committees approved the protocol before study initiation.

This was a phase IIa, multisite, randomized, double-blind, vehicle-controlled, parallel-group study (A3921214; NCT02001181) (Fig. S1; see Supporting Information). The study was conducted at five investigator sites in Canada between 5 December 2013 and 4 September 2014. Patients were randomized 1:1 to 2% (20 mg g⁻¹) tofacitinib ointment or matching vehicle ointment for 4 weeks. The proprietary ointment formulation contained known topical excipients. The ointment was packaged in tubes containing 60 g of the study drug. At each dispensing visit, a patient received a quantity of tubes that was sufficient to treat the patient’s baseline absolute body surface area (BSA) of treatment-eligible AD until their next dispensing visit. Tubes were weighed before they were dispensed and weighed again after return in order to estimate ointment usage. Tofacitinib or vehicle was applied twice daily to all AD areas, except those on hair-bearing scalp, at a target rate of approximately 3 mg cm⁻². Any new AD on treatment-eligible areas, including the groin or genitals, occurring after day 1 were also treated with the study drug. Patients were instructed to continue to treat all treatment-eligible AD areas identified on day 1, regardless of clearing or improvement. Patients were instructed not to bathe or shower for at least 4 h after application of the study drug.

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**What does this study add?**

- **Tofacitinib ointment showed significantly greater efficacy vs. vehicle across all study end points, with early onset of effect, and comparable safety/local tolerability with vehicle.**
- **JAK inhibition through topical delivery is potentially a promising treatment target for AD.**
- **This study provides important information to the medical research community regarding AD treatment options that have a new mechanism of action.**
Patient randomization at day 1 (baseline) was stratified by baseline AD severity as defined by the Physician’s Global Assessment (PGA) (5-point scale, gestalt static assessment) with a target of approximately 54 patients for ‘moderate’ AD (PGA score of 3) and 16 patients for ‘mild’ AD (PGA score of 2). A computer-generated central randomization schema was implemented in an automated web-based system. Patients, investigational site staff and study sponsors were blinded to treatment assignment for the study duration.

Protocol amendments are summarized in the Supporting Information (File S1; see Supporting Information). The full protocol and statistical analysis plan are also provided in File S1 (see Supporting Information).

Patients

Eligible patients were 18–60 years old with a diagnosis of clinically stable AD (≥ 1 month) for ≥ 6 months prior to the first study dose. Diagnosis of AD was performed by a board-certified dermatologist using Hanifin and Rajka criteria at screening/washout. Patients were required to have a PGA score of 2 (mild) or 3 (moderate), AD covering 2–20% of total BSA and a lichenification score ≤ 1 in each Eczema Area and Severity Index (EASI) body region with treatment-eligible AD. AD located on the scalp, palms and soles was excluded from the BSA calculation used to determine eligibility.

Exclusion criteria included the following: active forms of other dermatitides/eczematous conditions; evidence of skin conditions that would interfere with AD evaluation or treatment response; AD on the groin or genitals; evidence of active, latent or inadequately treated Mycobacterium tuberculosis infection; hepatitis B/C or HIV infection; history of disseminated or recurrent herpes zoster infection; infection requiring hospitalization < 6 months prior to the study; infection requiring oral or topical antimicrobial therapy < 2 weeks prior to the study; history of lymphoproliferative disorders or malignancies (except adequately treated or excised non-metastatic basal cell or squamous cell skin cancer or cervical carcinoma in situ) or previous treatment with oral or topical tofacitinib.

Patients were excluded who were not able to washout of treatments for AD (File S1; see Supporting Information); specifically, topical agents for ≥ 2 weeks prior to day 1, phototherapy or systemic therapy (immunosuppressive or cytotoxic) for ≥ 16 weeks or corticosteroid therapy (oral or injectable) for ≥ 4 weeks prior to screening/washout. Patients who were expected to require such therapy during the study were also excluded. Permitted and prohibited medications are detailed in File S1 (see Supporting Information).

Study outcomes

Clinical efficacy evaluations were modified to exclude the scalp, palms, soles, groin and genitals, even if these areas were being treated with the study drug. The primary efficacy analysis for tofacitinib vs. vehicle was the percentage change from baseline in the EASI total score at week 4. EASI total score was also evaluated at week 1 and week 2 as a secondary end point. Other secondary efficacy end points measured at weeks 1, 2 and 4 included the proportion of patients with a PGA of clear or almost clear and the proportion of patients with a PGA of clear or almost clear plus ≥ 2-point improvement from baseline, change from baseline in EASI Clinical Signs Severity Sum Score and percentage change from baseline in BSA. The proportion of patients achieving ≥ 50%, 75% or 90% reduction in EASI total score relative to baseline (EASI 50/75/90) was analysed post hoc. The Itch Severity Item (ISI) PRO used a single 0–10 numerical rating scale instrument to measure the change from baseline in ISI on days 2–14 (completed by the patient at home in a diary) and at week 2 and week 4 (completed by the patient in clinic). These end points are detailed in File S1 (see Supporting Information).

The incidence and severity of adverse events (AEs) [including treatment-area AEs, Medical Dictionary for Regulatory Activities (MedDRA) version 17.0], clinical laboratory abnormalities and vital sign abnormalities were monitored.

Predose blood samples for tofacitinib PK analysis were collected at day 1 (baseline), week 2 and week 4 (time point range 0.5–3 h). The lower limit of quantification (LLOQ) was 0.01 ng mL⁻¹.

Sample size

This was a phase IIa study using an estimation approach. The sample size (35 patients per group) was not powered for a statistical comparison of the efficacy of two treatment groups, although the sample size was adequate to provide reasonable efficacy estimates. This sample size provided an 80% probability to detect a difference of −26% between two treatment groups with an SD of 50% (based on the two-sided test and alpha = 0.2 level) for the primary efficacy end point (percentage change from baseline in EASI total score at week 4).

Statistics

All analyses were performed on the full analysis set (all patients who were randomized and received at least one dose of the study drug) using SAS/STAT software (version 13.1; SAS Institute Inc., Cary, NC, U.S.A.).

The primary efficacy end point and other continuous end points were analysed using a linear mixed model for repeated measures (MMRM) with no imputation for missing data. The model included all percentage changes from baseline in EASI total scores from week 1 to week 4 as dependent variables. Least squares (LS) means along with SE were calculated for each treatment group and P-values for treatment contrast were also calculated.

Binary end points with repeated measures were analysed using a generalized MMRM (no imputation for missing data). The proportions of patients achieving the end points were derived from the model. P-values for treatment contrast were calculated. Furthermore, a PGA response of clear or almost
clear, and a PGA response of clear or almost clear in addition to a ≥ 2-point improvement from baseline were also analysed using the Cochran–Mantel–Haenszel (CMH) approach,\textsuperscript{23,24} stratified by baseline PGA, with nonresponder imputation for missing values (sensitivity analysis). The difference in EASI 50/75/90 response was analysed post hoc using the CMH approach, stratified by baseline PGA, with nonresponder imputation for missing values. Descriptive statistics were provided for PK data.

**Results**

**Patients**

A total of 104 patients were screened and 69 patients were randomized and treated; four (6%) patients discontinued from the study (Fig. 1).

Baseline demographic and disease characteristics were balanced across the two treatment groups (Table 1). Most patients were female (54%) and white (80%) with a mean age of 31-$\pm$4 years (18–0–57–0) and a ‘moderate’ PGA score (72%). Overall mean EASI total score was 5–6, mean BSA was 6–8 and mean ISI score was 6–0.

Mean ointment application rate per dose from day 1 to week 4 was 2–4 and 2–5 mg cm$^{-2}$ for the tofacitinib and vehicle groups, respectively.

**Efficacy**

For the primary analysis at week 4, the LS mean (SE) percentage change from baseline in EASI total score was significantly greater ($P < 0.001$) for patients treated with tofacitinib $[-81\% (6\%)]$ vs. patients treated with vehicle $[-29\% (6\%)]$. LS mean percentage change from baseline in EASI total score for tofacitinib was also significantly higher ($P < 0.001$) vs. vehicle at weeks 1 and 2 (Fig. 2).

At week 4, the proportion (SE) of patients with a PGA of clear or almost clear for tofacitinib was 73% (7–0–7) vs. 22% (7–5) for vehicle and was significantly higher ($P < 0.05$) vs. vehicle at weeks 1, 2 and 4. The proportion (SE) of patients with a PGA of clear or almost clear plus ≥ 2-point improvement from baseline at week 4 for tofacitinib was 68% (8–2) vs. 13% (6–1) for vehicle, and was significantly higher vs. vehicle at week 2 ($P = 0.005$) and week 4 ($P < 0.001$) (Fig. 2). Week 1 response rates were 20% for tofacitinib and 0% for vehicle ($P = 0.008$; analysed separately using a CMH...
Table 1  Patient demographics and baseline disease characteristics

|                          | 2% tofacitinib twice daily (N = 35) | Vehicle twice daily (N = 34) |
|--------------------------|------------------------------------|------------------------------|
| Sex, n (%)               |                                   |                              |
| Male                     | 16 (46)                            | 16 (47)                      |
| Female                   | 19 (54)                            | 18 (53)                      |
| Age, years               |                                    |                              |
| Mean (SD)                | 32-4 (9-8)                         | 30-4 (10-4)                  |
| Median                   | 31-0                               | 27-0                         |
| Range                    | 18-0–53-0                          | 18-0–57-0                    |
| Height, cm               |                                    |                              |
| Mean (SD)                | 167-0 (7-1)                        | 168-3 (10-3)                 |
| Range                    | 152-5–182-0                        | 139-0–194-5                  |
| Weight, kg               |                                    |                              |
| Mean (SD)                | 82-8 (19-6)                        | 72-0 (18-4)                  |
| Range                    | 52-3–133-3                         | 39-9–128-3                   |
| Body mass index, kg m⁻²  |                                    |                              |
| Mean (SD)                | 29-7 (7-2)                         | 25-3 (5-9)                   |
| Range                    | 19-6–52-4                          | 17-7–46-0                    |
| Race, n (%)              |                                    |                              |
| White                    | 30 (86)                            | 25 (74)                      |
| Black                    | 1 (3)                              | 2 (6)                        |
| Asian                    | 3 (9)                              | 7 (21)                       |
| Other                    | 1 (3)                              | 0 (0)                        |
| Ethnicity, n (%)         |                                    |                              |
| Hispanic/Latino          | 0 (0)                              | 0 (0)                        |
| Non-Hispanic/Latino      | 35 (100)                           | 34 (100)                     |
| EASI total score         |                                    |                              |
| Mean (SD)                | 5-4 (2-6)                          | 5-7 (3-1)                    |
| Range                    | 1-4–13-3                           | 1-3–13-2                     |
| EASI clinical signs severity sum score |          |                              |
| Mean (SD)                | 14-7 (5-6)                         | 14-5 (6-0)                   |
| Range                    | 6-0–29-0                           | 5-0–29-0                     |
| Body surface area, %     |                                    |                              |
| Mean (SD)                | 6-4 (3-4)                          | 7-1 (4-5)                    |
| Range                    | 2-0–17-0                           | 2-0–18-0                     |
| PGA, n (%)               |                                    |                              |
| Clear                    | 0 (0)                              | 0 (0)                        |
| Almost clear             | 0 (0)                              | 0 (0)                        |
| Mild                     | 10 (29)                            | 9 (26)                       |
| Moderate                 | 25 (71)                            | 25 (74)                      |
| Severe                   | 0 (0)                              | 0 (0)                        |
| Itch Severity Item       |                                    |                              |
| Mean (SD)                | 6-5 (2-5)                          | 5-5 (2-2)                    |
| Range                    | 0-0–10-0⁰                         | 1-0–10-0⁰                   |
| Age of onset, years      |                                    |                              |
| Mean (SD)                | 12-0 (15-2)                        | 9-1 (11-9)                   |
| Range                    | 0-0–45-0                           | 0-0–55-4                     |
| Duration since diagnosis, years |       |                              |
| Mean                     | 21-0                               | 22-0                         |
| Range                    | 1-1–53-0                           | 2-4–52-4                     |

EASI, Eczema Area and Severity Index; PGA, Physician’s Global Assessment. ⁰One patient had a baseline Itch Severity Item score of 0.

The results of sensitivity analyses using the CMH approach at week 4 were consistent (data not shown).

At week 4, the LS mean (SE) change from baseline in EASI Clinical Signs Severity Sum Score for tofacitinib was −11.1 (0.78) vs. −3.5 (0.81) for vehicle and was significantly greater (P < 0.001) vs. vehicle at weeks 1, 2 and 4. In a post hoc analysis, the proportion of patients achieving EASI 50 and EASI 75 response was significantly higher for tofacitinib vs. vehicle at all time points (P < 0.05); for EASI 90, tofacitinib was significantly higher vs. vehicle at weeks 2 and 4 (P < 0.05) (Fig. 3).

At week 4, the LS mean (SE) percentage change from baseline in EASI total score was −76% (6.65) vs. −31% (6.85) for vehicle, and was significantly greater (P < 0.001) vs. vehicle at weeks 1, 2 and 4 (Fig. 2).

LS mean changes from baseline in ISI scores were significantly greater for tofacitinib vs. vehicle from day 2 to day 14 (diary-based LS mean) (P < 0.001) and at weeks 2 and 4 (clinic-based LS mean) (P < 0.001).

Images from selected patients demonstrated visual improvements in AD following tofacitinib vs. vehicle treatment (Fig. S2; see Supporting Information).

Safety

Overall, 30 of 69 patients (44%) experienced a treatment-emergent AE (TEAE) (MedDRA version 17.0, Table 2), most of which (89%) were mild. Two patients who were treated with vehicle permanently discontinued from the study as a result of AEs (treatment-area AEs of contact dermatitis).

The most frequently reported TEAEs by system organ class were Infections and Infestations [nine of 69 patients (13%) (Table S1; see Supporting Information)]. Infections occurred in six patients treated with tofacitinib [nasopharyngitis (n = 2), bronchitis (n = 1), furuncle (n = 1), gastroenteritis (n = 1) and viral upper respiratory tract infection (n = 1)] and three patients treated with vehicle [nasopharyngitis (n = 1) and upper respiratory tract infection (n = 1)]. All infections were mild/moderate and resolved before study completion, except nasopharyngitis in one patient treated with vehicle. The most frequently reported TEAEs were nasopharyngitis (described above), increased blood creatine phosphokinase [vehicle (n = 3)], contact dermatitis [vehicle (n = 3)] and headache [tofacitinib (n = 1), vehicle (n = 2)]. TEAEs in the treatment area were reported in two patients treated with tofacitinib [application site pain (n = 1), application site pruritus (n = 1)] and four patients treated with vehicle [application site pruritus (n = 1), contact dermatitis (n = 2), both contact dermatitis and skin irritation (n = 1)].

No deaths, severe AEs or serious AEs occurred (Table 2). No AEs of herpes infection (simplex or zoster), opportunistic infection or malignancy were reported. No patient met protocol-defined clinical laboratory discontinuation criteria.

Pharmacokinetics

All patients on 2% tofacitinib ointment who provided plasma samples had measurable plasma tofacitinib concentrations above the LLOQ at weeks 2 and 4. Median postdose tofacitinib
concentrations at weeks 2 and 4 were marginally higher than predose concentrations, suggestive of a flat concentration profile (Table S2; see Supporting Information). Median concentrations at week 4 were lower than at week 2 (Table S2; see Supporting Information). Observed concentrations appeared higher with higher treated percentage BSA at week 2 (Fig. S3; see Supporting Information); however, this trend was not apparent at week 4.

Discussion

In the current clinical study we showed that JAK inhibition can improve signs and symptoms of AD. Tofacitinib preferentially inhibits signalling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2. This inhibition blocks signalling through several cytokine receptors, including IL-2, IL-4, IL-7, IL-9, IL-13, IL-15 and IL-21. AD is a Th2-dominant inflammatory skin disease and the JAK–STAT pathway is essential for Th2 cell differentiation; in particular JAK1, JAK3 and STAT6 are involved in IL-4 signalling. Moreover, Th2 cell proliferation and JAK–STAT-mediated release of various cytokines are key in the inflammatory responses in AD. IL-4 has been implicated in the dysregulation of keratinocyte function in AD via the upregulation of chemokines and proinflammatory factors, and the downregulation of antimicrobial peptides and factors involved in skin barrier function. Additionally, upregulation of IL-31 has a role in pruritus. Tofacitinib inhibition of JAK1/JAK2 may block signalling via IL-31, thereby suppressing pruritus. This could explain the rapid onset of improvements in ISI scores observed in the current study. Thus, inhibition of the JAK–STAT pathway and cytokines such as IL-4, IL-13 and IL-31 is the likely mechanism of action for tofacitinib in AD. Taken together, the results of the current study, in conjunction with the report demonstrating the efficacy of the IL-4/IL-13 inhibitor dupilumab and a review of targeted biological therapies, support the involvement of the JAK–STAT pathway in the pathogenesis of AD, and also support the JAK–STAT pathway and cytokine inhibition as potential treatment targets for AD.

The current study showed that JAK kinase inhibition with 2% tofacitinib ointment twice daily in adults with mild-to-moderate AD as defined by PGA resulted in significant improvements vs. vehicle across all efficacy end points over 4 weeks, including the primary end point. End points were significantly improved with tofacitinib vs. vehicle from week 1, indicating a rapid onset of efficacy with increasing improvement up to week 4. Furthermore, a substantial and statistically significant reduction in pruritus from baseline was observed as early as 1 day after initiating tofacitinib treatment, which is particularly important given that AD is known as the ‘itch that rashes’ and pruritus has a profound negative impact on quality of life.

The mean ointment application rate per dose during the treatment period (~2.5 mg cm⁻²) was lower than the target rate of 3 mg cm⁻²; however, the observed mean rate was similar to the rate reported in patients instructed to apply a thin layer of a topical medication.

Dermal penetration of tofacitinib was demonstrated by measurable systemic levels of tofacitinib. Lower concentrations at week 4 may be due to onset of efficacy with the return of normal skin barrier function. At week 2, when skin barrier function is most likely still disrupted, the observed trend for higher plasma tofacitinib concentrations with higher treated percentage BSA is not unexpected, whereas at week 4, when significant disease improvement was observed, this trend was no longer apparent. Decreased patient adherence to treatment of the baseline decreased BSA for the full 4 weeks may also explain lower concentrations at week 4; however, this is not supported by the mean application rate (calculated using the baseline disease BSA), which was stable for both treatment groups for the interval from day 1 to week 2 and for the interval from week 2 to week 4 (data not shown).

The maximum observed concentration of 2.7 ± 0.4 mg ml⁻¹ (Table S2; see Supporting Information) has a margin of approximately 6.4-fold relative to the mean average concentration [17.3 ± 0.4 mg ml⁻¹], average concentration = area under the concentration curve (ng h ml⁻¹)/dosing interval (12 h)] of 5 mg twice daily oral tofacitinib based on the observed concentrations in the phase III clinical trials of patients with moderate-to-severe plaque psoriasis. An additional PK discussion is provided in the Supporting Information (File S1).

Safety issues with many available AD therapies include application site reactions, incidence of eczema herpeticum, possible increased risk of infections and malignancies, and corticosteroid side-effects such as atrophy, striae and hypothalamic–pituitary–adrenal axis suppression. TEAEs were infrequent for both tofacitinib and vehicle; of note, more TEAEs and treatment-area TEAEs were recorded for vehicle vs. tofacitinib. No patients treated with tofacitinib permanently discontinued from the study owing to AEs, compared with two patients treated with vehicle. No Serious AEs were reported. Tofacitinib ointment was well tolerated and had an acceptable safety and local tolerability profile in this phase IIa study with 4 weeks of treatment.

Comparison of the current study with existing or investigational AD therapies is limited owing to its short duration, the absence of an active comparator arm, and differences in instruments and populations. A recent report of oral tofacitinib use in six patients with refractory moderate-to-severe AD showed improvement in the signs of AD as measured by BSA and the SCORing of AD (SCORAD) index; however, the study was limited by the small sample size and absence of placebo control or blinding.

This was a short-term study with a small sample size. To confirm these proof-of-concept results, future study of JAK inhibition for the treatment of AD should include larger trials of longer duration with a broader range of AD severity (as measured by BSA and clinical signs, including greater lichenification) and patient demographic characteristics in both adult and paediatric patients. The inclusion of an active comparator and biomarker measures will aid in elucidating the relative efficacy and safety, and mechanism of action, respectively.
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In this 4-week, phase IIa study, inhibition of JAK with topical tofacitinib demonstrated significantly greater efficacy vs. vehicle, with early onset and acceptable safety/local tolerability profile. These results indicate that inhibition of the JAK–STAT pathway may be a new therapeutic target for AD and that additional studies are warranted to address the unmet need in the treatment of AD.

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Author contributions

Conception and design of the study/analyses: W.C.P., J.P., C.W., V.P., C.M., L.M., K.A.P., Y.P., M.G. and R.B. Data and statistical analyses: J.P., C.W., V.P., C.M., L.M. and W.C.P. Data

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Appendix

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**Supporting Information**

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

- **File S1.** Protocol amendments, statistical analysis plan and pharmacokinetic results.
- **Fig S1.** Study design.
- **Fig S2.** Images taken from patients with atopic dermatitis (on selected limbs/extremities) before and after treatment with tofacitinib or vehicle.
- **Fig S3.** Relationship of treated baseline percentage body surface area and observed plasma concentrations.
- **Fig S4.** Efficacy assessment scales training for Eczema Area and Severity Index components and static Physician’s Global Assessment score.
- **Table S1.** Treatment-emergent adverse events by system organ class and Medical Dictionary for Regulatory Activities version 17.0 preferred term (all causalities).
- **Table S2.** Descriptive summary of predose and postdose plasma tofacitinib concentrations at weeks 2 and 4.