



Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial

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Summary

Background New therapeutic options are needed for patients with psoriasis. Tofacitinib, an oral Janus kinase inhibitor, is being investigated as a treatment for moderate-to-severe chronic plaque psoriasis. In this study, we aimed to compare two tofacitinib doses with high-dose etanercept or placebo in this patient population.

Methods In this phase 3, randomised, multicentre, double-dummy, placebo-controlled, 12-week, non-inferiority trial, adult patients with chronic stable plaque psoriasis (for ≥ 12 months) who were candidates for systemic or phototherapy and had a Psoriasis Area and Severity Index (PASI) score of 12 or higher and a Physician's Global Assessment (PGA) of moderate or severe, and had failed to respond to, had a contraindication to, or were intolerant to at least one conventional systemic therapy, were enrolled from 122 investigational dermatology centres worldwide. Eligible patients were randomly assigned in a 3:3:3:1 ratio to receive tofacitinib 5 mg or 10 mg twice daily at about 12 h intervals, etanercept 50 mg subcutaneously twice weekly at about 3–4 day intervals, or placebo. Randomisation was done by a computer-generated randomisation schedule, and all patients and study personnel were masked to treatment assignment. The co-primary endpoints were the proportion of patients at week 12 with at least a 75% reduction in the PASI score from baseline (PASI75 response) and the proportion of patients achieving a PGA score of “clear” or “almost clear” (PGA response), analysed in the full analysis set (all patients who were randomised and received at least one dose of study drug). This study is registered with ClinicalTrials.gov, number NCT01241591.

Findings Between Nov 29, 2010, and Sept 13, 2012, we enrolled 1106 eligible adult patients with chronic plaque psoriasis and randomly assigned them to the four treatment groups (330 to tofacitinib 5 mg twice daily, 332 to tofacitinib 10 mg twice daily, 336 to etanercept 50 mg twice weekly, and 108 to placebo). Of these patients, 1101 actually received their assigned study medication (329 in the tofacitinib 5 mg group, 330 in the tofacitinib 10 mg group, 335 in the etanercept group, and 107 in the placebo group). At week 12, PASI75 responses were recorded in 130 (39.5%) of 329 patients in the tofacitinib 5 mg group, 210 (63.6%) of 330 in the tofacitinib 10 mg group, 197 (58.8%) of 335 in the etanercept group, and six (5.6%) of 107 in the placebo group. A PGA response was achieved by 155 (47.1%) of 329 patients in the tofacitinib 5 mg group, 225 (68.2%) of 330 in the tofacitinib 10 mg group, 222 (66.3%) of 335 in the etanercept group, and 16 (15.0%) of 107 in the placebo group. The rate of adverse events was similar across the four groups, with serious adverse events occurring in seven (2%) of 329 patients in the tofacitinib 5 mg group, five (2%) of 330 in the tofacitinib 10 mg group, seven (2%) of 335 in the etanercept group, and two (2%) of 107 in the placebo group. Three (1%) of 329 patients in the tofacitinib 5 mg group, ten (3%) of 330 in the tofacitinib 10 mg group, 11 (3%) of 335 in the etanercept group, and four (4%) of 107 patients in the placebo group discontinued their assigned treatment because of adverse events.

Interpretation In patients with moderate-to-severe plaque psoriasis, the 10 mg twice daily dose of tofacitinib was non-inferior to etanercept 50 mg twice weekly and was superior to placebo, but the 5 mg twice daily dose did not show non-inferiority to etanercept 50 mg twice weekly. The adverse event rates over 12 weeks were similar for tofacitinib and etanercept. This study indicates that in the future tofacitinib could provide a convenient and well-tolerated therapeutic option for patients with moderate-to-severe plaque psoriasis.

Funding Pfizer Inc.

Introduction

Moderate-to-severe plaque psoriasis is a chronic, immune-mediated, systemic disease that affects patients both physically and psychologically, leading to major quality-of-life impairment.¹ Interplay between the innate and adaptive immune systems and epidermal proliferation

and differentiation underlie the disease pathogenesis, causing sustained inflammation and epidermal hyperplasia, which ultimately results in the formation and persistence of psoriatic lesions.^{2–4} Patients with moderate-to-severe plaque psoriasis need treatment with phototherapy or systemic agents. However, long-term

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exposure to phototherapy could be associated with an increased risk of skin cancers,^{5,6} whereas prolonged use of classical systemic treatments (methotrexate, ciclosporin, and acitretin) is associated with organ toxicity (liver, kidney, and mucocutaneous toxicity, respectively) that limits their long-term usefulness.^{7–11}

Despite the availability of biological therapies, including tumour necrosis factor inhibitors and interleukin 12 or interleukin 23 inhibitors,^{8,10–12} patients with psoriasis who have extensive or severe disease still need new treatment options, because loss of treatment efficacy over time, immunogenicity, adverse events, and the need for parenteral administration can compromise the long-term usefulness of biologicals in some cases and have been cited by patients as reasons contributing to treatment discontinuation.^{13–16} Furthermore, 20–50% of patients do not achieve or lose satisfactory clinical responses to biologicals in the short-to-medium term, which leads to poor drug continuation rates and substantial patient dissatisfaction.^{14,16–18} Similarly, new, effective, well-tolerated, and convenient treatments with new mechanisms of action that address these latter problems are needed to achieve adequate clinical responses and provide patients and physicians with a broader range of therapies to reduce the psoriasis disease burden.

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) intracellular signalling pathway is used by many cytokines and is implicated in the pathogenesis of chronic immune-mediated and inflammatory diseases including psoriasis.¹⁹ Tofacitinib is an oral JAK inhibitor that mainly interferes with JAK1 and JAK3 signalling and has previously shown significantly better efficacy than placebo in a 12-week phase 2b dose-ranging study in patients with moderate-to-severe plaque psoriasis.²⁰

We report the results of the first phase 3 study comparing the efficacy and safety of two doses of tofacitinib (5 mg and 10 mg twice daily) versus etanercept 50 mg subcutaneously twice weekly or placebo for the treatment of moderate-to-severe chronic plaque psoriasis in patients who are candidates for systemic therapy or phototherapy. The 5 mg and 10 mg twice daily doses of tofacitinib were selected to offer the best balance of safety and efficacy based on the phase 2b study results,^{20,21} whereas the 50 mg twice weekly dose of etanercept is the highest approved dose for psoriasis treatment that also has a favourable safety profile.⁹

Methods

Participants

Eligible patients were recruited from 122 investigational dermatology centres worldwide (excluding the USA and Canada), and were 18 years of age or older diagnosed with chronic (≥ 12 months) stable plaque psoriasis; were candidates for systemic or phototherapy; had a Psoriasis Area and Severity Index (PASI) score of 12 or higher and a Physician's Global Assessment (PGA) of moderate or

severe; had psoriasis that involved at least 10% of their body surface area; and had failed to respond to, had a contraindication to, or were intolerant to at least one conventional systemic therapy (including ultraviolet therapy) approved for plaque psoriasis treatment.

Patients were excluded from the study if they had non-plaque or drug-induced forms of psoriasis, could not discontinue systemic therapies, had previously been treated with or had a contraindication to etanercept, had previously not responded to treatment with any tumour necrosis factor inhibitors, had evidence of active infection, or had previously participated in studies involving oral tofacitinib. Patients with clinically significant infections within 6 months before the study or a history of infection that needed antimicrobial therapy within 2 weeks before the study were also excluded.

Washout periods for previous psoriasis therapies were: at least 2 weeks for topical treatments (exceptions were non-medicated emollients; least potent [class 6 or 7] topical corticosteroids for the palms, soles, face, and intertriginous areas; salicylic acid preparations; and corticosteroid-free shampoos) and ultraviolet B phototherapy; at least 4 weeks for systemic treatments, excluding biologicals and psoralen plus ultraviolet A phototherapy; at least 8 weeks for adalimumab, infliximab, and alefacept; and at least 12 weeks for investigational therapies and ustekinumab.

The study was done in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines, and the study protocol was approved by the institutional review board or ethics committee at each site. Written informed consent was obtained from each patient before enrolment.

Study design

For this randomised, double-blind, double-dummy, placebo-controlled, parallel-group phase 3 study, patients were randomly assigned in a 3:3:3:1 ratio to receive tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, etanercept 50 mg subcutaneously twice weekly, or placebo (administered in a matched dosing schedule) for 12 weeks. The twice daily doses of tofacitinib (or matching placebo) were administered around 12 h apart, and the twice weekly doses of etanercept (or matching placebo) were administered around 3–4 days apart. Figure 1 summarises the administration schedules of active treatment and oral or injected placebo. An off-treatment follow-up (end of study) visit was done 2–4 weeks after the final dose of study drug.

Randomisation and masking

A computer-generated randomisation schedule was used to assign patients to the treatment groups. This randomisation schedule was generated by the Pfizer Groton Randomization Group. Randomisation was done at the country level. The study site contacted an interactive voice response system or web-based

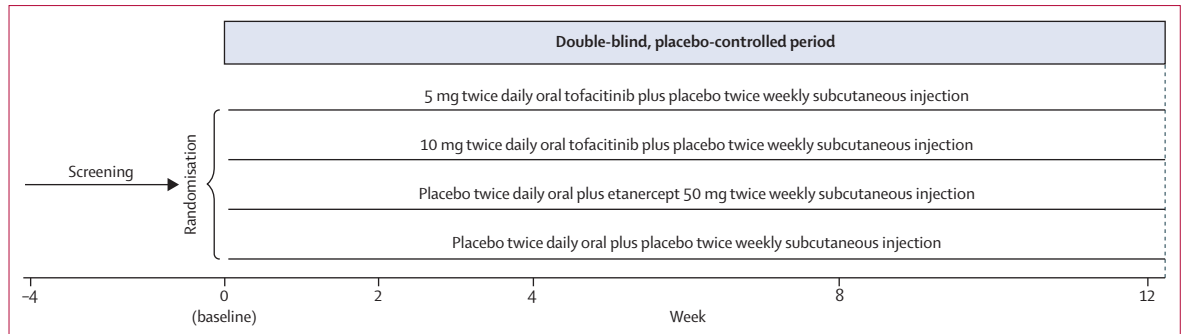


Figure 1: Study design

interactive response system, which associated that patient and their identification number with the next available randomisation number on the randomisation schedule. The randomisation schedule stratified patients according to number of previously failed systemic therapies (<3 or \geq 3). Stratification did not include any limit on the number of patients within a treatment group stratum. Patients and study personnel were masked to treatment assignment: the study drug packaging was labelled such that the patient and staff could not establish to which treatment group each patient was assigned. Placebo was provided as oral tablets matching those of tofacitinib to be given to the etanercept and placebo groups, and as prefilled syringes for subcutaneous injection matching those of etanercept, to be given to the tofacitinib and placebo groups.

Outcomes

The co-primary efficacy endpoints were the proportion of patients achieving at least a 75% reduction in PASI score from baseline at week 12 (PASI75 response) and the proportion of patients achieving a PGA score (on a five-point severity scale of 0 “clear”; 1 “almost clear”; 2 “mild”; 3 “moderate”; 4 “severe”) of “clear” or “almost clear” (PGA response) at week 12. The primary objectives were to assess the non-inferiority and superiority of tofacitinib 5 mg or 10 mg twice daily versus etanercept 50 mg twice weekly and placebo. The main secondary endpoints were the proportion of patients achieving at least a 50% reduction in PASI score (PASI50 response) or at least a 90% reduction in PASI score (PASI90 response) from baseline, reduction in itch severity item score (patient-reported itch severity in a 24 h period on a scale of 0 [no itching] to 10 [worst possible itching]), and a clinically meaningful decrease (\geq 5 point reduction) in Dermatology Life Quality Index (DLQI) score from baseline.²² Additional secondary endpoints not reported in this Article because of space limitations but included in the protocol are listed in the appendix.

Safety was assessed according to the incidence and severity of adverse events, clinical laboratory abnormalities, vital sign abnormalities, and ECG changes. Cardiovascular events were adjudicated by an independent, masked

cardiovascular safety endpoint adjudication committee consisting of external experts. All available histological material from potentially malignant tumours was reviewed by a central laboratory (Quintiles Central Laboratory, ERT Laboratories, and Canfield Scientific Incorporated), by prospective, masked over-read of local histopathology data, to confirm the findings.

Statistical analysis

The primary analysis population for efficacy was the full analysis set, which was defined as all patients who were randomly assigned for the study and received at least one dose of study drug. The safety analysis set comprised all patients who received at least one dose of study drug.

The sample size was established to have at least 95% power to establish non-inferiority of each dose of tofacitinib to etanercept for the efficacy comparison of PASI75 and PGA responses at week 12 within the 15% margin, at a 0.025 (one-sided) significance level. The sample sizes also provided at least 99% power to show superiority of each of the active treatments over placebo at week 12.

To preserve type I error, we used a fixed sequence procedure with six steps to assess each objective sequentially for the two coprimary endpoints. The first step tested non-inferiority of tofacitinib 10 mg twice daily versus etanercept 50 mg twice weekly and the second step tested superiority of tofacitinib 10 mg twice daily versus placebo; these testing steps were then repeated for tofacitinib 5 mg twice daily. The final two steps tested superiority of tofacitinib 10 mg twice daily and 5 mg twice daily to etanercept. Statistical significance could be claimed for an objective at a given dose only if the previous step in the sequence met the requirements for significance.

We used a normal approximation for the difference in binomial proportions for the comparisons. Because of the small size in one of the randomisation strata (use of three or more previous systemic therapies), we did not adjust this stratification factor in the primary analysis. We judged patients with missing values for all binary endpoints to be non-responders in efficacy assessments.

This study is registered with ClinicalTrials.gov, number NCT01241591.

See Online for appendix

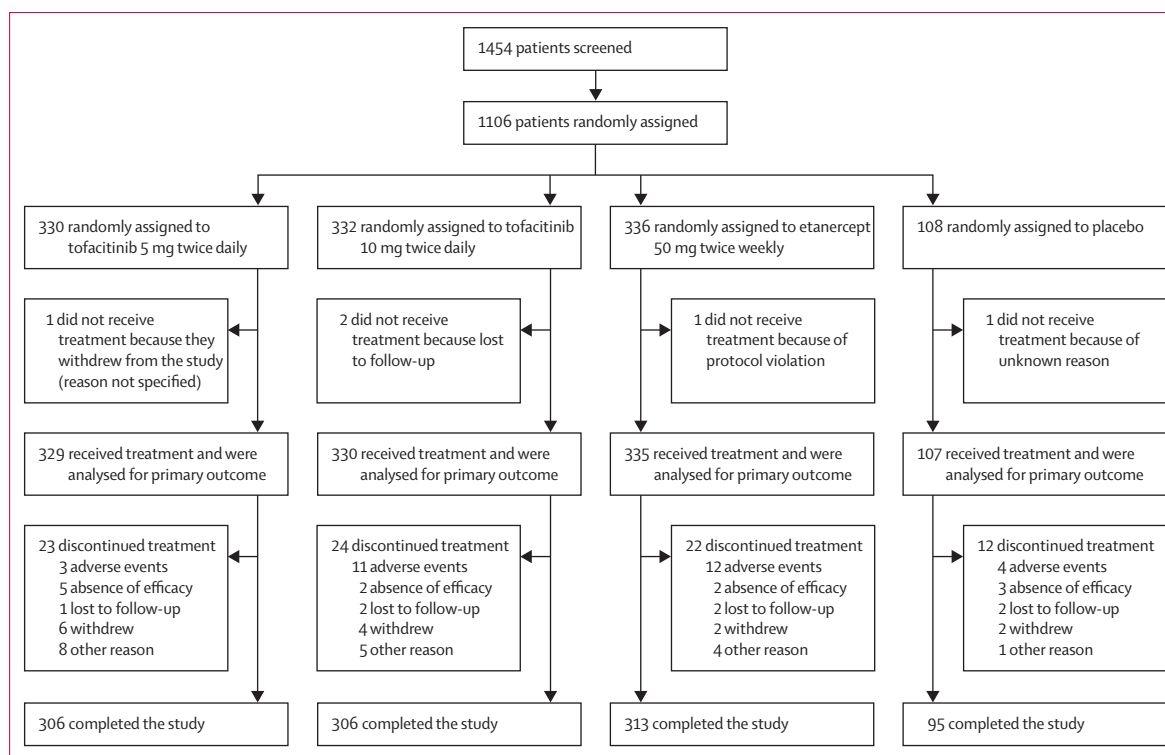


Figure 2: Trial profile

Role of the funding source

This study was designed and funded by Pfizer Inc. In collaboration with academic authors, authors employed by Pfizer were involved in the collection, analysis, and interpretation of data; the writing of the report; and in the decision to submit for publication. Study investigators gathered the data, which were maintained in a database by Pfizer and an external contract research organisation (ICON Clinical Research Ltd, Dublin, Ireland; and Atlas Medical Services, Istanbul, Turkey). All authors had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Between Nov 29, 2010, and Sept 13, 2012, 1454 patients from 122 dermatology centres worldwide were screened for inclusion, of whom 1106 eligible participants were enrolled and randomly assigned to the four treatment groups: 330 to tofacitinib 5 mg twice daily, 332 to tofacitinib 10 mg twice daily, 336 to etanercept 50 mg twice weekly, and 108 to placebo). Of these patients, 1101 actually received study medication (329 in the tofacitinib 5 mg group, 330 in the tofacitinib 10 mg group, 335 in the etanercept group, and 107 in the placebo group) and therefore comprised the full analysis set. Most patients (1020 [93%] of 1106) completed the study (figure 2).

The baseline demographic and disease characteristics of the patients were similar between the treatment groups (table 1). Most patients were white men, with a median

age of 44 years (IQR 34–53) and a median weight of 83 kg (IQR 72–95). More than half of patients had severe psoriasis (PASI score ≥ 20). Most patients (1029 [94%] of 1101) had received previous systemic therapies and 113 (10%) had previous exposure to, or a contraindication to, biological agents. Of the 1101 participants who received the study drugs, 968 (88%) were in the stratum of patients with fewer than three previously failed systemic therapies; therefore, we do not present the stratified results.

A PASI75 response at week 12 was achieved by 130 (39.5%) of 329 patients in the tofacitinib 5 mg twice daily group, 210 (63.6%) of 330 in the tofacitinib 10 mg twice daily group, 197 (58.8%) of 335 in the etanercept twice weekly group, and six (5.6%) of 107 in the placebo group. The corresponding proportions of PGA responders at week 12 were 155 (47.1%) in the tofacitinib 5 mg group, 225 (68.2%) in the tofacitinib 10 mg group, 222 (66.3%) in the etanercept group, and 16 (15.0%) in the placebo group (table 2). For both coprimary endpoints, tofacitinib 10 mg twice daily was non-inferior to etanercept and was superior to placebo, whereas tofacitinib 5 mg twice daily did not meet the non-inferiority criteria versus etanercept but met the superiority criteria versus placebo (table 2). However, the superiority of tofacitinib 5 mg twice daily to placebo could not be claimed because of the failed non-inferiority test in the predefined testing procedure that controls for type I error. Figure 3 and table 2 present the proportions of patients achieving a PASI75 response, PASI90 response, and a PGA response.

| | Tofacitinib 5 mg twice daily (n=329) | Tofacitinib 10 mg twice daily (n=330) | Etanercept 50 mg twice weekly (n=335) | Placebo (n=107) |
|--|---|--|--|-------------------|
| Age (years) | 44.0 (18–73) | 44.0 (19–75) | 42.0 (18–74) | 46.0 (21–81) |
| Weight (kg) | 83.0 (36.8–150.0) | 84.0 (36.3–168.0) | 82.0 (48.0–143.5) | 80.2 (46.5–130.0) |
| Men | 236 (72%) | 238 (72%) | 233 (70%) | 71 (66%) |
| Race | | | | |
| White | 289 (88%) | 285 (86%) | 292 (87%) | 90 (84%) |
| Asian | 16 (5%) | 17 (5%) | 20 (6%) | 7 (7%) |
| Other | 23 (7%) | 27 (8%) | 22 (7%) | 8 (8%) |
| Duration of psoriasis (years) | 16.0 (1–56) | 17.0 (1–60) | 18.0 (1–62) | 17.0 (1–57) |
| PASI score | 21.0 (12.0–56.3) | 21.0 (12.0–62.3) | 19.4 (12.0–63.6) | 19.5 (12.4–54.6) |
| PGA | | | | |
| Mild | 6 (2%) | 4 (1%) | 4 (1%) | 3 (3%) |
| Moderate | 264 (80%) | 275 (83%) | 271 (81%) | 88 (82%) |
| Severe | 59 (18%) | 51 (16%) | 60 (18%) | 16 (15%) |
| Body surface area affected (%) | 28.0% (9.0–84.0) | 28.0% (10.0–87.0) | 25.0% (9.5–93.0) | 26.0% (11.0–79.0) |
| DLQI score | 12.0 (0–30) | 13.0 (0–30) | 12.0 (0–30) | 11.5 (0–30) |
| Psoriatic arthritis | 59 (18%) | 78 (24%) | 71 (21%) | 26 (24%) |
| Previous psoriasis treatment | | | | |
| Phototherapy | 236 (72%) | 236 (72%) | 242 (72%) | 76 (71%) |
| Systemic treatment (conventional systemic, biological and/or phototherapies) | 308 (94%) | 307 (93%) | 315 (94%) | 99 (93%) |
| Biological agent* | 35 (11%) | 29 (9%) | 37 (11%) | 12 (11%) |

Data are median (range) or n (%). DLQI=Dermatology Life Quality Index. PASI=Psoriasis Area and Severity Index. PGA=Physician's Global Assessment. *Includes patients with a contraindication to biologicals.

Table 1: Baseline characteristics of the full analysis set

The percentage of PASI75 responders was larger in patients who received tofacitinib 10 mg twice daily than in those who received etanercept at week 4 (64 [19.4%] of 330 vs 27 [8.1%] of 335; $p<0.0001$) and week 8 (167 [50.6%] of 330 vs 138 [41.2%] of 335; $p=0.0144$); these rates were also numerically higher than in the tofacitinib 5 mg twice daily group (33 [10.0%] of 329 at week 4 and 90 [27.4%] of 329 at week 8; figure 3A). Similarly, median time to PASI75 response was generally shorter with tofacitinib 10 mg twice daily than with etanercept or with tofacitinib 5 mg twice daily (data not shown). PASI50 and PASI90 response rates over time, and the corresponding differences between treatment groups, were similar to those based on the PASI75 outcome (figure 3C; data not shown).

The decrease in median PASI score from baseline to week 12 was similar for tofacitinib 10 mg twice daily and etanercept; these reductions were greater than those reported with tofacitinib 5 mg twice daily or placebo (figure 3D). Similar trajectories were recorded for absolute and percentage change from baseline in total and component PASI scores throughout the 12 weeks. During the treatment period, 44 (4.0%) patients had a worsening of their PASI score of 25% or more from baseline: 15 (4.6%) with tofacitinib 5 mg twice daily, six (1.8%) with tofacitinib 10 mg twice daily, six (1.8%) with etanercept, and 17 (15.9%) with placebo. During the post-treatment follow-up period, only one patient in

the placebo group had worsening of PASI score of at least 25% from baseline. No patients who had active treatment experienced a worsening of PASI score of 25% or more from baseline during the follow-up period.

Mean itch severity item scores at baseline were 5.2 (SE 0.2) for tofacitinib 5 mg twice daily, 5.3 (0.2) with tofacitinib 10 mg twice daily, 5.2 (0.2) with etanercept 50 mg twice weekly, and 5.2 (0.3) with placebo; the corresponding scores at week 12 were 2.0 (0.1), 1.3 (0.1), 1.7 (0.1), and 4.8 (0.3), respectively. Decreases in scores with active treatment were greater than the clinically important difference of 1.64 previously identified in patients with moderate-to-severe plaque psoriasis.²³

At week 12, a clinically meaningful improvement in DLQI score (a reduction by five points or more) was achieved by 191 (66.3%) of 288 patients in the tofacitinib 10 mg group, 226 (78.2%) of 289 in the tofacitinib 5 mg group, 218 (74.7%) of 292 in the etanercept group, and 28 (31.8%) of 88 in the placebo group, in patients with a baseline score of 5 or higher ($p<0.0001$ for each active treatment vs placebo; table 2).

Only three of 329 (1%) patients in the tofacitinib 5 mg group, ten (3%) of 330 in the tofacitinib 10 mg group, 11 (3%) of 335 in the etanercept group, and four (4%) of 107 in the placebo group discontinued treatment because of adverse events (table 3). The percentage of patients experiencing serious or severe adverse events was low and was similar across the

| | Tofacitinib 5 mg twice daily (n=329) | Tofacitinib 10 mg twice daily (n=330) | Etanercept 50 mg twice weekly (n=335) | Placebo (n=107) |
|--|--------------------------------------|---------------------------------------|---------------------------------------|--------------------|
| PASI50 response | 216 (65.7%; 2.6) | 266 (80.6%; 2.2) | 269 (80.3%; 2.2) | 22 (20.6%; 3.9) |
| Difference vs placebo | 45.1 (4.7) | 60.0 (4.5) | 59.7 (4.5) | .. |
| p value vs placebo | <0.0001 | <0.0001 | <0.0001 | .. |
| Difference vs etanercept | -14.6 (3.4) | 0.3 (3.1) | .. | .. |
| p value vs etanercept | <0.0001 | 0.92 | .. | .. |
| PASI75 response* | 130 (39.5%; 2.7) | 210 (63.6%; 2.6) | 197 (58.8%; 2.7) | 6 (5.6%; 2.2) |
| Difference vs placebo | 33.9 (3.5) | 58.0 (3.5) | 53.2 (3.5) | .. |
| p value vs placebo | <0.0001 | <0.0001 | <0.0001 | .. |
| Difference vs etanercept | -19.3 (3.8) | 4.8 (3.8) | .. | .. |
| p value vs etanercept | <0.0001 | 0.20 | .. | .. |
| PASI90 response | 69 (21.0%; 2.2) | 119 (36.1%; 2.6) | 108 (32.2%; 2.6) | 1 (0.9%; 0.9) |
| Difference vs placebo | 20.0 (2.4) | 35.1 (2.8) | 31.3 (2.7) | .. |
| p value vs placebo | <0.0001 | <0.0001 | <0.0001 | .. |
| Difference vs etanercept | -11.3 (3.4) | 3.8 (3.7) | .. | .. |
| p value vs etanercept | 0.0009 | 0.30 | .. | .. |
| Median PASI scores† | 7.5 (0.0–57.0) | 3.4 (0.0–55.2) | 3.2 (0.0–35.6) | 15.3 (0.7–52.8) |
| PGA response* | 155 (47.1%; 2.8) | 225 (68.2%; 2.6) | 222 (66.3%; 2.6) | 16 (15.0%; 3.4) |
| Difference vs placebo | 32.2 (4.4) | 53.2 (4.3) | 51.3 (4.3) | .. |
| p value vs placebo | <0.0001 | <0.0001 | <0.0001 | .. |
| Difference vs etanercept | -19.2 (3.8) | 1.9 (3.6) | .. | .. |
| p value vs etanercept | <0.0001 | 0.60 | .. | .. |
| PGA score of clear | 37 (11.2%; 1.7) | 84 (25.4%; 2.4) | 65 (19.4%; 2.2) | 2 (1.9%; 1.3) |
| Difference vs placebo | 9.4 (2.2) | 23.6 (2.7) | 17.5 (2.5) | .. |
| p value vs placebo | <0.0001 | <0.0001 | <0.0001 | .. |
| Difference vs etanercept | -8.2 (2.8) | 6.1 (3.2) | .. | .. |
| p value vs etanercept | 0.0033 | 0.06 | .. | .. |
| Clinically meaningful decrease in DLQI (≥5 point reduction from baseline)‡ | 191/288 (66.3%; 2.8) | 226/289 (78.2%; 2.4) | 218/292 (74.7%; 2.6) | 28/88 (31.8%; 5.0) |
| Difference vs placebo | 34.5 (5.7) | 46.4 (5.5) | 42.8 (5.6) | .. |
| p value vs placebo | <0.0001 | <0.0001 | <0.0001 | .. |
| Difference vs etanercept | -8.3 (3.8) | 3.5 (3.5) | .. | .. |
| p value vs etanercept | 0.0271 | 0.31 | .. | .. |

The data in this table are for the full analysis set (with non-responder imputation). Data are n (%; SE), mean difference (SE), median (range), or n/N (%; SE). DLQI=Dermatology Life Quality Index. PASI=Psoriasis Area and Severity Index. PGA=Physician's Global Assessment. *Coprimary endpoint. †Observed cases. ‡In patients with DLQI ≥5 at baseline. The statistical tests compared the 97.5% lower confidence bound of the difference to -15% for non-inferiority comparison, or to 0 for superiority comparison. The 97.5% lower confidence bounds for tofacitinib 5 mg twice daily compared with etanercept were: -26.8% for PASI75 response and -26.6% for PGA response; and those for tofacitinib 5 mg twice daily compared with placebo were 27.1% for PASI75 response and 23.5% for PGA response. The 97.5% lower confidence bounds for tofacitinib 10 mg twice daily compared with etanercept were -2.6% for PASI75 response and -5.2% for PGA response; and those for tofacitinib 10 mg twice daily compared with placebo were 51.3% for PASI75 response and 44.8% for PGA response.

Table 2: Clinical responses at week 12

active treatment groups (table 3). The most common adverse events were infections (most frequently involving the nasopharyngeal and upper respiratory tracts; appendix pp 5–6). Injection-site reactions occurred more frequently in patients who received etanercept, whereas adverse events of increases in cholesterol and creatine phosphokinase were more common in patients who received tofacitinib (appendix pp 5–6).

No deaths occurred during the 12 weeks of treatment. One case of gastric cancer occurred in the tofacitinib 10 mg twice daily group, which was diagnosed after study completion. Non-melanoma skin cancer (basal cell

carcinoma in all cases) was diagnosed in four patients during the 12-week treatment period (one in the tofacitinib 5 mg group, one in the tofacitinib 10 mg group, and two in the etanercept group). Major adverse cardiac events (defined as any myocardial infarction, cerebrovascular accident [stroke or transient ischaemic attack], or cardiovascular death) were reported in one patient receiving tofacitinib 5 mg twice daily (myocardial infarction) and in one patient receiving etanercept 50 mg twice weekly (cerebrovascular accident).

Serious infections (treated infections that needed parenteral antimicrobial therapy, admission to hospital for treatment, or infections that met other criteria

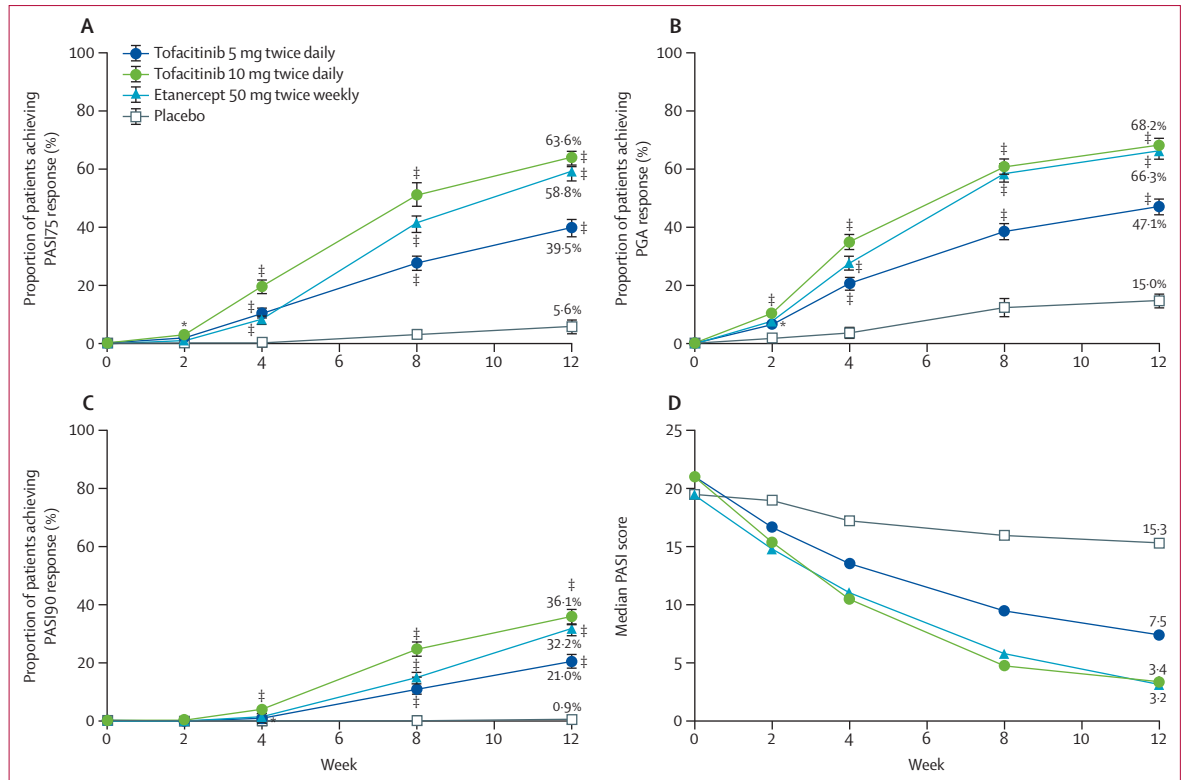


Figure 3: Patient outcomes
 Proportion of patients achieving (A) a PASI75 response (full analysis set, with non-responder imputation), (B) a PGA response (full analysis set, with non-responder imputation), and (C) a PASI90 response (full analysis set, with non-responder imputation) to week 12; and (D) median PASI score to week 12 (full analysis set, observed cases). Error bars are standard errors. **p*<0.05 vs placebo. †*p*<0.001 vs placebo. ‡*p*<0.0001 vs placebo. PASI=Psoriasis Area and Severity Index. PGA=Physician's Global Assessment.

| | Tofacitinib 5 mg twice daily (n=329) | Tofacitinib 10 mg twice daily (n=330) | Etanercept 50 mg twice weekly (n=335) | Placebo (n=107) |
|---------------------------------|--------------------------------------|---------------------------------------|---------------------------------------|-----------------|
| Patients with any TEAE | 180 (55%) | 198 (60%) | 192 (57%) | 55 (51%) |
| Patients with serious TEAEs | 7 (2%) | 5 (2%) | 7 (2%) | 2 (2%) |
| Patients with severe TEAEs | 7 (2%) | 6 (2%) | 7 (2%) | 5 (5%) |
| Discontinuation because of TEAE | 3 (1%) | 10 (3%) | 11 (3%) | 4 (4%) |

TEAE=treatment-emergent adverse event.

Table 3: Incidence of treatment-emergent adverse events (safety population)

meaning that they had to be classified as a serious adverse event) developed in six patients (two in each group) receiving active treatment (tofacitinib 5 mg twice daily: perforated diverticulitis and extradural abscess; tofacitinib 10 mg twice daily: pneumonia and paronychia; etanercept 50 mg twice weekly: bronchitis and perineal abscess), all of whom recovered. Five cases of herpes zoster infection (all non-serious) occurred in the active treatment groups (one with tofacitinib 5 mg twice daily, two with tofacitinib 10 mg twice daily, and two with etanercept 50 mg twice daily). No serious infection or herpes zoster cases were reported with placebo. Appendix pp 7–9 summarises all the reported treatment-emergent infections.

For tofacitinib 5 mg and 10 mg twice daily, dose-dependent increases in HDL cholesterol (median percentage increase from baseline at week 12 of 10.3% [IQR 0.0–20.8], median absolute increase 5.0 mg/dL [IQR 0.0–9.7] for the 5 mg dose and 11.8% [3.3–22.8], 5.8 mg/dL [1.9–10.8] for the 10 mg dose) and LDL cholesterol (median percentage increase from baseline at week 12 of 5.8% [IQR –6.2 to 19.2], median absolute increase 5.9 mg/dL [IQR –6.2 to 20.9] and 8.9% [–5.9 to 21.7], 9.1 mg/dL [–7.0 to 23.0], respectively) became evident by week 4 and stabilised thereafter. The mean ratio of LDL cholesterol to HDL cholesterol decreased slightly from baseline at week 4 (–0.1 [SE 0.03] for both tofacitinib doses) and stabilised for the remainder of the study (–0.1 [0.03] for tofacitinib 5 mg and –0.1 [0.04] for tofacitinib 10 mg at week 12). A non-progressive, dose-related increase in creatine phosphokinase was recorded in tofacitinib recipients (appendix pp 5–6). No cases of rhabdomyolysis were reported.

Mean changes from baseline in lymphocyte count ($\times 10^3/\text{mm}^3$) at week 12 were 0.1 (SE 0.03) in the tofacitinib 5 mg group, 0.1 (0.03) in the tofacitinib 10 mg group, 0.3 (0.03) in the etanercept group, and 0.1 (0.04) in the placebo group. Two patients (one receiving tofacitinib 5 mg twice daily who had a baseline

lymphocyte count of 550 cells per μL , and one receiving tofacitinib 10 mg twice daily who had a baseline lymphocyte count of 920 cells per μL) had confirmed nadir lymphocyte counts lower than 500 cells per μL (460 cells per μL and 490 cells per μL , respectively) during treatment; neither of these patients developed a serious infection. Mean changes from baseline in haemoglobin at week 12 were -0.1 g/dL (SE 0.04) in the tofacitinib 5 mg group, -0.4 (0.05) in the tofacitinib 10 mg group, 0.2 (0.05) in the etanercept group, and 0.1 (0.07) in the placebo group. Confirmed haemoglobin values lower than 10 g/dL were recorded in two patients during the study (one each in the two tofacitinib treatment groups); baseline values in these patients were 12.7 g/dL in the patient in the tofacitinib 5 mg group and 13.1 g/dL in the patient in the tofacitinib 10 mg group, and their respective nadirs were 9.7 g/dL and 8.4 g/dL. Blood pressure, ECG parameters, weight, and physical examination findings were generally similar across all four treatment groups at baseline and week 12 (data not shown).

Discussion

Tofacitinib 10 mg twice daily was non-inferior to etanercept 50 mg twice weekly in the treatment of plaque psoriasis as measured by PASI75 and PGA responses. Although a substantial number of patients who received tofacitinib 5 mg twice daily achieved PASI75, PGA, and DLQI responses, this dose did not meet the statistical criterion for non-inferiority to etanercept. Although the superiority of tofacitinib 5 mg twice daily to placebo could not be claimed because of the failed non-inferiority test in the predefined statistical testing procedure that controlled for type I error, improved PASI75 and PGA response rates were recorded with tofacitinib 5 mg twice daily versus placebo, which is consistent with results from a phase 2b study.²⁰ Improvements versus placebo in PASI50 and PASI90 response were also noted with tofacitinib 5 mg and 10 mg twice daily in the present study.

Reductions in itch severity occurred with both tofacitinib doses, with similar itch severity reported at week 12 with tofacitinib 5 mg twice daily and etanercept 50 mg twice weekly. Rapid and significant reductions in patient-reported itch severity with tofacitinib 5 and 10 mg twice daily have been reported in a phase 2b study, with significant improvements as early as 2 or 3 days after treatment initiation.²⁴ Improvements in itch severity with tofacitinib exceeded the estimated clinically important difference of 1.64 in the phase 2b study.²³ An additional article focusing on itch severity in this study is currently in progress.

These data provide confirmation of findings from previous studies suggesting that signalling through the JAK pathway is an important component of psoriasis pathogenesis, and support the clinical benefit of targeted inhibition of JAK family members (panel).¹⁹ The JAK–STAT pathway has a key role in activating

signals induced by several inflammatory cytokines involved in psoriatic inflammation, such as interleukin 2, interleukin 12, interleukin 20, interleukin 22, interleukin 23, interferon α/β , and interferon γ .²⁵ The degree of clinical response was consistent with previous phase 2b results of tofacitinib in patients with moderate-to-severe psoriasis.²⁰ This trial is the first phase 3 study to describe the non-inferior efficacy of an oral agent (with 210 [64%] of 330 patients who received tofacitinib 10 mg twice daily achieving a PASI75 response at week 12) versus a parenteral biological agent (with 197 [59%] of 335 of those who received etanercept achieving the same response) in plaque psoriasis. Many patients cite injection-related issues as factors that contribute to the burden of biological treatment regimens;¹³ oral drugs could overcome these issues, although the effect of associated laboratory monitoring procedures on patient satisfaction remains to be established.

The onset of effects of tofacitinib 10 mg twice daily on PASI75 and PGA responses were clearly evident by week 4 and seemed to occur more quickly than for etanercept 50 mg twice weekly. Rapid treatment response is generally associated with increased patient compliance.^{26,27} Tofacitinib also led to improvements in patients' quality of life.

Etanercept is a well-established biological agent with a favourable safety profile in patients with moderate-to-severe plaque psoriasis.²⁸ In our present study, rates of events associated with immunomodulation, such as infection, were similar for tofacitinib and etanercept. Frequencies and types of other adverse events were also generally similar across treatment groups and were consistent with previous studies.²⁰ Additionally, as an oral agent, tofacitinib offers the benefit of an administration route that bypasses the risk of injection site-related adverse events associated with biological therapies such as etanercept.

Tofacitinib has previously been associated with raised cholesterol levels in patients with rheumatoid arthritis,^{29–32} and our study similarly reported increases in both LDL and HDL cholesterol. However, the potential effect of tofacitinib on cardiovascular events (if any) in patients with psoriasis, who themselves are already at increased risk for cardiovascular disease, remains unknown.³³ Mean increases in creatine phosphokinase were modest and were not associated with rhabdomyolysis in the present study. In view of the role of JAK signalling in lymphopoiesis and haemopoiesis, we monitored changes in lymphocyte counts and haemoglobin concentration. Changes in these parameters were modest; few patients had abnormal levels and they tended to have low baseline values.

Since this study was designed to assess non-inferiority of tofacitinib to etanercept, the quite short treatment duration (12 weeks) meant that the conclusions that could be made regarding safety were limited to the duration of the trial; further assessment of the longer

Panel: Research in context**Systematic review**

Psoriasis vulgaris is a chronic inflammatory disease that leads to major changes in patient quality of life in its moderate-to-severe forms. Psoriasis-associated skin and systemic inflammation results from the interaction of genetic and environmental factors, leading to exacerbated immune responses involving several cytokines and signalling pathways in immune cells. Small molecules targeting the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) intracellular signalling pathway have shown potent inhibitory effects. These effects can inhibit the signalling arising from the activity of several inflammatory cytokines involved in psoriasis pathogenesis, thereby establishing the rationale for the development of specific JAK inhibitors for the treatment of psoriasis. The small molecule tofacitinib is one of these oral inhibitors that preferentially inhibits JAK1 and JAK3. We searched PubMed and Medline, with no date or language restrictions, for published articles using the terms “tofacitinib” and “psoriasis”, and selected only those publications from registered studies in human beings. Our search identified three publications, all of which were trials undertaken by Pfizer, that reported the results of one phase 1 and two phase 2 (a and b) randomised, placebo-controlled studies in patients with moderate-to-severe plaque psoriasis. These studies provided a rationale for us to undertake a large-scale, phase 3 clinical trial to compare the efficacy and safety of tofacitinib 5 mg and 10 mg twice daily versus placebo and etanercept, one of the most widely used biologicals, in patients with moderate-to-severe psoriasis.

Interpretation

In our study, the efficacy of oral tofacitinib 10 mg twice daily was superior to placebo and non-inferior to etanercept 50 mg twice weekly. Rates of adverse events were similar between the etanercept and tofacitinib groups, without any new safety signals. This study is the first to show non-inferiority of an oral treatment to a biological drug for the treatment of moderate-to-severe psoriasis, and establishes the relevance of targeted inhibition of the intracellular JAK-STAT pathway in this disorder. Furthermore, the oral route of administration of tofacitinib is a potentially appealing attribute in terms of patients' acceptance, since many patients with psoriasis report dissatisfaction with available phototherapy and parenteral treatments because of logistical and injection-related issues;^{33,14} this factor needs further investigation in long-term prospective studies.

term efficacy and safety of tofacitinib in patients with psoriasis is underway. The statistical testing procedure used to assess the non-inferiority of tofacitinib versus etanercept also limited our ability to draw conclusions about the superiority of tofacitinib 5 mg twice daily compared with placebo.

In conclusion, this study is the first phase 3 trial of an oral agent (tofacitinib 10 mg twice daily) to show similar efficacy and safety to a biological agent (etanercept) for the treatment of moderate-to-severe plaque psoriasis. Additionally, the 5 mg twice daily dose of tofacitinib provided benefit to a substantial number of patients. Long-term studies of tofacitinib in plaque psoriasis are ongoing to confirm the efficacy and safety profile beyond the 12-week period assessed in this trial. If further results confirm these findings, in the future tofacitinib could provide a convenient and well-tolerated therapeutic option for patients with moderate-to-severe plaque psoriasis.

Contributors

HB was involved in data collection, data analysis, data interpretation, literature search and writing of the report. PCMvdK participated in data collection, data analysis, data interpretation, and writing of the report. RS was involved in patient recruitment, collection of data, interpretation of data, writing of the report, and in the decision to submit for publication. AK was involved in data collection, analysis, and interpretation. FV was involved in the literature search, data collection, and data interpretation. J-HL contributed to the study design, data interpretation, and the writing of the report. VY participated in data collection. SC was involved in data collection, data interpretation, and finalisation of the report. JPa was accountable for the execution, monitoring, delivery, and reporting of the study, and for the safety review in the role of physician-clinician. JPr contributed to study amendments, study medical monitoring, data collection, data analysis, data interpretation, and editing of the report. PG was involved in the study design, data collection, data analysis, data interpretation, and organisation of the report. HT contributed to study design, data analysis, data interpretation, manuscript concept, and reviewing and editing of the report. MT participated in the data collection, data analysis, data interpretation, and writing of the report. HV participated in collection and interpretation of the data. He also participated in drafting the report, had major suggestions for its content, and approved the final version. RW participated in the study design, data interpretation, report review, and report approval. All authors reviewed and approved the final version.

Declaration of interests

HB has provided consultancy services for AbbVie, Amgen, Boehringer, Celgene, Janssen, Leo Pharma, Lilly, Novartis, MSD, Pfizer, and Sandoz. He has also acted as an adviser for AbbVie, Amgen, Boehringer, Celgene, Janssen, Leo Pharma, Lilly, Novartis, Pfizer, and Sandoz; has served on speaker's bureaus for AbbVie, Amgen, Celgene, Janssen, Leo Pharma, Lilly, Novartis, and Pfizer; and has received a research grant from Pfizer. PCMvdK has provided consultancy services for Celgene, Centocor, Almirall, Amgen, Pfizer, Philips, Abbott, Ely Lilly, Galderma, Novartis, JanssenCilag, Leo Pharma, Sandoz, and Mitsubishi. He has also done clinical trials for Basilea, Pfizer, Ely Lilly, Amgen, AbbVie, Philips Lighting, JanssenCilag, and Leo Pharma. RS has served on speaker's bureaus for Pfizer, Schülke and Mayr, Lohmann & Rauscher, Meda Pharmaceuticals, Menarini Pharmaceuticals, Stockhausen, and Smith & Nephew; has had consulting agreements with Pfizer, Novartis, Lohmann & Rauscher, Urgo, Chemomedica, Schülke & Mayr, and Pantec Biotechnologies; and has received research and educational grants from Stockhausen, 3M-Woundcare, Smith & Nephew, Lohmann & Rauscher, Enjo Commercials, Urgo, Chemomedica, and Schülke & Mayr. FV has been a principal investigator, member of a scientific advisory board, or speaker for AbbVie, Janssen, Eli Lilly, Merck, Novartis, and Pfizer. SC has been a consultant and/or speaker for Pfizer, AbbVie, Novartis, Merck, and Janssen-Cilag. JPa, JPr, PG, HT, MT, HV, and RW are employees of Pfizer Inc. AK, J-HL, and VY declare no competing interests.

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