Treatment of palmoplantar psoriasis with infliximab: a randomized, double-blind placebo-controlled study

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Abstract

Background Palmpoplantar psoriasis is a difficult to treat variant of plaque psoriasis.
Objective To study the safety and efficacy of infliximab in non-pustular palmoplantar psoriasis.
Methods Patients with non-pustular palmoplantar psoriasis affecting at least 10% of their palms and soles and with a modified palmoplantar psoriasis area and severity index (m-PPPASI) of at least eight were recruited. Patients were randomized (1:1) to receive infliximab 5 mg/kg or placebo at weeks 0, 2 and 6. Patients initially randomized to placebo received infliximab at weeks 14, 16 and 20 whereas patients randomized to infliximab received additional infliximab infusions every 8 weeks until week 22.
Results Twenty four (24) patients were randomized in this study. At week 14, 33.3% and 66.7% of patients treated with infliximab achieved m-PPPASI 75 and m-PPPASI 50 respectively compared to 8.3% for both m-PPPASI 75 (P = 0.317) and m-PPPASI 50 (P = 0.009) for patients randomized to placebo. A reduction of 50.3% in the mean surface area of palms and soles affected with psoriasis was seen at week 14 in patients randomized to infliximab as compared to an increase of 14.9% in patients randomized to placebo (P = 0.009).
Conclusions This pilot study did not reach its primary endpoint of m-PPPASI 75 at week 14. However, infliximab was observed to be more efficacious than placebo in improving PPSA and with respect to the percentage of patients reaching m-PPPASI 50 at week 14. Larger and longer term studies are needed for severe patients to better assess the efficacy of infliximab in palmoplantar psoriasis.

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Conflicts of interest
Dr Bissonnette has been a speaker, consultant, investigator and/or advisory board member for Abbott Laboratories, Amgen-Wyeth, Astellas Pharma, Centocor, Janssen Ortho, Novartis and Schering-Plough. He has received compensation in the form of grants and/or honoraria from these companies. No conflicts of interest exist.

Dr Poulin has been a speaker, consultant, investigator and/or advisory board member for Abbott Laboratories, Amgen-Wyeth, Astellas Pharma, Centocor, Ortho Biotech, EMD Serono and Schering-Plough. He has received compensation in the form of grants and/or honoraria from these companies. No conflicts of interest exist.

Dr Guenther has been a speaker, consultant, investigator and advisory board member for Abbott Laboratories, Amgen-Wyeth, Astellas Pharma, Centocor, Janssen Ortho, Novartis and Schering Plough and Schering-Plough Canada. She has received compensation in the form of grants and/or honoraria from these companies. No conflicts of interest exist.

Dr Lynde has been a speaker, consultant, investigator and/or advisory board member for Abbott Laboratories, Amgen-Wyeth, Astellas Pharma, Centocor, Janssen Ortho and Schering-Plough. He has received compensation in the form of grants and/or honoraria from these companies. No conflicts of interest exist.

Dr Bolduc has been a speaker, consultant, investigator or advisory board member for, Abbott Laboratories, Amgen-Wyeth, Biogen, Celgene, Centocor, Galderma, Genentech, Leo Pharma, Medimmune, Novartis and Schering-Plough Canada. She has received compensation in the form of honoraria from these companies. No conflicts of interest exist.

Dr Nigen has been a speaker, consultant, investigator and/or advisory board member for Abbott Laboratories, Amgen-Wyeth, Astellas Pharma, Centocor, Janssen Ortho, Novartis and Schering-Plough Canada. He has received compensation in the form of honoraria from these companies. No conflicts of interest exist.
Introduction

Moderate to severe palmoplantar psoriasis refers to a debilitating form of plaque psoriasis affecting the palms and the soles. Topical treatment results are often disappointing, probably because of poor penetration through the thick stratum corneum. Few controlled studies have been published on the use of systemic treatments for non-pustular variants of palmoplantar psoriasis.

Infliximab is an intravenous chimeric anti-TNF-alpha (tumour necrosis factor) monoclonal antibody approved for the treatment of moderate to severe plaque psoriasis. Following 10 weeks of infliximab, 75.5% to 80% of patients have been reported to achieve PASI 75, making this biologic one of the most effective systemic treatments for plaque psoriasis. However, the clinical response of palmoplantar plaque psoriasis to infliximab treatment has never been studied. Given the very high efficacy of infliximab in plaque psoriasis, the objective of this study was to determine if infliximab would also be similarly safe and efficacious in plaque palmoplantar psoriasis.

Methods

Patient population

This was a double blind, placebo controlled, multicentre study conducted at four centres in Canada. Patients 18 years of age or older with non-pustular palmoplantar psoriasis were recruited. The study was approved by an ethics committee and written informed consent from each participant was obtained before any study procedures were performed. Patients were randomized (1:1) to receive either courses of intravenous infliximab at 5 mg/kg at weeks 0, 2, 6, 14 and 22 or 3 infusions of placebo at weeks 0, 2 and 6 followed by intra-venous infliximab at 5 mg/kg at weeks 14, 16 and 20 and placebo again at week 22. Patients who were randomized to receive infliximab received placebo at week 16 and week 20 to preserve the blind. Infliximab (Remicade) was obtained from Schering-Plough Canada, Inc. (Montreal, QC, Canada).

A computer generated randomization list was generated using a spreadsheet (Excel, Microsoft) that randomly assigned a zero or one to a patient (infliximab or placebo). The spreadsheet calculation was refreshed until the treatments were evenly distributed. Sealed envelopes with treatment assignment were provided to each centre. Centres opened each envelope on day 0 in numerical order of the patient treated and the unblinded pharmacist prepared normal saline with infliximab or provided normal saline alone (placebo). Investigators, patients, and site personnel who were involved with patients including personnel who administered infliximab were kept blinded throughout the study.

To be eligible, patients were required to have a modified palmoplantar psoriasis area and severity index (m-PPASI) of at least eight with at least 10% of the total surface of their palms and soles affected by psoriasis at baseline with evidence of plaque psoriasis elsewhere on their bodies. The m-PPASI evaluates erythema, infiltration and desquamation as well as the area affected with psoriasis on each palm and each sole. For calculation of the affected area, each palm represents 20% of the calculation and each sole 30%. To be eligible, patients also had to have failed to respond to 4 weeks of treatment with potent or superpotent topical corticosteroids or systemic therapies.

Patients had to either have a negative Protein Purified Derivate (PPD) or have initiated Tuberculosis (TB) prophylaxis before the first infusion of infliximab. Female patients had to have a negative pregnancy test at screening. The main exclusion criteria included pregnancy, opportunistic, serious, chronic or recurrent infections including hepatitis B or C, malignancies, chest X-rays positive for or suspicious of TB, a history of lymphoproliferative disease or elevated aspartate or alanine aminotransferase levels more than twice the upper limit of normal. Washout periods from day 0 were 2 weeks for topical treatments or UVB phototherapy, 4 weeks for non-biological systemic treatments for psoriasis and PUVA therapy and 90 days for biological therapy for the treatment of psoriasis. Patients were not prevented from using non-medicated emollients.

Efficacy and safety evaluations

The primary endpoint was the percentage of patients treated with infliximab compared with placebo reaching a 75% improvement in the m-PPASI (m-PPASI 75) at week 14.

Secondary endpoints included the physician’s global assessment for palmoplantar psoriasis (PGA), palmoplantar psoriasis surface area (PPSA) and DLQI at week 14 for patients who received infliximab or placebo. PPSA is the percentage of the palms and soles covered with psoriasis. The improvement over time in m-PPASI, PPSA, PGA and DLQI from day 0 to week 26 was also evaluated to study the efficacy of infliximab administered for 22 weeks.

Safety was evaluated at each visit through assessment of recorded vital signs, routine chemistry and haematology tests and by adverse event (AE) reporting. Autoantibodies (ANA and Anti-DNA) were not evaluated in this trial.
**Statistical analysis**

A sample size of 24 had a power of 0.83 to detect a difference of 55% (in absolute percentage points) between the null hypothesis and the alternate hypothesis (efficacy as defined by the percentage of patients reaching m-PPPASI 75) assuming a 20% m-PPPASI 75 rate in placebo patients and a significance level of 0.05.

Fisher’s exact test was used to determine the statistical significance of the primary endpoint, while an ANOVA was performed to determine statistical significance between groups, treatments and over time for PPSA, PGA and DLQI. A Student’s t-test was used to compare PPSA, PGA and DLQI between patients randomized to placebo and infliximab at a given time point.

Analysis was performed on the intent-to-treat population in which all patients receiving at least one dose of infliximab or placebo were included in the efficacy and safety analyses. Missing values were imputed as non-responders for calculation of percentage of patients reaching m-PPPASI 75 and those having a reduction in m-PPPASI of 50% or more (m-PPPASI 50), whereas last observation carried forward was used for missing values in calculating mean PGA, DLQI and PPSA.

**Results**

**Demographics and patient disposition**

A total of 24 patients were recruited between February 2007 and July 2008. Patient disposition is provided in Fig. 1, whereas demographics are shown in Table 1. Some patients had severe disease with as much as 85% of their palms and soles covered with psoriasis, whereas others had milder disease with 13% of their palms and soles involved with psoriasis. There was no statistical difference in disease severity between the two groups at baseline measured with m-PPPASI (P = 0.601), DLQI (P = 0.370), PPSA (P = 0.710) and PGA (P = 0.207). The overall analysis at baseline between the two groups also showed no significant difference.

| Table 1 Baseline demographic and clinical characteristics of infliximab and placebo groups. PPSA – percentage of area involved (palms and soles) covered with psoriasis. PGA – physician’s global assessment of induration, erythema and scaling on a scale from 0 – clear to 5 – very severe |
|---------------------------------|----------------|
| **Infliximab group (n = 12)**   | **Placebo group (n = 12)** |
| Male n (%)                       |                  |
| 5 (42.7)                         | 4 (33.3)         |
| Age (mean ± SD)                  |                  |
| 57.8 ± 12.4                      | 49.9 ± 14.7      |
| Caucasian, n (%)                 |                  |
| 12 (100)                         | 12 (100)         |
| m-PPPASI (mean % ± SD)           |                  |
| 24.1 ± 11.4                      | 26.7 ± 12.4      |
| PPSA (mean ± SD)                 |                  |
| 37.1 ± 21.0                      | 40.4 ± 21.6      |
| DLQI (mean ± SD)                 |                  |
| 9.8 ± 4.4                        | 11.9 ± 6.9       |
| PASI (mean ± SD)                 |                  |
| 6.5 ± 3.0                        | 7.1 ± 3.3        |
| PGA for palmoplantar psoriasis, n (%) |              |
| 3 Moderate                       |                  |
| 7 (58)                           | 3 (25)           |
| 4 Severe                         |                  |
| 4 (33)                           | 8 (66)           |
| 5 Very severe                    |                  |
| 1 (8)                            | 1 (8)            |

**Figure 1** Flow diagram of the trial.
Fourteen of 24 patients had at least 10% of the surface area of their soles and 17 of 24 patients had at least 10% of the surface of their palms covered with psoriasis. At baseline, 2 (8.3%) patients suffered only from palmar psoriasis, 2 (8.3%) patients suffered from plantar psoriasis only and 20 (83.3%) patients suffered from both.

**m-PPPASI score**

There was a decrease in m-PPPASI over time reaching a minimum at week 20 (Fig. 2) ($P < 0.001$). At week 14, 33.3% (4 of 12) of patients randomized to infliximab reached m-PPPASI 75 compared to 8.3% (1 of 12) on placebo ($P = 0.317$). A total of 66.7% (8 of 12) of patients randomized to infliximab reached m-PPPASI 50 at week 14 compared to 8.3% (1 of 12) on placebo ($P = 0.009$).

Of the patients who were initially randomized to infliximab, 58.3% (95% CI 28.5–83.5) and 75.0% (95% CI 42.8–93.3) reached m-PPPASI 75 and m-PPPASI 50 respectively at week 26, while 33.3 (95% CI 11.2–64.5) and 58.3 (95% CI 28.5–83.5) of patients who were initially randomized to placebo and crossed over to infliximab reached m-PPPASI 75 and m-PPPASI 50 respectively at week 26. Moreover, at week 26, 29.1% (95% CI 13.4–51.2) reached m-PPPASI 90 and 16.6% (95% CI 5.4–38.1) reached m-PPPASI 100 for patients in both groups.

Figures 3–4 show photographs of the soles and palms at day 0, week 14 and week 26 of patients randomized to infliximab and placebo.
Palmoplantar psoriasis surface area

Palmoplantar psoriasis surface area, the surface area of the palms and soles affected by psoriasis, decreased over time to reach a minimum at week 20 (Fig. 5) \( (P = 0.002) \). At week 14, there was a significant difference between infliximab and placebo in mean PPSA over time \( (P = 0.034) \). The mean PPSA at week 14 was significantly lower than that at day 0 for patients randomized to infliximab \( (P = 0.002) \) but not for patients randomized to placebo \( (P = 0.750) \).

There was a decrease of 65.9% at week 26 in mean PPSA in patients who were initially randomized to infliximab \( (P = 0.003) \).

Physician’s global assessment

Physician’s global assessment decreased over time to reach a minimum at week 20 (Fig. 6) \( (P < 0.001) \). The difference between placebo and infliximab was not statistically significant \( (P = 0.348) \) at week 14. At week 14, 25% of patients had a PGA of 0 or 1.
Table 2  Summary of adverse events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Day 0 to week 14</th>
<th>Week 14 to week 22</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infliximab (3.27 PYs)</td>
<td>Placebo (2.71 PYs)</td>
</tr>
<tr>
<td></td>
<td>Events</td>
<td>Events/ PY*</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>Total AE</td>
<td>32</td>
<td>9.77</td>
</tr>
<tr>
<td>Infectious AE†</td>
<td>5</td>
<td>1.53</td>
</tr>
<tr>
<td>Serious AE†</td>
<td>1</td>
<td>0.31</td>
</tr>
<tr>
<td>Serious infectious AE</td>
<td>1</td>
<td>0.31</td>
</tr>
<tr>
<td>AE leading to withdrawal</td>
<td>1</td>
<td>0.31</td>
</tr>
</tbody>
</table>

*PY, patient-year.
†The total number of serious AE includes the number of serious infectious AE. The total number of infectious AE also includes the number of serious infectious AE.

pared to 8.3% for placebo. At week 26, 50% of patients had a PGA of 0 or 1 compared to 25% for patients randomized to placebo and then crossed over to infliximab.

Dermatology life quality index
The mean DLQI was 9.75 at day 0, 4.50 at week 14 and 3.67 at week 26 for patients randomized to infliximab (Fig. 7). The mean DLQI for patients randomized to placebo and then crossed over to infliximab at week 14 was 11.92 at day 0, 9.25 at week 14 and 6.58 at week 26. The difference between placebo and infliximab was not statistically significant (P = 0.248) at week 14.

Safety analysis
Adverse event(s) are presented in Table 2 as events per patient-year (PY). No cases of exacerbation of palmoplantar psoriasis and no cases of pustular palmoplantar psoriasis were reported during this study. Three serious AEs were reported: one case of cellulitis on the right cheek that occurred at week 21, one case of fractured sternum due to a car accident and one case of hepatitis at week 14. This latter patient (non-drinker) initially presented with fatigue, nausea and a decrease in appetite and ultimately developed jaundice. AST and ALT levels were normal at baseline and increased to a maximum of 1377 U/L and 2242 U/L respectively. Serologies were negative for hepatitis A, B and C. At the time of the AE, the patient was taking Lipitor, ASA, hydrochlorothiazide, glucosamine with chondroitin and vitamins. The patient was discontinued from the study and eventually had a full recovery. According to the principal investigator, the sternum fracture was not related to infliximab, whereas the cellulitis and hepatitis were possibly and probably related respectively.

Discussion
The current study demonstrated evidence of improvement in palmoplantar plaque psoriasis among patients randomized to infliximab as shown by the statistically significant decrease in PPSA and the percentage of patients achieving m-PPPASI 50 at week 14, although the primary endpoint, defined as a difference between infliximab and placebo in the percentage of patients reaching m-PPPASI 75 at week 14, was not met. This is probably due to the small sample size: The study was powered to detect a difference of 55% points between placebo and infliximab and only a 25% point effect size was observed. Sample size calculation performed before this study was initiated assumed a 75% m-PPPASI 75 rate at week 14 in patients randomized to infliximab. However, the maximum percentage of patients reaching m-PPPASI 75 in the current study was 66.7% at week 20. In view of the fact that palmoplantar psoriasis is notoriously difficult to treat, it might have been better to use a lower expected m-PPPASI 75 rate to calculate sample size. This would have resulted in a study with a larger sample size.

Another possible explanation for not reaching the primary endpoint is the inclusion of patients with milder PPP, as responses to treatment in patients with milder disease may be more difficult to detect. There is no universally accepted definition of what is mild, moderate and severe PPP. All patients included in this study had a PGA of moderate or higher. However, patients were eligible for this study if they had a body surface area of at least 10% of palms and soles covered with psoriasis. Some physicians may consider that these patients had mild instead of moderate psoriasis. This might have influenced the results of this study.

The impact of palmoplantar psoriasis on QoL can be dramatic when the disease prevents walking or working. However, the current trial did not show a statistically significant difference in DLQI between patients randomized to placebo and infliximab. DLQI is probably not the ideal tool to measure QoL in patients with palmoplantar psoriasis as many questions are more related to factors associated with extensive lesions or lesions elsewhere on the body. This may be the reason the mean DLQI was relatively low at baseline which could have made it more difficult to detect differences between groups. At the time this study was initiated, there was no QoL tool designed specifically for assessment of patients with
palmoplantar psoriasis. However, Farley et al. recently published a QoL questionnaire specific for hand and foot psoriasis. This type of questionnaire should be used, possibly in association with the DLQI, in future studies performed on palmoplantar psoriasis.

In general, infliximab was well tolerated by patients with palmoplantar psoriasis. There was one serious AE of hepatitis that was evaluated by the investigator as probably related to infliximab. Idiosyncratic cases of severe hepatitis have been rarely reported in patients treated with infliximab.\textsuperscript{5–7} In addition, infliximab phase III trials in plaque psoriasis demonstrated a higher incidence rate of hepatic enzyme elevation compared with placebo (4% vs. 0%), an observation not similarly observed in infliximab trials for rheumatoid arthritis, Crohn’s disease and psoriatic arthritis.\textsuperscript{1,2} Patients with severe forms of psoriasis may be at greater risk of developing sub-clinical liver disease, including steatohepatitis. The prevalence of baseline liver abnormalities in palmoplantar plaque psoriasis patients is unknown. This patient had a very rapid rise in liver enzymes suggesting that measuring transaminases every 3 months or even every month may not have been enough to detect early hepatitis in this case. A heightened index of suspicion is warranted in patients treated with infliximab for palmoplantar plaque psoriasis, and other severe or recalcitrant forms of psoriasis, who develop symptoms such as nausea, vomiting, fatigue, jaundice or darker urine.

A number of cases and series of exacerbation or new onset of pustular palmoplantar psoriasis have been reported in patients treated with anti-TNF-alpha for various indications including psoriasis.\textsuperscript{8–10} In addition, a small placebo controlled study using etanercept for the treatment of pustular palmoplantar psoriasis and palmoplantar pustulosis showed no difference between the placebo and the active treatment group suggesting that anti-TNF-alpha may not be the treatment of choice in patients with pustular palmoplantar psoriasis.\textsuperscript{11} In the current study, no cases of exacerbation of palmoplantar psoriasis and no development of pustular palmoplantar psoriasis were seen suggesting that some patients with non-pustular palmoplantar psoriasis can be treated with anti-TNF-alpha agents without experiencing pustular exacerbations. These findings need to be confirmed by larger trials.

In conclusion, although this pilot study did not reach its primary endpoint of m-PPPASI 75 at week 14, infliximab was observed to be more efficacious than placebo in improving, PPSSA and with respect to the percentage of patients reaching m-PPPASI 50 at week 14. The small sample size and the inclusion of patients with lower m-PPPASI may explain why there was no statistically significant difference in the primary endpoint. Larger and longer term studies are needed for severe patients to better assess the efficacy of infliximab in palmoplantar psoriasis.

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References