# Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review

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**ABSTRACT**

**Objective.** *To review the evidence on the clinical effectiveness of etanercept and infliximab for the treatment of active and progressive psoriatic arthritis (PsA) in patients with an inadequate response to standard treatment (including DMARD therapy).*

**Methods.** *A systematic review was conducted. The literature search covered a range of 13 medical databases and submissions were provided by the manufacturers of etanercept and infliximab. Randomised controlled trials (RCTs) of etanercept or infliximab that reported outcomes of disease activity in PsA were reviewed.*

**Results.** *There were two good quality double-blind, placebo-controlled RCTs each for etanercept and infliximab. The results demonstrated that after initial treatment (12 weeks for etanercept and 14 or 16 weeks for infliximab) both drugs had statistically significant beneficial effects compared with placebo on ACR 20, 50 and 70, PsARC and HAQ scores. Efficacy was not dependent upon concomitant methotrexate. Results at 24 weeks indicated that the response to treatment is maintained. Effects on psoriasis were beneficial, particularly with infliximab. Uncontrolled radiographic assessment data at one year indicated a beneficial effect of both etanercept and infliximab on the progression of joint disease.*

**Conclusion.** *Our review indicates that both etanercept and infliximab are efficacious in the treatment of PsA with beneficial effects on both joint and psoriasis symptoms and on functional status. There are limited data indicating that etanercept and infliximab can delay joint disease progression. Further long-term data are required to confirm and consolidate the evidence base for both drugs.*

## Introduction

Psoriatic arthritis (PsA) is an inflammatory arthritis that is distinct from rheumatoid arthritis (RA) and closely associated with psoriasis (1-3). It is diagnosed when a patient with psoriasis has a distinctive pattern of peripheral and/or spinal arthropathy (4). Most, but not all, of these patients will test negative for rheumatoid factor (RhF). The majority of patients will have developed psoriasis before any joint disease, however, joint involvement appears before or concurrently with psoriasis in 35% of cases (4). There are still some residual difficulties in defining PsA consistently across studies (2, 3).

The health burden of PsA can be considerable (1, 4). PsA is a life-long condition but its severity and hence its impact fluctuates over time (5). In addition to an adverse impact on quality of life, PsA, particularly the more severe polyarticular disease, carries about a 60% higher risk of mortality relative to the general population (6, 7). Ideally PsA should be diagnosed early and treated aggressively in order to minimise joint damage (8). Most treatments for PsA have been borrowed from those used for RA; non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying anti-rheumatic drugs (DMARDs) are widely used (4). Thus, disease that is unresponsive to NSAIDs and particularly polyarticular disease, has normally been treated with DMARDs in order to reduce joint damage and prevent disability (9). Tumour necrosis factor (TNF) is one of several pro-inflammatory cytokines that have been implicated in the pathogenesis of both psoriasis and PsA (10, 11) and etanercept and infliximab are among a number of new biological agents that target TNF. Unlike the older DMARDs etanercept and infliximab have gained

European Agency for the Evaluation of Medicinal Products approval for clinical use in the treatment of PsA; specifically for the treatment of disease that is unresponsive to DMARDs. They were granted their product licences in the United Kingdom (UK) 2003 and 2004 respectively.

In the UK the National Institute for Health and Clinical Excellence (NICE), which is an independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health, issues guidance on the use of new technologies within the National Health Service. In 2004 NICE commissioned the Centre for Reviews and Dissemination (CRD), as an independent academic centre, to review the evidence on the clinical effectiveness of etanercept and infliximab for the treatment of active and progressive PsA in patients with an inadequate response to standard treatment (including DMARD therapy).

## Methods

We conducted a systematic review of the available evidence. A literature search was conducted which covered a range of 13 medical databases including MEDLINE, EMBASE, the National Research Register, the Cochrane Central Register of Controlled Trials and a number of Internet resources. All databases were searched from inception to July 2004 and the bibliographies of all included studies were reviewed. The full list of sources and the search strategy is available from the authors. In addition, submissions were provided by the manufacturers of etanercept and infliximab, which provided additional data on published or soon to be published trials.

Studies eligible for inclusion in the review were randomised controlled trials (RCTs) of etanercept or infliximab in the treatment of adult patients with PsA. Only trials using placebo or an active control and which reported outcomes of disease activity were eligible. Two reviewers independently selected the studies for the review and any discrepancies were resolved by consensus, consulting a third reviewer when necessary. No language restrictions were applied to study selection.

Data were extracted into predesigned forms. All relevant data were extracted by one reviewer and independently checked for accuracy by a second reviewer. The trials were assessed for quality using a checklist compiled from criteria specified in CRD Report No. 4 (12) and the quality of each study was summarised as a quality rating: Excellent, Good, Satisfactory, or Poor (See Table I). Two reviewers performed this quality assessment independently and the quality rating was agreed on by consensus.

Relative risks (RRs) and mean differences were calculated for the primary outcomes with 95% confidence intervals (CIs); the primary outcome variables were those derived from the American College of Rheumatology (ACR) (ACR 20, ACR 50, ACR 70), the Psoriatic Arthritis Response Criteria (PsARC), Psoriasis Area and Severity Index (PASI) based measures, those of function and quality of life (Health Assessment Questionnaire (HAQ)) and those of radiological assessment of disease progression. The presence of dactylitis in the hands and feet and the presence/absence of enthesopathy were recorded when reported. PsARC was developed for a trial of sulphasalazine in psoriatic arthritis (13). PsARC has not been validated but responses assessed by it do parallel those identified with ACR 20. Although PsARC was developed for assessment of psoriatic arthritis, it does not incorporate an assessment of psoriasis. PASI assesses psoriasis by combing an extent and a severity score for each of four body areas (head, trunk, upper extremities and lower extremities). The clinical diversity of the trials in terms of, for example, adult status, disease severity, and concomitant medication was considered. Where the trials were not clinically diverse (not heterogeneous) the data were pooled. Pooled RRs (95% CI) or weighted mean differences (WMD) (95% CI) were calculated using a fixed effect model. A fixed effect model was considered most appropriate because of the small number of trials included in the meta-analysis, and the resultant smaller estimation of between-study variance (14). Statistical heterogeneity was investigated using the Q statistic (Chi-Squared test); where it was statistically significant, pooled results are not reported.

A total of four trials investigating the

**Table I.** Quality assessment tool.

| | |
|---|---|
| 1 | Were the eligibility criteria for the study adequately specified? |
| 2 | Was an a priori power calculation for adequate sample size performed? |
| 3 | Was the sample size adequate for the analysis of the primary outcome variable? |
| 4 | Was the number of participants who were randomised stated? |
| 5 | Was the method used to assign participants to treatment groups truly random? |
| 6 | Was the trial described as double-blind? |
| 7 | Was allocation of treatment concealed? |
| 8 | Were the individuals administering the treatment blinded to the treatment allocation? |
| 9 | Were the outcome assessors blinded to the treatment allocation? |
| 10 | Were the participants blinded to the treatment allocation? |
| 11 | Was the blinding procedure successful? |
| 12 | Were adequate details of the treatment groups at baseline presented? |
| 13 | Were the treatment groups comparable at baseline? |
| 14 | Were the treatment groups similar in terms of co-interventions that could influence the results? |
| 15 | Was participant compliance with the assigned treatment adequate? |
| 16 | Were all participants who were randomised accounted for at the end of the trial? |
| 17 | Was a valid ITT analysis performed? |
| 18 | Were at least 80% of those randomised included in the follow-up assessment? |

*Quality rating*

| | |
|---|---|
| Excellent: | The answer is 'Yes' to all of the criteria. |
| Good: | The answer is 'Yes' to all of the following criteria: 1, 3, 4, 6, 10, 12-14, 16-18. |
| Satisfactory: | The answer is 'Yes' to all of the following criteria: 1, 3, 6, 13, 17. |
| Poor: | The answer is NOT 'Yes' to one or more of the criteria listed for 'Satisfactory'. |

**Table II.** Inclusion criteria and baseline data for the RCTs or etanercept and infliximab in PsA.

| Inclusion criteria for number of swollen joints/tender joints | Mease 2000 ≥ 3 / ≥ 3 | | Mease 2004 ≥ 3 / ≥ 3 | | IMPACT ≥ 5 / ≥ 5 | | IMPACT2 ≥ 5 / ≥ 5 | |
|---|---|---|---|---|---|---|---|---|
| Inclusion criteria for previous treatment | An inadequate response to NSAIDs | | An inadequate response to NSAIDs | | An inadequate response to NSAIDs and at least one DMARD | | An inadequate response to NSAIDs | |
| | Etanercept (n = 30) | Placebo (n = 30) | Etanercept (n = 101) | Placebo (n = 104) | Infliximab (n = 52) | Placebo (n = 52) | Infliximab (n = 100) | Placebo (n = 100) |
| Age in years | Median 46.0 | Median 43.5 | 47.6 | 47.3 | 45.7 | 45.2 | 47.1 | 46.5 |
| Male (%) | 53 | 60 | 57 | 45 | 58 | 58 | 71 | 51 |
| Duration of PsA (years) | 9.0 | 9.5 | 9.0 | 9.2 | 11.7 (9.8) | 11 (6.6) | 8.4 (7.2) | 7.5 (7.8) |
| Duration of psoriasis (years) | 19.0 | 17.5 | 18.3 | 19.7 | 16.9 (10.9) | 19.4 (11.6) | - | - |
| Number of prior DMARDS | 1.5 | 2.0 | 1.6 | 1.7 | ≥ 1 | ≥ 1 | - | - |
| Patients on concomitant methotrexate (%) | 47% | 47% | 45% | 49% | 46% | 65% | 47% | 45% |
| Tender Joint Count | Median 22.5 | Median 19.0 | 20.4 | 22.1 | 23.7 (13.7) | 20.4 (12.1) | 24.6 (14.1) | 25.1 (13.3) |
| Swollen Joint Count | Median 14.0 | Median 14.7 | 15.9 | 15.3 | 14.6 (7.5) | 14.7 (8.2) | 13.9 (7.9) | 14.4 (8.9) |
| HAQ (0 to 3) | Median 1.3 | Median 1.2 | 1.1 | 1.1 | 1.2 (0.7) | 1.2 (0.7) | 1.1 (0.6) | 1.1 (0.6) |

Values are mean (standard deviation) unless otherwise stated.

efficacy of the interventions of interest were identified by the search strategies (15-18). At the time the searches were conducted two trials were available only as conference abstracts or confidential company reports but have since been published in full (17, 18). A total of 265 patients were included in the etanercept trials (two trials) and 304 included in the infliximab trials (two trials).

## Results

The baseline characteristics of the populations in the four trials that met the inclusion criteria for the review are summarised in Table II. All patients had been diagnosed with PsA for at least 6 months, with a negative rheumatoid factor and active disease including five or more swollen and five or more tender joints. The proportion of patients with spine involvement, arthritis mutilans and erosions at baseline was not reported for three of the four trials so the severity of disease across the populations was unclear. Although the inclusion criteria in terms of disease activity were higher in the infliximab trials, the average baseline characteristics indicate that the four trial populations were similar and are likely to be representative of a population with PsA requiring DMARD or biologic therapy.

All trials reported data on the following outcome measures: PsARC, ARC 20, ACR 50 and ACR 70, HAQ and PASI. With the exception of the Mease 2000 trial (15), which took PsARC, the primary outcome variable in the trials was ACR 20.

*Efficacy of etanercept*

Both RCTs of etanercept for the treatment of PsA were double-blind and placebo-controlled and both were rated as Good on the quality rating. In both trials etanercept was administered by subcutaneous (SC) injection twice weekly at a dose of 25 mg. The double-blind placebo controlled phase lasted 12 weeks in the smaller trial (Mease 2000) and for at least 24 weeks in the larger trial (Mease 2004). In both trials the controlled phase was followed by an open-label follow-up, during which all patients received etanercept.

The outcome data and pooled results , where calculated, are summarised in Table III. Twelve week data for ACR 20, 50 and 70 and PsARC responses were available from the two trials (15, 16) and individual trial results favoured etanercept over placebo and all pooled results were statistically significant. There was no statistical heterogeneity in the pooling for any outcome. Across the two trials at 12 weeks almost 85% of patients treated with etanercept achieved a PsARC response and around 65% of patients treated with etanercept achieved an ACR 20 response, demonstrating a basic degree of efficacy in terms of arthritis-related symptoms. Around 45% of patients treated with etanercept achieved ACR 50 and around 12% achieved ACR 70 responses respectively, demonstrating a good level of efficacy. Subgroup analyses conducted on the Mease 2004 (16) data revealed that the effect of etanercept was not dependent upon patients' concomitant use, or not, of methotrexate. The data for percentage improvement in HAQ score also demonstrated significant treatment benefit.

Controlled data at 24 weeks were available from only one trial (Mease 2004). At 24 weeks the treatment effect for all joint disease outcome measures and functional status assessed by the change in HAQ score was statistically significantly greater with etanercept than with placebo. The size of treatment effect did not appear greater at 24 weeks than at 12 weeks. Subgroup analyses conducted on the Mease 2004 (16) data revealed that the effect of etanercept was not dependent upon patients' concomitant use of methotrexate.

The published data for the effect of etanercept on psoriasis were limited: the Mease 2000 trial provided results for PASI 75 and PASI 50 at week 12, based on 38 evaluable patients, and week 24 results for PASI 50, 75 and 90 were available from the Mease 2004 trial (n = 128) (Table III). All treatment differences favoured etanercept although not all reached statistical significance, probably because of the small numbers of patients with psoriasis

**Table III.** Etanercept efficacy data – outcomes at 12 weeks and 24 weeks.

| Trial | Duration | Outcomes | Etanercept | Placebo | RR or mean difference (95% CI) | Pooled RR (95% CI), p (Chi-square test) for heterogeneity |
|---|---|---|---|---|---|---|
| | | *PsARC* | | | | |
| Mease 2000 | 12 weeks | | 26/30 (87%) | 7/30 (23%) | 3.71 (1.91, 7.21) | |
| Mease 2004 | 12 weeks | | 73/101 (72%) | 32/104 (31%) | 2.35 (1.72, 3.21) | |
| | | | | | | 2.60 (1.96, 3.45), p = 0.22 |
| Mease 2004 | 24 weeks | | 71/101 (70%) | 24/104 (23%) | 3.05 (2.10, 4.42) | |
| | | *ACR20* | | | | |
| Mease 2000 | 12 weeks | | 22/30 (73.0%) | 4/30 (13%) | 5.50 (2.15, 14.04) | |
| Mease 2004 | 12 weeks | | 60/101 (59%) | 16/104 (15%) | 3.86 (2.39, 6.23) | |
| | | | | | | 4.19 (2.74, 6.42), p = 0.51 |
| Mease 2004 | 24 weeks | | 50/101 (50%) | 14/104 (13%) | 3.68 (2.17, 6.22) | |
| | | *ACR50* | | | | |
| Mease 2000 | 12 weeks | | 15/30 (50.0%) | 1/30 (3%) | 15.00 (2.11, 106.49) | |
| Mease 2004 | 12 weeks | | 38/101 (38%) | 4/104 (4%) | 9.78 (3.62, 26.41) | |
| | | | | | | 10.84 (4.47, 26.28), p = 0.70 |
| Mease 2004 | 24 weeks | | 37/101 (37%) | 4/104 (4%) | 9.52 (3.52, 25.75) | |
| | | *ACR70* | | | | |
| Mease 2000 | 12 weeks | | 4/30 (13%) | 0/30 (0%) | 9.00 (0.51, 160.17) | |
| Mease 2004 | 12 weeks | | 11/101 (11%) | 0/104 (0%) | 23.68 (1.41, 396,53) | |
| | | | | | | 16.28 (2.20, 120.54), p = 0.63 |
| Mease 2004 | 24 weeks | | 9/101 (9%) | 1/104 (1%) | 9.27 (1.20, 71.83) | |
| | | *HAQ% improvement from baseline (mean (SD))*[*] | | | | |
| Mease 2000 | 12 weeks | | 64.2 | 9.9 | 54.3 % p < 0.001 | |
| Mease 2004 | 12 weeks | | 53.5 | 6.3 | 47.20% p < 0.001 | |
| | | | | | | 48.99 (38.53, 59.44), p = 0.56 |
| Mease 2004 | 24 weeks | | 54% | 6% | 48% p = 0.0001 | |
| | | *PASI 75* | | | | |
| Mease 2000 | 12 weeks | | 5/19 (26%) | 0/30 (0%) | 11.00 (0.65, 186.02) | |
| Mease 2004 | 24 weeks | | 15/66 (23%) | 2/62 (3%) | 7.05 (1.68, 29.56) | |
| | | *PASI 50* | | | | |
| Mease 2000 | 12 weeks | | 8/19 (42%) | 4/19 (21%) | 2.00 (0.72, 5.53) | |
| Mease 2004 | 24 weeks | | 31/66 (47%) | 11/62 (18%); | 2.65 (1.46, 4.80) | |
| | | *PASI 90* | | | | |
| Mease 2004 | 24 weeks | | 4/66 (6%) | 2/62 (3%) | 1.88 (0.36, 9.90) | |
| | | *TSS Mean (SD) annualised rate of progression* | | | | |
| Mease 2004 | 24 weeks | | -0.03 (0.73) | 0.53 (1.39) | -0.56 (-0.86, -0.26) | |

[*]Some data not shown for reasons of commercial confidentiality.

of a sufficient extent to be assessed.

Radiographic assessment data were available from the Mease 2004 trial; at 24 weeks the mean total Sharp score (TSS) annualised rate of progression was statistically significantly lower in etanercept treated patients compared with placebo patients (Table III) and at one year the mean annualised rate of progression TSS for all etanercept patients was -0.03 indicating that on average no clinically significant progression of joint erosion had occurred.

*Efficacy of infliximab*

Both infliximab trials (known as the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT) and IMPACT2 trials) were double-blind and placebo-controlled in adult patients with active PsA and were rated as Good by the quality assessment. Infliximab (5 mg/kg) or placebo was infused at weeks 0, 2, 6 and 14 in both trials. Further infusions of infliximab were administered to all patients at eight-week intervals; in an open label fashion in the IMPACT trial with further follow-up at week 50 and under controlled, blinded conditions in the IMPACT2 trial with follow-up at week 24. In the IMPACT2 trial patients with an inadequate response (less than 10% improvement) at week 16 were offered an early escape but the trial blinding was maintained.

The primary outcome variable in both trials was the percentage achieving an ACR 20 response. Data were available at 14 weeks from IMPACT2 and 16 weeks from IMPACT and week 24 from IMPACT2 (Table IV). At 14 to 16 weeks approximately 76% of patients treated with infliximab achieved PsARC and approximately 62% achieved ACR 20 responses, demonstrating a clear degree of efficacy in terms of arthritis-related symptoms.

This level of efficacy was not dependent upon patients' concomitant use, or not, of methotrexate. In both trials over a third of patients treated with infliximab achieved an ACR 50 response and 15 to 29% achieved an ACR 70 response demonstrating a considerable degree of efficacy. The treatment differences at week 24 reflected the findings at week 14. All treatment differences, from individual trials and from pooled analyses for scores on PsARC, ACR 20, 50 and 70, and mean improvement in HAQ were statistically significantly in favour of infliximab. Uncontrolled follow-up data at week 50 from the IMPACT trial indicates that the ACR 20, 50 and 70 and the PsARC responses to infliximab are maintained (18).

The effect of infliximab on psoriasis was markedly beneficial. After 14/16 weeks of treatment almost all patients who were evaluable for psoriasis (n = 105) achieved a PASI 50 at week 14/16 compared with 0 to 10% with placebo (n = 104). Similarly, 68% in IMPACT

**Table IV.** Infliximab efficacy data – outcomes at 14 – 16 weeks and 24 weeks.

| Trial | Duration | Outcome | Infliximab | Placebo | RR or mean difference (95% CI) | Pooled RR (95% CI), p (Chi-square test) for heterogeneity |
|---|---|---|---|---|---|---|
| | | *PsARC* | | | | |
| IMPACT | 16 weeks | | 39/52 (75%) | 11/52 (21%) | 3.55 (2.05, 6.13) | |
| IMPACT2 | 14 weeks | | 77/100 (77%) | 27/100 (27%) | 2.85 (2.03, 4.01) | |
| | | | | | | 3.05 (2.29, 4.08), p = 0.51 |
| IMPACT2 | 24 weeks | | 70/100 (70%) | 32/100 (32%) | 2.19 (1.60, 2.99) | |
| | | *ACR20* | | | | |
| IMPACT | 16 weeks | | 34/52 (65%) | 5/52 (10%) | 6.80 (2.89, 16.01) | |
| IMPACT2 | 14 weeks | | 58/100 (58%) | 11/100 (11%) | 5.27 (2.95, 9.44) | |
| | | | | | | 5.75 (3.55, 9.30), p = 0.63 |
| IMPACT2 | 24 weeks | | 54/100 (54%) | 16/100 (16%) | 3.38 (2.08, 5.48) | |
| | | *ACR50* | | | | |
| IMPACT | 16weeks | | 24/52 (46%) | 0/52 (0%) | 49.00 (3.06, 785.06) | |
| IMPACT2 | 14 weeks | | 36/100 (36%) | 3/100 (3%) | 12.00 (3.82, 37.70) | |
| | | | | | | 17.29 (6.02, 49.65), p = 0.33 |
| IMPACT2 | 24 weeks | | 41/100 (41%) | 4/100 (4%) | 10.25 (3.81, 27.55) | |
| | | *ACR70* | | | | |
| IMPACT | 16 weeks | | 15/52 (29%) | 0/52 (0%) | 31.00 (1.90, 504.86) | |
| IMPACT2 | 14 weeks | | 15/100 (15%) | 1/100 (1%) | 15.00 (2.02, 111.41) | |
| | | | | | | 20.33 (4.01, 103.15), p = 0.67 |
| IMPACT2 | 24 weeks | | 27/100 | 2/100 | 13.50 ( 3.30, 55.26) | |
| | | *HAQ mean (SD) % improvement from baseline* | | | | |
| IMPACT | 16 weeks | | 49.80 (8.2) | -1.6 (8.3) | 51.40 (48.08, 54.72) | |
| IMPACT2 | 14 weeks | | 48.6 (43.3) | -18.4 (90.5) | 67.00 (47.34, 86.66) | |
| | | | | | | 51.83 (48.56, 55.10), P = 0.13 |
| IMPACT2 | 24 weeks | | 46.0 (42.5) | -19.4 (102.8) | 65.40 (43.60, 87.20) | |
| | | *PASI 50* | | | | |
| IMPACT | 16 weeks | | 22/22 (100%) | 0/17 (0%) | 35.22 (2.29, 542.00) | |
| IMPACT2 | 14 weeks | | 82/83 (99%) | 9/87 (10%) | 9.55 (5.14, 17.74) | |
| | | | | | | 11.09 (6.00, 20.49), p = 0.34 |
| IMPACT2 | 24 weeks | | 75/83 (90%) | 8/87 (9%) | 9.83 (5.06, 19.09) | |
| | | *PASI 75* | | | | |
| IMPACT | | | 15/22 (68%) | 0/17 (0%) | 24.26 (1.55, 378.66) | |
| IMPACT2 | | | 64/83 (77%) | 2/87 (2%) | 33.54 (8.48, 132.65) | |
| | | | | | | 31.47 (9.23, 107.36), p = 0.84 |
| IMPACT2 | 24 weeks | | 60/83 (72%) | 1/87 (1%) | 62.89 (8.92, 443.47 ) | |
| | | *PASI 90* | | | | |
| IMPACT | | | 8/22 (36%) | 0/17 (0%) | 13.30 (0.82, 215.46) | |
| IMPACT2 | | | 41/83 (49%) | 0/87 (0%) | 86.95 (5.44, 1390.95) | |
| | | | | | | 47.58 (7.02, 322.49), p = 0.32 |
| IMPACT2 | 24 weeks | | 39/83 (47%) | 0/87 (0%) | 82.76 (5.17, 1325.04) | |
| | | *Presence of enthesopathy (in feet)* | | | | |
| IMPACT2 | 24 weeks | | 20/100 (20%) | 37/100 (37%) | 0.54 (CI 0.34, 0.86) | |
| | | *Presence of at least one dactylitis digit* | | | | |
| IMPACT2 | 24 weeks | | 12/100 (12%) | 34/100 (34%) | 0.35 ( 0.19, 0.64) | |

and 77% in IMPACT2 achieved a PASI 75 compared with 0 to 2% in the placebo group. The pooled relative risks in favour of infliximab over placebo were large and all were statistically significant, although the confidence intervals were wide due to the small amount of data. Data from the IMPACT2 study indicate that this level of efficacy was maintained at 24 weeks.

Data on the presence of enthesopathy and dactylitis were reported at 24 weeks and showed significant improvements in both these outcomes. Radiographic assessment data at one year from the IMPACT trial have been reported (19). Using modification of the van der Heijde-Sharp scoring method that included bilateral 2nd through 5th DIP joints, the annual rate of progression after one year of infliximab treatment was -1.58 compared to a rate of 7.7 at baseline, with 84% of patients having no disease progression at one year. These data are from an uncontrolled follow-up phase of the trial and it is unclear what proportion of trial patients were included in this assessment.

**Discussion**

The literature searches conducted for this review were comprehensive and we were able to include all RCTs available to date. Other efficacy data were not included in the review because RCTs represent the best design of clinical study by which to evaluate the efficacy of an intervention. This is particularly true for trials in PsA, for which there is a large and appreciable placebo response, rendering the results of uncontrolled studies unreliable (20).

A potential limitation of our review could stem from the difficulties in assessing the activity of PsA and its response to therapy. There are a number of outcome measures that are used, none of which has been clearly identified as optimal for PsA (21). This point is illustrated by the range of endpoints included in the trials of etanercept and infliximab and by the fact that even these trials, conducted on similar drugs at approximately the same time, have not used all the same outcome measures. In our clinical evaluation, we have made use of the main outcome measures as reported in all the included clinical trials - namely PsARC, ACR 20, 50 and 70, HAQ and PASI. These measures all have their limitations (21, 22) and while the primary outcomes chosen did vary between studies, we were still able to identify comparable data from a number of trials that allowed some comparison of the magnitude of benefits seen across trials. In addition, we have reported more objective measures of joint disease such as radiological assessments; unfortunately these data are currently very sparse in published PsA trials. We have also included data on enthesopathy and dactylitis where available; again, refinement of these outcomes are in development for use in PsA trials (22).

Our review demonstrates that there is only a limited amount of RCT-based efficacy data for both etanercept and infliximab. However, all four trials were of good quality and they do provide a clear indication of an initial response to treatment (at 12 weeks with etanercept and at 14 to 16 weeks with infliximab) with a good level of efficacy in terms of beneficial effects on arthritis and psoriasis and functional status assessed by the HAQ score, and with continued efficacy at 24 weeks for both drugs.

The level of efficacy demonstrated for both etanercept and infliximab in the first three months of treatment (approximately) is similar and both drugs demonstrated efficacy against psoriasis. The relative risks in favour of infliximab over placebo being particularly impressive suggesting that the anti-psoriatic efficacy of infliximab may be better than that of etanercept. However, not all patients included in the trials were evaluable for psoriasis and definitive conclusions cannot be drawn from such a limited pool of data. This finding does, however, reflect those of a recent systematic review of treatments for psoriasis (23).

All trials of etanercept and infliximab in PsA included a significant proportion of patients who took concomitant methotrexate. Analysis of these subgroups found no indication of a lack of effect of either drug when administered without methotrexate or, conversely, of any synergistic effect when combined with methotrexate. Although methotrexate is used in clinical practice for the treatment of PsA this is supported by an extremely limited trials evidence base (24, 25). The infliximab licence in RA (though not PsA) requires the concomitant use of methotrexate in order to limit the development of antibodies to infliximab and associated tachyphylaxis. As the discrepancy between the licences for the two indication suggests, there is uncertainty regarding this issue. The effects of methotrexate need proper investigation to establish if it does indeed have a role in terms of efficacy or safety when combined with anti-TNF drugs.

Despite their demonstrable efficacy in short-term treatment it is important to remember that PsA is a chronic disease and evidence of long-term benefit is required for both drugs. Long-term controlled trials of both etanercept and infliximab are required to confirm that symptomatic benefits for joint and skin disease and improvements in function and the beneficial effects on joint disease progression are maintained; such trials in RA are usually 1 to 2 years in duration. A long term trial would ideally compare the efficacy of these anti-TNF drugs with each other and with the best other available treatment, for example methotrexate. Such a trial should gather comparative data on HAQ and radiographic progression and safety. With regards to safety, in addition to a long term controlled trial, a long-term observational registry for patients with PsA seems in our view justified.

Although the evidence base for neither etanercept nor infliximab can be said to be strong, compared to other treatments used in PsA the evidence supporting their use is convincing in terms of the quality of data and size of treatment effect. Recent reviews of traditional DMARD therapy for PsA e.g. methotrexate, sulphasalazine, ciclosporin etc, have demonstrated that existing therapies are used without a firm and extensive evidence base (20). Recently a randomised trial of leflunomide in PsA did demonstrate a sig-

nificant effect on both joints and skin (26). Nevertheless, it remains clear that the evidence regarding the anti-TNF agents as a class of drug is better than that for alternative agents in this condition.

A number of new and promising agents for the treatment of PsA are emerging. The use of adalumimab has also recently been reported in PsA in a single trial. While this agent did not fall within our remit, this agent showed similar magnitude of responses with regard to joint and skin outcomes (27).

## Conclusions

The data available indicate that both etanercept and infliximab are efficacious in the treatment of PsA with beneficial effects on both joint and psoriasis symptoms and on functional status. There are some limited data indicating that etanercept and infliximab can both delay joint disease progression. Further long-term data are required to confirm and consolidate the evidence base for both drugs.

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