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Etanercept and Infliximab for the Treatment of Psoriatic Arthritis: A systematic review

Nerys Woolacott[1], Christian Asseburg[2], Anita Kainth[1], Zarnie Khadjesari[1], Kate Misso[1], Kate Light[1], Ian Bruce[3], Rob Riemsma[1]

[1] Centre for Reviews and Dissemination, University of York, York. [2] Centre for Health Economics, University of York, York. [3] ARC Epidemiology Unit, University of Manchester, Manchester

Psoriatic arthritis is defined as an inflammatory arthropathy associated with psoriasis which is usually negative for rheumatoid factor (RhF) (an antibody produced by plasma cells and found in around 70% of cases of RA). It is a hyperproliferative and inflammatory arthritis that is distinct from rheumatoid arthritis (RA) and closely associated with psoriasis. Overall, because psoriatic arthritis involves both skin and joints it can result in significant quality of life impairment and joint deformity and psychosocial disability. Due to the lack of a precise definition and diagnostic marker for psoriatic arthritis, it is difficult to gauge its prevalence. The UK adjusted prevalence of psoriatic arthritis in the primary care setting has been estimated to be 0.3%.

In the United Kingdom both etanercept (Enbrel®) and infliximab (Remicade®) are recently licensed drugs for the treatment of adults with active and progressive psoriatic arthritis in patients who have responded inadequately to disease modifying anti-rheumatic drugs (DMARDs). Both etanercept and infliximab are new biologic agents, which target pathologic T cell activity (anti-TNF drugs).

Other therapies available for the treatment of psoriatic arthritis are DMARDs such as sulphasalazine, methotrexate and ciclosporin, all of which have limitations to their use due to limited efficacy or serious long-term adverse effects. In addition, there is a new DMARD, leflunomide, which is the only drug other than etanercept and infliximab which is licenced for the treatment of psoriatic arthritis.

Methods

A systematic review evaluated the clinical efficacy and adverse effects of etanercept and infliximab. The efficacy of DMARDs in the treatment of psoriatic arthritis was also reviewed and, where data allowed, treatments were compared in an evidence synthesis utilising a Bayesian mixed treatment comparison analysis.

Number and quality of studies

Our review of the clinical evidence identified a total of 17 studies: three trials of the efficacy of the interventions of interest (two for etanercept and one for infliximab) and 14 trials of the efficacy of the DMARDs.

	Mease 2000[1]		Mease 2004[2]		Antoni 2004[3]	
	Etanercept (n=30)	Placebo (n=30)	Etanercept (n=101)	Placebo (n=104)	Infliximab (n=52)	Placebo (n=52)
Age in years	Median 46.0	Median 43.5	Mean 47.6	Mean 47.3	Mean 45.7	Mean 45.2
Male (%)	53	60	57	45	58	58
Duration of psoriatic arthritis (mean years)	9.0	9.5	9.0	9.2	11.7 (SD 9.8)	11.0 (SD 6.6)
Duration of psoriasis (mean years)	19.0	17.5	18.3	19.7	16.9 (SD 10.9)	19.4 (SD 11.6)
Number of prior DMARDS (mean)	1.5	2.0	1.6	1.7	-	-
Proportion of patients with numbers of previous DMARDs	-	-	27% = 0 40% = 1 20% = 2	21%=0, 50% =1 19% =2	All patients ≥ 1	All patients ≥ 1
Concomitant methotrexate	47%	47%	45%	49%	46%	65%
Tender Joint Count	Median 22.5	Median 19.0	Mean 20.4	Mean 22.1	Mean 23.7 (SD 13.7)	Mean 20.4 (SD 12.1)
Swollen Joint Count	Median14.0	Median14.7	Mean 15.9	Mean 15.3	Mean 14.6 (SD 7.5)	Mean 14.7 (SD 8.2)
HAQ (0 to 3)	Median1.3	Median 1.2	Mean 1.1	Mean 1.1	Mean 1.2 (SD 0.7)	Mean 1.2 (SD 0.7)

Efficacy of etanercept and infliximab

The trials of the efficacy of etanercept and infliximab were all double-blind and placebo controlled trials and were rated 'Good' by the quality assessment. A total of 265 patients were included in the etanercept trials and 104 included in the infliximab trial.

Across the two available trials, at 12 weeks, around 65% of patients treated with etanercept achieved an ACR 20. Similarly, at 16 weeks, 65% of patients treated with infliximab achieved an ACR 20. Thus both drugs demonstrated a basic degree of efficacy in terms of arthritis-related symptoms. In addition, around 45% of patients treated with etanercept and those treated with infliximab achieved an ACR 50 and around 12% treated with etanercept and 29% treated with infliximab achieved an ACR 70, demonstrating a good level of efficacy. In addition, almost 85% of patients treated with etanercept and 75% of patients treated with infliximab achieved a PsARC which is the only compound disease outcome measure that has been specifically defined for psoriatic arthritis. The PASI results indicate some beneficial effect of etanercept on psoriasis at 12 weeks and a good effect of infliximab on psoriasis; however, the data are sparse. The statistically significant reduction (improvement) in HAQ score with etanercept and with infliximab compared to placebo indicates a beneficial effect of both drugs on function. All the results are limited by the very small number of patients studied.

For etanercept similar results were seen at 24 weeks, except that the results for PASI 75 now achieved statistical significance. Uncontrolled follow-up of patients indicates that treatment benefit of both etanercept and infliximab may be maintained for at least 50 weeks.

Radiographic data for (TSS annualised rate of) disease progression at 12 months were available for etanercept: this was statistically significantly lower in etanercept treated patients than in placebo patients. There were no radiographic assessments of infliximab, so nothing can be determined about its potential or otherwise to delay the progression of joint disease.

Evidence synthesis

A Bayesian evidence synthesis completed the clinical evaluation. The evidence synthesis utilized mixed treatment comparison methodology and focused on response rates to therapy in terms of PsARC and changes in HAQ conditional on whether the patient responds to therapy. Only etanercept and infliximab could be included in the evidence synthesis due to a lack of appropriate data on DMARDs. The results of the evidence synthesis confirm that the response rate to infliximab is slightly higher than with etanercept (0.83 compared with 0.77) and that both are significantly higher than the response to placebo (0.25). The evidence synthesis shows that responders to either treatment experience a statistically significant improvement in HAQ scores, but do not differ substantially between the two active treatments.

DMARDs

The available drug treatments for psoriatic arthritis, with the exception of sulphasalazine and possibly leflunomide, have not been investigated thoroughly. The available limited data indicate some degree of efficacy for all DMARDs but the evidence for IM gold and azathroprine is particularly weak and may not be reliable.

Outcomes	Treatment	Control	RR or mean difference (95% CI) relative to placebo
PsARC	Etanercept* (n=131)	Placebo* (n=134)	*2.60 (1.96, 3.45) p<0.00001
	Infliximab (n=52)	Placebo (n=52)	3.55 (2.05, 6.13) p<0.01.
ACR20	Etanercept* (n=131)	Placebo* (n=134)	*4.19 (2.74, 6.42) p<0.00001
	Infliximab (n=52)	Placebo (n=52)	6.80 (2.89, 16.01) p<0.01.
ACR50	Etanercept* (n=131)	Placebo* (n=134)	*10.84 (4.47, 26.28) p<0.00001
	Infliximab (n=52)	Placebo (n=52)	49.00 (3.06, 785.06) (p<0.01
ACR70	Etanercept* (n=131)	Placebo* (n=134)	*16.28 (2.20, 120.54) p=0.006)
	Infliximab (n=52)	Placebo (n=52)	31.00 (1.90, 504.86)p<0.01
HAQ% reduction from baseline (mean (SD)	Etanercept* (n=131)	Placebo* (n=134)	*48.99 (38.53, 59.44) p<0.00001
	Infliximab (n=52)	Placebo (n=52)	51.4 (28.3, 74.5); p<0.01.
PASI 75	Etanercept* (n=85)	Placebo* (n=81)	*1.61 (0.52, 4.99) p=0.41
	Infliximab (n=22)	Placebo (n=17)	24.26 (1.55, 378.66) p=0.004

*Pooled values from two trials[1, 2]

Conclusions

- The limited data available indicate that both etanercept and infliximab are efficacious in the treatment of psoriatic arthritis with beneficial effects on both joints and psoriasis symptoms, and on functional status.
- Short-term data indicate that etanercept can delay joint disease progression. Further long-term data are required, to confirm and consolidate the evidence base for etanercept.
- There are no controlled data as yet to indicate that infliximab can delay joint disease progression.
- Further data are required to confirm the findings of the currently available trials and to demonstrate that response is maintained and that disease progression is delayed in the long-term.
- A 2-year controlled trial of etanercept versus best care (probably methotrexate or leflunomide) is warranted; such a trial should gather comparative data on HAQ and radiographic progression.
- Randomised controlled trials investigating the effects of the biologics in combination with methotrexate, with reference to any synergistic effect and the possibility of tachyphylaxis are warranted.

References

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For further details contact Dr Nerys Woolacott, Research Fellow, Centre for Reviews and Dissemination, University of York, York YO10 5DD. Email: nw11@york.ac.uk