



Etanercept and Efalizumab for the Treatment of Moderate to Severe Psoriasis: A systematic review

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Psoriasis is a common inflammatory skin disease, with estimates of its world prevalence ranging from 0.5 to 4.6%, and UK prevalence estimated at around 1.5%. Psoriasis is a chronic disorder that can be physically and emotionally debilitating and which can require life-long treatment.

In the United Kingdom both etanercept (Enbrel®) and efalizumab (Raptiva®) have recently been licensed for the treatment of adults with moderate to severe plaque psoriasis (the most common form of psoriasis). Both etanercept and efalizumab are new biologic agents, which target pathologic T cell activity.

Other therapies available for the treatment of moderate to severe psoriasis include phototherapy and systemic agents such as ciclosporin, methotrexate and retinoids; all of which have limitations to their use due to serious long-term adverse effects.

Aim of the review

To evaluate the clinical efficacy of etanercept and efalizumab in the treatment of moderate to severe psoriasis.

Methods

Extensive searches were carried out. RCTs investigating etanercept, efalizumab or more traditional therapies for moderate to severe psoriasis were included. Primary outcomes were derived from the Psoriasis Area and Severity Index (PASI). Where data allowed, all treatments were compared in an evidence synthesis utilising a mixed treatment comparison implemented as a Bayesian hierarchical model.

Number and quality of studies

We identified a total of eight RCTs of the efficacy of the interventions of interest (three of etanercept and five of efalizumab) and 24 RCTs of the efficacy of the other treatments for moderate to severe psoriasis.

The trials of the efficacy of the interventions were all double-blind and placebo controlled and generally of good quality, but three of the five efalizumab trials (unpublished) were poorly reported. All were of adults with clinically stable plaque psoriasis. Most patients had baseline BSA \geq 10% and PASI \geq 10 or 12.

Details of RCTs of Efficacy of Etanercept and Efalizumab

	Reference	Duration	Intervention	Comparison
Etanercept	Leonardi, 2004, USA	12 wks	Etanercept 25mg SC twice a wk (n=162) Etanercept 50mg SC twice a wk (n=164)	Placebo (n=166)
	Elewski, 2003, USA, Canada & Europe	12 wks	Etanercept 25mg SC twice a wk (n=196) Etanercept 50mg SC twice a wk (n=194)	Placebo (n=178)
	Gottlieb, 2003, USA	24 wks	Etanercept 25mg SC twice a wk (n=57)	Placebo (n=55)
Efalizumab	Lebwohl, 2003, USA	12 wks	Efalizumab 1mg/kg SC once a wk (n=232) Efalizumab 2mg/kg SC once a wk (n=243)	Placebo (n=122)
	Gordon, 2003, USA	12 wks	Efalizumab 1mg/kg SC once a wk (n=369)	Placebo (n=187)
	ACD2058g, 2004,	12 wks	Efalizumab 1mg/kg SC once a wk (n=162)	Placebo (n=170)
	ACD2600g, 2004,	12 wks	Efalizumab 1mg/kg SC once a wk (n=450)	Placebo (n=236)
	IMP24011, 2004,	12 wks	Efalizumab 1mg/kg SC once a wk (n=529)	Placebo (n=264)

Etanercept: proportion of patients achieving PASI 75

All treatment differences were statistically significantly in favour of etanercept over placebo. Similar results were found for the other outcome measures. On average, 12 weeks treatment

Reference	Etanercept	Placebo	RR (95% CI)
<i>12 week follow-up, Etanercept 25 mg twice a week</i>			
Leonardi 2004	55/162 (34.0%)	6/166 (3.6%)*	9.39 (4.30, 20.90)
Elewski 2003	67/196 (34.2%)	6/193 (3.1%)*	11.00 (5.04, 24.38)
Gottlieb 2003	17/57 (29.8%)	1/55 (1.8%)	16.40 (2.98, 95.36)
Pooled RR			10.69 (95% CI: 6.15, 18.57)
Test for heterogeneity			Q=0.281 (df=2), P=0.869
<i>12 week follow-up, Etanercept 50 mg twice a week</i>			
Leonardi 2004	81/164 (49.4%)	6/166 (3.6%)*	13.66 (6.35, 30.04)
Elewski 2003	96/194 (49.5%)	6/193 (3.1%)*	15.92 (7.38, 34.95)
Pooled RR			14.80 (95% CI: 8.40, 26.06)
Test for heterogeneity			Q=0.070 (df=1), P=0.791
<i>24 week follow-up, Etanercept 25 mg twice a week</i>			
Gottlieb 2003	32/57 (56.1%)	3/55 (5.5%)	10.29 (3.67, 30.57)

*Where a trial had more than one intervention arm, results from the placebo arm have been reported more than once

with etanercept 25 mg resulted in 62% of patients achieving a PASI 50, 33% achieving a PASI 75, 11% a PASI 90 and 40% were assessed as clear or almost clear. Improvement in quality of life as assessed by mean percentage change in DLQI was around 59% with etanercept 25 mg twice a week compared with 9% with placebo.

Efalizumab: proportion of patients achieving PASI 75

Across the five trials 12 weeks efalizumab treatment resulted in an average of 55% of patients achieving PASI 50, 27% achieving PASI 75, 25% achieving PASI 90 and 27% achieving clear or minimal psoriasis status. The mean change from baseline in DLQI score averaged across four trials was 45.5% for efalizumab-treated patients compared to 15.2% for placebo-treated patients.

Reference	Efalizumab	Placebo	RR (95% CI)
<i>12 week follow-up, Efalizumab 1 mg/kg once a week</i>			
Lebwohl, 2003 ² USA	52/232 (22.4%)	6/122 (4.9%)*	4.56 (2.02, 10.31)
Gordon, 2003 ³ USA	98/369 (26.6%)	8/187 (4.3%)*	6.21 (3.09, 12.49)
IMP24011, 2004 ²⁸	163/529 (31.0%)	11/264 (4%)	7.40 (4.09, 13.37)
Pooled RR			6.34 (95% CI: 4.27, 9.42)
Test for heterogeneity			Q=0.89 (df=2), P=0.64
<i>12 week follow-up, Efalizumab 2 mg/kg once a week</i>			
Lebwohl, 2003 ² USA	69/243 (28.4%)	6/122 (4.9%)*	5.77 (2.68, 12.78)

*Where a trial had more than one intervention arm, results from the placebo arm have been reported more than once

Other treatments for moderate to severe psoriasis

Only infliximab and ciclosporin have had their efficacy demonstrated in placebo-controlled RCTs. Whilst clinical experience has demonstrated excellent efficacy of PUVA and methotrexate, no placebo-controlled trials have been conducted. In clinical trials, methotrexate appears to be as effective as ciclosporin. The trials of other treatments, acitretin, Re-PUVA, and NBUVB, in comparison with PUVA, provide only limited evidence, demonstrating some degree of effectiveness but making it difficult to draw firm conclusions regarding relative efficacy.

Evidence synthesis

The available data permitted the inclusion of etanercept (25 mg and 50 mg), efalizumab, infliximab, ciclosporin, methotrexate, Fumaderm and placebo in this mixed-treatment comparison which was implemented as a Bayesian hierarchical model.

In terms of mean response rate, when response is taken as PASI 75, infliximab appears the most effective followed by methotrexate and ciclosporin, then etanercept 50 mg. These findings for the PASI 75 level of response are mirrored in the results for the PASI 50 and PASI 90.

	Probability of a Response			Relative Risks		
	Mean	2.5% CI	97.5% CI	Mean	2.5% CI	97.5% CI
Response =PASI 75						
Supportive Care	3%	2%	4%	1.00	1.00	1.00
Etanercept 50mg	50%	25%	74%	15.69	7.79	24.67
Etanercept 25mg	35%	17%	56%	10.98	5.34	18.24
Efalizumab	27%	14%	41%	8.35	4.45	13.35
Ciclosporin	55%	37%	75%	17.30	10.74	25.38
Fumaderm	27%	5%	63%	8.49	1.49	20.17
Infliximab	79%	55%	95%	24.89	15.97	33.62
Methotrexate	59%	23%	89%	18.56	7.04	30.00

Conclusions

Etanercept and efalizumab are both more efficacious than placebo in the treatment of moderate to severe psoriasis over a 12- week treatment period. Etanercept and efalizumab do not appear to be more efficacious than older therapies for moderate to severe psoriasis.

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