

Efalizumab

Concise evaluated information to support the managed entry of new medicines in the NHS

Summary

- Efalizumab (*Raptiva*) is a recombinant, humanised, monoclonal antibody that inhibits T-cell activity. It is licensed for the treatment of adults with moderate to severe plaque psoriasis who have failed to respond to, or have contraindications to, or who are intolerant to other systemic therapies. It is given by weekly subcutaneous injection.
- The efficacy and safety of efalizumab have been assessed in a number of randomised clinical trials, of which only two have been reported in full. These have shown that efalizumab produces a statistically superior response compared to placebo in patients with plaque psoriasis, as measured by both primary and secondary clinical endpoints.
- The most common adverse effects of efalizumab include mild to moderate flu-like symptoms. There is, at present, no clear evidence of a causal link between use of efalizumab and malignancy but vigilance is advised. Efalizumab may reduce host immunity to infections.
- There are no data comparing efalizumab with other systemic treatments for psoriasis, including other biological agents.

Introduction

Psoriasis is a chronic, inflammatory skin disorder affecting approximately 1.2 million people in the UK.¹ Plaque psoriasis (*psoriasis vulgaris*) accounts for about 80% of cases and is characterised by widely-distributed thickened, scaly patches. It causes significant morbidity as a result of psychological disability and impaired quality of life.¹

Although topical medications usually suffice, about 25% of patients with psoriasis will require systemic therapy, phototherapy, or both.² The most frequently used such treatments include ciclosporin, methotrexate, oral retinoids and psoralen plus ultraviolet light (PUVA), all of which have significant toxicity. The recognition of the role of T-cell interactions in the pathogenesis of psoriasis has led to the development of a number of 'biological' treatments, of which efalizumab, a humanised, monoclonal antibody, is an example. Efalizumab binds to the α -subunit of leucocyte-function-associated antigen-1 (LFA-1), blocking its interaction with intercellular-adhesion molecule-1 (ICAM-1) and thus inhibiting T-cell activity.³

Evidence

The safety and clinical efficacy of efalizumab have been assessed in five randomised, double-blind, placebo-controlled trials.³ In all five, treatment with efalizumab led to a statistically significant improvement, compared with placebo, in the primary response measure.³ Only two trials have been reported in full. Both recruited subjects at least 18 years of age, diagnosed with moderate to severe plaque psoriasis of at least 6 months duration. Further selection criteria included involvement of at least 10% of body surface and a minimum Psoriasis and Severity Index (PASI) score of 12.0 at screening. The primary response measure in both trials was the proportion of subjects (estimated

Brand Name, (Manufacturer): *Raptiva* (Serono Limited)

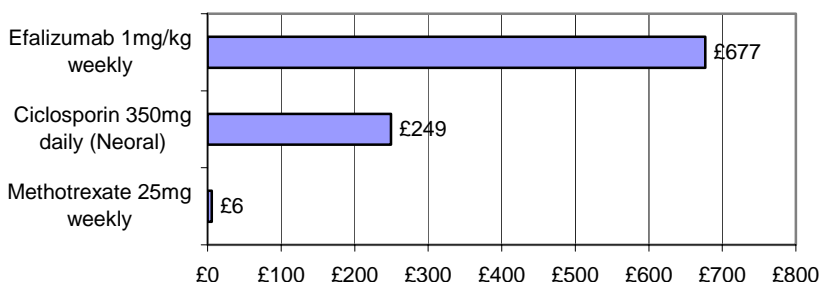
BNF Therapeutic Class: Drugs affecting the immune response (13.5.3 – subject to possible amendment)

Licensed Indications: Treatment of adults with moderate to severe psoriasis, who have failed to respond to, or who have contraindications to, or who are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA. A dermatologist should initiate treatment.

Dosage and Administration: An initial single dose of 0.7mg/kg body-weight followed by weekly subcutaneous injections of 1.0mg/kg body-weight (maximum single dose should not exceed a total of 200mg).

Marketed: October 2004.

Cost Comparisons: For 28 days treatment for a 70kg adult - the cost of efalizumab is based on use of a single-use vial (at £169.20) weekly. (Prices from the Drug Tariff and company literature October 2004).



N.B. Doses shown for general comparison and do not imply therapeutic equivalence. Graph illustrates cost differences between efalizumab and other systemic therapies for psoriasis.

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from intention-to-treat analysis) achieving at least a 75% improvement in this score (PASI-75). Secondary response measures are detailed in Appendix II and included both physician-based and patient-based assessments. Exclusion criteria included concomitant phototherapy and/or systemic therapy for psoriasis.

Of the published trials, one enrolled 597 subjects into the first of three consecutive 12-week study phases.⁴ At the start of the first phase, subjects were randomly allocated to one of three subcutaneous regimens; placebo (n=122), or to an initial conditioning dose of efalizumab (0.7mg/kg) followed by 11 weekly doses of 1.0mg/kg (n=232) or 2mg/kg (higher than the licensed dose, n=243). At the end of this phase, an improvement of 75% or more in the PASI score was achieved by 5%, 22%, and 28% of these groups, respectively (P<0.001 for both comparisons with placebo).

Patients who received active treatment and achieved an improvement at 12 weeks of 50% or more in the PASI score, were then randomly allocated to an extended treatment phase of a further 12 weeks with efalizumab at a dose of 2mg/kg weekly, 2mg/kg every other week, or placebo. Those with a lower score were randomly allocated to efalizumab 4mg/kg weekly or placebo. The results from this extension phase (see Appendix II) showed that the response to efalizumab was sustained and that a higher dose was effective in previous non-responders. During the final 12-week follow-up phase, after treatment withdrawal, a PASI-50 response was sustained by 30% of subjects who had received efalizumab for 24 weeks.

In the second fully-reported trial, 556 subjects were assigned to a 0.7mg/kg initial dose of efalizumab followed by 11 weekly doses of 1.0mg/kg (n=369) or to placebo (n=187).⁵ At the completion of the study period, a PASI-75 response was achieved by 27% and 4% of subjects, respectively (P<0.001). This corresponds to a difference of 22.3% (95% CI 15.8% to 29.5%). The mean improvements in PASI score from baseline were 52% and 19%, respectively (P<0.001).

Of the 345 subjects who received

efalizumab and completed the first 12 weeks of the study, 342 elected to enter an open-label, 12-week extension study. At its completion, 43.8% of subjects achieved $\geq 75\%$ improvement and 66.6% a $\geq 50\%$ improvement in PASI scores.⁷ A separate study has reported sustained responses to efalizumab in patients treated for up to 24 months.⁷

Neither of the two fully published studies enrolled subjects matching the target population defined in the SPC, that is, patients who have failed to respond, or are intolerant or have contraindications to other systemic therapies. However, an ongoing study includes a cohort (n= 526) of such 'high-need' patients (defined as those for whom at least two currently available systemic therapies were unsuitable). At 12 weeks, the proportion of 'high-need' patients on efalizumab achieving a PASA-75 score was 29.5%, compared to 2.7% on placebo (P<0.001); in the 'non-high-risk' patients, the respective proportions were 34.8% and 7.5%.⁸

The efficacy of efalizumab has not been evaluated in comparative studies with other systemic therapies.

Safety

Flu-like symptoms (headache, fever, chills, nausea and myalgia) have been observed with a frequency of approximately 41% among efalizumab recipients (vs. 24% with placebo) and are reported to diminish after initiation of treatment. Other common effects (>10%) include leucocytosis and lymphocytosis. Antibodies to efalizumab have been detected with an incidence of 6%, but have no obvious effects on the pharmacokinetic profile or clinical efficacy of efalizumab.³

Efalizumab may affect host defences against infections. It is not known whether it can increase the risk of malignancies and lymphoproliferative disorders. Use with other immunosuppressive systemic anti-psoriasis treatments is not recommended.³

Place in Therapy

Efalizumab is the first biological agent to be marketed for psoriasis. Similar agents currently under investigation for this condition include etanercept and infliximab. For both of these

drugs there are considerably more data on long-term safety.

Clinical trials have shown efalizumab to have modest clinical efficacy based on a PASI-75 response.³ Use of a PASI-50 endpoint, as recommended by some authorities as a more clinically realistic outcome,⁹ increases the estimate of efficacy of efalizumab compared to placebo.

To date, trials have been exclusively placebo-controlled. This limitation, together with cost considerations, suggests that efalizumab will remain a second-line agent pending comparative studies with other systemic therapy. Limited evidence from longer-term studies indicates that efalizumab has sustained efficacy. However, if therapy is initiated, efalizumab should only be continued beyond 12 weeks in those patients who have responded to treatment.

Key Papers

4. Lebwohl M *et al.* A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N Engl J Med* 2003; **349**: 2004-2013

5. Gordon KB *et al.* Efalizumab for patients with moderate to severe plaque psoriasis. A randomized controlled trial. *JAMA* 2003; **290**: 3073-3080

Appendix I: Bibliography Appendix II: Table of Clinical Trials

Risk Management Issues:

Efalizumab has to be stored in a refrigerator (2°C to 8°C) and reconstituted before use. It may be self-administered but patients must be trained in reconstitution and injection techniques. Injection sites should be rotated.

Because of the risk of thrombocytopenia, platelet counts should be monitored at initiation and monthly at the start of therapy. With continued treatment, three monthly monitoring of platelets is suggested.³

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The information contained in this document will be superseded in due course.
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Appendix I

Bibliography

References

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2. Griffiths CEM *et al.* A systematic review of treatment for severe psoriasis. Health Technology Assessment Monographs 2000; **4**: 1-125.
3. Serono Ltd. Efalizumab – Summary of Product Characteristics. September 2004.
4. Lebwohl M *et al.* A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. N Engl J Med 2003; **349**: 2004-2013.
5. Gordon KB *et al.* Efalizumab for patients with moderate to severe plaque psoriasis. A randomized controlled trial. JAMA 2003; **290**: 3073-3080.
6. Papp KA *et al.* Efficacy and safety of 24-week continuous efalizumab therapy in patients with moderate to severe chronic plaque psoriasis. Poster 2. Scientific experiences of efalizumab; 2nd EADV Spring Symposium, Budapest 2004.
7. Gottlieb AB *et al.* Long-term efalizumab therapy safely maintains psoriasis area and severity index improvement: preliminary results from an open-label study. Scientific experience of efalizumab. Poster 4. AAD Winter Meeting, Washington 2004.
8. Sterry I W *et al.* Efalizumab for patients with moderate to severe chronic plaque psoriasis: results of the international, randomized, controlled phase III Clinical Experience Raptiva (CLEAR) Trial. Poster 03v presented at the ECP, Paris, October 2004.
9. Carlin CS *et al.* A 50% reduction in the Psoriasis Area and Severity Index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. J Am Acad Dermatol 2004; **50**: 859-866.

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Appendix II

Table of pivotal, published, randomised, controlled trials of efalizumab in psoriasis

Ref No	Trial Design	Trial Population	Treatment	Treatment Outcomes			
5	<p>Double-blind, randomised, placebo-controlled, parallel group, multicentre, phase 3 study.</p> <p>12-week first treatment phase followed by 12-week extended treatment phase and a further 12-week follow-up phase after drug discontinuation.</p>	<p>597 subjects with moderate to severe plaque psoriasis of at least 6 months duration and stable for at least 3 months.</p> <p>Age 18 to 70 years, minimum PASI score of 12.0, candidacy for systemic treatment.</p> <p>All phototherapy and other systemic therapy for psoriasis discontinued.</p>	<p>First treatment phase:</p> <ul style="list-style-type: none"> • placebo (n= 122), or • initial dose of efalizumab 0.7mg/kg followed by 11 weekly doses of 1.0mg/kg (n=232), or • initial dose of efalizumab 0.7mg/kg followed by 11 weekly doses of 2.0mg/kg (n=243). <p>Numbers withdrawing from each group because of adverse effects were 1, 7 and 6, respectively.</p> <p>Extended treatment phase for those with a PASI-50 response:</p> <ul style="list-style-type: none"> • placebo, or • an initial dose of efalizumab 0.7mg/kg followed by 2mg/kg weekly, or • an initial dose of efalizumab 0.7mg/kg followed by 2mg/kg every other week. <p>Extended treatment phase for those without a PASI-50 response:</p> <ul style="list-style-type: none"> • placebo, or • two initial doses of efalizumab 0.7mg/kg followed by 4mg/kg weekly. 	Percentage of subjects with $\geq 75\%$ improvement in PASI at 12 weeks			
				Efalizumab 1mg/kg	22% (52/232)	P < 0.001 for comparison with placebo	
				Efalizumab 2mg/kg	28% (69/243)		
				Placebo	5% (6/122)		
							Percentage of subjects with $\geq 50\%$ improvement in PASI at 12 weeks
				Efalizumab 1mg/kg	52% (120/232)	P < 0.001 for comparison with placebo	
				Efalizumab 2mg/kg	57% (138/243)		
				Placebo	16% (19/122)		
							Percentage of subjects with $\geq 75\%$ improvement in PASI at end of 12 weeks who achieved a $\geq 75\%$ improvement at 24 weeks
				Efalizumab 1mg/kg	78% (31/40)	P < 0.001 for comparison with placebo	
				Efalizumab 2mg/kg	77% (30/39)		
				Placebo	20% (8/40)		
							Percentage of subjects with improvement of $\geq 50\%$ but $\leq 75\%$ in PASI at end of 12 weeks who achieved $\geq 75\%$ improvement at 24 weeks
				Efalizumab 2mg/kg/weekly	53% (25/47)	P < 0.001 vs. placebo	
				Efalizumab 2mg/kg/two-weekly	29% (13/45)	P = 0.002 vs. placebo	
Placebo	4% (2/46)						
			Percentage of subjects with improvement of $\leq 50\%$ in PASI at end of 12 weeks who achieved $\geq 75\%$ improvement at 24 weeks				
Efalizumab 4mg/kg/weekly	13% (15/118)	P = 0.02 vs. placebo					
Placebo	2% (1/59)						

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Ref No	Trial Design	Trial Population	Treatment	Treatment Outcomes			
6	Double-blind, randomised, placebo-controlled, parallel-group, multicentre, phase 3 study. 12 weeks duration.	556 subjects with moderate to severe plaque psoriasis of at least 6 months duration. Age 18 to 75 years, minimum PASI score of 12.0, candidacy for systemic treatment. All phototherapy and other systemic therapy for psoriasis discontinued. Location – USA and Canada (30 centres).	Initial dose of efalizumab 0.7mg/kg followed by 11 weekly doses of 1.0mg/kg (n=369). Placebo (n=187). Numbers withdrawing from each group because of adverse effects were 7 and 2, respectively.	Percentage of subjects with ≥ 75% improvement in PASI at 12 weeks			
				Efalizumab 1mg/kg	27% (98/369)	Difference = 22.3% (95% CI, 15.8% to 29.5%) P < 0.001	
				Placebo	4% (8/187)		
				Percentage of subjects with ≥ 50% improvement in PASI at 12 weeks	Efalizumab 1mg/kg	59% (216/369)	P < 0.001
				Placebo	14% (26/187)		
				Approximate mean improvement from baseline in PASI at 12 weeks	Efalizumab 1mg/kg	52%	P < 0.001
				Placebo	19%		
				Percentage of subjects reaching; 'minimal' or 'clear' status on Physicians Overall Lesion Severity Scale at 12 weeks	Efalizumab 1mg/kg	26%	P < 0.001
				Placebo	3%		
				Percentage of subjects reaching 'excellent' or 'cleared' on Physicians Global Assessment Scale at 12 weeks	Efalizumab 1mg/kg	33%	P < 0.001
				Placebo	5%		
				Mean improvement (%) in Dermatology Life Quality Index at 12 weeks	Efalizumab 1mg/kg	47%	P < 0.001
				Placebo	14%		
				Mean improvement in Itching Visual Analogue Scale at 12 weeks	Efalizumab 1mg/kg	38%	P < 0.001
				Placebo	- 0.2%		
				Mean improvement in Psoriasis Symptom Assessment (PSA) frequency scale at 12 weeks	Efalizumab 1mg/kg	48%	P < 0.001
				Placebo	18%		
				Mean improvement in PSA severity scale at 12 weeks	Efalizumab 1mg/kg	47%	P < 0.001
				Placebo	17%		