

Effects of Biologic Therapies on the Severity of Skin Symptoms and Quality of Life in Patients with Plaque-type Psoriasis: A Meta-Analysis

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Abstract

The efficacy of biologic treatments is well established in the treatment of moderate-to-severe plaque psoriasis. The purpose of this research was to compare PASI-75 response rates from randomized controlled trials (RCTs) and review quality of life data for biologic therapies.

A literature search was conducted to identify RCTs evaluating labeled doses for alefacept, efalizumab, etanercept and infliximab in psoriasis patients. A Mantel-Haenszel fixed-effects model was used to calculate relative risk (RR) with 95% confidence intervals for patients achieving PASI-75 responses after induction therapy (10 to 12 weeks of therapy) with a biologic versus placebo. Due to data limitations, quality of life (QoL), as measured by the disease-specific Dermatology Life Quality Index and generic Short Form 36, could not be assessed through statistical modeling. However, published data from RCTs were reviewed to assess the impact of treatment on QoL.

Patients treated with infliximab 5mg/kg were most likely to achieve PASI-75 vs. placebo (RR=25.48; CI=14.04-46.23); followed by etanercept 50 mg twice weekly (RR=11.92; CI=8.17-17.39); etanercept 25 mg twice weekly (RR=10.68; 6.15-18.57); efalizumab 1-2 mg/kg per week (RR=7.47; CI=5.20-10.73); and alefacept (RR=3.37; CI=2.18-5.23). Relative risks of achieving PASI 50 and 90 were also higher for infliximab; results for all PASI scores were confirmed with a random-effects model. Improvement in PASI-75 was consistent with better quality of life. A literature synthesis revealed that significantly higher numbers of patients on treatment with biologics achieved a clinically meaningful decrease in Dermatology Life Quality Index (DLQI) vs. placebo-treated patients. Additionally, 47% of the patients treated with infliximab achieved a DLQI of 0 at week 10 vs. less than 25% of the patients treated with etanercept 50mg BIW at week 12.

This analysis suggests that treatment with infliximab in the first 10/12 weeks is more effective than other biologics for chronic plaque psoriasis and leads to improvements in the patient's quality of life.

Background

- Psoriasis is a chronic, life-long inflammatory disease of the skin which affects 1-3% of US and European populations. Approximately 25% of patients have moderate-to-severe disease.¹
- The impact of psoriasis on quality of life (QoL) is comparable to that associated with other chronic diseases such as depression, diabetes and congestive heart failure², and is greater than that experienced with other dermatological diseases such as acne, basal cell carcinoma and viral warts.³
- Patients with moderate-to-severe disease require phototherapy or other systemic treatment throughout their lives. However, use of these therapies can be limited due to short- and long-term adverse effects and tolerance. For example, phototherapy increases the risk of developing skin cancer.
- Several biological therapies targeting the T-cells involved in the underlying disorder are now licensed for the treatment of adults with moderate-to-severe psoriasis who have failed to respond to, or are intolerant of, other systemic therapies. These agents offer a viable alternative to existing treatments.

Objectives

- To assess the relative efficacies of alefacept, efalizumab, etanercept and infliximab in chronic plaque psoriasis.
- To review QoL data for biologic therapies.

Methods

- A comprehensive literature search using electronic databases (Medline, Embase) and manual searches of reference lists was undertaken to identify all relevant randomized controlled trials (RCTs) described in published papers and congress abstracts evaluating the use of alefacept, efalizumab, infliximab or etanercept in patients with psoriasis.
- Unpublished studies were excluded from the analysis.
- Data was extracted for PASI 50, PASI 75 and PASI 90 response rates, and DLQI for infliximab, etanercept, alefacept and efalizumab at the primary trial endpoints (10/12 weeks). Only results consistent with doses recommended in the product labels were used in the analysis.
- The Mantel-Haenszel method was used to estimate the pooled relative risk (RR) under the assumption of a fixed effects model. A confidence interval for the pooled RR was calculated.
- Heterogeneity was estimated across trials, and the null hypothesis (study effects were homogeneous) was tested.
- Treatments were also compared in an evidence synthesis with endpoints jointly modeled using an ordered probit random effects model.
- Data for changes from baseline in DLQI are presented. Standard deviations were calculated using reported P values. Where exact P values were not available (e.g. "P<0.001"), a conservative approach of setting the values equal to the expressed upper limit (i.e. P=0.001) was taken. The general variance approach for mean differences on the same scale was used to calculate pooled mean differences and 95% CI.

Results

- Three randomised controlled trials were included for alefacept^{4,5,6} and four each for efalizumab^{7,8,9,10}, etanercept^{11,12,13,14} and infliximab.^{15,16,17,18} Trials are summarised in Table 1.
- All studies are placebo-controlled; most presented results for a short-term (induction), double-blind period.

Table 1. Summary of Included Trials

Reference	Participants	Duration	Intervention	Comparison
Ellis 2001	N=229 Adults Clinically stable plaque psoriasis; >10% BSA; baseline PASI >12	24 wks	Alefacept 0.025 mg/kg (n=57) Alefacept 0.075 mg/kg (n=55) Alefacept 0.125 mg/kg (n=58)	Placebo (n=59)
Kreuger 2002	N=553 Adults Clinically stable plaque psoriasis; >10% BSA; baseline PASI >12	12 wks	Cohort 1 (n=183) Cohort 2 (n=184)	Placebo (n=186)
Lebwohl, 2003	N=507 Adults Clinically stable plaque psoriasis; >10% BSA; baseline PASI >12	12 wks	Alefacept 10mg (n=173) Alefacept 15mg (n=166)	Placebo (n=168)
Lebwohl, 2003	N=597 Adults Clinically stable moderate to severe plaque psoriasis; >10% BSA; baseline PASI >12	12 wks	Efalizumab 1mg/kg SC once a wk (n=232)	Placebo (n=122)
Gordon, 2003	N=556 Adults Clinically stable moderate to severe plaque psoriasis; >10% BSA; baseline PASI >12	12 wks	Efalizumab 1mg/kg SC once a wk (n=369)	Placebo (n=187)
Leonardi, 2005	N=332 Adults Clinically stable moderate to severe plaque psoriasis; >10% BSA; baseline PASI >12	12 wks	Efalizumab 1mg/kg SC once a wk (n=162)	Placebo (n=170)
Papp, 2005	N=793 Adults (of whom 524 were 'high need', at least 2 systemic therapies unsuitable) Clinically stable moderate to severe plaque psoriasis; >10% BSA; baseline PASI >12	12 wks	Efalizumab 1mg/kg SC once a wk (n=529)	Placebo (n=264)
Leonardi, 2003	N=652 Adults Clinically stable plaque psoriasis; >10% BSA; baseline PASI >10	12 wks	Etanercept 25mg SC once a wk (n=160) Etanercept 25mg SC twice a wk (n=162) Etanercept 50mg SC twice a wk (n=164)	Placebo (n=166)
Papp, 2005	N=583 Adults Clinically stable plaque psoriasis; >10% BSA; baseline PASI >10	12 wks	Etanercept 25mg SC twice a wk (n=196) Etanercept 50mg SC twice a wk (n=194)	Placebo (n=193)
Gottlieb, 2003	N=112 Adults Clinically stable plaque psoriasis; >10% BSA	24 wks	Etanercept 25mg SC twice a wk (n=57)	Placebo (n=55)
Tyring, 2006	N=112 Adults Clinically stable plaque psoriasis; >10% BSA; baseline PASI >10	96 wks	Etanercept 50mg SC twice a wk (n=311)	Placebo (n=307)
Chaudhari 2001	N=33 Adults Clinically stable plaque psoriasis; >5% BSA	10 wks	Infliximab 5 mg/kg (n=11) Infliximab 10 mg/kg (n=11)	Placebo (n=11)
Gottlieb, 2004	N=249 Adults Clinically stable plaque psoriasis; >10% BSA; baseline PASI >10	10 wks	Infliximab 3 mg/kg (n=99) Infliximab 5 mg/kg (n=99)	Placebo (n=51)
Reich, 2005	N=378 Adults Clinically stable plaque psoriasis; >10% BSA; baseline PASI >12	50 wks	Infliximab 5 mg/kg (n=301)	Placebo (n=77)
Menter, 2007	N=835 Adults Clinically stable plaque psoriasis; >10% BSA; baseline PASI >12	50 wks	Infliximab 3 mg/kg (n=313) Infliximab 5 mg/kg (n=314)	Placebo (n=209)

Fixed-Effects Model (PASI-75)

- The pooled RRs for each biologic versus placebo suggest that infliximab is the most effective option in terms of achieving PASI 75. Infliximab is followed by etanercept 50 mg twice weekly, etanercept 25 mg twice weekly, efalizumab, and finally alefacept. (Table 2 and Figure 1)
- Two sensitivity analyses were conducted to assess the extent of statistical heterogeneity associated with infliximab. In the first analysis, the smallest study (Chaudhari et al. 2001), which also had the lowest RR, was excluded. This approach provided the best fit: the pooled RR (95%CI) for infliximab is 22.08 (p=16, 53.21) (Q=0.712, df=1, p=0.397). In the second example, the largest study (Reich et al. 2005), with the highest RR, was excluded. This approach similarly improved model fitting but to a lesser degree (RR 11.44 [4.75, 27.5], Q=2.25, df=1, p=0.133).

Table 2. PASI 75 Response Rates Using the Mantel-Haenszel Fixed Effect Model

Reference	Infliximab	Placebo	RR (95% CI)
Alefacept 7.5 mg (IV) / 15 mg (IM)			
Ellis, 2001	48/170 (28.2%)	6/59 (10.2%)	2.78 (1.25, 6.15)
Kreuger, 2004	53/367 (14.4%)	7/186 (3.8%)	3.84 (1.78, 8.27)
Lebwohl, 2005	56/339 (16.5%)	8/168 (4.8%)	3.47 (1.69, 7.11)
Pooled RR			3.37 (2.18, 5.23)
Test for heterogeneity			Q=0.344 (df=2), P=0.842
Efalizumab 1 mg/kg			
Lebwohl, 2003	52/232 (22.4%)	6/122 (4.9%)	4.56 (2.02, 10.31)
Gordon, 2003	98/369 (26.6%)	8/187 (4.3%)	6.21 (3.09, 12.49)
Leonardi, 2005	63/162 (38.9%)	4/170 (2.4%)	16.53 (6.16, 44.37)
Papp, 2005	166/529 (31.4%)	11/264 (4.2%)	7.53 (4.17, 13.61)
Pooled RR			7.47 (5.20, 10.73)
Test for heterogeneity			Q=4.16 (df=3), P=0.244
Etanercept 25mg			
Leonardi, 2003	55/162 (34.0%)	6/166 (3.6%)	9.39 (4.16, 21.21)
Papp, 2005	67/194 (34.2%)	6/193 (3.1%)	11.00 (4.89, 24.75)
Gottlieb, 2003	17/57 (29.8%)	1/55 (1.8%)	16.40 (2.26, 119.10)
Pooled RR			10.68 (6.15, 18.57)
Test for heterogeneity			Q=0.28 (df=2), P=0.869
Etanercept 50mg			
Leonardi, 2003	81/164 (49.4%)	6/166 (3.6%)	13.67 (6.14, 30.43)
Papp, 2005	96/194 (49.5%)	6/193 (3.1%)	15.92 (7.15, 35.44)
Tyring, 2006	147/311 (47.3%)	15/306 (4.9%)	9.64 (5.81, 16.02)
Pooled RR			11.92 (8.17, 17.39)
Test for heterogeneity			Q=1.29 (df=2), P=0.526
Infliximab 5 mg/kg			
Chaudhari 2001	9/11 (81.8%)	2/11 (18.2%)	4.50 (1.25, 16.25)
Gottlieb, 2004	87/99 (87.9%)	3/51 (5.9%)	14.94 (4.97, 44.89)
Reich, 2005	242/301 (80.4%)	2/77 (2.6%)	30.95 (7.87, 121.68)
Menter, 2007	237/314 (75.5%)	4/208 (1.9%)	39.25 (14.84, 103.80)
Pooled RR			25.48 (14.04, 46.23)
Test for heterogeneity			Q=8.742 (df=3), P=0.033

Random Effects Model (PASI-75, PASI-50, PASI-90)

- The random effects Bayesian hierarchical model was a better fit than the fixed effects model and yielded similar results: infliximab was the most effective in achieving PASI 75 response, followed by etanercept 50mg BIW, etanercept 25mg BIW, efalizumab, and alefacept.
- The PASI 75 response rate for infliximab was 82.9% and was significantly better than etanercept 50mg BIW (50.1%), etanercept 25mg BIW (35.9%), efalizumab (29.4%) and alefacept (18.2%). (Table 3)
- Trends for PASI 50 and PASI 90 were similar to results seen for PASI 75.

Table 3. Results for PASI 75 Response Using Random Effects Model

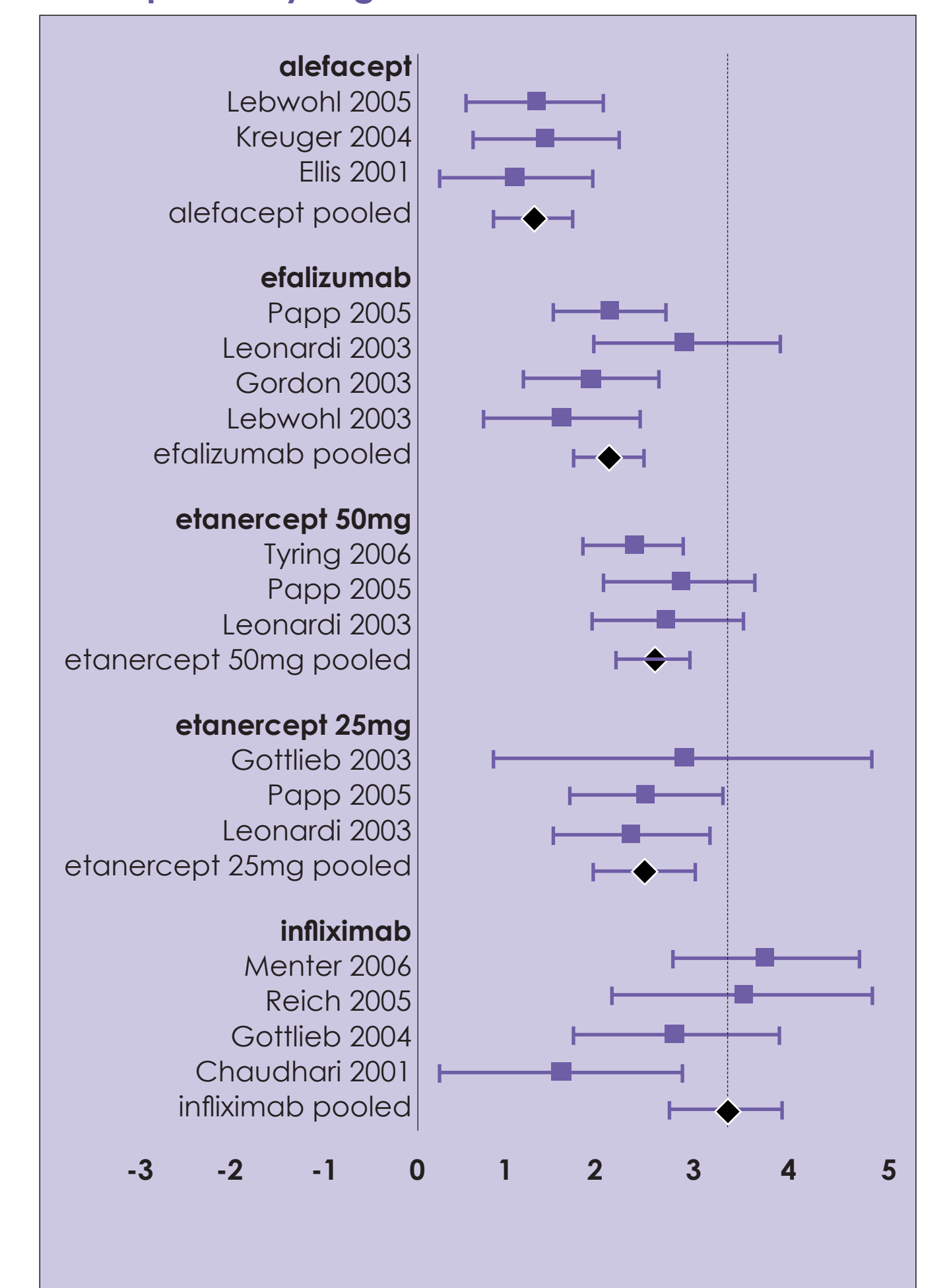
Treatment	Probability of a Response			Relative risk		
	Mean	2.5% CI	97.5% CI	Mean	2.5% CI	97.5% CI
Response = PASI 50						
Supportive Care	0.143	0.1219	0.1669	1.0	1.0	1.0
Alefacept	0.4044	0.3373	0.4713	2.84	2.28	3.44
Efalizumab 1 mg/kg	0.556	0.498	0.6107	3.91	3.36	4.50
Etanercept 25 mg BIW	0.6258	0.5552	0.6958	4.34	3.74	5.19
Etanercept 50 mg BIW	0.7525	0.6986	0.8048	5.29	4.58	6.12
Infliximab 5 mg/kg	0.9406	0.9172	0.9604	6.62	5.65	7.69
Response = PASI 75						
Supportive Care	0.04001	0.03189	0.05001	1.0	1.0	1.0
Alefacept	0.1777	0.1343	0.2243	4.48	3.21	5.89
Efalizumab 1 mg/kg	0.2939	0.2452	0.3435	7.41	5.96	9.09
Etanercept 25 mg BIW	0.3592	0.2928	0.4317	9.06	7.03	11.53
Etanercept 50 mg BIW	0.5001	0.4348	0.5691	12.36	10.22	15.55
Infliximab 5 mg/kg	0.8102	0.7592	0.8567	20.49	16.28	25.37
Response = PASI 90						
Supportive Care	0.005815	0.004139	0.008012	1.0	1.0	1.0
Alefacept	0.04503	0.02979	0.06393	7.88	4.92	11.50
Efalizumab 1 mg/kg	0.09438	0.07069	0.1213	16.50	12.08	21.93
Etanercept 25 mg BIW	0.1289	0.09218	0.1732	22.58	15.58	31.87
Etanercept 50 mg BIW	0.2202	0.1729	0.2754	38.62	28.21	52.51
Infliximab 5 mg/kg	0.5427	0.4721	0.6164	95.74	67.74	131.30

Table 4. Effects of biologic therapies on quality of life assessed by the dermatology life quality index (DLQI)

Agent	Reduction in DLQI from baseline		
	Placebo	Treatment	Mean difference
Alefacept			
Feldman et al., 2004	1.8	4.4	2.6
Finlay et al., 2003 (15 mg)	2.7	4.9	2.2
Finlay et al., 2003 (10 mg)	2.7	3.8	1.1
Ellis et al., 2003 (0.025 mg/kg)	1.7	4.0	2.3
Ellis et al., 2003 (0.075 mg/kg)	1.7	4.4	2.7
Ellis et al., 2003 (0.150 mg/kg)	1.7	3.2	1.5
Pooled mean difference (95% CI)			1.65 (1.23, 2.07)
Efalizumab 1 mg/kg			
Menter et al., 2004	1.9	5.6	3.7
Ortonne et al., 2005	2.6	5.7	3.4
Pooled mean difference (95% CI)			3.54 (2.05, 5.02)
Etanercept 25 mg BIW			
Kreuger et al., 2005	0.73	7.47	6.64
Feldman et al., 2005	1.4	6.45	5.05
Pooled mean difference (95% CI)			5.66 (3.27, 8.04)
Etanercept 50 mg BIW			
Tyring et al., 2006	2.67	8.64	5.97
Kreuger et al., 2005	0.73	7.98	7.25
Feldman et al., 2005	1.4	6.89	5.49
Pooled mean difference (95% CI)			6.07 (3.99, 8.16)
Infliximab 5 mg/kg			
Gottlieb et al., 2004	2.6	10.3	7.7
Reich et al., 2005	0.4	10.3	9.9
Pooled mean difference (95% CI)			8.52 (4.95, 12.08)

BIW, twice weekly; CI, confidence interval.

Figure 1. Forest Plot of Relative Risk (95%CI) for PASI 75 Response by Logarithm Scale



DLQI

- Infliximab treatment was also associated with numerically greater improvements from baseline in organ-specific QoL (vs placebo) as assessed by the DLQI.
- 47.1% of patients receiving infliximab reported that psoriasis no longer had any effect on their health-related QoL (DLQI, 0) at week 10 compared with 1.3% in the placebo group (P<0.001).⁶
- Less than 25% of patients receiving etanercept 50mg reported that psoriasis no longer had any effect on their health-related QoL (DLQI, 0) at week 12.¹⁹

Conclusions

- Results from both fixed-effects and random-effects models suggest that induction therapy with infliximab is more likely to result in PASI 75 response vs. other biologic therapies.
- Infliximab treatment was associated with numerically greater improvements from baseline in organ-specific QoL (vs placebo) as assessed by the DLQI.
- Shortcomings of this meta-analysis include the lack of long term data, the limited number of studies for each agent, and systematic differences between studies that cannot be corrected with statistical techniques.
- However, these factors are unlikely to explain the large differences between response rates for infliximab and other treatments.

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