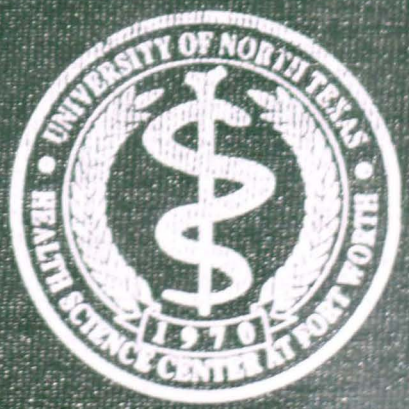
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To evaluate and compare efficacy and safety of biological agents in the treatment of plaque psoriasis, data was identified through four parallel systematic reviews. Randomized, controlled, double-blind, monotherapy trials of alefacept , efalizumab, etanercept and infliximab were selected. Sixteen studies comprising 7,931 patients met inclusion criteria. Efficacy was measured by pooled relative risk (RR) and number needed to treat (NNT) of PASI 75 achievement as compared to placebo. Each biological agent was efficacious ($p<.001$); however, there was a graded response for achievement of PASI 75. The risk of one or more adverse event was increased in the alefacept, efalizumab, and infliximab groups compared to placebo.

SAFETY AND EFFICACY OF ALEFACEPT, EFALIZUMAB, ETANERCEPT, AND INFLIXIMAB IN TREATING MODERATE TO SEVERE PLAQUE PSORIASIS: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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THESIS

Presented to the Graduate Council of the University of North Texas Health Science Center at Fort Worth in Partial Fulfillment of the Requirements for the Degree of MASTER OF SCIENCE By Angela K. Brimhall, Fort Worth, TX, May 3, 2007.

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CHAPTER I

INTRODUCTION

The introduction of biological agents for the treatment of psoriasis has created renewed clinical and basic science interest in this chronic, immune-mediated disease[1] with psychological morbidity comparable to heart disease, cancer and diabetes.[2] The exact etiology of psoriasis is yet to be elucidated, although current evidence indicates autoimmune,[3, 4] genetic,[5] infectious,[6] environmental[7] and psychological[8] components of disease onset and promotion.

Biological agents can be divided into three main groups: monoclonal antibodies, fusion proteins and cytokines.[9] Alefacept was the first biological agent designed and introduced for the treatment of psoriasis in January 2003.[10] It is a fully human receptor-antibody fusion protein which binds to CD2 on activated memory T leukocytes.[11] Subsequently, efalizumab, the humanised form of a murine antibody against CD11a [the alpha subunit of Leukocyte Function Associated Antigen – 1 (LFA-1)], was approved by the Food and Drug Administration (FDA) for psoriasis in October 2003.[12] Etanercept, a fully human fusion protein composed of a dimeric soluble p75 tumour necrosis factor (TNF) receptor and a human IgG Fc fragment, received FDA approval in November 1998 for adult rheumatoid arthritis and has since been approved for juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and most recently for plaque psoriasis in April 2004.[13] Infliximab is a chimeric IgG1κ monoclonal antibody with human constant and murine variable regions that bind specifically to tumour necrosis factor-alpha (TNF-α).[14]

It was first approved for active and fistulising Crohn's disease in August 1998, with subsequent indications approved for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, paediatric Crohn's disease and most recently in September 2006 for severe psoriasis. Adalimumab, a fully human monoclonal IgG1 antibody targeted against TNF, has not to date been approved for psoriasis, with approvals currently for rheumatoid arthritis, psoriatic arthritis and most recently Crohn's disease (March 2007). It has not been included in this initial meta-analysis study.

These biological agents have been extensively studied with differing degrees of efficacy reported. This study was designed first to summarise clinical trial efficacy data enabling a quantitative, indirect comparison between agents, as no current direct "head-to-head" data between biological agents is available. Meta-analysis is a well established method for summarising data[15-18] and carries the highest citation power when compared to other scientific study designs, including randomized controlled trials.[19]

The second objective of this study was to independently summarise safety events described in published manuscripts and FDA reports of clinical trials of alefacept, efalizumab, etanercept and infliximab to allow quantitative evaluation of the risk these agents incur in psoriasis patients. Randomised controlled trials are typically powered to measure clinical efficacy but often lack sample size and/or trial duration to adequately capture safety events. Another limiting factor of randomised controlled trials is the inability of patients with significant disease to tolerate placebo treatment and extensive treatment wash-out periods prior to study participation. This issue has raised ethical debate.[20-23] One method to minimise these weaknesses is the pooling of results from

individual randomised trials using meta-analysis. This amplifies the statistical power of current trials without exposing additional patients to placebo.[24, 25] This study uses meta-analysis to pool clinical trial data from alefacept, efalizumab, etanercept and infliximab trials in psoriasis patients to create an objective frame of reference for the quantitative comparison of efficacy and safety without the cost and risk of additional clinical trials.

CHAPTER II

METHODS

Search

Four systematic literature searches were performed independently using structurally identical search strategies by two authors. The Cochrane Handbook for Systematic Reviews of Interventions 4.2.5[26] guidelines were utilized in searching MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. All four were searched from inception to June 2005; an updating search was conducted in July 2006 to capture reports from the interim period. The search terms used were: *psoriasis, psoria*, Controlled Clinical Trial, Clinical Trial, Clinical Trial Phase I, Clinical Trial Phase II, Clinical Trial Phase III, Clinical Trial Phase IV, Controlled Clinical Trial,* and *Randomized Controlled Trial.* Unique to each biological agent search were the terms: *alefacept, Amevive®*, and *222535-22-0; efalizumab, Raptiva®* and *214745-43-4; etanercept, Enbrel®* and *185243-79-0;* and *infliximab, Remicade®* and *17-277-31-3.* Industry sponsors were contacted to obtain data from unpublished or

unidentified clinical studies. FDA reports were reviewed to collect intention-to-treat and unreported endpoints.

Selection

Titles, abstracts and full reports were screened in English to select randomised, controlled, double-blind, monotherapy trials of alefacept, efalizumab, etanercept or infliximab in the treatment of patients with moderate to severe psoriasis (see **Figure 1**). Studies were individually evaluated by pre-defined criteria on points of randomisation, masking of allocation, intention to treat analysis, placebo control, attrition, use of other systemic therapies and comparable baseline demographics between placebo and treatment groups. Sixteen studies including 7,931 patients (5,454 treatment and 2,477 placebo patients) met the pre-defined inclusion criteria: three trials of alefacept (n=1,289); five trials of efalizumab (n=3,130); four trials of etanercept (n=2,017); and four trials of infliximab (n=1,495). These studies were found to be methodologically homogeneous with very similar baseline demographics, inclusion criteria and exclusion criteria for participating subjects. **Table 1** summarises the key aspects of each study that met the pre-defined criteria for inclusion in these analyses.

Data Abstraction

Efficacy outcomes abstracted were 75% and 90% improvement in the Psoriasis Area and Severity Index (PASI 75 and 90 respectively) at 10-14 weeks of treatment. Only etanercept and infliximab reported PASI 90 endpoints. FDA reports were consulted to corroborate efficacy data and to abstract safety data unreported in peer-reviewed literature.[10, 12, 13]

Two safety endpoints were abstracted for patients who received at least one dose of study drug. The first was the number of patients who experienced one or more adverse events. We defined an adverse event according to 61 FR 37320 under regulation 21 CFR Part 312 which states, "an adverse event is any untoward medical occurrence that may present itself during treatment or administration with a pharmaceutical product, and which may or may not have a causal relationship with the treatment."[27] The second safety endpoint abstracted was the number of patients who experienced one or more serious adverse events (SAEs). A serious adverse event was defined under the same code as "any untoward medical occurrence that at any dose results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; creates persistent or significant disability/incapacity, or a congenital anomaly/birth defect."[27]

Statistical Analysis

A pooled estimate of the Relative Risk (RR) of PASI 75 achievement and PASI 90 achievement was computed using the Mantel-Haenszel method. Because of the homogeneity of studies selected, results for fixed and random effects were very similar. Although our analysis satisfies the statistical requirements of the fixed effects model, the more conservative random effects data are reported. Bioequivalent or equivalent FDA approved doses were pooled for each biological agent. In addition, RR of PASI 75 was computed for combined doses and results are reported within the text. PASI 90 data were pooled and reported where available. Safety was evaluated by RR of one or more AEs and SAEs for all doses. All dosages were combined for comparison. These data are presented as forest plots in the succeeding figures (see **Figures 2 – 9**).

In cases where zero-event data was observed, a constant continuity correction of 0.5 was added to enable computation of the RR. The Number Needed to Treat (NNT) and the Number Needed to Harm (NNH) was calculated as the inverse of the absolute risk difference between treatment and control groups. These endpoints were chosen for their ease of clinical application.[28] Confidence intervals for the NNT and NNH were calculated by the substitution metod.[29] The heterogeneity of randomised controlled trials was measured by the Q statistic.

CHAPTER III

RESULTS

Efficacy

Efficacy was measured by PASI 75 and PASI 90 which are well validated endpoints of significant psoriasis treatment response.[30] The PASI score captures disease severity as measured by body surface area affected, encompassing induration, scale and erythema of psoriatic plaques in four specified body areas. It does not include a quality of life component. The p value for heterogeneity as measured by the Q statistic was appreciably greater than 0.05 for each efficacy comparison refuting statistical heterogeneity and supporting statistical homogeneity for valid comparisons between trials. All efficacy endpoints were measured during the controlled period. Although all trials were considered monotherapy and excluded other systemic psoriatic therapies, the application of mild to moderate strength topical corticosteroids to the palms, soles, groin and scalp were allowed in most studies.

Alefacept

Three alefacept studies met our pre-defined criteria for inclusion.[31-33] Similar data subsequently published in the Journal of the European Academy of Dermatology and Venereology in July 2003 were not included.[34-36] In two trials, alefacept was administered by 30 second intravenous (IV) infusion and in the third by intramuscular (IM) injection. Pharmacodynamic studies determined a 150-200% bioequivalence between IM and IV dosing of alefacept[37] mitigating a comparison of 7.5 mg of IV

alefacept[32] with 15 mg of IM alefacept.[33] Patients in the earliest published trial reported a median body weight of 100 Kg, enabling an equitable comparison of 0.075 mg Kg^{-1} IV [31] with 7.5 mg IV[32] and subsequently 15 mg IM[33] dosing.

Figure 2 presents the forest plot with overall RR of 3.70 (95% CI=2.38-5.75, p<.001) for achievement of PASI 75 in the 1,001 patients treated with bioequivalent doses (0.075 mg Kg^{-1} IV, 7.5 mg IV, or 15 mg IM) of alefacept. The NNT to attain PASI 75 was 8 (95% CI=5.05-12.20) after 12 weekly injections and 2 weeks of observation. The RR of achieving PASI 75 for 1,289 psoriasis patients on any study dose of alefacept (0.025 mg Kg^{-1} IV, 0.075 mg Kg^{-1} IV, 0.150 mg Kg^{-1} IV, 7.5 mg IV, 10 mg IM, or 15 mg IM) was 3.20 (95% CI=2.09-4.92, p<.001). The NNT remained 8 (95% CI=6.76-11.90) in the comprehensive dose analysis.

Efalizumab

Five randomised controlled trials of efalizumab met our inclusion criteria.[38-42] **Figure 3** presents forest plot data including five studies with overall RR of 7.34 (95% CI=5.23-10.30, p < .001, n=2,721) for achievement of PASI 75 in patients who received efalizumab 1mg Kg^{-1} by SC injection QW as compared to placebo. The NNT was 4 (95% CI=3.36-5.24) after 12 weekly injections. An overall RR of 7.33 (95% CI=5.28-10.17, p<.001) was realised for all patients receiving 1 or 2 mg Kg^{-1} SC of efalizumab as compared to placebo. This endpoint was measured in 3,130 patients (2,151 treatment and 979 placebo patients) after 12 weekly doses of efalizumab or placebo treatment. The NNT remained 4 (95% CI=3.58-4.90) in this analysis.

Etanercept

Four reports of etanercept use in psoriasis met our pre-defined inclusion criteria.[43-46] Randomised controlled trials conducted in psoriatic arthritis patients were excluded due to concomitant use of methotrexate and substantially lower baseline PASI scores compared to subjects in plaque psoriasis trials.[47, 48] The FDA has approved two dosing schedules of etanercept for psoriasis, i.e. an induction dose of 50 mg BIW for the initial 12 weeks followed by a maintenance regimen of 50 mg QW or 25 mg BIW. These dosing schedules were analysed separately. All administration of etanercept was by subcutaneous injection (SC).

Figure 4A, presents forest plot data summarising the overall RR of PASI 75 as 10.20 (95% CI=5.87-17.72, p<.001) for 844 psoriasis patients treated with 25 mg BIW of etanercept. The NNT was 4 (95% CI=2.96-4.10) for achievement of PASI 75 after 12 weeks of etanercept treatment. In **Figure 4B**, patients dosed with etanercept 50 mg BIW achieved an increased RR of 11.73 (95% CI=8.04-17.11, p<.001) with a NNT of 3 (95% CI=2.07-2.49). Combined analysis of 25 mg QW, 25 mg BIW or 50 mg BIW of etanercept generated an overall RR of 10.43 (95% CI=7.20-15.11, p<.001). The NNT was 3 (95% CI=2.41-3.72) for the combined dose analysis. **Figure 4C**, describes the achievement of PASI 90 with overall RR of 21.44 (95% CI=9.52-48.26, p < .001) for 1,334 patients treated with 50 mg of etanercept BIW. The NNT increased to 5 (95% CI=4.29-5.88) for the achievement of PASI 90.

Infliximab

Four reports of infliximab for psoriasis met our inclusion criteria.[49-52] As with etanercept, psoriatic arthritis data were excluded.[53, 54] All doses of infliximab were administered by

slow IV infusion over a 2-3 hour period. Analysing the approved 5 mg Kg^{-1} dose, the overall RR of PASI 75 was 17.40 (6.41-47.19, p<.001) in 1,072 patients. This was measured at week 10 following three IV infusions of infliximab or placebo administered at week 0, 2, and 6 (**Figure 5A**). When pooling results from all dosages (3, 5 or 10 mg Kg^{-1}), a similar overall RR of 16.52 (95% CI=5.96-45.80, p<.001) was observed in 1,495 patients. The NNT was to 2 for both analyses (95% CI=1.24-1.38 and 1.28-1.45 respectively). **Figure 5B** further shows that the 714 patients administered 5 mg Kg^{-1} of infliximab were nearly 50 times more likely to achieve PASI 90 when compared to 336 patients administered placebo (RR=49.42, 95% CI=16.01-152.54, p<.001). The NNT remained 2 for PASI 90 (95% CI=1.67-2.31).

Safety

Patients with one or more AEs and one or more SAEs were pooled to evaluate safety. All events were analysed with total number of patients dosed as the denominator.[55] The Q statistic was greater than 0.05 for each analysis refuting mathematical heterogeneity and supporting mathematical homogeneity for valid comparison between trials. All safety endpoints were measured during the controlled period.

Alefacept

The number of patients with incidence of one or more adverse events with IM dosing was not reported by Lebwohl et al[33] or FDA medical reviews. As a result, we pooled the total adverse events for IV dosing (see **Figure 6A**). The overall risk was 9% higher for patients treated with alefacept compared to patients treated with placebo (RR=1.09, 95% CI=1.01-1.18, p=.03). The Number Needed to Harm (NNH) was 15 (95% CI = 7.63-

142.86). Common AEs were pharyngitis, chills, and headache. With intramuscular dosing, the most common AEs were headache, pruritus, and infection. Seventy to eighty percent of these infections were coded as "common cold(s)" per FDA reports.[10] The incidence of SAEs was greater in IV-dosed patients and lower in IM-dosed patients compared to placebo (see **Figure 6B**). The pooled RR for incidence of SAEs in alefacept treated patients was not statistically significant (RR=1.40, CI=0.56-3.48, p=0.47). The most common SAEs were coronary artery disorder (n=4), cellulitis (n=3), and myocardial infarction (n=3), none of which occurred in the placebo group. Both AEs and SAEs were measured at week 24 after 12 weeks of alefacept treatment followed by 12 weeks of observation.

Efalizumab

Fifteen percent more efalizumab treated patients experienced one or more adverse events when compared to placebo treated patients (RR=1.15, 95% CI=1.09-1.20, p<.001, see **Figure 7A**). This effect was pooled from data for 3,128 patients. The NNH was 9 (95% CI=7.30-13.88). The most common adverse events were headaches, infection and chills. **Figure 7B** summarises the incidence of one or more SAEs in efalizumab patients. The pooled RR was 1.43 and not statistically significant in a comprehensive analysis of all five trials (95% CI=0.71-2.90, p=0.32, n=3,128). A sensitivity analysis was conducted excluding one trial with distinct criteria excluding potential subjects with "hospital admission for cardiac disease, stroke or pulmonary disease within the past year."[41] Sensitivity analysis of the four remaining trials resulted in a RR of 1.15 (95% CI=1.09-1.21, p<.001) for AEs and a statistically significant RR of 1.92 (95% CI=1.05-3.51,

p=0.03, see **Figure 7C**) for SAEs. The NNH was 9 (95% CI=6.85-14.29) and 60 (95% CI=35.71-166.67) for the sensitivity analyses of AEs and SAEs, respectively. Common SAEs as reported in FDA reviews included hospitalisation for psoriasis flare (n=17), serious infection (n=7) [including cellulitis (n=2), sepsis (n=1), gastroenteritis (n=2), pneumonia (n=2)] and thrombocytopenia (n=5). Incidence of both AEs and SAEs were measured cumulatively throughout the first 12 weeks of treatment.

Etanercept

The RR of one or more AEs was not significantly increased for etanercept treated patients (RR=1.05, 95% CI=0.96-1.16, p=0.28, see **Figure 8A**). This was also true for incidence of SAEs (RR=1.17, 95% CI=0.59-2.33, p=0.66, see **Figure 8B**). The most common adverse events reported were injection site reaction, headache and upper respiratory tract infection. The most common serious adverse events were malignancy (n=10), serious infection (n=4) and worsening psoriasis (n=3). Both AEs and SAEs were measured cumulatively over 12-24 weeks of etanercept treatment.

Infliximab

Neither Chaudhari et al[49] nor FDA medical reviews reported incidence of AEs in the relatively small initial infliximab trial. During the remaining trials, 18% more treatment patients experienced one or more AEs compared to placebo (RR=1.18, 95% CI=1.07-1.29, p<.001, see **Figure 9A**). The NNH was 9 (95% CI=5.99-19.61). The most common AEs were upper respiratory tract infection, headache, increased hepatic enzymes and infection. The incidence of SAEs for infliximab patients did not reach statistical significance (RR=1.26, 95% CI=0.56-2.84, p=0.58 see **Figure 9B**). Some of the most

common SAE(s) reported were malignancy (n=12), serious infection (n=6), serious infusion reaction (n=4) and lupus-like syndrome (n=4). Both AEs and SAEs were measured across 10-30 weeks of infliximab treatment.

CHAPTER IV

DISCUSSION

This is a quantitative meta-analysis of efficacy and safety data for randomised controlled trials of alefacept, efalizumab, etanercept and infliximab in patients with moderate to severe psoriasis. The measured efficacy of biological agents over a 10-14 week course of treatment and observation was impressive with RR of PASI 75 achievement rounding to 4, 7, 12 and 19 for maintenance doses of alefacept, efalizumab, etanercept and infliximab compared with placebo, respectively. The corresponding numbers needed to treat were 8, 4, 3 and 2. Through indirect comparison[24, 25] of these efficacy endpoints, all similarly compared to placebo, the decreasing rank order of efficacy can be concluded as infliximab, etanercept, efalizumab and alefacept. The design and execution of head-to-head trials to compare biological and traditional agents for psoriasis on points of efficacy and safety is encouraged for direct comparison.

This report also quantifies the statistically significant increased risk of adverse events for patients in randomised controlled trials of alefacept, efalizumab and infliximab. Patients need to be aware of the 9%, 15% and 18% increased risk of experiencing one or more adverse events on alefacept, efalizumab and infliximab, respectively, as compared to placebo. The corresponding NNH are 15, 9 and 9. In our analysis, alefacept, etanercept and infliximab did not carry an increased risk of SAEs using current pooled clinical trial data. Results for efalizumab were mixed with sensitivity analysis, resulting in an increased risk of serious adverse event relating predominantly to psoriatic flare. A recent

review of this risk documents a small (1-3%) risk of a "generalised inflammatory flare" and appropriate treatment strategies.[56] As experience and awareness with efalizumab increases, it is anticipated that hospitalisation (i.e. SAE) will be significantly reduced. Strengths of this study include incorporation of data from multiple sources, including FDA reports. In addition, the inclusion of only high quality studies with largely homogeneous populations further strengthens the validity of the pooled results. Choosing to report the results as both RRs and NNT/NNH provides simple clinical application.[28] Limitations of our analysis include a relatively short duration of treatment studied (10-30 weeks). This is secondary to the short duration of placebo control in the pooled trials, suggesting that other methods of control beyond placebo may be preferable to extend the inferential potential of future analyses.[57] Caution must be exercised in interpreting our results due to different methodologies, including individual dosing schedules and differing routes of admission, utilised with the four biologic agents.

Adalimumab, a fifth biological agent, is a fully human monoclonal IgG1 antibody targeted against TNF. It was not included in this analysis due to the limited availability of clinical trial data and FDA reports for psoriasis patients at the "cut-off" period of data collection. A recent clinical trial comparing adalimumab to placebo in 1,212 subjects found 71% vs. 6.5% achievement of PASI 75 after 16 weeks of treatment.[58] The incidence of any adverse event was 62.2% vs. 55.5% for adalimumab and placebo respectively. The serious adverse event rate was 1.8% for both groups. Open label analysis extended up to 52 weeks without evidence of rebound psoriasis in patients re-randomised to placebo. As further data is made available, future meta-analyses will

include adalimumab, in addition to break out analysis of individual safety events, other measures of efficacy and quality of life endpoints.

The purpose of this study is to provide dermatologists with an initial, objective tool to more effectively educate patients regarding the safety and efficacy of biological agents. In the absence of head-to-head studies among biological agents and the paucity of studies between traditional agents and biological agents, our analysis may help guide choice of therapy for individual patients.[59, 60, 61] As with all therapeutic decisions, clinicians must carefully weigh the risk of each individual agent with the likelihood of disease improvement after a full and forthright discussion with each patient. As further studies of this type become available, the ability of dermatologists to make evidence-based therapeutic decisions for their patients will be enhanced.

APPENDIX A:

ABBREVIATIONS AND ACRONYMS

ABBREVIATIONS AND ACRONYMS

FDA = United States Food and Drug Administration

PASI 75 = 75% improvement in the Psoriasis Area and Severity Index

PASI 90 = 90% improvement in the Psoriasis Area and Severity Index

AE(s) = Adverse Event(s)

SAE(s) = Serious Adverse Event(s)

RR = Relative Risk

LFA-1 = Leukocyte Function Antigen - 1

TNF = Tumour Necrosis Factor

TNF-α = Tumour Necrosis Factor Alpha

FR = Federal Register

CFR = Code of Federal Regulations

IV = Intravenous Infusion

IM = Intramuscular Injection

SC = Subcutaneous Injection

NNT = Number Needed to Treat

NNH = Number Needed to Harm

QW = Once per Week

BIW = Twice per Week

APPENDIX B:

TABLES 1-3

Table 1. Clinical Trial Characteristics and Design

Name of Lead Author	Year Published	Journal	Placebo Controlled	Randomized	Double-Blind	Monotherapy[0]	Dose and Dosing Schedule(s)	Route of Administration	Last Week of Controlled Trial	Last Week Reported	Number of Patients Randomized	Mean Age	Women %	Mean Baseline PASI	Weight (kg)	Primary Endpoint
Alefacept																
Ellis[31]	2001	NEJM	+	+	+	+	0.025, 0.075, or 0.150 mg Kg^{-1} QW x 12 weeks	IV	24	24	229	48	29%	16*	100†	Mean change in PASI at week 14
Krueger[32]	2002	JAAD	+	+	+	+	7.5 mg QW x 12 weeks x 2 courses	IV	48	48	553	45	30%	NR	92	PASI 75 at week 14
Lebwohl[33]	2003	ARCH	+	+	+	+	10 or 15 mg QW x 12 weeks	IM	24	24	507	45	34%	14†	84*	PASI 75 at week 14
Efalizumab																
Lebwohl[38]	2003	NEJM	+	+	+	+	1 or 2 mg Kg^{-1} § QW x 12 weeks	SC	24	36	597	46	35%	20	93	PASI 75 at week 12
Gordon[39]	2003	JAMA	+	+	+	+	1 mg Kg^{-1} § QW x 12 weeks	SC	12	12	556	45	31%	19	94	PASI 75 at week 12
Leonardi[40]	2005	JAAD	+	+	+	+	1 or 2 mg Kg^{-1} § QW x 12 weeks	SC	12	24	498	44	28%	19	93	PASI 75 at week 12
Papp[41]	2006	IJD	+	+	+	+	1 mg Kg^{-1} § QW x 12 weeks	SC	12	12	686	46	35%	19	93	"Evaluate safety and tolerability"
Dubertret[42]	2006	BJD	+	+	+	+	1 mg Kg^{-1} § QW x 12 weeks	SC	12	12	793	45	33%	23	NR	PASI 75 at week 12
Etanercept																
Leonardi[43]	2003	NEJM	+	+	+	+	25 mg QW, 25 mg BIW, or 50 mg BIW x 24 weeks	SC	12	24	672	45	33%	18	95	PASI 75 at week 12
Gottlieb[44]	2003	ARCH	+	+	+	+	25 mg BIW x 24 weeks	SC	24	24	112	47	38%	19	91	PASI 75 at week 12
Papp[45]	2005	BJD	+	+	+	+	25 or 50 mg BIW x 24 weeks	SC	12	24	611	45	34%	16†	NR	PASI 75 at week 12
Tyring[46]	2006	LANC	+	+	+	+	50 mg BIW x 12 weeks	SC	12	12	622	46	32%	18	NR	PASI 75 at week 12
Infliximab																
Chaudhari[49]	2001	LANC	+	+	+	+	5 or 10 mg Kg^{-1} at week 0, 2, & 6	IV inf	10	10	33	44	30%	23	89.3	PGA week 10
Gottlieb[50]	2004	JAAD	+	+	+	+	3 or 5 mg Kg^{-1} at week 0, 2, & 6	IV inf	10	30	249	44	30%	19†	NR	PASI 75 at week 10
Reich[51]	2005	LANC	+	+	+	+	5 mg Kg^{-1} at week 0, 2, 6, 14, 22, 30, 38, & 46	IV inf	24	46	378	43	29%	23	NR	PASI 75 at week 10
Menter[52]	2006	JAAD	+	+	+	+	3 or 5 mg Kg^{-1} at week 0, 2, 6, 14, 22, 30, 36, 44, & 50 or week 0, 2, 6, and "as needed"	IV inf	14	50	835	44	33%	20	91.9	PASI 75 at week 10

Legend - Table 1.
*mean of reported medians

Table 2. Number Needed to Treat (NNT)

	PASI 75	PASI 90
Alefacept	8 (CI=5.05-12.20)	n/a
Efalizumab	4 (CI=3.36-5.24)	n/a
Etanercept	3 (CI=2.07-2.49)	5 (CI=4.29-5.88)
Infliximab	2 (CI=1.24-1.38)	2 (CI=1.67-2.31)

Table 3. Number Needed to Harm (NNH)

	Any Adverse Event
Alefacept	15 (CI=7.63-142.86)
Efalizumab	9 (CI=7.30-13.88)
Etanercept	NS
Infliximab	9 (CI=5.99-19.61)

APPENDIX C:

FIGURES 1 – 9

Figure 1.

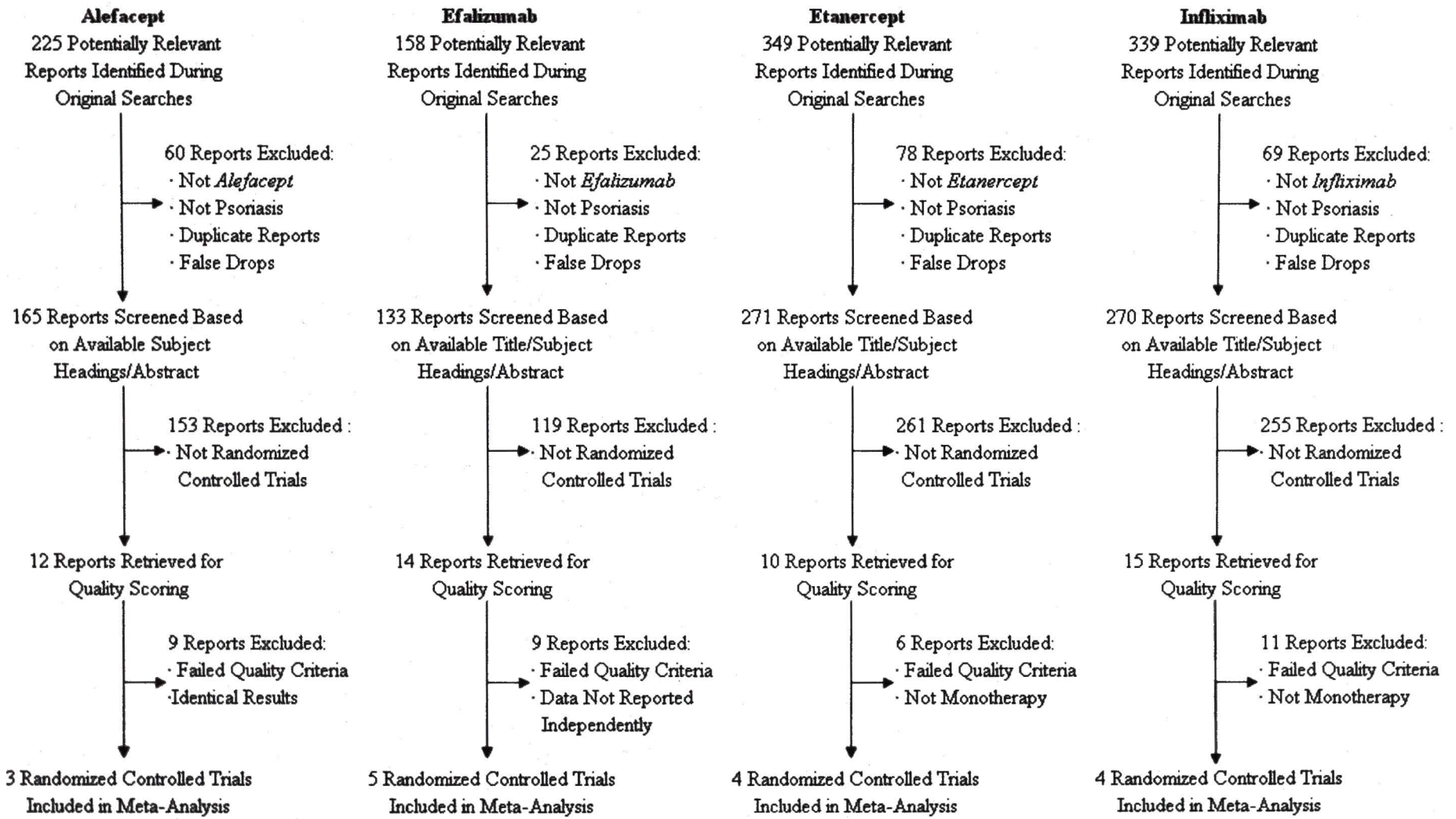

Alefacept
225 Potentially Relevant Reports Identified During Original Searches
60 Reports Excluded:
· Not Alefacept
· Not Psoriasis
· Duplicate Reports
· False Drops
165 Reports Screened Based on Available Subject Headings/Abstract
153 Reports Excluded :
· Not Randomized Controlled Trials
12 Reports Retrieved for Quality Scoring
9 Reports Excluded:
· Failed Quality Criteria
·Identical Results
3 Randomized Controlled Trials Included in Meta-Analysis
Efalizumab
158 Potentially Relevant Reports Identified During Original Searches
25 Reports Excluded:
· Not Efalizumab
· Not Psoriasis
· Duplicate Reports
· False Drops
133 Reports Screened Based on Available Title/Subject Headings/Abstract
119 Reports Excluded :
· Not Randomized Controlled Trials
14 Reports Retrieved for Quality Scoring
9 Reports Excluded:
· Failed Quality Criteria
· Data Not Reported Independently
5 Randomized Controlled Trials Included in Meta-Analysis
Etanercept
349 Potentially Relevant Reports Identified During Original Searches
78 Reports Excluded:
· Not Etanercept
· Not Psoriasis
· Duplicate Reports
· False Drops
271 Reports Screened Based on Available Title/Subject Headings/Abstract
261 Reports Excluded :
· Not Randomized Controlled Trials
10 Reports Retrieved for Quality Scoring
6 Reports Excluded:
· Failed Quality Criteria
· Not Monotherapy
4 Randomized Controlled Trials Included in Meta-Analysis
Infliximab
339 Potentially Relevant Reports Identified During Original Searches
69 Reports Excluded:
· Not Infliximab
· Not Psoriasis
· Duplicate Reports
· False Drops
270 Reports Screened Based on Available Title/Subject Headings/Abstract
255 Reports Excluded :
· Not Randomized Controlled Trials
15 Reports Retrieved for Quality Scoring
11 Reports Excluded:
· Failed Quality Criteria
· Not Monotherapy
4 Randomized Controlled Trials Included in Meta-Analysis

FIGURE 2. Alefacept Efficacy Evaluation

Achievement of PASI 75

Citation	RR	Alefacept	Placebo	n	p
Ellis et al, 2001	3.22	18 / 55	6 / 59	114	0.005
Krueger et al, 2002	3.84	53 / 367	7 / 186	553	<.001
Lebwohl et al, 2003	3.94	35 / 166	9 / 168	334	<.001
Combined	**3.70**	**106 / 588**	**22 / 413**	**1001**	**<.001**

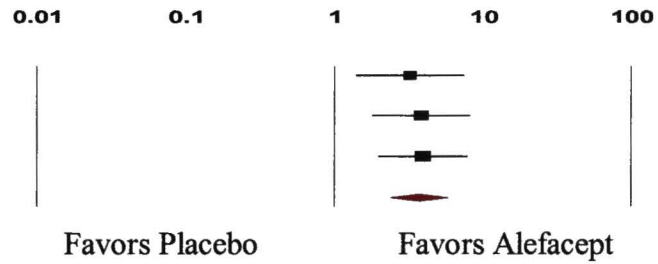


FIGURE 3. Efalizumab Efficacy Evaluation

Achievement of PASI 75

Citation	RR	Efalizumab	Placebo	n	p
Gordon et al, 2003	6.21	98 / 369	8 / 187	556	< .001
Lebwohl et al, 2003	4.56	52 / 232	6 / 122	354	< .001
Leonardi et al, 2005	16.53	63 / 162	4 / 170	332	< .001
Papp et al, 2006	7.94	106 / 450	7 / 236	686	< .001
Dubertret et al, 2006	7.53	166 / 529	11 / 264	793	< .001
Combined	**7.34**	**485 / 1742**	**36 / 979**	**2721**	**< .001**

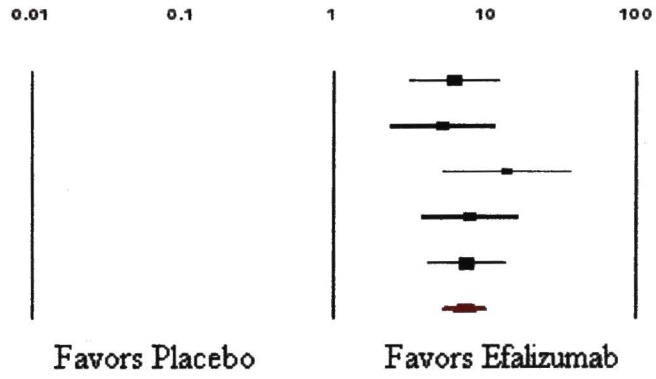
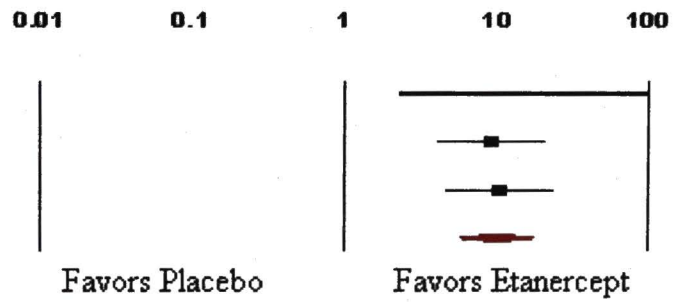


FIGURE 4. Etanercept Efficacy Evaluation

A. Achievement of PASI 75 on 25 mg BIW

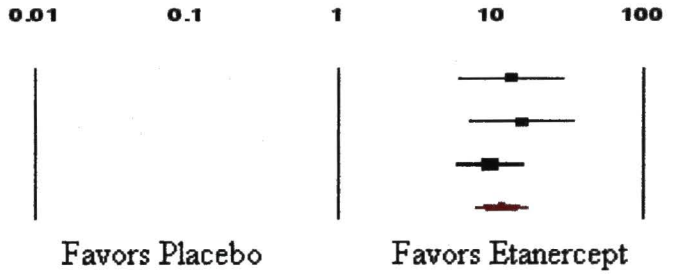
Citation	RR	Etanercept	Placebo	n	p
Gottlieb et al, 2003	16.40	17 / 57†	1 / 55†	112	<.001
Leonardi et al, 2003	9.22	55 / 167	6 / 168	335	< .001
Papp et al, 2005	10.41	66 / 204	6 / 193	397	< .001
Combined	**10.20**	**138 / 428**	**13 / 416**	**844**	**< .001**

†Modified Intention To Treat



B. Achievement of PASI 75 on 50 mg BIW

Citation	RR	Etanercept	Placebo	n	p
Leonardi et al, 2003	13.50	81 / 168	6 / 168	336	<.001
Papp et al, 2005	15.92	96 / 194	6 / 193	387	< .001
Tyring et al, 2006	9.80	147 / 311	15 / 311	622	< .001
Combined	**11.73**	**324 / 673**	**27 / 672**	**1345**	**< .001**



C. Achievement of PASI 90 on 50 mg BIW

Citation	RR	Etanercept	Placebo	n	p
Leonardi et al, 2003	36.44	36 / 164	1 / 166	330	<.001
Papp et al, 2005	39.79	40 / 194	1 / 193	387	< .001
Tyring et al, 2006	15.99	65 / 311	4 / 306	617	< .001
Combined	**21.43**	**141 / 669**	**6 / 665**	**1334**	**< .001**

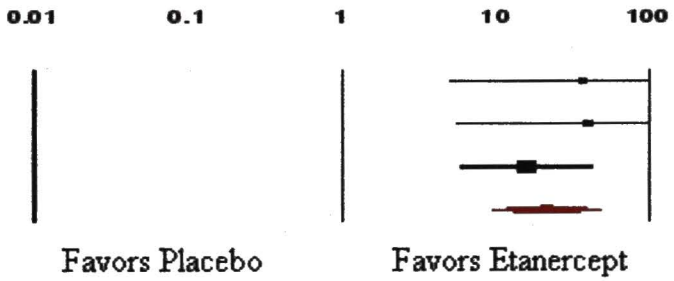
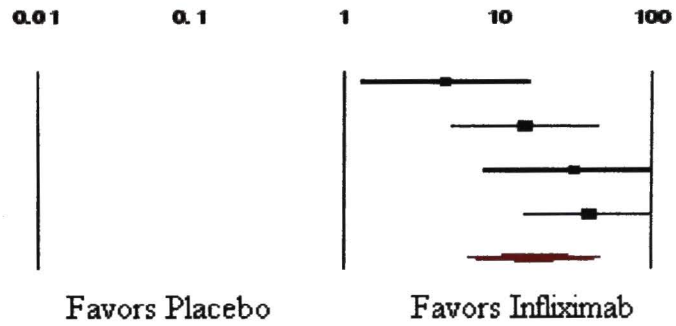


FIGURE 5. Infliximab Efficacy Evaluation

A. Achievement of PASI 75

Citation	RR	Infliximab	Placebo	n	p
Chaudhari et al, 2001	4.50	9 / 11	2 / 11	22	0.003
Gottlieb et al, 2004	14.94	87 / 99	3 / 51	150	< .001
Reich et al, 2005	30.95	242 / 301	2 / 77	378	< .001
Menter et al, 2006	39.25	237 / 314	4 / 208	522	< .001
Combined	**17.40**	**575 / 725**	**11 / 347**	**1072**	**< .001**



B. Achievement of PASI 90

Citation	RR	Infliximab	Placebo	n	p
Gottlieb et al, 2004	29.36	57 / 99	1 / 51	150	<.001
Reich et al, 2005	44.00	172 / 301	1 / 77	378	< .001
Menter et al, 2006	94.06	142 / 314	1 / 208	522	< .001
Combined	**49.42**	**371 / 714**	**3 / 336**	**1050**	**< .001**

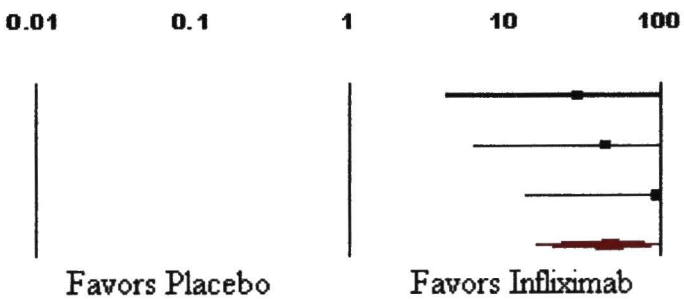
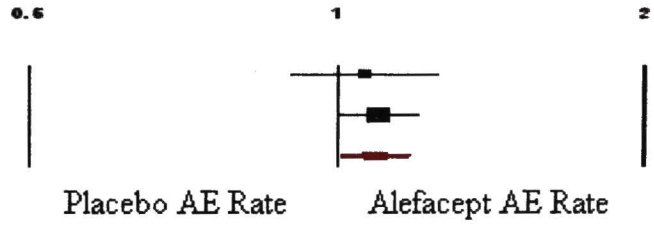


FIGURE 6. Alefacept Safety Evaluation

A. Incidence of AE

Citation	RR	Alefacept	Placebo	n	p
Ellis et al, 2001	1.06	135 / 170	44 / 59	229	0.44
Krueger et al, 2002	1.10	310 / 367*	143 / 186*	553	0.03
Combined	**1.09**	**445 / 537**	**187 / 245**	**782**	**0.03**

*Data from FDA reports



B. Incidence of SAE

Citation	RR	Alefacept	Placebo	n	p
Ellis et al, 2001	4.51	13 / 170*	1/59*	229	0.10
Krueger et al, 2002	1.82	18 / 367*	5 / 186*	553	0.22
Lebwohl et al, 2003	0.74	15 / 339	10 / 168	507	0.45
Combined	**1.40**	**46 / 876**	**16 / 413**	**1289**	**0.47**

*Data from FDA reports

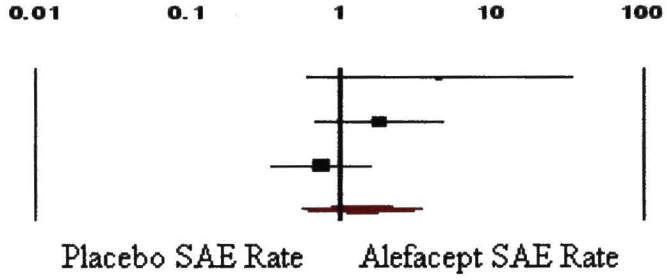
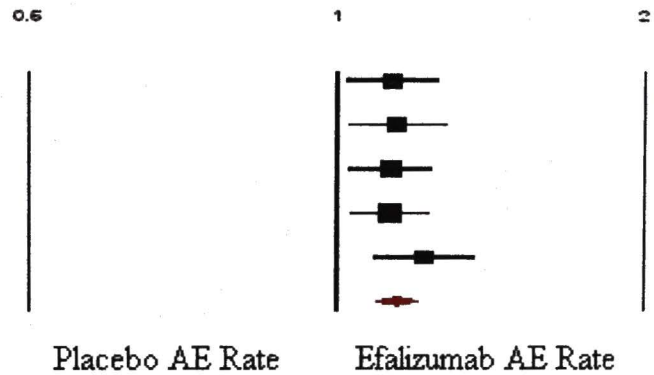


FIGURE 7. Efalizumab Safety Evaluation

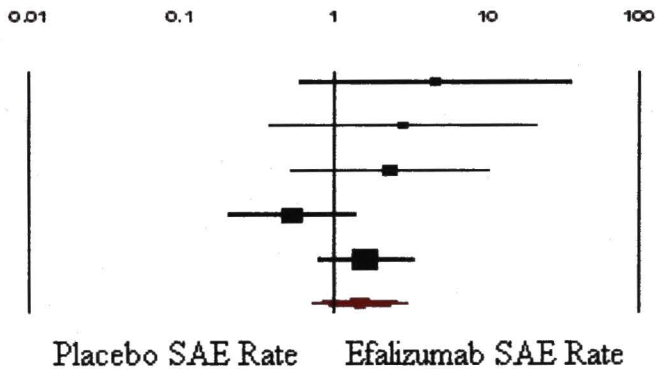
A. Incidence of AE

Citation	RR	Efalizumab	Placebo	n	p
Gordon et al, 2003	1.13	296 / 368	133 / 187	555	0.01
Lebwohl et al, 2003	1.15	406 / 475	91 / 122	597	0.004
Leonardi et al, 2005	1.13	283 / 328	130 / 170	498	0.006
Papp et al, 2006	1.13	369 / 449	172 / 236	685	0.005
Dubertret et al, 2006	1.22	383 / 529	157 / 264	793	<.001
Combined	**1.15**	**1737 / 2149**	**683 / 979**	**3128**	**<.001**



B. Incidence of SAE

Citation	RR	Efalizumab	Placebo	n	p
Gordon et al, 2003	4.57	9 / 368	1 / 187	555	0.11
Lebwohl et al, 2003	2.83	11 / 475	1 / 122	597	0.29
Leonardi et al, 2005	2.07	8 / 328	2 / 170	498	0.34
Papp et al, 2006	0.53	8 / 449	8 / 236	685	0.19
Dubertret et al, 2006	1.61	29 / 529	9 / 264	793	0.20
Combined	**1.43**	**65 / 2149**	**21 / 979**	**3128**	**0.32**



C. Sensitivity Analysis of SAE

Citation	RR	Efalizumab	Placebo	n	p
Gordon et al, 2003	4.57	9 / 368	1 / 187	555	0.11
Lebwohl et al, 2003	2.83	11 / 475	1 / 122	597	0.29
Leonardi et al, 2005	2.07	8 / 328	2 / 170	498	0.34
Dubertret et al, 2006	1.61	29 / 529	9 / 264	793	0.20
Combined	**1.92**	**57 / 1700**	**13 / 743**	**2443**	**0.03**

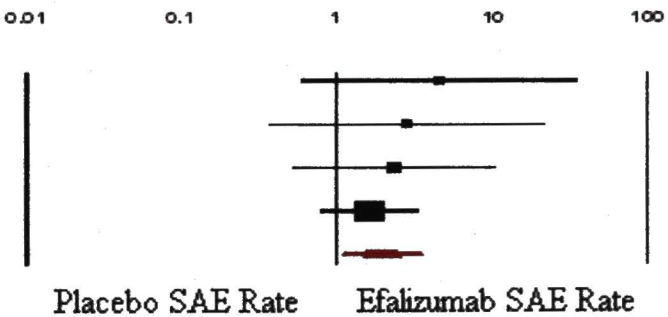
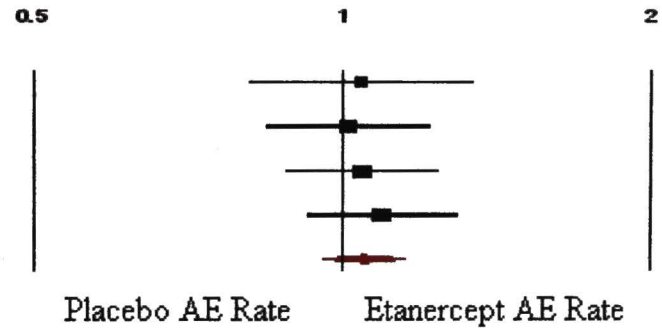


FIGURE 8. Etanercept Safety Evaluation

A. Incidence of AE

Citation	RR	Etanercept	Placebo	n	p
Gottlieb et al, 2003	1.04	40 / 57*	37 / 55*	112	0.74
Leonardi et al, 2003	1.02	235 / 486*	79 / 166*	652	0.87
Papp et al, 2005	1.05	201 / 390*	95 / 193*	583	0.60
Tyring et al, 2006	1.10	153 / 312	137 / 306	618	0.29
Combined	**1.05**	**629 / 1245**	**348 / 720**	**1965**	**0.28**

*Data from FDA reports



B. Incidence of SAE

Citation	RR	Etanercept	Placebo	n	p
Gottlieb et al, 2003	0.97	2 / 57	2 / 55	112	0.97
Leonardi et al, 2003	0.61	9 / 486*	5 / 166*	652	0.37
Papp et al, 2005	2.47	10 / 390*	2 / 193*	583	0.22
Tyring et al, 2006	1.96	6 / 312	3 / 306	618	0.33
Combined	**1.17**	**27 / 1245**	**12 / 720**	**1965**	**0.66**

*Data from FDA reports

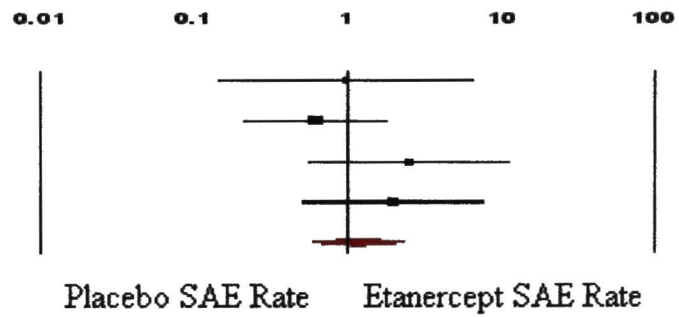
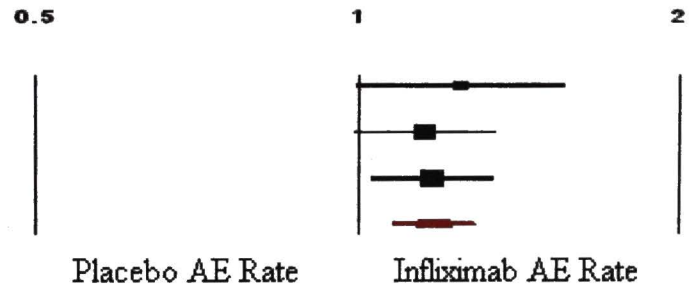


FIGURE 9. Infliximab Safety Evaluation

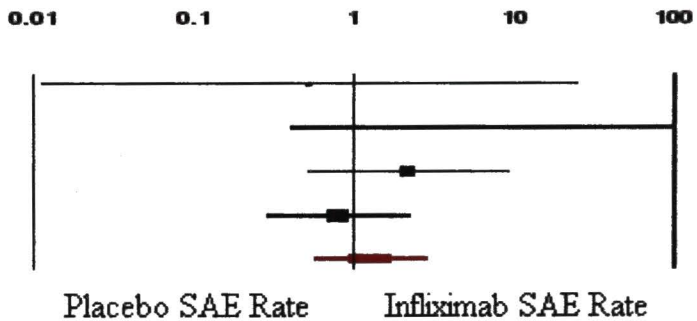
A. Incidence of AE

Citation	RR	Infliximab	Placebo	n	p
Gottlieb et al, 2004	1.25	154 / 197	32 / 51	248	0.02
Reich et al, 2005	1.15	244 / 298	54 / 76	374	0.04
Menter et al, 2006	1.17	412 / 627	116 / 207	834	0.01
Combined	**1.18**	**810 / 1122**	**202 / 334**	**1456**	**<.001**



B. Incidence of SAE

Citation	RR	Infliximab	Placebo	n	p
Chaudhari et al, 2001	0.52	0 / 22	0 / 11	33	0.74
Gottlieb et al, 2004	6.57	12 / 197	0 / 51	248	0.12
Reich et al, 2005	2.17	17 / 298	2 / 76	374	0.28
Menter et al, 2006	0.79	12 / 627	5 / 207	834	0.66
Combined	**1.26**	**41 / 1144**	**7 / 345**	**1489**	**0.58**



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