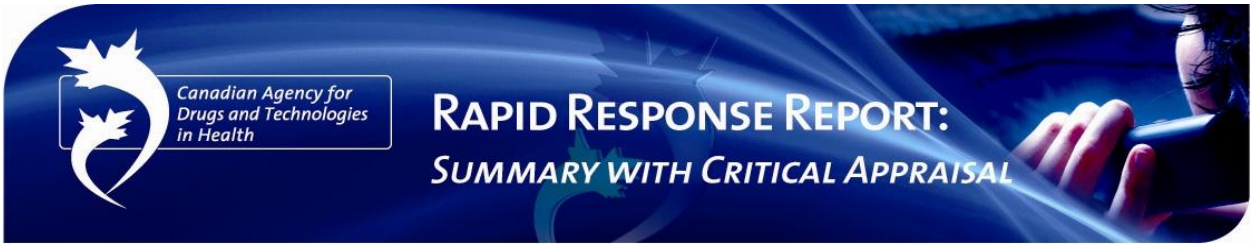

TITLE: Infliximab versus Methotrexate, Etanercept, Adalimumab, and Ustekinumab for Plaque Psoriasis: A Review of the Comparative Clinical Efficacy, Safety and Cost Effectiveness

DATE: 30 July 2012

CONTEXT AND POLICY ISSUES

According to large-scale population studies conducted in the United Kingdom in 2006, psoriasis affects 1.5% of individuals and if these prevalence rates are apply to the Canadian population, more than 500,000 Canadians could be diagnosed with psoriasis.[1] The most common clinical form of psoriasis is plaque psoriasis, encompassing approximately 80% of psoriasis patients.[2,3] Plaque psoriasis is a chronic, relapsing, inflammatory skin disorder characterized by red plaques, usually covered by silvery white scales, distributed over extensor body surfaces and the scalp.[4,5] These psoriatic plaques are caused by the erroneous activation of T-cells, which trigger inflammation and rapid turnover of skin cells.[1]

Psoriasis disease severity is primarily measured by a psoriasis area and severity index (PASI), which is a score from 0 (no disease) to 72 (maximal disease) based on the redness, scaliness, and thickness of the lesions and the affected body surface area.[2,6] In clinical trials, PASI measurements are compared to baseline scores and the most well-established clinical endpoint is a 75% reduction in score from baseline (PASI 75).[5,6] Another tool used to assess disease severity is the dermatology life quality index (DLQI), a 10-item questionnaire used to assess health-related quality of life (HRQoL) in patients with skin conditions.[7]

There are a variety of management options for psoriasis, but no permanent cure.[4] Mild-to-moderate forms of psoriasis are treated with topical therapy and phototherapy, while moderate-to-severe forms (PASI score ≥10) require systemic or biologic therapy.[2] These therapies include: the disease-modifying anti-rheumatic drug, methotrexate; the tumor necrosis factor-alpha (TNF-α) blockers, adalimumab, etanercept, and infliximab; and the inhibitor of interleukin (IL)-12 and IL-23, ustekinumab. Infliximab has been recommended for the treatment of adults with very severe plaque psoriasis that have failed to respond to standard therapies such as methotrexate, cyclosporine, or ultraviolet radiation, or are intolerant to these treatments.[8]

The purpose of this review is to examine the comparative clinical efficacy, safety, and cost-effectiveness of infliximab versus methotrexate, etanercept, adalimumab, or ustekinumab for the treatment of adults with plaque psoriasis.

RESEARCH QUESTIONS

1. What is the comparative clinical efficacy of infliximab versus methotrexate, etanercept, adalimumab or ustekinumab for the treatment of adults with plaque psoriasis?
2. What is the comparative safety of infliximab versus methotrexate, etanercept, adalimumab or ustekinumab for the treatment of adults with plaque psoriasis?
3. What is the cost-effectiveness of infliximab versus methotrexate, etanercept, adalimumab or ustekinumab for the treatment of adults with plaque psoriasis?

KEY MESSAGE

Infliximab was found to be more effective than methotrexate, etanercept, adalimumab, and ustekinumab through meta-analyses and one randomized controlled trial. Limited data on safety found that the use of infliximab was associated with an increased risk of experiencing an adverse event than methotrexate or 50 mg etanercept. Despite having a high efficacy, the recommended dose of 5mg/kg infliximab was found to be less cost effective than methotrexate, 25 mg etanercept, adalimumab, or 90 mg ustekinumab.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2012, Issue 6), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and June 27, 2012.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with plaque psoriasis
Intervention	Infliximab
Comparator	Methotrexate, etanercept, adalimumab, ustekinumab
Outcomes	Clinical effectiveness, length of effect, number of treatments for control of symptoms, adverse events, cost effectiveness
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), economic evaluations

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications or included in a selected systematic review, or were published prior to 2007.

Critical Appraisal of Individual Studies

The quality of included systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[9] The quality of RCTs were evaluated using the Downs and Black instrument.[10] A guidelines for appraisal of economic studies by Drummond et al. was used to assess the quality of included cost-effectiveness studies.[11] A numeric score was not calculated for each study. Instead, strengths and limitations of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 100 citations. Upon screening titles and abstracts, 79 citations were excluded and 21 potentially relevant articles were retrieved for full-text reviews. An additional two potentially relevant reports were identified through grey literature searching. Of the 23 potentially relevant reports, 12 were included in this review. The study selection process is outlined in a PRISMA flowchart (Appendix 1). Six systematic reviews, one RCT, and five economic evaluations met inclusion criteria.

Summary of Study Characteristics

Details on study characteristics of the clinical studies and economic evaluations can be found in Appendices 2 and 3, respectively

Country of origin.

Of the six systematic reviews, four were from Germany[12-15] and two were from the USA.[16,17] The open-label RCT[7] was from Germany. Of the economic evaluations, one each came from Spain,[18] Italy,[19] Germany,[20] USA,[21] and the UK.[22]

Study design

Six systematic reviews,[12-17] one open-label RCT,[7] and five economic evaluations[18-22] were included in this review. Meta-analyses of RCTs were performed in all of the included systematic reviews. In all the included economic evaluations, a cost-effectiveness analysis was performed using trial data from a literature search of the relevant drugs for the treatment of patients with moderate-to-severe plaque psoriasis.[18,20-23] The third party payer's perspective was used in all of the economic studies.

Patient population

All studies included patients with moderate-to-severe plaque psoriasis that underwent treatment with biologic agents. Of the systematic reviews, two specified the criteria in which patients would be classified as having moderate-to-severe plaque psoriasis. One systematic review[14] included

studies of patients with a PASI score ≥7 and another review[15] included studies of patients with plaque psoriasis involving >10% of body surface area. The open-label RCT included patients with plaque psoriasis involving >10% of their body surface area and a PASI score 12.[7] All of the economic studies focused on the treatment of patients with moderate-to-severe plaque psoriasis.

Interventions and comparators

All studies compared the use of intravenous infliximab at a dose of 5 mg/kg and/or 3 mg/kg to at least one other biologic agent. All systematic reviews included studies that used subcutaneous etanercept at a dose of 25 mg or 50 mg twice-weekly.[12-17] Four systematic reviews also included studies that administered subcutaneous adalimumab at an initial dose of 80 mg followed by 40 mg every other week.[12-14,16] Two systematic reviews included studies that used ustekinumab at 45 mg or 90 mg doses.[12,13] The RCT compared the use of infliximab to methotrexate given at 15 to 20 mg/week.[7] All of the economic studies included etanercept and adalimumab, while only one study[18] included ustekinumab and one study[22] included methotrexate.

Outcomes measured

All of the included studies used PASI 75 as a clinical endpoint, which refers to a 75% reduction in the PASI score from baseline. Four systematic reviews[13,15-17], and one economic study[22] used PASI 50 and PASI 90 as an outcome in addition to PASI 75. One systematic review[17] examined the incidence of adverse events. The open-label RCT,[7] and one economic study[21] considered changes in the dermatology life quality index (DLQI) as an outcome.

Summary of Critical Appraisal

A summary of critical appraisal of individual studies can be found in Appendix 4.

All systematic reviews were based on comprehensive literature searches and meta-analyses were performed using RCTs. The methodology used to pool data in the meta-analyses was well detailed and appropriate. Three meta-analyses[13,15,16] employed a mixed-treatment comparison evidence synthesis while the other studies compared each treatment to placebo individually. The scientific quality of included studies was assessed in three of the six reviews.[12,13,16] Publication bias was not assessed in any of the systematic reviews. One weakness of all of the systematic reviews was the lack of head-to-head trials included in the meta-analysis as the majority of existing trials are placebo-controlled.

The RCT described an adequate method of randomization and losses to follow-up.[7] In addition, an active comparator was used rather than placebo and all patients received assigned treatments. One weakness of this study was the lack of blinding in the patients and outcome assessors, which may bias the efficacy and safety results. For example, increased safety concerns regarding infusion-related reactions related to infliximab may have led to more hospitalizations. In addition, patients were able to switch between treatments if necessary, which may affect reported adverse events due to an imbalance in study medication exposure. No statistical analysis was performed for the safety data, making it difficult to compare numbers between the two treatment groups.

All of the economic evaluations were conducted in a similar manner in that a literature review of the relevant drugs was performed. The main limitation of the included economic studies was the

source of data used to generate the economic models. The use of data from prospective controlled trials may not be generalizable to real-life conditions and the majority of the data was from placebo-controlled trials rather than head-to-head trials. In addition, all of the studies were conducted in various countries and may not be applicable to other countries due to drug costs and guidelines used to plan out the course of treatments.

Summary of Findings

Individual study findings are summarized in Appendix 5 and 6 for clinical and economic studies, respectively.

What is the comparative clinical efficacy of infliximab versus methotrexate, etanercept, adalimumab or ustekinumab for the treatment of adults with plaque psoriasis?

All of the systematic reviews performed meta-analyses using mainly placebo-controlled trials to compare the efficacy of biologic agents to treat patients with moderate-to-severe plaque psoriasis. Two systematic reviews[12,17] reported risk difference (RD) of achieving PASI 75 when compared with placebo, while the remaining systematic reviews[13-16] reported relative risk (RR) of achieving PASI 75 when compared to placebo. In all of the systematic reviews, infliximab at the standard dose of 5 mg/kg was superior in efficacy to etanercept, adalimumab, ustekinumab, and methotrexate. This rank in efficacy was determined by comparing the risk of achieving PASI 75 using each drug versus placebo. The meta-analyses that performed mixed-treatment comparisons also calculated the probability of achieving a PASI 75 response and found that infliximab had the highest probability of response compared with etanercept, adalimumab, ustekinumab, methotrexate, supportive care, and placebo.[13,15,16]

This difference in infliximab superiority increased when PASI 90 was used as an outcome, which is the probability of achieving an even more complete recovery (90%) from baseline.[13,15-17] Therefore, according to meta-analyses of placebo-controlled trials, patients had the greatest chance of achieving PASI 75 when on infliximab therapy compared to other biologic and non-biologic agents. High-dose ustekinumab (90 mg) was the next most efficacious treatment followed by low-dose ustekinumab (45mg).[12,13] All systematic reviews also found that treatment with infliximab and adalimumab was superior to etanercept and one systematic review[16] found that all of these agents were superior to conventional systemic therapies such as methotrexate.

The open-label RCT compared the efficacy of infliximab at a dose of 5 mg/kg to methotrexate and found that infliximab was significantly more effective in achieving PASI 75 at weeks 16 and 26.[7] The proportion of patients achieving PASI 50 and PASI 90 was also significantly higher in the infliximab group than the methotrexate group. Similar results were obtained when physician global assessment (PGA) and DLQI was analyzed.

What is the comparative safety of infliximab versus methotrexate, etanercept, adalimumab or ustekinumab for the treatment of adults with plaque psoriasis?

One systematic review found that there was an 18% increased risk of experiencing one or more adverse events for patients taking infliximab when compared to placebo within 10 to 30 weeks of treatment.[17] In this review, the safety of etanercept at a dose of 50 mg twice-weekly was also examined. There was a 5% increase risk of experiencing one or more adverse events for patients taking 50 mg etanercept compared to placebo within 12 to 24 weeks of treatment. The

most common adverse events experienced with infliximab were upper respiratory tract infection, headache, increased hepatic enzymes, and infection.

In the open-label RCT, the incidence of adverse events and severe adverse events was higher in the infliximab group compared to the methotrexate group.[7] Statistical significance of this difference was not reported. There were more withdrawals due to adverse events in the infliximab group compared to the methotrexate group, and the majority of these events were infusion-related reactions as infliximab is administered intravenously while methotrexate was given in tablet form.

What is the cost-effectiveness of infliximab versus methotrexate, etanercept, adalimumab or ustekinumab for the treatment of adults with plaque psoriasis?

In all of the economic evaluations, sensitivity analyses found that all calculated cost ratios were sensitive to variations in PASI 75 efficacy and the cost of the drug.

One study from Spain found that adalimumab had the best incremental cost-effectiveness ratio (ICER) with a mean cost of €8013 per PASI 75 responder, followed by 25 mg etanercept and 45 mg ustekinumab.[18] The pharmaceutical company sales price was used to determine drug cost. Infliximab was found to be the most efficacious, but the least cost effective due to the high cost of treatment. For 10 weeks of 5 mg/kg infliximab treatment, the cost per PASI 75 responder was €10,523; for 24 weeks, it was €17,122.

One study from Italy attempted to look at longer-term treatments using biologic agents for plaque psoriasis using drug costs from the National Drug Formulary.[19] When compared to etanercept and adalimumab at week 24 and weeks 48-50, infliximab was more cost-effective than 50 mg etanercept given twice-weekly. However, infliximab was not as cost-effective as adalimumab or 25 mg etanercept given twice-weekly.

Two studies, one from Germany[20] and one from the USA[21] conducted cost-effectiveness analyses of biological agents for the remission induction phase of plaque psoriasis therapy. Both studies found that the most cost-effective treatment for achieving PASI 75 was infliximab administered at 3 mg/kg, which is not the recommended treatment dose for patients with moderate-to-severe plaque psoriasis. Infliximab administered at the recommended treatment dose of 5 mg/kg was less cost-effective than adalimumab and 90 mg ustekinumab.[20,21] In both studies, etanercept at 25 mg or 50 mg was the least cost-effective agent when compared to infliximab, adalimumab, and ustekinumab.

One study was conducted in North America but used drug pricing and guidelines from the UK to generate the economic model.[22] QALYs and ICERs were calculated compared with supportive care and adalimumab was found to be most cost effective (£30,538/QALY), followed by etanercept at 25 mg and 50 mg dosage. Infliximab provided the most benefit, but its high cost outweighed the benefit, resulting in an ICER of £42,492/QALY. Methotrexate treatment was found to be cost saving when compared to supportive care due to costs saved through reduced hospitalizations exceeding drug-related costs.

Limitations

In all of the included systematic reviews and economic evaluations, the definition for moderate-to-severe plaque psoriasis differed or was not specified, which may affect the ability to generalize results and to compare results between studies. Also, there were no included trials that were head-to-head comparisons involving infliximab, limiting the ability to directly compare the biologic agents of interest to infliximab and determine which is the most efficacious. In addition, the majority of trials used for both meta-analyses and economic analyses were no longer than 24 weeks in duration, showing a lack of long-term data that would be useful in a disease such as plaque psoriasis where therapy would be required for life. The available data on maintenance treatment beyond 24 weeks are scarce and heterogeneous.[12] There was overlap of included RCTs between systematic reviews, which may have resulted in an overestimation of the strength of evidence available. There were fewer studies that included methotrexate or ustekinumab as a comparator as methotrexate is typically used as first-line therapy prior to biologic therapies and ustekinumab is a newer drug.

The PASI was used as the clinical endpoint in all of the included trials, and it is the most common assessment measure for plaque psoriasis. However, the PASI is not an ideal measure of the severity of psoriasis and may be inaccurate in assessing the extent of disease.[24] In addition, the PASI may not reflect how the disease is affecting the patient's quality of life, a measure that is addressed with the DLQI. A small number of included studies (n=2) employed the DLQI as an outcome measure.

None of the economic studies were performed using Canadian data. The studies conducted in Europe used European prices and treatment guidelines, thus limiting their applicability in the Canadian setting and making it difficult to compare results between analyses. All of the economic studies used data from clinical trials, which may not be representative of real-life settings. Only one study[22] used QALY as an outcome while all other studies used the PASI 75 score, limiting comparability of cost-effectiveness results to other disease areas.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

According to meta-analyses of placebo-controlled RCT trials, infliximab at a dose of 5 mg/kg appears to be more effective than methotrexate, etanercept, adalimumab, and ustekinumab for achieving PASI 75 in patients with moderate-to-severe plaque psoriasis. One open-label RCT found infliximab to be more effective than methotrexate.[7]

Limited evidence was identified regarding the comparative safety of infliximab versus methotrexate, etanercept, adalimumab, and ustekinumab. Infliximab was found to be associated with an increase in the incidence of adverse events when compared with placebo, and with a slight increase when compared to 50 mg etanercept or methotrexate.

Results from economic evaluations varied due to the use of drug prices and guidelines from different countries. Infliximab administered at 3 mg/kg was found to be more cost effective than etanercept, adalimumab, and ustekinumab in two studies, but this is not the recommended treatment dose for plaque psoriasis. This may emphasize a need for further economic analyses and consideration when determining an appropriate treatment regimen. Infliximab administered at the currently recommended dose of 5 mg/kg was found to be less cost effective than methotrexate, 25 mg etanercept, adalimumab, and 90 mg ustekinumab. From the trial data, infliximab was found to be the most efficacious, but this is offset by its high cost.

Traditional systemic agents such as methotrexate for the treatment of moderate-to-severe plaque psoriasis can provide effective control in many cases, but biologic agents such as infliximab, etanercept, adilimumab, and ustekinumab provide alternate treatment options. Infliximab, with its efficaciousness, may be an attractive option for these patients. Additional head-to-head trials will need to be performed to determine direct comparative effectiveness, but a number of systematic reviews have found infliximab to be superior to other biologic agents for the treatment of plaque psoriasis, through indirect comparison.

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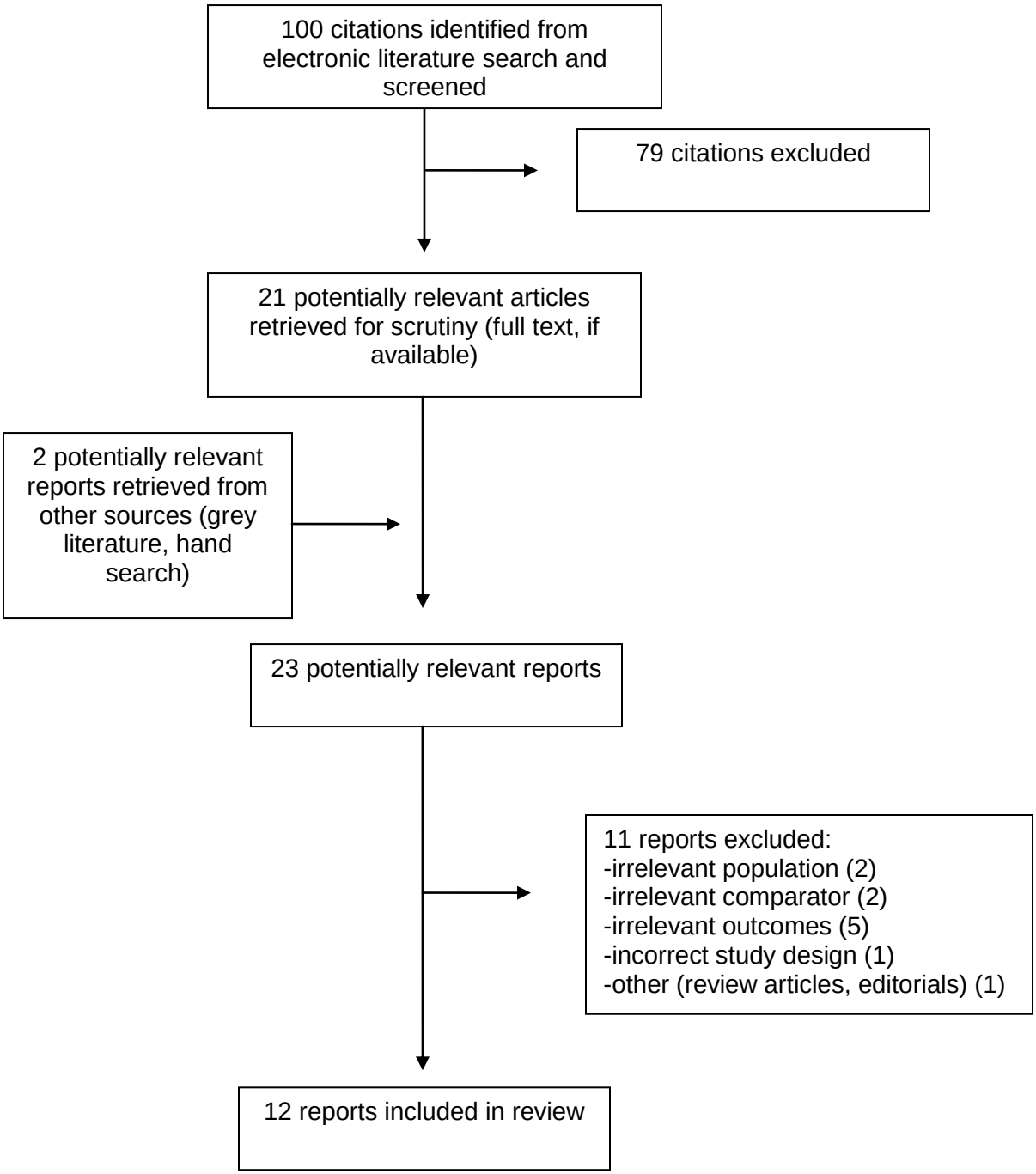
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention*	Comparator	Clinical Outcomes Measured
Lucka[12] 2012 Germany	Systematic review and meta-analysis May 2005-July 2011	27 prospective clinical trials (20 RCTs) longer than 16 weeks including patients with moderate-to-severe psoriasis undergoing systemic therapy 7 RCTs eligible for meta-analysis	Infliximab Etanercept 2x25 mg/week or 2x50 mg/week Adalimumab Ustekinumab 45 mg or 90 mg at weeks 0 and 4, then every 12 weeks	Placebo	PASI 75 response rate
Reich[13] 2012 Germany	Systematic review and network meta-analysis Jan 1995-Oct 2008	20 RCTs including adult patients with plaque psoriasis who were treated with adalimumab, efalizumab, etanercept, infliximab, or ustekinumab as monotherapy	Infliximab IV 5 mg/kg at weeks 0, 2, 6, then every 8 weeks Etanercept 2x50 mg/week Adalimumab 80 mg at week 0, 40 mg at week 1, then 40 mg every 2 weeks Ustekinumab 45 or 90 mg at weeks 0 and 4, then every 12 weeks	Placebo Methotrexate (one RCT, compared to adalimumab) Etanercept (one RCT, compared to ustekinumab)	PASI 50, PASI 75, and PASI 90 response rates
Bansback[16] 2009 USA	Systematic review and network meta-analysis Until Jan 2007	22 RCTs including 9704 patients with moderate-to-severe psoriasis who received systemic therapies	Infliximab IV 5 mg/kg (4 RCTs including 1495 patients) Etanercept 2x 50 mg/week (4 RCTs including 1965 patients) Adalimumab 40 mg bi-weekly (3 RCTs including 1630 patients)	Placebo Methotrexate 15-22.5 mg weekly (one RCT, compared to adalimumab)	PASI 50, PASI 75, and PASI 90 response rates

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention*	Comparator	Clinical Outcomes Measured
Brimhall[17] 2008 USA	Systematic review and meta-analysis Until July 2006	16 RCTs including 7931 patients with moderate-to-severe plaque psoriasis undergoing treatment with alefacept, efalizumab, etanercept, or infliximab	Infliximab IV 5 mg/kg (4 RCTs including 1495 patients) Etanercept (4 RCTs including 2017 patients)	Placebo	PASI 50, PASI 75, and PASI 90 response rates Adverse events
Schmitt[14] 2008 Germany	Systematic review and meta-analysis Until Dec 2007	24 RCTs including 9384 patients with moderate-to-severe chronic plaque psoriasis (PASI score ≥7) undergoing biologic and nonbiologic systemic treatments 16 double-blind, placebo-controlled RCTs eligible for meta-analysis	Infliximab IV 5 mg/kg (3 RCTs including 1050 patients) Etanercept: 2x25 mg/week (3 RCTs including 829 patients) or 2x50 mg/week (3 RCTs including 1335 patients) Adalimumab (one RCT including 1212 patients)	Placebo	PASI 75 response rate
Reich[15] 2008 Germany	Systematic review and network meta-analysis Jan 2004-Dec 2006	16 RCTs including 6520 patients with active but clinically stable plaque psoriasis (≥10% body surface area) undergoing treatment with alefacept, efalizumab, etanercept, or infliximab	Infliximab IV 5 mg/kg every 2-8 weeks (4 RCTs including 1495 patients) Etanercept (4 RCTs including 1965 patients)	Placebo	PASI 50, PASI 75 and PASI 90 response rates
Barker[7] 2011 Germany	Open-label RCT 26 weeks	868 adult patients with moderate-to-severe plaque psoriasis (PASI score ≥12, >10% body surface area) never before treated with methotrexate	Infliximab IV 5 mg/kg at weeks 0, 2, 6, 14 and 22	Methotrexate 15 mg/week with a dose increase to 20 mg/week at week 6 (tablet)	PASI 75 response rate at week 16 and week 26, PGA score at week 16 and week 26, HRQoL

HRQoL=health-related quality of life; IV=intravenous; PASI= psoriasis area and severity index; PGA=physician global assessment; RCT=randomized controlled trial
*Only interventions of interest were indicated within systematic reviews

APPENDIX 3: Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Type of Economic Evaluation, Study Perspective	Patient Population	Interventions	Comments
Ferrandiz[18] 2012 Spain	Cost-effectiveness analysis Spanish National Health System (health care payer) perspective	Patients with moderate-to-severe plaque psoriasis	Infliximab 5 mg/kg Etanercept 2x25 mg/week or 2x50 mg/week Adalimumab 80 mg at week 0 followed by 40 mg every 2 weeks Ustekinumab 45 mg or 90 mg	Decision tree built using data from placebo-controlled RCTs Outcome: patient achieving PASI 75 Source of drug costs: pharmaceutical company sales price Cost of placebo assumed to be zero dollars All costs were in euros Incremental cost-effectiveness ratio calculated Sensitivity analysis based on most and least favourable scenarios for each treatment Source of funding: industry
de Portu[19] 2010 Italy	Cost-effectiveness analysis Italian third party payer's perspective (National Health Service)	Patients with moderate-to-severe plaque psoriasis (assume 80 kg weight)	Infliximab 5 mg/kg Etanercept 2x25 mg/week or 2x50 mg/week Adalimumab 80 mg initial dose followed by 40 mg every other week	Outcome: patients achieving PASI 75 Time horizon: 24 weeks (short-term) and 48-50 weeks (long-term) Source of drug costs: National Drug Formulary All costs were in euros Incremental cost-effectiveness ratio calculated One-way and two-way sensitivity analysis Source of funding: not stated
Schmitt-Rau[20] 2010 Germany	Cost-effectiveness analysis German third-party payer's perspective	Patients with moderate-to-severe plaque psoriasis (assume 80 kg weight)	Infliximab 5 mg/kg or 3 mg/kg Etanercept 2x25 mg/week or 2x50 mg/week Adalimumab 80 mg loading dose followed by 40 mg every other week Ustekinumab 45 mg or 90 mg	Outcome: patient achieving PASI 75 Time horizon: 12 weeks Source of drug costs: pharmacy retail prices as listed in the German 'Rote Liste' Costs were calculated on the basis of the German physicians' fee schedule and treatments based on European psoriasis guidelines Cost of placebo assumed to be zero dollars

First Author, Publication Year, Country	Type of Economic Evaluation, Study Perspective	Patient Population	Interventions	Comments
				All costs were in euros Incremental cost effectiveness relative to placebo One-way sensitivity analysis Source of funding: not stated
Nelson[21] 2008 USA	Cost-effectiveness analysis Third-party payer's perspective	Patients with moderate-to-severe plaque psoriasis (assume 80 kg weight)	Infliximab 3 mg/kg or 5 mg/kg Etanercept 2x25 mg/week or 2x50 mg/week Adalimumab 40 mg every other week	Outcome: patient achieving minimally important difference in DLQI and PASI 75 Time horizon: 12 weeks Source of drug costs: average wholesale price of drug Costs were calculated on the basis of the 2006 Medicare fee and physician reimbursement schedule, manufacturer's published guidelines, clinical practice, and dosage used in the RCTs Cost of placebo assumed to be zero dollars All costs were in USD One-way sensitivity analysis Source of funding: industry
Sizto[22] 2008 UK	Cost-effectiveness analysis	Patients with moderate-to-severe plaque psoriasis	Infliximab 5 mg/kg Etanercept 2x25 mg/week or 2x50 mg/week Adalimumab 40 mg every other week Methotrexate 15-25 mg/week	Outcome: patient achieving PASI 50/75/90, QALYs compared with supportive care Time horizon: 12-16 weeks (depending on trial and drug) Source of drug costs: British National Formulary Analysis followed a clinical pathway determined by established UK guidelines All costs were in British pounds One-way sensitivity analysis Source of funding: industry (manufacturer of adalimumab)

DLQI=dermatology life quality index; PASI=psoriasis area severity index

APPENDIX 4: Summary of Critical Appraisal

First Author, Publication Year	Strengths	Limitations
Systematic Reviews		
Lucka[12] 2012	• Comprehensive literature search based on pre-defined criteria • Summary of study characteristics provided • Quality of included studies assessed	• Number of patients per included trial not stated • Very few trials included in meta-analysis • Risk of publication bias not assessed
Reich[13] 2012	• Comprehensive literature search based on pre-defined criteria • Grey literature was searched • Summary of study characteristics provided • Quality of studies assessed	• Number of patients per included trial not stated • Risk of publication bias not assessed
Bansback[16] 2009	• Comprehensive literature search based on pre-defined criteria • Grey literature was searched • Summary of study characteristics provided • Reasons for study exclusions detailed • Quality of included studies assessed	• Study selection and data extraction not performed in duplicate independently • Risk of publication bias not assessed
Brimhall[17] 2008	• Comprehensive literature search based on pre-defined criteria • Grey literature was searched • Summary of study characteristics provided	• Unclear if quality of included studies were considered • Risk of publication bias not assessed • No direct head-to-head trials were identified for inclusion in the meta-analysis
Schmitt[14] 2008	• Comprehensive literature search based on pre-defined criteria • Summary of study characteristics provided • Separate analyses were performed for qualitative and quantitative measures	• Unclear if quality of included studies were considered • Risk of publication bias not assessed • Unclear if grey literature was included • No direct head-to-head trials were identified for inclusion in the meta-analysis
Reich[15] 2008	• Comprehensive literature search based on pre-defined criteria • Summary of study characteristics provided • Both random and fixed-effect analyses were performed	• Unclear if quality of included studies were considered • Risk of publication bias not assessed • No direct head-to-head trials were identified for inclusion in the meta-analysis
Randomized controlled trial		
Barker[7] 2011	• Method of randomization described • Description of losses to follow-up • Active comparator used • All patients received assigned treatments	• Power calculation not performed to determine sample size • Patients and outcome assessors not blinded • Crossover design may affect data reporting • No statistical analysis was performed on the safety data
Economic Evaluations		
Ferrandiz[18] 2012	• Research question clearly stated • The source for effectiveness data was stated • Effectiveness data was drawn from a literature review of each relevant drug and meta-analysis performed for efficacy data • Length of each treatment was specified in the analysis	• Cost effectiveness was based on short-term data, limiting applicability to long-term treatment • Cost of diagnostic tests not included • Cost of drugs based on prices in Spain, which may differ in other countries
de Portu[19] 2010	• Research question clearly stated • The source for effectiveness data was stated	• Data were based on drug costs in Italy, limiting generalizability of findings • Lack of head-to-head trials identified in

First Author, Publication Year	Strengths	Limitations
	• Both short and long-term trials were considered • Cost-effectiveness of infliximab compared to other agents was calculated	analysis • Data from RCTs may not correspond to outpatient setting • Costs other than medication costs not considered
Schmitt-Rau[20] 2010	• Research question clearly stated • The source for effectiveness data was stated • Effectiveness data was drawn from a literature review of each relevant drug	• Cost effectiveness was based on one 12-week treatment course, limiting applicability to long-term treatment • Data from RCTs may not correspond to outpatient setting • Data were based on guidelines and fees in Germany only, limiting the generalizability of findings • All included RCTs compared treatment to placebo, which may limit comparability between treatments
Nelson[21] 2008	• Research question clearly stated • The source for effectiveness data was stated • Effectiveness data was drawn from a systematic review of each relevant drug	• Cost effectiveness was based on one 12-week treatment course, limiting applicability to long-term treatment • Data from RCTs may not correspond to outpatient setting • All included RCTs compared treatment to placebo, which may limit comparability between treatments
Sizto[22] 2008 UK	• Research question clearly stated • The source for effectiveness data was stated • Effectiveness data was drawn from review of the literature of each relevant drug • The primary outcome was clearly reported (QALY)	• Time horizon was not explicitly stated • Lack of long-term data identified • Data was based on pricing of drugs and guidelines in the UK, limiting generalizability • Data from RCTs may not correspond to outpatient setting

APPENDIX 5: Summary of Findings – Clinical

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Systematic Reviews		
Lucka[12] 2012	RD for achieving PASI 75 compared to placebo (95% CI) **Infliximab:** 0.78 (0.72-0.83) **Etanercept 2x25 mg/week:** 0.45 (0.34-0.56) **Etanercept 2x50 mg/week:** 0.56 (0.49-0.62) **Adalimumab:** 0.60 (0.45-0.74) **Ustekinumab 45 mg:** 0.70 (0.64-0.77) **Ustekinumab 90 mg:** 0.77 (0.71-0.83) After 24 weeks, a decrease in efficacy for infliximab, adalimumab and etanercept was observed.	"Among the biologics, infliximab and ustekinumab can be considered the most efficacious treatments for psoriasis after 24 weeks of treatment with PASI 75 responses of 82% (infliximab) and 76.1% as well as 85.0% (45 mg and 90 mg dose ustekinumab)…The available data on maintenance treatment beyond 24 weeks are extremely scarce and heterogeneous." (p. 10, 12)
Reich[13] 2012	A network meta-analysis was performed using Bayesian methods. RR for achieving PASI 50 compared to placebo (95% CI) **Infliximab:** 7.3 (6.6-8.1) **Etanercept 2x25 mg/week:** 5.1 (4.4-5.8) **Etanercept 2x50 mg/week:** 6.0 (5.4-6.6) **Ustekinumab 45 mg:** 6.9 (6.3-7.6) **Ustekinumab 90 mg:** 7.1 (6.5-7.8) RR for achieving PASI 75 compared to placebo (95% CI) **Infliximab:** 22.6 (19.3-26.5) **Etanercept 2x25 mg/week:** 10.9 (8.6-13.7) **Etanercept 2x50 mg/week:** 14.7 (12.5-17.1) **Ustekinumab 45 mg:** 19.5 (16.8-22.6) **Ustekinumab 90 mg:** 22.6 (19.3-26.5) RR for achieving PASI 90 compared to placebo (95% CI) **Infliximab:** 100.2 (76.0-126.9) **Etanercept 2x25 mg/week:** 28.1 (19.3-39.8) **Etanercept 2x50 mg/week:** 45.2 (35.2-56.8) **Ustekinumab 45 mg:** 74.2 (59.5-93.0) **Ustekinumab 90 mg:** 84.8 (68.6-104.6) Probability of achieving PASI 75, % (95% CI) **Infliximab:** 80 (70-87) **Etanercept 2x25 mg/week:** 39 (30-48) **Etanercept 2x50 mg/week:** 52 (45-59) **Ustekinumab 45 mg:** 69 (62-75) **Ustekinumab 90 mg:** 74 (68-80)	"Infliximab has the highest estimated mean probability of response or relative risks followed by ustekinumab 90 mg, ustekinumab 45 mg, adalimumab, etanercept 50 mg, etanercept 25 mg, efalizumab and placebo…There is an estimated 93% probability that infliximab is the most effective treatment followed by an 81% probability that ustekinumab 90 mg is the second most effective treatment and a 79% probability that ustekinumab 45 mg is the third most-effective treatment." (p. 181, 184)
Bansback[16] 2009	A mixed-treatment comparison evidence synthesis was employed. RR for achieving PASI 50 compared to placebo (95% CI) **Infliximab:** 6.68 (5.90-7.55) **Etanercept 2x50 mg/week:** 5.28 (4.58-6.02)	"Our findings suggest that, based on the efficacy outcome probability of a PASI 50, PASI 75 or PASI 90 response, treatment with TNF inhibitors is superior is superior to T-cell modulators and treatment with adalimumab or infliximab is superior to conventional systemic therapies and to etanercept." (p. 216)

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	Methotrexate: 4.74 (3.52-5.73) **Adalimumab:** 6.33 (5.52-7.16) RR for achieving PASI 75 compared to placebo (95% CI) **Infliximab:** 18.93 (15.98-22.52) **Etanercept 2x50 mg/week:** 11.73 (9.40-14.29) **Methotrexate:** 9.76 (6.08-13.19) **Adalimumab:** 16.71 (13.57-20.1) RR for achieving PASI 90 compared to placebo (95% CI) **Infliximab:** 84.51 (65.17-109.8) **Etanercept 2x50 mg/week:** 34.74 (24.77-46.68) **Methotrexate:** 25.99 (12.41-41.38) **Adalimumab:** 65.61 (47.49-87.79) Sensitivity analysis identified dosage to be an important determinant of outcome. Probability of achieving PASI 75 (95% CI) **Infliximab:** 81 (75-86) **Etanercept 2x50 mg/week:** 50 (43-58) **Methotrexate:** 42 (27-54) **Adalimumab:** 71 (63-79)	
Brimhall[17] 2008	A pooled estimate of RR was computed using the Mantel-Haenszel method and random effects model. RR for achieving PASI 75 compared to placebo (95% CI) **Infliximab:** 17.40 (6.41-47.19) **Etanercept 2x25 mg/week:** 10.20 (5.87-17.72) **Etanercept 2x50 mg/week:** 11.73 (8.04-17.11) RR for achieving PASI 90 compared to placebo (95% CI) **Infliximab:** 49.42 (16-01-152.54) **Etanercept 2x50 mg/week:** 21.44 (9.52-48.26) RR for experiencing one or more AEs compared to placebo (95% CI) **Infliximab:** 1.18 (1.07-1.29) – most common AEs were upper respiratory tract infection, headache, increased hepatic enzymes and infection (within 10-30 weeks of treatment) **Etanercept:**1.05 (0.96-1.16, P=0.28) – most common AEs were injection-site reaction, headache, and upper respiratory tract infection (within 12-24 weeks of treatment)	"The RR of PASI 75 achievement was, respectively, 4, 7, 12 and 19 for maintenance doses of alefacept, efalizumab, etanercept and infliximab compared with placebo…Through indirect comparison of these efficacy endpoints, all similarly compared with placebo, the decreasing rank order of efficacy can be concluded as infliximab, etanercept, efalizumab and alefacept. It is stressed that this study is not a head-to-head trial and does not replace the need for future direct comparator trials." (p. 282)

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	RR for experiencing one or more SAEs compared to placebo (95% CI) **Infliximab:**1.26 (5.99-19.61, P=0.58) – most common SAEs were malignancy, infection, infusion reaction, and lupus-like syndrome (within 10-30 weeks of treatment) **Etanercept:** 1.17 (0.59-2.33, P=0.66) – most common SAEs were malignancy, infection, and worsening psoriasis (within 12-24 weeks of treatment) Unless otherwise indicated, all p-values were less than 0.001.	
Schmitt[14] 2008	Response rates of studies considered qualitatively homogenous were pooled by applying a random effects model. RD for achieving PASI 75 compared to placebo (95% CI) **Infliximab:** 0.77 (0.72-0.81) **Etanercept 2x25 mg/week:** 0.30 (0.25-0.35) **Etanercept 2x50 mg/week:** 0.44 (0.40-0.48) **Adalimumab:** 0.64 (0.61-0.68) All P-values were less than 0.00001.	"Infliximab is the most effective treatment option for moderate-to-severe psoriasis, followed by adalimumab. Patients receiving infliximab have an excess chance of 77% over placebo to achieve substantial clinical benefit after 10 weeks of treatment…After 24 weeks of treatment the initial response rates are maintained by infliximab and adalimumab" (p. 522)
Reich[15] 2008	A fixed-effects Mantel-Haenszel model was used to pool RCTs by outcome and dose. Both fixed- and random-effects models were tested in a Bayesian hierarchical model. Pooled RR (fixed effects) for achieving PASI 50 compared to placebo (95% CI) **Infliximab:** 7.35 (4.65-11.61) **Etanercept 2x25 mg/week:** 5.41 (4.10-7.14) **Etanercept 2x50 mg/week:** 5.85 (4.77-7.17) Pooled RR (fixed effects) for achieving PASI 75 compared to placebo (95% CI) **Infliximab:** 25.48 (14.04-46.23) **Etanercept 2x25 mg/week:** 10.68 (6.15-18.57) **Etanercept 2x50 mg/week:** 11.92 (8.17-17.39) Pooled RR (fixed effects) for achieving PASI 90 compared to placebo (95% CI) **Infliximab:** 53.94 (17.65-164.89) **Etanercept 2x50 mg/week:** 23.32 (10.38-52.37) Probability of achieving PASI 75 at 24 weeks, % **Infliximab:** 79.20 **Etanercept 2x25 mg/week:** 51.02 **Etanercept 2x50 mg/week:** 56.44	"According to a fixed-effects model, the pooled RR of patients experiencing a 75% decrease in the PASI after 10 to 12 weeks of treatment compared to placebo was 25.48 for infliximab, 11.92 for etanercept 50 mg twice weekly, 10.68 for etanercept 25 mg twice weekly, 7.41 for efalizumab, and 3.37 for alefacept. Similar trends emerged using analyses by random-effects models…That both the fixed- and random-effects models give similar results supports our conclusions of improved outcomes with infliximab." (p. 1247)

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Randomized controlled trial		
Barker[7] 2011	Percentage of patients achieving PASI 75 at week 16 **Infliximab:** 78 **Methotrexate:** 42 Percentage of patients achieving PASI 75 at week 26 **Infliximab:** 77 **Methotrexate:** 66 PASI reduction from baseline to study endpoint **Infliximab:** 83% **Methotrexate:** 54% A significantly greater proportion of patients taking infliximab achieved PASI 75 at weeks 16 and 26 (P<0.001). The proportion of patients achieving PASI 50, PASI 75 and PASI 90 was significantly higher in the infliximab group than the methotrexate group at all visits (P<0.001) except for week 2 for PASI 90. PGA score of cleared (0) or minimal (1) at week 16 **Infliximab:** 76% **Methotrexate:** 38% PGA score of cleared (0) or minimal (1) at week 26 **Infliximab:** 73% **Methotrexate:** 28% A significantly greater proportion of patients taking infliximab achieved a PGA score of cleared or minimal at weeks 16 and 26 (P<0.001). Improvement in HRQoL was greater in the infliximab group than in the methotrexate group as measured by the DLQI, SF-36 and EQ-5D metrics. Percentage of patients experiencing at least one AE up to week 16 **Infliximab:** 64 (infusion-related reactions, nasopharyngitis, headache most common) **Methotrexate:** 63 (nasopharyngitis, fatigue, headache, nausea most common) Percentage of patients experiencing at least one SAE up to week 16 **Infliximab:** 6 **Methotrexate:** 2	"RESTORE1 demonstrates greater efficacy of infliximab compared with MTX in both skin and HRQoL measures in MTX-naïve patients with moderate-to-severe plaque psoriasis. Infliximab was significantly more effective in achieving PASI 75 and PGA score of cleared or minimal at weeks 16 and 26. A greater proportion of infliximab patients achieved most secondary endpoints, including PASI 50 and PASI 90 response." (p. 1115)

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	<u>Percentage of patients experiencing at least one SAE up to week 26</u> **Infliximab:** 7 **Methotrexate:** 3 <u>Percentage of WDAEs up to week 26</u> **Infliximab:** 12 (infusion-related reaction most common) **Methotrexate:** 4	

AE=adverse events; CI=confidence interval; DLQI=dermatology life quality index; HRQoL=health-related quality of life; RD=risk difference; RR=relative risk; SAE=serious adverse event; SF-36=36-item short form health survey; WDAE=withdrawal due to adverse event

APPENDIX 6: Summary of Findings – Economic

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Ferrandiz[18] 2012	**Base Case** ICER – cost per PASI 75 responder gained (euros) **Infliximab (10 weeks):** 10,523 **Infliximab (24 weeks):** 17,112 **Etanercept 2x25 mg/week (12 weeks):** 9110 **Etancercept 2x25 mg/week (24 weeks):** 11,213 **Etanercept 2x50 mg/week (12 weeks):** 12,797 **Adalimumab:** 8013 **Ustekinumab 45 mg:** 9627 **Ustekinumab 90 mg:** 17,981 Sensitivity analyses ICERs were sensitive to variations in PASI-75 efficacy.	"…the present study shows that adalimumab is the drug with the best cost-efficacy ratio in the short-term (clearance period) management of the patients, with a mean cost of 8013 (range 7568€ to 8515€) per PASI 75 responder. Due to its low cost, etanercept (at a dosage of 25 mg twice a week) was the second most efficient biological agent, despite its much lower efficacy as compared to others. The third most efficient biologic was ustekinumab at a dose of 45 mg, the dose indicated in the product's technical specifications for patients weighing less than 100 kg…Although infliximab had the highest efficacy, it was the least efficient drug because the cost of treatment is much higher than that of the remaining agents." (p. 772, 775)
de Portu[19] 2010	After 24 weeks ICER of infliximab versus other agents (euros) **Etanercept 2x25 mg/week:** 9,647.13 **Etanercept 2x50 mg/week:** more effective and less costly **Etanercept 50 mg/week:** 33,632.20 **Adalimumab:** 16,068.94 After 48-50 weeks ICER of infliximab versus other agents (euros) **Etanercept 2x50 mg/week:** more effective and less costly **Etanercept 50 mg/week:** 3,943.06 **Adalimumab:** 22,506.62 Sensitivity analyses ICERs were sensitive to price variations.	"Based on the outcome measures selected for this analysis, infliximab seems to be cost-effective. This is due to its high effectiveness in terms of both PASI and improvement in QoL scores when compared with etanercept and adalimumab. Infliximab resulted in both lower costs and greater efficacy and thus can be considered a dominant therapy compared with high dosage of etanercept both after 24 and 48 weeks." (p 11)
Schmitt-Rau[20] 2010	Incremental cost effectiveness of treatment versus placebo for patient achieving PASI 75 (euros) **Infliximab 3 mg/kg:** 10,568.19 **Infliximab 5 mg/kg:** 12,501.29 **Etanercept 2x25 mg/week:** 16,895.57 **Etanercept 2x50 mg/week:** 22,724.93 **Adalimumab:** 11,286.51 **Ustekinumab 45 mg:** 13,099.30 **Ustekinumab 90 mg:** 12,089.28 One-way sensitivity analyses Cost effectiveness ratios were sensitive to variations in PASI-75 efficacy and the cost of the drug.	"Interestingly, the most cost-effective biological treatment in our setting, expressed in cost per patient achieving a PASI-75 improvement during a 12-week treatment course, is infliximab 3 mg/kg, the dose that is not recommended for plaque-type psoriasis. The next most cost-effective agents are adalimumab, ustekinumab 90 mg and infliximab 5 mg/kg)" (p. 240)
Nelson[21] 2008	Incremental cost effectiveness of treatment versus placebo for patient achieving PASI 75 (USD) **Infliximab 3 mg/kg 3 infusions:** 8,797 **Infliximab 5 mg/kg 3 infusions:** 10,422	"The most cost-effective medications, in terms of cost per patient achieving the DLQI MID, were etanercept, infliximab and adalimumab. In terms of cost per patient achieving PASI-75 improvement, adalimumab and infliximab

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	Etanercept 2x25 mg/week: 14,254 **Etanercept 2x50 mg/week:** 18,738 **Adalimumab:** 11,657 Incremental cost effectiveness of treatment versus placebo for patient achieving minimal important difference in DLQI (USD) **Infliximab 3 mg/kg 3 infusions:** 3,508 **Infliximab 5 mg/kg 3 infusions:** 4,322 **Etanercept 2x25 mg/week:** 3,599 **Etanercept 2x50 mg/week:** 6,645 **Adalimumab:** 3,511 One-way sensitivity analyses Cost effectiveness ratios were sensitive to variations in PASI-75 efficacy and average wholesale price at a level of variance of ±5%.	were the most cost-effective medications…the most cost-effective treatment regimen of infliximab in our analysis is a dose of 3 mg/kg IV for 3 infusions, rather than the current recommended treatment dose of 5 mg/kg IV for 3 infusions." (p. 132)
Sizto[22] 2008	ICER versus supportive care (pounds) **Infliximab:** 42,492/QALY **Etanercept 2x25 mg/week:** 37,284/QALY **Etanercept 2x50 mg/week:** 38,358/QALY **Adalimumab:** 30,538/QALY **Methotrexate:** -29,759/QALY Infliximab strategy cost the most, while methotrexate treatment were found to be cost saving due to costs saved through reduced hospitalizations were greater than drug-related costs. One-way sensitivity analyses ICER estimates were sensitive to certain alternative assumptions including changing the number of days hospitalized owing to nonresponse to treatment.	"Of the available biologic therapies, adalimumab was the most cost effective (approximately £30,000 per QALY vs. supportive care). Infliximab provided the most benefit (i.e. the most incremental QALYs vs. supportive care), as its trials included the highest response rates; however, the cost of the drug and the related infusions outweighed the benefit that it provided (an ICER of £42,000 per QALY compared with supportive care)." (p. 1269-1270)

DLQI=dermatology life quality index; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year