NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (review)

This document is a summary of the evidence and views submitted by consultees and the Assessment Group. It highlights key issues for discussion at the first Appraisal Committee meeting. NICE prepares the overview before it receives consultees' comments on the assessment report. The sources of evidence used in the preparation of this document are given in appendix A.

1 Background

1.1 The condition

Psoriatic arthritis is an inflammatory arthritis affecting the joints and connective tissue and associated with psoriasis of the skin or nails. The prevalence of psoriasis in the general population is estimated at 2–3%. The prevalence of inflammatory arthritis in people with psoriasis is estimated at up to 30%. At least 20% of people with psoriasis have severe psoriatic arthritis with progressive joint lesions. Psoriatic arthritis is a progressive disorder ranging from mild synovitis to severe progressive erosive arthropathy. People with psoriatic arthritis presenting with oligoarticular disease progress to polyarticular disease and a large percentage develop joint lesions and deformities which progress over time. Despite clinical improvement with current disease-modifying antirheumatic drug (DMARD) treatment, radiological joint damage has been shown in up to 47% of people with psoriatic arthritis at a median interval of 2 years.

Psoriatic arthritis can affect people's ability to carry out daily activities and to work, which can have a significant impact on quality of life. The impact of severe psoriasis on health-related quality of life is considered to be similar to that of other major medical conditions including diabetes, heart disease, and

cancer. People with psoriatic arthritis have a higher self-rated disease severity than those with psoriasis only. People with psoriatic arthritis have a 60% higher risk of mortality than the general population and their life expectancy is estimated to be approximately 3 years shorter.

Most people with psoriatic arthritis develop skin symptoms before joint symptoms, although joint symptoms may appear first, or symptoms may appear simultaneously. Psoriatic arthritis usually develops in the 10 years following a diagnosis of psoriasis. The rheumatic characteristics of psoriatic arthritis include joint stiffness, pain, and swelling, and tenderness of the joints and surrounding ligaments and tendons. Symptoms can range from mild to very severe.

A lack of clear diagnostic criteria and markers for psoriatic arthritis has made it difficult to gauge its prevalence in the UK. In August 2006 an international consortium of rheumatologists with a special interest in psoriatic arthritis, the CASPAR (ClASsification criteria for Psoriatic ARthritis) group, published simple classification criteria, which were derived from statistical analyses of observed data from cohorts of people with psoriatic arthritis from 30 clinics in 13 countries (n = 588) compared with control groups consisting of people with other inflammatory arthropathies (n = 536). These criteria were found to be highly specific (0.987) and sensitive (0.914).

Assessing the effectiveness of treatments for psoriatic arthritis relies on having outcome measures that accurately and sensitively measure disease activity. Outcomes of effectiveness are based on measures of the anti-inflammatory response (such as the Psoriatic Arthritis Response Criteria [PsARC], and the American College of Rheumatology response criteria [ACR 20/50/70]) of psoriatic skin lesions (psoriasis area and severity index [PASI]), functional measures (health assessment questionnaire [HAQ]) and radiological assessments of disease progression, quality of life and overall global assessments (see table 1). Overall response criteria have not yet been

clearly defined. For further information please see the pages 31-34 of the Technology Assessment Report.

1.2 Current management

The aim of psoriatic arthritis treatment is to relieve symptoms, slow disease progression, and maintain function and quality of life. To effectively manage psoriatic arthritis, both skin and joint conditions need to be treated, especially if both are seriously affected. Non-steroidal anti-inflammatory drugs (NSAIDs) and local corticosteroid injections are widely used. Disease that is unresponsive to NSAIDs, in particular polyarticular disease, should be treated with DMARDs (currently, methotrexate and sulphasalazine are considered the DMARDs of choice) to reduce the joint damage and prevent disability. Aggressive treatment of early stage progressive psoriatic arthritis can help to improve prognosis.

NICE has produced guidance on ‘Etanercept and infliximab for the treatment of adults with psoriatic arthritis’ (NICE technology appraisal guidance 104) and ‘Adalimumab for the treatment of psoriatic arthritis’ (NICE technology appraisal guidance 125), see appendix B for the recommendations.

2 The technologies

Table 1 Summary description of technologies

Non-proprietary name	Adalimumab	Etanercept	Infliximab
Proprietary name	Humira	Enbrel	Remicade
Manufacturer	Abbott Laboratories	Wyeth Pharmaceuticals	Schering-Plough
Dose	40 mg administered every other week	25 mg administered twice weekly, or 50 mg administered once weekly	5 mg/kg given as an intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.
Acquisition cost (British National Formulary edition 58)	Prefilled pen or prefilled syringe: 40 mg – £357.50	Prefilled syringe: 25 mg – £89.38 50 mg – £178.75 Powder for reconstitution (with solvent): 25 mg vial – £89.38	Powder for reconstitution: 100-mg vial – £419.62

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary mammalian expression system. Its mechanism of action is thought to be its competitive inhibition of tumour necrosis factor (TNF) binding to cell surface TNF receptors, preventing TNF-mediated cellular responses by rendering TNF biologically inactive.

Infliximab is a chimeric human-murine IgG1 monoclonal antibody produced by recombinant DNA technology. Infliximab inhibits the functional activity of TNF-alpha.

Adalimumab is a recombinant human monoclonal antibody expressed in Chinese hamster ovary cells. Adalimumab binds specifically to TNF and neutralises its function by blocking its interaction with the p55 and p75 cell-surface TNF receptors.

3 The evidence

3.1 Clinical effectiveness

The Assessment Group identified two placebo-controlled RCTs in patients with PsA for each of the technologies: 2 for etanercept, 2 for infliximab and 2 for adalimumab.

Etanercept

The Assessment Group identified two double-blind, placebo-controlled randomised controlled trials (RCTs) of etanercept in adults with active psoriatic arthritis:

- Mease 2000 (n = 60), in which treatment with etanercept (25 mg twice weekly) or placebo was administered for 12 weeks.
- Mease 2004 (n = 205) in which treatment with etanercept (25 mg twice weekly) or placebo was administered for 24 weeks.

The inclusion criteria for both trials were:

- active psoriatic arthritis (defined as more than three swollen joints and more than three tender or painful joints, although only the more recent trial specified stable plaque psoriasis), **and**
- psoriatic arthritis that had not responded adequately to NSAIDs.

Patients were not required to have active psoriasis at baseline but 77% of people treated with etanercept and 73% of people treated with placebo did.

The Assessment Group conducted a meta-analysis of the outcomes for etanercept at 12 weeks and the results are shown in table 2.

Table 2 Meta-analysis of etanercept efficacy data – outcomes at 12 weeks (page 51 of the Technology Assessment Report)

Trial	Outcomes	Etanercept	Placebo	RR[a] or mean difference (95% CI[b])
	PsARC[c]			
Mease 2000		26/30 (87%)	7/30 (23%)	3.71 (1.91 to 7.21)
Mease 2004		73/101 (72%)	32/104 (31%)	2.35 (1.72 to 3.21) p < 0.001
	Pooled RR (95% CI), p I^2			2.60 (1.96 to 3.45) p < 0.00001 I^2 = 34%
	ACR[d] 20			
Mease 2000		22/30 (73.0%)	4/30 (13%)	5.50 (2.15 to 14.04)
Mease 2004		60/101 (59%)	16/104 (15%)	3.86 (2.39 to 6.23) p < 0.001
	Pooled RR (95% CI), p I^2			4.19 (2.74 to 6.42) p < 0.00001 I^2 = 0%
	ACR 50			
Mease 2000		15/30 (50.0%)	1/30 (3%)	15.00 (2.11 to 106.49)
Mease 2004		38/101 (38%)	4/104 (4%)	9.78 (3.62 to 26.41) p < 0.001
	Pooled RR (95% CI), p I^2			10.84 (4.47 to 26.28) p < 0.00001 I^2 = 0%
	ACR 70			
Mease 2000		4/30 (13%)	0/30 (0%)	9.00 (0.51 to 160.17)
Mease 2004		11/101 (11%)	0/104 (0%)	23.68 (1.41 to 396.53) p < 0.001
	Pooled RR (95% CI), p I^2			16.28 (2.20 to 120.54) p = 0.006) I^2 = 0%
	HAQ[e] % change from baseline (mean [SD[f]])			
Mease 2000		(n = 29) –64.2 (38.7)	(n = 30) –9.9 (42.9)	–54.3 (33.47 to 75.13)
Mease 2004		(n = 96) –53.5 (43.4)	(n = 99) –6.3 (42.7)	–47.20 (35.11 to 59.29)
	Pooled WMD[g] (95% CI),p I^2			–48.99 (38.53 to 59.44) p < 0.00001 I^2 = 0%

[a] Relative risk; [b] confidence interval; [c] Psoriatic Arthritis Response Criteria; [d] American College of Rheumatology response criteria; [e] health assessment questionnaire; [f] standard deviation; [g] weighted mean difference

At 24 weeks the treatment effect for all joint disease outcome measures was statistically significantly greater with etanercept than with placebo, though this data was only available for one trial, Mease 2004. At 24 weeks, total sharp score (TSS) annualised rate of progression was statistically significantly lower in people treated with etanercept than people treated with placebo (total sharp score –0.56; 95% confidence interval [CI] –0.86 to –0.26).

At 24 weeks the treatment effect on psoriasis favoured etanercept with relative risks (RRs) for PASI 75 of 7.05 (95% CI 1.68 to 29.56), PASI 50 of 2.65 (95% CI 1.46 to 4.80) and PASI 90 of 1.88 (95% CI 0.36 to 9.90). At 1 year the mean annualised rate of progression total sharp score (TSS) for all people was –0.03 (standard deviation [SD] 0.87) indicating that on average no clinically significant progression of joint erosion had occurred.

Infliximab

The Assessment Group identified two double-blind, placebo-controlled RCTs of infliximab for the treatment of psoriatic arthritis:

- IMPACT (n = 104) in which participants were randomised to receive infusions of infliximab (5 mg/kg) or placebo at weeks 0, 2, 6 and 14 with follow-up at week 16.
- IMPACT 2 (n = 200) in which people were randomised to receive infusions of placebo or infliximab 5 mg/kg at weeks 0, 2, 6, 14 and 22, with assessments at weeks 14 and 24.

All participants had been diagnosed with psoriatic arthritis for at least 6 months, with a negative rheumatoid factor and active disease including more than five swollen and/or tender joints.

In both RCTs the inclusion criteria required that participants' psoriatic arthritis should have inadequately responded to at least one DMARD. IMPACT 2 also required people to have active plaque psoriasis with at least one qualifying target lesion (2 cm or more in diameter). Both studies reported longer-term

open-label follow-up of people: after 50 weeks in IMPACT and 54 weeks in IMPACT 2.

The baseline characteristics of the trial populations were similar. However the trial population included people with less severe psoriatic arthritis than stipulated in the marketing authorisation because approximately half of the people in the IMPACT and fewer than half in the IMPACT 2 RCT had psoriatic arthritis that had failed to respond to two or more DMARDs.

The Assessment Group conducted a meta-analysis of the outcomes for infliximab at 14 weeks and the results are shown in table 3.

Table 3 Meta-analysis of infliximab efficacy data – outcomes at 14 weeks (page 57 of the Technology Assessment Report)

Trial	Outcomes	Infliximab	Placebo	RR[a] or mean difference (95% CI[b])
	PsARC[c]			
IMPACT		40/52 (76.9%)	7/52 (13.5%)	5.71 (2.82 to 11.57)
IMPACT 2		77/100 (77%)	27/100 (27%)	2.85 (2.03 to 4.01)
	Pooled RR (95% CI), p I^2			3.44 (2.53 to 4.69), p < 0.0001 I^2 = 68%
	ACR[d] 20			
IMPACT		35/52 (67.3%)	6/52 (11.5%)	5.83 (2.68 to 12.68)
IMPACT 2		58/100 (58%)	11/100 (11%)	5.27 (2.95 to 9.44)
	Pooled RR (95% CI), p I^2			5.47 (3.43 to 8.71) I^2 = 0%
	ACR 50			
IMPACT		19/52 (36.5%)	1/52 (1.9%)	19.00 (2.64 to 136.76)
IMPACT 2		36/100 (36%)	3/100 (3%)	12.00 (3.82 to 37.70)
	Pooled RR (95% CI), p I^2			13.75 (5.11 to 37.00), p < 0.0001 I^2 = 0%
	ACR 70			
IMPACT		11/52 (21.2%)	0/52 (0%)	23.00 (1.39 to 380.39)
IMPACT 2		15/100 (15%)	1/100 (1%)	15.00 (2.02 to 111.41)
	Pooled RR (95% CI), p I^2			17.67 (3.46 to 90.14), p = 0.001 I^2 = 0%
	PASI[e] 50			
IMPACT		22/22 (100%)	0/16 (0%)	33.26 (2.17 to 510.71)
IMPACT 2		[redacted]	[redacted]	[redacted]
	Pooled RR (95% CI), p I^2			10.58 (5.47 to 20.48) , p < 0.0001[f] I^2 = 0%
	PASI 75			
IMPACT		15/22 (68.2%)	0/16 (0%)	22.91 (1.47 to 356.81)

IMPACT 2		[redacted]	[redacted]	[redacted]
	Pooled RR (95% CI), p I^2			26.68 (7.79 to 91.44), p < 0.0001[f] I^2 = 0%
	PASI 90			
IMPACT		8/22 (36.4%)	0/16 (0%)	12.57 (0.78 to 203.03)
IMPACT 2		[redacted]	[redacted]	[redacted]
	Pooled RR (95% CI), p I^2			40.01 (5.93 to 270.15), p < 0.0001[f] I^2 = 0%
	HAQ[g] % change from baseline (mean (SD))			
IMPACT		(n = 48) – 49.8 (56.8)	(n = 47) 1.6 (56.9)	–51.4 (–74.27 to –28.54)
IMPACT 2		(n = 100) – 48.6 (43.3)	(n = 100) 18.4 (90.5)	–67.00 (–86.66 to –47.33)
	Pooled WMD[h] (95% CI), p I^2			–60.37 (–75.28 to –45.46) I^2 = 3%

[a] Relative risk; [b] confidence interval; [c] Psoriatic Arthritis Response Criteria; [d] American College of Rheumatology response criteria; [e] health assessment questionnaire; [f] combined 14 and 16 week data; [g]standard deviation; [h] weighted mean difference

The IMPACT 2 trial maintained randomisation for 24 weeks. The data for all measures of joint disease, psoriasis and HAQ are similar to those observed at the earlier 14-week follow-up, suggesting that the benefits of infliximab are maintained for up to 24 weeks of treatment and for longer-term follow-up (50 weeks for IMPACT and 54 weeks for IMPACT 2), although the data for the latter were uncontrolled and may therefore be unreliable.

In terms of radiographic assessment, there was no significant change from baseline in the total modified van der Heijde-Sharp score for infliximab-treated people followed up at 50 weeks ([n = 70] –1.72 [5.82], IMPACT) or 54 weeks (infliximab/infliximab –0.94 (3.4); placebo/infliximab 0.53 [2.6], IMPACT 2), suggesting infliximab may inhibit progression of joint damage. However, as with other post-24-week outcomes, there was no placebo group for comparison.

Adalimumab

The Assessment Group identified two double-blind and placebo-controlled RCTs of adalimumab in adults with active psoriatic arthritis:

- ADEPT (n = 313) in which people were randomised to adalimumab (administered every other week at a dose of 40 mg) or placebo, with a follow-up of 24 weeks.
- Genovese 2007 (n = 100) in which people were randomised to adalimumab (administered every other week at a dose of 40 mg) or placebo, with a follow-up of 12 weeks. In both trials the controlled phase was followed by a follow-up period during which open-label adalimumab was given to all people.

The inclusion criteria for both RCTs required adults to have active psoriatic arthritis (defined in both trials as more than three swollen joints and more than three tender or painful joints, with active psoriatic skin lesions or a documented history of psoriasis). Overall, the baseline characteristics demonstrate that the trial populations were similar and represented people who require DMARD or biologic therapy.

The Assessment Group conducted a meta-analysis of the outcomes for adalimumab at 12 weeks and the results are shown in table 4.

Table 4 Meta-analysis of adalimumab efficacy data – outcomes at 12 weeks (page 63 of the Technology Assessment Report)

Trial	Outcomes	Adalimumab	Placebo	RR[a] or mean difference (95% CI[b])
	PsARC[c]			
ADEPT		94/151 (62%)	42/162 (26%)	2.40 (1.80 to 3.20)
Genovese 2007		26/51 (51%)	14/49 (24%)	1.78 (1.06 to 3.00)
	Pooled RR (95% CI), p I^2			2.24 (1.74 to 2.88) p < 0.0001 I^2 = 0%
	ACR[d] 20			
ADEPT		88/151 (58%)	23/162 (14%)	4.10 (2.75 to 6.14)
Genovese 2007		20/51 (39%)	8/49 (16%)	2.40 (1.17 to 4.94)
	Pooled RR (95% CI), p I^2			3.65 (2.57 to 5.17) p < 0.0001 I^2 = 38%
	ACR 50			
ADEPT		54/151 (36%)	6/162 (4%)	9.66 (4.28 to 21.79)
Genovese 2007		13/51 (25%)	1/49 (2%)	12.49 (1.70 to 91.90)
	Pooled RR (95% CI), p I^2			10.08 (4.74 to 21.44) p < 0.0001 I^2 = 0%
	ACR 70			
ADEPT		30/151 (20%)	1/162 (1%)	32.19 (4.44 to 233.11)
Genovese 2007		7/51 (14%)	0/49 (0%)	14.42 (0.85 to 5.26)
	Pooled RR (95% CI), p I^2			26.05 (5.18 to 130.88) p < 0.0001 I^2 = 0%
	HAQ[e] change from baseline (mean [SD[f]])			
ADEPT		–0.4 (0.5)	–0.1 (0.5)	–0.3 (–0.41 to –0.19)
Genovese 2007		–0.3 (0.5)	–0.1 (0.3)	–0.2 (–0.36 to –0.04), p = 0.015
	Pooled WMD[g] (95% CI), p I^2			–0.27 (–0.36 to –0.18) p < 0.0001 I^2 = 0.6%

[a] Relative risk; [b] confidence interval; [c] Psoriatic Arthritis Response Criteria; [d] American College of Rheumatology response criteria; [e] health assessment questionnaire; [f] standard deviation; [g] weighted mean difference

The ADEPT trial was open label and measured several outcomes at 48 weeks compared with placebo. Both ACR response rates and mean HAQ scores at weeks 48 and 104 appear to have remained stable relative to the randomised observations of these outcomes at weeks 12 and 24. Similarly, rates of PASI response reported at 48 weeks appeared largely consistent with the earlier randomised observations. Disease progression as measured by total sharp score was reported at week 48 and week 144 demonstrating that the efficacy of adalimumab was maintained long term.

3.1.1 Efficacy of all three biologics

The Assessment Group was able to conduct an indirect comparison of etanercept, infliximab and adalimumab because all of the trials compared the treatments with placebo. All the trials identified in the systematic review were used in the analysis; although not all trials provided data for of all outcomes analysed. The results of this evidence synthesis highlighted the superior efficacy of biologics (etanercept, infliximab and adalimumab) over placebo across the outcomes evaluated.

Although most people in the trials had previously received at least one DMARD, no trial specified that participants' psoriatic arthritis had to have failed to respond to at least two DMARDs (people whom the current British Society for Rheumatology guidelines consider eligible for biologic treatment) as a recruitment criterion. Therefore, trial participants were not precisely representative of people receiving these agents in practice, and were likely to have had less severe disease, having often received biologic therapy after failing a single DMARD. Most studies used the ACR 20, however it should be noted that ACR 20 is not frequently used in routine clinical practice to measure response to a biologic treatment.

Overall, biologic treatment appears to have had a broadly beneficial effect on skin disease in people with psoriatic arthritis and, although less frequently reported than joint outcomes, results (PASI response) were generally statistically significant, though confidence intervals were wide – possibly

because of the small sample size of people evaluable for psoriasis in the trials.

The indirect comparison of the three drugs indicated that infliximab is associated with the highest probability of response on joint and skin outcomes. The response in joint disease appeared greater with etanercept than with adalimumab, whereas the skin response appeared greater with adalimumab than with etanercept, though these differences were not statistically significant. In those people who had a PsARC response to treatment the highest mean reductions in HAQ were seen with infliximab and etanercept.

The probability of PsARC response to each one of the biologic treatments being appraised are summarised in table 5.

Table 5 Probability of PsARC[a] response to biologics (page 66 of the Technology Assessment Report)

	Mean	Credible intervals	
		2.50%	97.50%
Placebo	0.249	0.178	0.317
Etanercept	0.741	0.566	0.832
Infliximab	0.797	0.672	0.886
Adalimumab	0.568	0.444	0.713

[a] Psoriatic Arthritis Response Criteria

Table 6 and table 7 shows the change in health assessment questionnaire (HAQ) for biologics in people whose psoriatic arthritis responded and did not respond to treatment, respectively.

Table 6 Change in HAQ[a] in people whose psoriatic arthritis responded to treatment (page 66 of the Technology Assessment Report)

	Mean	Credible intervals	
		2.50%	97.50%
Placebo	–0.218	–0.314	–0.128
Etanercept	–0.624	–0.815	–0.438
Infliximab	–0.653	–0.796	–0.509
Adalimumab	–0.423	–0.539	–0.296

[a] Health assessment questionnaire

Table 7 Change in HAQ[a] in people whose psoriatic arthritis did not respond to treatment (page 66 of the Technology Assessment Report)

	Mean	Credible intervals	
		2.50%	97.50%
Placebo	0	0	0
Etanercept	–0.185	–0.390	0.015
Infliximab	–0.191	–0.337	–0.046
Adalimumab	–0.064	–0.188	0.065

[a] Health assessment questionnaire

All three agents appeared to have beneficial effects on functional status as measured by HAQ. Only changes greater than –0.3 have been considered as clinically meaningful improvement in psoriatic arthritis.

For all three biologics the changes in HAQ for people whose psoriatic arthritis did not respond to treatment were below the minimum clinically significant threshold, and only the HAQ scores for people treated with infliximab were statistically significant. People who had shown no response to placebo were used as a baseline in the evidence synthesis.

The probability of PASI and ACR responses to biologics are summarised in tables 8 and 9, respectively.

Table 8 Probability of PASI response to biologics (page 67 of the Technology Assessment Report)

		Mean	Credible intervals	
			2.50%	97.50%
PASI[a] 50	Placebo	0.130	0.092	0.175
	Etanercept	0.403	0.236	0.592
	Infliximab	0.913	0.823	0.968
	Adalimumab	0.738	0.552	0.881
PASI 75	Placebo	0.044	0.028	0.065
	Etanercept	0.177	0.085	0.313
	Infliximab	0.769	0.594	0.901
	Adalimumab	0.477	0.275	0.693
PASI 90	Placebo	0.018	0.010	0.026
	Etanercept	0.074	0.032	0.145
	Infliximab	0.557	0.347	0.767
	Adalimumab	0.257	0.120	0.452

[a] Psoriasis area and severity index

Table 9 Probability of ACR response to biologics (page 68 of the Technology Assessment Report)

		Mean	Credible intervals	
			2.50%	97.50%
ACR[a] 20	Placebo	0.137	0.108	0.168
	Etanercept	0.609	0.459	0.750
	Infliximab	0.678	0.533	0.805
	Adalimumab	0.560	0.429	0.686
ACR 50	Placebo	0.053	0.040	0.070
	Etanercept	0.362	0.231	0.516
	Infliximab	0.433	0.288	0.594
	Adalimumab	0.315	0.209	0.438
ACR 70	Placebo	0.018	0.012	0.025
	Etanercept	0.158	0.087	0.260
	Infliximab	0.203	0.114	0.326
	Adalimumab	0.131	0.077	0.205

[a] American College of Rheumatology response criteria

The ACR 20 is generally accepted to be the minimal clinically important difference that indicates some response to a particular intervention in terms of arthritis-related symptoms. The credible intervals for all three biologics overlap each other but none overlap with those for placebo.

A comparison of the effectiveness evidence syntheses conducted by the manufacturers and the Assessment Group can be found in table 5.14, pages 73 and 74 of the technology assessment report.

Serious adverse event and withdrawal rates across non-randomised studies and large RCTs are shown in table 10.

Table 10 Serious adverse event and withdrawal rates across non-randomised studies and large RCTs (page 94 of the Technology Assessment Report)

	Patients (%)				
Drug	Serious infections	Cancer	Tuberculosis	Mortality	Withdrawals because of adverse events
Etanercept	0.6–13.2	1–5.7	0–1.4	0–3.1	0–13.6
Infliximab	0.8–13.8	0.16–5.1	0.06–4.6	0.06–2.0	6.4–12.8
Adalimumab	0.4–5.1	0.1–1.1	0–0.4	0.5– 0.9	5.8–10.7

There were no RCTs that directly compared the three drugs. The estimates for adverse events were derived from studies that were heterogeneous in terms of participants, study design and treatment regimens.

3.2 Cost effectiveness

The Assessment Group performed a systematic review of published literature and identified three studies (Olivieri et al. [2008], Bansback et al. [2007] and Bravo Vergel [2006]) that met the inclusion criteria for the cost-effectiveness review. Three submissions were also received from Abbott Laboratories (for adalimumab), Schering-Plough (for infliximab) and Wyeth Pharmaceuticals (for etanercept).

The study by Olivieri et al. was difficult to compare with the other studies because in Olivieri et al. all biologics were considered as a group compared with DMARDs. There were no model results. The economic evaluation was made together with before-and-after studies and the effectiveness evidence based on a single trial. This produced an incremental cost-effectiveness ratio

(ICER) of around €40,000 (£34,700) per quality-adjusted life year (QALY) gained for biologics.

The study by Bansback et al. compared etanercept with ciclosporin and leflunomide. The economic model focused on response according to PsARC and associated HAQ score, with changes in HAQ and further withdrawals modelled over 10 years. Mease 2004 was the source of evidence for response rates and HAQ. The base-case results show an ICER of around £28,000 per QALY gained for etanercept compared with ciclosporin and £38,000 per QALY gained for etanercept compared with leflunomide.

The Bravo Vergel study compared etanercept with infliximab and palliative care. The model included response according to PsARC and associated HAQ score. Changes in HAQ and further withdrawals were modelled over 40 and 10 years. Evidence from Mease 2000, Mease 2004 and IMPACT was used to model the PsARC response. The ICER for etanercept was between £26,361 and £30,628 per QALY gained depending on the rebound (deterioration experienced in HAQ at treatment withdrawal) scenario, used compared with palliative care. Infliximab was the most effective strategy with the higher QALYs produced.

3.2.1 Manufacturer submissions

Etanercept

A published cost-effectiveness model originally used to support a submission to NICE in 2004 was adapted to incorporate additional effectiveness evidence and new comparators. The adjusted model compares the costs and benefits associated with etanercept, infliximab, adalimumab and best supportive care. Best supportive care was assumed to be ciclosporin based on the limited DMARD options available for this group and because first or second line DMARDs in people with psoriatic arthritis are generally leflunomide and either sulphasalazine or methotrexate.

The base case results and the probabilistic sensitivity analysis for etanercept are summarised in tables 11 and 12, respectively.

Table 11 Base-case results comparing the least effective regimen with the next least effective (page 38 of the manufacturer submission)

	QALYs[a]	Cost (£)	ICER[b] (£ per QALY gained)
Etanercept	6.90	65,650	12,480
Adalimumab	6.54	61,381	Extendedly dominated by etanercept
Infliximab	6.39	66,867	Dominated by adalimumab
Best supportive care	5.96	53,860	

[a] Quality-adjusted life year; [b] incremental cost-effectiveness ratio

Table 12 Probabilistic sensitivity analysis results (page 38 of the manufacturer submission)

	QALYs[a]	Cost (£)	ICER[b] (£ per QALY gained)
Etanercept	6.91	65,994	12,351
Adalimumab	6.53	61,396	Extendedly dominated by etanercept
Infliximab	6.45	67,159	Dominated by adalimumab
Best supportive care	5.95	54,204	

[a] Quality-adjusted life year; [b] incremental cost-effectiveness ratio

Infliximab

In the economic analysis submitted by the manufacturer of infliximab four treatment alternatives were compared. These included maintenance treatment with a TNF-α inhibitor (infliximab, adalimumab or etanercept) followed by a sequence of DMARDs. The comparator was palliative care comprising DMARDs. For the health-economic model, the incremental treatment effects for the comparative treatments were estimated for infliximab, etanercept and adalimumab.

The model structure in terms of the cohort flow had a first cycle of 0-12 weeks, a second cycle of 13–24 weeks, and annual cycles thereafter. At the end of the first cycle, all people were assessed for their PsARC response. Those

who had responded to treatment at 12 weeks continued with their current treatment, but then had an annual probability of withdrawing from treatment and moving onto palliative care. Those who had not responded to treatment at 12 weeks had their treatment withdrawn and moved onto palliative care. The parameters used in the base case estimates are summarised in table 13.

Table 13 Parameters used in the base case estimates for infliximab cost-effectiveness analysis (page 63 of the manufacturer submission)

Cohort size	1	Proportion with psoriasis	66%
Female percentage	50%	Rebound equal to gain or natural history	Gain
Age	45 years	Quality of life algorithm	Gray
HAQ[a]	1.14	Base year for costs	2008
PASI[b]	11.0	Time horizon	40 years

[a] Health assessment questionnaire; [b] psoriasis area and severity index

The direct drug costs for the TNF-α inhibitors were obtained from BNF56. Tables 14, 15 and 16 show the base-case results for a person weighing 60 kg, 70 kg and 80 kg, respectively.

Table 14 Base-case results for a person weighing 60 kg (page 65 of the manufacturer submission)

	QALY[a]	Treatment cost	Total cost	ICER[b] (per QALY gained)
Palliative care	6.10	£0	£64,704	£0
Adalimumab	7.89	£40,931	£99,278	£19,246
Etanercept	8.62	£51,484	£108,481	£17,327
Infliximab	8.65	£52,505	£107,954	£16,942

[a] Quality-adjusted life year; [b] incremental cost effectiveness ratio compared with palliative care

Table 15 Base-case results for a person weighing 70 kg (vial optimising) (page 66 of the manufacturer submission)

	QALY[a]	Treatment cost	Total cost	ICER[b] (per QALY gained)	ICER[c] (per QALY gained)
Palliative care	6.10	£0	£64,704	£0	£0
Adalimumab	7.89	£40,931	£99,278	£19,246	£19,246 (ED[d])
Etanercept	8.62	£51,484	£108,481	£17,327	£12,606
Infliximab	8.65	£60,266	£115,715	£19,982	£274,755

[a] Quality-adjusted life year; [b] incremental cost-effectiveness ratio compared with palliative care; [c] ICER compared with next least costly alternative; [d] extendedly dominated

Table 16 Base-case results for a person weighing 80 kg (page 66 of the manufacturer submission)

	QALY[a]	Treatment cost	Total cost	ICER[b] (per QALY gained)	ICER[c] (per QALY gained)
Palliative care	6.10	£0	£64,704	£0	£0
Adalimumab	7.89	£40,931	£99,278	£19,246	£19,246 (ED[d])
Etanercept	8.62	£51,484	£108,481	£17,327	£12,606
Infliximab	8.65	£68,026	£123,475	£23,022	£569,511

[a] Quality-adjusted life year; [b] incremental cost-effectiveness ratio compared with palliative care; [c] ICER compared with next least costly alternative; [d] extendedly dominated

The one-way sensitivity analysis showed that TNF-α inhibitors were cost effective compared with palliative care in all of the sensitivity analysis except the algorithm for estimating quality of life. Most of the ICERs were below £30,000 per QALY gained, ranging from £16,882 per QALY gained for people weighing 60 kg treated with infliximab when the baseline PASI score was reduced from 11.0 to 9.0, to the highest ICER which was £32,552 per QALY gained for people weighing 80 kg when the rate of HAQ progression under natural history was halved from 0.072 to 0.036.

Adalimumab

The manufacturer of adalimumab used an individual sampling model to simulate the disease progression of a cohort of people with psoriatic arthritis over a lifetime horizon under different treatment sequences. A 3-month cycle was used. Baseline characteristics from the ADEPT trial for people for whom two previous DMARDs had failed were used in the base-case analysis.

The cost of all drugs used in the analysis was calculated based on the recommended dosages and vial prices given in the Monthly Index of Medical Specialties. The model assumed that four 100 mg vials of infliximab were required per infusion, based on an average person weighing 80kg. The base-case results for adalimumab are summarised in table 17.

Table 17 Results of base-case scenario (page 98 of the manufacturer submission)

	Mean QALY[a] (95% CI[b])	Mean Cost (£) (95% CI)	ICER[c] (£ per QALY gained)
DMARD[d]	7.47 (6.81–7.57)	47,537 (35,751–55,661)	–
Adalimumab	8.33 (7.16–9.34)	73,072 (61,748–80,705)	29,827
Etanercept	8.33 (7.17–9.39)	80,381 (67,178–85,679)	Dominated
Infliximab	8.49 (7.20–9.56)	104,772 (89,946–113,112)	199,596

[a] Quality-adjusted life year; [b] confidence interval; [c] incremental cost-effectiveness ratio (for a therapy relative to the next most effective alternative); [d] disease-modifying antirheumatic drug

The manufacturer of adalimumab performed sensitivity analysis surrounding effectiveness, disease progression, utility, costs and assuming rebound to natural history. Adalimumab had a lower ICER per QALY gained than etanercept and infliximab.

3.2.2 Assessment Group's critique of the manufacturers economic analysis

The Assessment Group critiqued the manufacturers' economic models and updated the model from the previous NICE technology appraisal 104 - etanercept and infliximab for the treatment of adults with psoriatic arthritis, taking account of the cost and health impact of the patients' psoriasis and joint disease and the impact of therapy.

The approach used in Wyeth (etanercept) and Abbott (adalimumab) models, i.e., the use of DMARDs as a comparator to biologics may be criticised if it is considered unrealistic for people for whom two or more DMARDs had previously failed, as defined in the British Society of Rheumatology guidelines, to receive a third DMARD.

In estimating the treatment effect, the Abbott and Schering-Plough models used data sources relating to comparators not included in the model, such as golimumab, and the implications of this were not clear. It was uncertain

whether the relative treatment effects could be transferred from one biologic to another.

In the Wyeth submission, data from an existing synthesis for adalimumab and the Mease 2004 trial were used to estimate effects. Although data were included from a number of trials in the adalimumab mixed treatment comparisons (MTC), the Assessment Group noted that the manufacturer didn't search for new evidence.

Schering-Plough's submission assumed that RCTs might overestimate the absolute response rates, and adjusted the expected effectiveness of biologics in their model while and Wyeth did not.

Withdrawals after 3 months because of adverse events and lack of efficacy were estimated from a single dataset (BSR register) in all of the industry models. The Assessment Group noted that there are other potential biologic registry datasets available which could have been synthesised.

The Assessment Group noted that the prediction of initial change in HAQ and longer-term changes in HAQ using PASI as an explanatory variable in the Wyeth model was questionable. There was no evidence to suggest that one component of the disease is a good predictor of the other, although there may be a correlation between joint and skin response, which has not been explored in any detail by the industry models. The Assessment Group also noted that there were some considerable differences in the sources of costs and the costing methodology used in the three manufacturer models.

The Assessment Group noted that the manufacturers' models gave markedly different results. These differences can be partly explained by the choice of comparator, different baseline characteristics of participants, placebo effects and sequential biologic treatments assumed in the models.

The key features of each of the industry models are summarised in table 6.10 (page 136-138) of the Technology Assessment Report, with a full description of the three industry models provided in Appendix 10.7 (page 241 of the

Technology Assessment Report). A full critique of the industry models is also presented in Appendix 10.8 (page 271) of the Technology Assessment Report.

3.2.3 Assessment Group economic assessment

The Assessment Group updated the economic model developed for NICE technology appraisal 104 - etanercept and infliximab for the treatment of adults with psoriatic arthritis. This model allowed the three biological therapies to be compared. A probabilistic decision analytic model was developed to estimate the incremental costs and incremental QALYs of the three biological therapies compared with palliative care over a lifetime horizon (40 years), only. The price year was 2008/2009 and costs and benefits were discounted at a rate of 3.5%.

Model structure

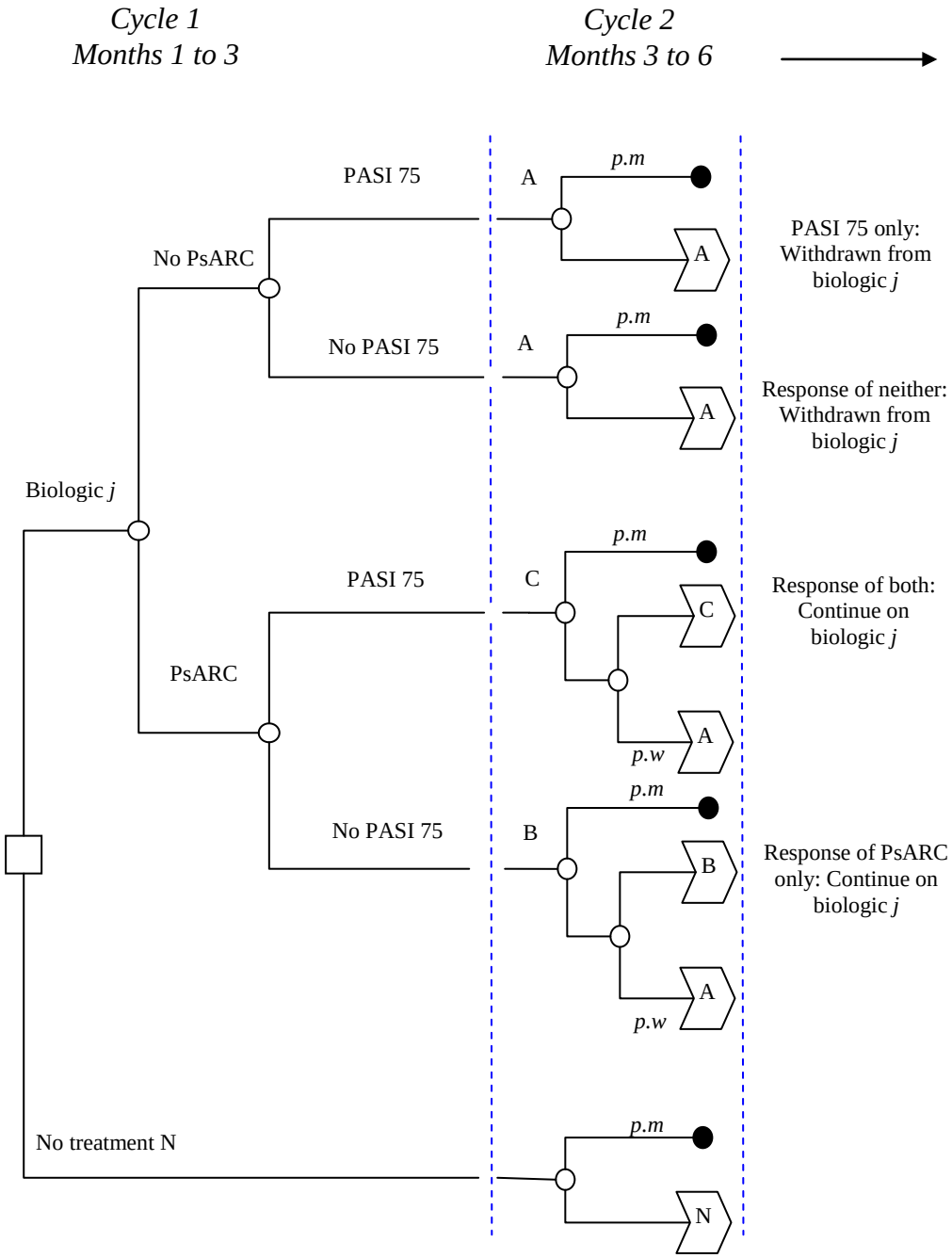
The decision analytical model followed a cohort of people, which represented the average characteristics of participants in the RCTs, and had a Markov structure (see figure 1). People in the cohort were 47 years old, had been diagnosed with psoriatic arthritis 7 years previously, were assumed to weigh 70 kg and had psoriatic arthritis that had inadequately responded to at least two DMARDS. People in the treatment arm received etanercept, infliximab or adalimumab and people in the control arm received palliative care. People's response to treatment was assessed between 12 and 16 weeks. People who responded to treatment stayed in the treatment arm, and treatment was discontinued in people whose psoriatic arthritis failed to adequately respond to treatment – these people went on to receive palliative care.

The following assumptions were included in the model:

- People in the initial 3-month trial period had some improvement in HAQ (even if they did not reach the PsARC threshold).
- People who had a PASI 75 response would gain at least a 75% improvement in psoriasis compared with baseline PASI.

- People continuing on biologic therapy maintained their initial improvement in HAQ.
- The same ongoing risk of withdrawal from biologic therapy was used for all biologics, which represented withdrawal because of reduction in efficacy, adverse events or other reasons.

Figure 1 Structure of the decision model, assuming people continue beyond 3 months if they achieve a PsARC response



Key: A – Withdrawn from biologic *j*. B – Continue on biologic *j* with response of arthritis but not of psoriasis. C – Continue on biologic *j* with response of both arthritis and psoriasis. N – No treatment.
P.m – Probability of mortality (any cause).
P.w – Probability of withdrawal from biologic after first 3 months.
Nodes: White circle – chance node. Black circle – terminal node (death from any cause). Arrow - Markov node

Health utility was measured as a function of HAQ and PASI based on linear regressions of EQ5D utility versus HAQ and PASI provided by the manufacturers based on RCT evidence. Further information can be found on page 118 of the assessment report.

The Assessment Group base-case model assumed a cohort of people with psoriatic arthritis with a baseline HAQ of 1.05, the mean of HAQ across the RCTs, and a PASI of 7.5, which represents mild-to-moderate psoriasis. It assumed that the response to arthritis and psoriasis might be correlated.

The base-case model assumed treatment with at least two DMARDS had failed in people included but that they had never been treated with biologics at baseline. The Assessment Group also modelled the cost effectiveness of sequencing biologic therapies if the first-line biologic is withdrawn. The base-case analysis reported the lifetime costs and QALYs of the three biologic treatments in people with mild-to-moderate psoriatic arthritis, which is presented as an incremental analysis ranking the alternative strategies by mean cost. The base case is shown in table 18.

Table 18 Results of the base-case analysis (page 125 of the Technology Assessment Report)

Strategy	QALY[a]	Cost (£)	Incremental QALY	Incremental cost	ICER[b] (£ per QALY gained)	PCE[c] 20K	PCE 30K[d]
Palliative care	5.241	42,205				0.414	0.282
Adalimumab	6.642	66,408	1.401	24,202	Ex dom[e]	0.044	0.020
Etanercept	7.115	72,172	0.473	5763	15,986	0.524	0.566
Infliximab	7.430	89,107	0.315	16,935	53,750	0.018	0.132

[a] Quality-adjusted life year; [b] incremental cost-effectiveness ratio; [c] probability that the treatment is cost effective at a threshold of £20,000 per QALY; [d] probability that the treatment is cost effective at a threshold of £30,000 per QALY; [e] extendedly dominated

The base-case analysis in the Assessment Group's model assumed a lifetime (40-year) time horizon for costs and QALYs, a baseline HAQ of 1.05, a baseline PASI of 7.5, rebound equal to gain and incorporates the correlation between PsARC and PASI 75 outcomes. The results for the base case

showed that infliximab was the most effective treatment (QALYs of 7.43), followed by etanercept (QALYs of 7.11), then adalimumab (QALYs of 6.64). Infliximab was also the most costly treatment (£89,107), followed by etanercept (£72,172), then adalimumab (£66,408). The ICER of etanercept compared with palliative care was £15,986 per QALY gained. The ICER for infliximab compared with etanercept was £53,750 per QALY gained. Adalimumab was extendedly dominated by a combination of etanercept and palliative care (that is, if 81% of the population were treated with etanercept and the remainder with palliative care it would have generated more QALYs for the same cost of adalimumab). Etanercept had the highest probability of being cost effective with a 52% and 57% probability of being cost effective at willingness-to-pay thresholds between £20,000 and £30,000 per QALY gained, respectively.

The total lifetime discounted health associated with palliative care was about 5.24 QALYs because the base-case scenario assumed that utility declined fairly rapidly in people with uncontrolled arthritis, and may have been less than 0 (representing a health state worse than death) in later years.

Results of sensitivity analyses

The Assessment Group conducted a univariate sensitivity analysis assuming different scenarios. The Assessment Group presented the results according to whether the ICER was less than £20,000 per QALY gained, between £20,000 to £30,000 per QALY gained or greater than £30,000 per QALY gained. The results are shown in table 19.

Table 19 Cost effectiveness of the strategies under different scenarios (page 131 of the Technology Assessment Report)

#	Description	Adalimumab	Etanercept	Infliximab
1	Base case	Ex dom[a]	< 20k[b]	> 30k[c]
2	Rebound in HAQ[d] is small after withdrawal (base case = initial gain)	Ex dom	< 20k	> 30k
3	Rapid worsening in HAQ with no treatment (upper 95% of CI[e])	Ex dom	< 20k	> 30k
4	Log-PASI[f] utility function (Abbott Laboratories) (Base case linear)	Ex dom	< 20k	> 30k
5	No correlation between PASI 75 and PsARC[g] (base case = 0.4)	Ex dom	< 20k	> 30k
6	RCT[h] results fully generalisable to clinical practice (no adjustment for placebo effect)	Ex dom	< 20k	> 30k
9	Exponential HAQ-cost function (Abbott Laboratories) (base case linear)	Ex dom	< 20k	> 30k
12	Inpatient treatment for uncontrolled psoriasis	< 20k	Dom	< 20k
13	Cost per 3 month per 1 unit change in HAQ is £183 (US data) (base case £103)	Ex dom	< 20k	> 30k
14	Change in utility per 1 unit change in HAQ is –0.45 (Wyeth Pharmaceuticals) (base case –0.29)	Ex dom	< 20k	> 30k
15	HAQ improves while on drug (lower 95% of CI) (base case no change)	Ex dom	< 20k	30k
16	High rate of withdrawal (upper 95% of CI)	Ex dom	< 20k	> 30k
17	Low rate of withdrawal (lower 95% of CI)	Ex dom	< 20k	> 30k
18	All treatments have the same probability of PsARC response at 3 months	Ex dom	< 20k	> 30k
19	All treatments have the same probability of psoriasis responses (PASI 50, 75 and 90) at 3 months	Ex dom	< 20k	> 30k
20	Cost of drugs as in Wyeth Pharmaceuticals submission	Ex dom	< 20k	> 30k
22	All biologics have the same change in HAQ at 3 months for a PsARC responder	< 20k	< 20k	> 30k
23	3 vials of infliximab (base case: 4 vials)	Ex dom	< 20k	< 20k
26	Rebound to natural history after withdrawal (Base case: rebound to initial gain)	Ex dom	> 30k	> 30k
31	No costs of psoriasis (base case: UK data)	Ex dom	< 20k	> 30k
32	Schering-Plough estimates of cost per PASI point without phototherapy	Ex dom	< 20k	> 30k
33	Schering-Plough estimates of cost per PASI point with phototherapy	< 20k	< 20k	20k–30k[i]
34	The effectiveness of biologic therapy lasts no longer than 10 years, compared with palliative care	Ex dom	20k–30k	> 30k

[a] Extendedly dominated; [b] mean incremental cost-effectiveness ratio is less than £20,000 per QALY; [c] mean ICER is less than £20,000 per QALY gained; [d] health assessment

questionnaire; [e] confidence interval; [f] psoriasis area and severity index; [g] Psoriatic Arthritis Response Criteria; [h] randomised controlled trial; [i] Mean ICER is between £20,000 and £30,000 per QALY gained

Further details can be found in table 6.6 of the Technology Assessment Report (pages 127–129).

Results of subgroup analyses

The Assessment Group also considered subgroup analysis, modelling a cohort with a worse baseline health-related quality of life (HAQ score of 1.8 based on the BSR biologics register) and a baseline PASI of 12.5, corresponding to moderate-to-severe psoriasis, and a cohort without skin involvement (PASI of 0) which is thought to represent 50% of people with psoriatic arthritis (table 20).

Table 20 Subgroup analyses (pages 132–133 of the Technology Assessment Report)

#	Description		QALY[a]	Cost (£)	ICER[b] (£ per QALY gained)	PCE20k[c]	PCE30k[d]
10	Baseline HAQ[e] 1.8 (BSR[f] register) (Base case 1.05)	N[g]	2.132	46,703		0.458	0.314
10		A[h]	3.439	71,044	Ex dom[i]	0.040	0.016
10		E[j]	3.902	76,824	17,023	0.482	0.548
10		I[k]	4.209	93,770	55,099	0.020	0.122
11	Baseline PASI[l] 12.5 (Base-case 7.5)	N	4.879	66,871		0.374	0.256
11		A	6.320	88,203	14,809	0.110	0.056
11		E	6.775	95,553	16,154	0.432	0.410
11		I	7.135	108,651	36,364	0.084	0.278
7	Baseline PASI 12.5, and continue after 3 months only if respond to both PsARC[m] & PASI 75 (base-case PsARC only)	N	4.879	66,871		0.354	0.212
7		E	5.398	74,172	Ex dom	0.050	0.078
7		A	5.855	80,199	13,660	0.232	0.078
7		I	6.832	102,369	22,703	0.364	0.632
8	Baseline PASI 12.5, and continue after 3 months if respond to either PsARC or PASI 75	N	4.879	66,871		0.374	0.258
8		A	6.514	91,119	14,829	0.198	0.072
8		E	6.779	95,619	17,007	0.326	0.296
8		I	7.312	112,560	31,794	0.102	0.374
21	Baseline PASI 12.5, and annual inpatient treatment for uncontrolled psoriasis (Base-case UVB[n])	N	4.879	171,901		0.190	0.084
21		A	6.320	181,009	6323	0.138	0.056
21		I	7.135	191,873	13,327	0.660	0.832
21		E	6.775	195,112		0.012	0.028
30	Baseline PASI 0 (base case 7.5)	N	5.783	28,933		0.424	0.306
30		A	7.126	54,556	Ex dom	0.016	0.014
30		E	7.626	59,534	16,603	0.552	0.616
30		I	7.873	78,368	76,132	0.008	0.064

[a] Quality-adjusted life year; [b] incremental cost-effectiveness ratio; [c] probability that the treatment is cost-effective at a threshold of £20,000 per QALY; [d] probability that the treatment is cost-effective at a threshold of £30,000 per QALY; [e] health assessment questionnaire; [f] British Society for Rheumatology; [g] palliative care; [h] adalimumab; [i] extendedly dominated; [j] etanercept; [k] infliximab

The Assessment Group presented an analysis which compared the sequencing of different biological therapies in people with mild-to-moderate skin disease if a first biologic has failed (see table 21). The ICERs depended on which drug was used as first-line therapy, and was therefore ineligible for use as second-line therapy.

Table 21 Costs and QALYs[a] of biologics used as second-line therapy for people with mild-to-moderate skin disease if first biologic fails (page 133 of the Technology Assessment Report)

Scenario	Description	Treatment	QALY	Cost **(£)**	ICER[b] assuming **infliximab** was used **first** line **(**£ per QALY gained)	ICER assuming **etanercept** was used **first** line **(£** per QALY gained**)**	ICER assuming **adalimumab** was used **first** line **(£** per QALY gained**)**
24	Second-line biologic if first failed for inefficacy	Palliative care	5.241	42,205			
24		Adalimumab	5.889	53,349	Extendedly dominated	17,182	NA[c]
24		Etanercept	6.234	57,418	15,309	NA	15,309
24		Infliximab	6.512	69,152	NA	25,363	42,220
25	Second-line biologic if first failed for adverse events	Palliative care	5.241	42,205			
25		Adalimumab	6.334	59,809	Extendedly dominated	16,103	NA
25		Etanercept	6.699	63,846	11,067	NA	11,067
25		Infliximab	6.938	76,842	NA	28,176	54,218

[a] Quality-adjusted life years; [b] incremental cost-effectiveness ratio; [c] therapy is not available for second-line use because it failed as first-line therapy

Comparison between manufacturers' and Assessment Group models

Key differences between the three industry models and the current Assessment Group model included: the choice of comparator; heterogeneity; failure to consider alternative correlations between response types; how initial PsARC response was determined; how the change in HAQ was determined; no consideration of alternative decision rules about continuing beyond the initial 3-month period; generating withdrawals rates from a single observational study; the costs of drugs; drug administration and monitoring; and the healthcare costs associated with treating arthritis and psoriasis if these were not controlled by biologics.

For further details please refer to the Technology Assessment Report (pages 135–145).

4 Issues for consideration

- Does the Committee consider that differences in the RCT design (patient population, definitions of response and progression) enable comparisons between the three biological treatments?

- Does the Committee consider that differences in the RCT design (patient population, definitions of response and progression) enable comparisons between the three biological treatments?

- What is the Committee's view on the availability and quality of long-term data on both skin and joint component of psoriatic arthritis for the biological treatments?

- What is the Committee's view of the generalisability of RCT evidence to the UK given that the population included patients with less severe psoriatic arthritis than the marketing authorisation or current NICE guidance?

- Does the Committee consider that the different choice of primary outcome between manufacturers is appropriate to assess the effectiveness of the biological treatments?

- Does the committee consider the biological treatments to be effective in treating the psoriasis component of the disease?

- Does the Committee consider that generalisability of adverse event data for etanercept, infliximab and adalimumab in PsA, which are derived primarily from patients with RA or other indications to be appropriate?

- Does the Committee consider the model assumptions by the manufacturers of etanercept, infliximab and adalimumab appropriate?

- Does the Committee consider that there is sufficient evidence available to consider the sequencing of the different biological treatments?

5 Authors

João Vieira
Technical Lead

Eleanor Donegan
Technical Adviser

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Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York:

- Rodgers, Mark et al., Centre for Reviews and Dissemination, University of York, York, December 2009.

B Submissions or statements were received from the following organisations:

I Manufacturers/sponsors

- Wyeth Pharmaceuticals
- Schering-Plough Ltd
- Abbott Laboratories Ltd

Appendix B:

Etanercept and infliximab for the treatment of adults with psoriatic arthritis (NICE technology appraisal guidance 104)

Guidance

1.1. Etanercept, within its licensed indications, is recommended for the treatment of adults with severe active psoriatic arthritis only when the following criteria are met.

- The person has peripheral arthritis with three or more tender joints and three or more swollen joints.
- The psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying anti-rheumatic drugs (DMARDs), administered either individually or in combination.

1.2. Etanercept treatment should be discontinued in patients whose psoriatic arthritis has not shown an adequate response when assessed using the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks. An adequate response is defined as:

- an improvement in at least two of the four PsARC criteria, one of which has to be joint tenderness or swelling score, with no worsening in any of the four criteria.

1.3. Infliximab, within its licensed indications, is recommended for the treatment of adults with severe active psoriatic arthritis if, under the circumstances outlined in section 1.1, treatment with an anti-TNF (tumour necrosis factor) agent is considered appropriate and the person has been shown to be intolerant of, or have contraindications to, treatment with etanercept or has major difficulties with self administered injections.

1.4. Infliximab treatment should be discontinued in patients whose psoriatic arthritis has not responded adequately at 12 weeks. An adequate response is defined in section 1.2.

1.5. It is recommended that the use of etanercept or infliximab for psoriatic arthritis should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of psoriatic arthritis. If a person has both psoriatic arthritis and psoriasis their treatment should be managed by collaboration between a rheumatologist and a dermatologist.

Adalimumab for the treatment of psoriatic arthritis (NICE technology appraisal guidance 125)

Guidance

1.1 Adalimumab, within its licensed indication, is recommended as an option for the treatment of adults with active and progressive psoriatic arthritis only when the following criteria are met.

- The person has peripheral arthritis with three or more tender joints and three or more swollen joints.
- The psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying anti-rheumatic drugs (DMARDs), administered either individually or in combination.

1.2 Adalimumab treatment should be discontinued after 12 weeks in adults whose psoriatic arthritis has not shown an adequate response when assessed using the psoriatic arthritis response criteria (PsARC). For the purposes of this guidance, an adequate response is defined as:

- an improvement in at least two of the four PsARC criteria, one of which has to be joint tenderness or swelling score, with no worsening in any of the four criteria.

1.3 It is recommended that the use of adalimumab for the treatment of psoriatic arthritis in adults should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of psoriatic arthritis.