Scottish Medicines Consortium

adalimumab 40mg pre-filled syringe for subcutaneous injection (Humira®) No. (218/05)

Abbott

New indication: treatment of active and progressive psoriatic arthritis in adults when response to disease-modifying anti-rheumatic drugs has been inadequate

4 November 2005

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Adalimumab (Humira®) is accepted for use within NHS Scotland for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

Adalimumab improves symptoms of arthritis and psoriasis and may slow the progression of joint damage in patients with active psoriatic arthritis.

Chairman,
Scottish Medicines Consortium

Adalimumab 40mg pre-filled syringe for subcutaneous injection (Humira®)

Indication

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

Dosing information

40mg by subcutaneous injection every two weeks.

UK launch date

8th August 2005

Comparator medications

The other two tumour necrosis factor (TNF)-antagonists marketed in the UK, infliximab and etanercept, are licensed for treatment of adults who have active and progressive psoriatic arthritis (PsA) and have had an inadequate response to disease-modifying anti-rheumatic drugs (DMARDs). Leflunomide, a DMARD, is licensed for treatment of adult patients with active PsA and would probably be used before TNF-antagonist treatment was considered.

Cost of relevant comparators

Drug	Dosing regimen	Annual cost (£)
Adalimumab	**40mg sc injection every 2 weeks**	**9295**
Etanercept	25mg sc injection twice a week	9296
Infliximab	5mg/kg iv infusion weeks 0, 2, 6 then every 8 weeks	10910*#

£14687 in first year; * for 60kg to 80kg patient, for those weighing <60kg annual cost would be £8183 (£11015 in first year); sc = subcutaneous; iv = intravenous; costs from eVadis in August 2005

Summary of evidence on comparative efficacy

Adalimumab is an IgG1 monoclonal antibody that binds to TNF preventing it binding to TNF receptors and thereby antagonising its physiological activity.

A double-blind study recruited 100 adults with moderate to severely active PsA, defined by at least three swollen joints and at least three tender joints, having an inadequate response to DMARD therapy as assessed by the investigator. They were randomised, with stratification for concurrent use of DMARDs, to adalimumab 40mg by subcutaneous (sc) injection every two weeks or placebo. The primary outcome, proportion of patients achieving at least 20% improvement in their American College of Rheumatology score (ACR20) at 12 weeks, was assessed in all patients who received at least one dose of study drug on an intention-to-treat (ITT) basis. This was significantly greater with adalimumab compared to placebo: 39% vs. 16%, with significantly greater proportions of adalimumab-treated patients achieving at least 50% and 70% improvements in this score (ACR50 and ACR70), and PsA response criteria (PsARC) at 12 weeks: 25%, 14% and 51%, respectively, vs. 2%, 0% and 24%, respectively, with placebo. Quality of life, assessed via mean change in disability index of the health assessment questionnaire (HAQ), significantly improved with adalimumab compared to

placebo: -0.3 vs. -0.1 (on a 0-3 scale). In these groups respectively, 32 and 30 patients had a target psoriatic lesion suitable for assessment and these were assessed as clear or almost clear on the physician's global assessment (PGA) scale at 12 weeks in significantly more patients who received adalimumab, compared to placebo: 41% vs. 7%.

A double-blind study recruited 313 adults with moderate to severely active PsA, defined by at least three swollen joints and at least three tender joints, who had failed to respond to non-steroidal anti-inflammatory drug (NSAID) therapy. They were randomised, with stratification for concurrent methotrexate use and degree of psoriasis (<3% or ≥3% of body surface area) to adalimumab 40mg sc injection every two weeks or placebo for 24 weeks. Patients who failed to achieve at least a 20% reduction in both swollen joint count and tender joint count on two consecutive assessments at least four weeks apart could receive rescue medication with corticosteroids or DMARDs after assessment at week 12. The primary outcome, proportion of patients achieving an ACR20 response at 12 weeks, was assessed in patients who received at least one dose of study drug on an ITT basis. This was significantly greater with adalimumab compared to placebo: 58% vs. 14%, with significantly greater proportions of adalimumab-treated patients also achieving ACR50, ACR70 and PsARC responses at 12 weeks: 36%, 20% and 62%, respectively, vs. 3.7%, 0.6% and 26%, respectively, with placebo. After 12 weeks, 4 and 16 patients in the respective groups received rescue therapy and were considered non-responders in subsequent analyses. At week 24 adalimumab was associated with significantly greater ACR20, ACR50, ACR70 and PsARC response rates: 57%, 39%, 23% and 60%, respectively, vs. 15%, 5.5%, 1.2% and 23%, respectively, with placebo. In the subgroup of 138 patients with psoriasis affecting at least 3% of their body surface, significantly more adalimumab-treated patients, compared to those given placebo, were assessed as having clear or almost clear skin on the PGA and achieved at least 50%, 75% and 90% improvement from baseline on the psoriasis area and severity index (PASI50, PASI75 and PASI90;) on an ITT basis at week 12: 59%, 72%, 49% and 30%, respectively, vs. 2.9%, 15%, 4.3% and 0%, respectively, with placebo. At 24 weeks, the respective rates with adalimumab were 67%, 75%, 59% and 42%, which were significantly greater than those with placebo: 10%, 12%, 1.5% and 0%.

There were significant improvements with adalimumab, compared to placebo, in mean changes from baseline for the quality of life outcomes: HAQ, -0.4 vs. -0.1 (on a 0-3 scale) at weeks 12 and 24; functional assessment of chronic illness therapy-fatigue (FACIT-F), 6.5 vs. 0.6 and 7.1 vs. 0.1 (on a 0-52 scale) at weeks 12 and 24, respectively; and dermatology life quality index (DLQI), -5.6 vs. -0.4 and -6.1 vs. -0.7 (on a 0-30 scale) at weeks 12 and 24, respectively. All short-form 36 (SF-36) domains significantly improved with adalimumab at week 24, except for role-emotional.

Summary of evidence on comparative safety

In common with other TNF-antagonists, adalimumab is associated with increased incidences of infection, including opportunistic infections and tuberculosis, probably due to suppression of the immune system, which may also mask signs of fever. The relative deficiency of TNF produced by TNF-antagonists may also initiate auto-immune processes, with development of antinuclear and double-stranded DNA antibodies and lupus-like syndromes, although the latter remain uncommon. TNF-antagonists have rarely been associated with demyelinating disease, including multiple sclerosis. There is concern that TNF-antagonists, by continually inhibiting pro-inflammatory molecules may increase the risks of cancer, particularly lymphoproliferative malignancies. Currently, there is no clinical evidence of this. However, long-term data are required to exclude it. Adalimumab and etanercept are associated with allergic reactions, but do not require to be administered in hospital. In contrast, infliximab must be administered in hospital because it has been associated with serious acute infusion-related reactions, including anaphylactic shock and delayed hypersensitivity reactions.

Summary of clinical effectiveness issues

British Society for Rheumatology (BSR) guidelines for anti-TNF therapy in PsA recommend TNF-antagonists for patients with peripheral PsA who have failed to respond to adequate therapeutic trials of at least two standard DMARDs. In the small and large trials described previously only 56% and 42% of patients, respectively, had previously received treatment with at least two DMARDs. Therefore, the populations within these studies may differ from Scottish patients who would receive this drug in accordance with the BSR guideline and it is possible that benefits observed in practice may differ from those observed in these trials. Additional sub group analysis provided by the manufacturer indicated that treatment effect with the sub group of patients who had received previous treatment with at least two DMARDs was similar to the treatment effect observed in the trial population overall.

Adalimumab is licensed as monotherapy, not in combination with DMARDs, for treatment of PsA. In the smaller trial described previously 68% of patients received concomitant DMARD therapy and in the larger trial about 50% of patients received concomitant methotrexate. In the latter trial, subgroup analyses indicated that ACR20, ACR50 and ACR70 response rates with adalimumab in combination with methotrexate were similar in those with adalimumab alone: 55%, 36% and 22% vs. 59%, 42% and 23%, respectively, suggesting that in this trial population methotrexate was no longer effective.

There are no trials directly comparing adalimumab with other TNF-antagonists for treatment of arthritic and psoriatic symptoms in patients with PsA, therefore relative efficacy is unclear.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis, based on a micro-simulation model of the patients' experience over time. Adalimumab was compared with a sequence of DMARDs in the main analysis, but this was extended to compare with the other TNF-antagonists. Clinical data were taken from the main clinical trial (up to 24 weeks of follow-up), the open label study (to 48 weeks) and extrapolation (essentially assuming no disease progression). QALY gains were estimated by mapping data from measures in the trial. Over the lifetime of a patient the estimated additional cost per QALY gained for adalimumab compared to DMARDs was just below £19k, although over 10 years it was £29k. The model showed that adalimumab would dominate etanercept (i.e. be cheaper and give more QALYs) although both differences are small.

The choice of comparator and modelling approach were broadly acceptable. The results were analysed appropriately and extensive sensitivity analysis was conducted on the lifetime "cost per QALY" result. Adalimumab remains cost–effective compared to DMARDs for time horizons of ten years and over using baseline assumptions.

Adalimumab may be said to have similar costs and benefits to etanercept, which has previously been recommended for use by SMC.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The manufacturer estimates the medicines budget impact of treating all eligible patients with adalimumab would be £3.8m in year 1 and thereafter £3.3m per year up to year 5. These figures include the cost of adalimumab and also the costs associated with testing and monitoring. Testing and monitoring costs accounted for around 4% of the total cost. This includes assessing patients at 12 weeks and stopping the treatment of those who are not responding. It is based on 541 patients being treated in Scotland and all receiving adalimumab from year one onwards, subject to response. This budget impact would be incurred with other anti-TNF agents and therefore if adalimumab is accepted for use the net costs will be less

Guidelines and protocols

The 2005 BSR guideline for anti-TNF therapy in PsA recommends TNF-antagonists for patients with peripheral PsA who have failed to respond to adequate therapeutic trials of at least two standard DMARDs (leflunomide, sulfasalazine, methotrexate or ciclosporin) and have active disease, defined as three or more swollen joints and three or more tender joints on two separate occasions one month apart. A response to TNF-antagonist therapy is defined as achieving a PsARC at 12 weeks for joint disease and for skin disease a PASI75 response. Patients who do not achieve a PsARC response should discontinue treatment, but can be considered for treatment with a different TNF-antagonist.

Additional information

After review of a full submission, the SMC issued advice on 12th July 2004 that etanercept is accepted for use within NHS Scotland for the treatment of active and progressive PsA in adults. It is the first drug to be licensed for this indication and not only improves symptoms of arthritis and psoriasis, but may slow the progression of joint damage (at least over a period of one year). SMC has not reviewed a submission for infliximab in this indication.

NICE is conducting a technology appraisal of etanercept and infliximab for treatment of PsA, that is expected to be published in January 2006. The September 2005 final appraisal determination notes that etanercept may be used for the treatment of adults with severe active PsA who have three or more tender joints and three or more swollen joints and have not responded to adequate trials of at least two standard DMARDs. It should be discontinued at three months if the patient has not achieved a PsARC response. Infliximab is recommended for the treatment of adults with severe active PsA, as defined previously for etanercept, who are intolerant to etanercept.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 14 October, 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The under noted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

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Mease PJ, Sharp JT, Ory P et al. Adalimumab treatment effects on radiographic progression of joint disease in patients with psoriatic arthritis: results from ADEPT. Proceedings from the Annual European Congress of Rheumatology (EULAR) 2005, Vienna, Austria. FRI0212

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Kavanaugh AF, Ritchlin CT, Malaise MG et al. Adalimumab treatment with and without methotrexate in patients with moderate to severe psoriatic arthritis: results from ADEPT Proceedings from the Annual European Congress of Rheumatology (EULAR) 2005, Vienna, Austria. FRI0227