
Abbott welcomes the opportunity to comment on the assessment report developed by the Liverpool Reviews and Implementation Group for this appraisal. The executive summary outlines the key points regarding Abbott’s assessment of the clinical and cost-effectiveness of adalimumab for the treatment of AS. Information provided in italics has been quoted from the assessment report. Please note that these comments have considered only the evidence provided in the assessment report, as the Liverpool Reviews and Implementation Group (LRIG) economic model has not been released at the time of writing. Where possible Abbott has suggested alternative model configurations to be run following review of the evidence presented in the assessment report.

Executive Summary

- Anti-TNF agents are highly effective for patients with severe active AS who have failed conventional therapy.
- The British Society for Rheumatology (BSR) guidelines for anti-TNF agents ensure that therapy is offered only to patients with sustained active disease for at least four weeks and who have failed to respond to NSAID therapy.
- The evidence does not support that patients with active disease experience spontaneous remission in the absence of anti-TNF therapy.
- The evidence indicates that withdrawal from anti-TNF therapy leads to rapid relapse.
- Clinical evidence indicates that inflammation can be suppressed over time using anti-TNF agents. Therefore, the LRIG model should be based on differential BASFI progression over time for anti-TNF agents compared to conventional therapy.
- Long-term discontinuation rates may be lower for AS than for RA as there are limited treatment options for AS patients stopping anti-TNF agents, as supported by observational studies.
- It is important to consider the costs for this disease from a societal perspective.
- Utility-regression relationships should be based on measured utilities, BASDAI and BASFI measured for the same patients, as derived from the adalimumab RCTs.

Overall, on consideration of the evidence base, Abbott considers that adalimumab is a highly clinically and cost-effective chronic therapy for severe active AS for patients who have failed conventional therapy. Further details of the evidence supporting this position are provided on the following pages.
Lack of evidence for spontaneous resolution without anti-TNF therapy

Based on an analysis of data included in the model submitted by Abbott, the assessment group has hypothesised in the report that some patients with AS may experience a spontaneous resolution in their condition without anti-TNF therapy:

‘many patients showed evidence of a natural improvement in condition over time, to the extent that some achieved a very good recovery whilst remaining on placebo [Page 126 of the assessment report]’

AS is a chronic progressive disease. Its progressive nature means that initiation of the disease usually occurs in the sacroiliac joints and tends to progress up the spine, leading to advanced and occasionally total spinal ankylosis. It is argued that the evidence on natural history of AS does not support the concept of spontaneous resolution of disease, as noted by Dougados and colleagues in the era before licensing of anti-TNF agents for AS¹:

‘Management of ankylosing spondylitis (AS) is challenged by the progressive nature of the disease. To date, no intervention is available that alters the underlying mechanism of inflammation in AS. Currently available conventional treatments are palliative at best, and often fail to control symptoms in the long term. Current drug treatment may perhaps induce a spurious state of “disease remission,” which is merely a low level of disease activity.’ [Dougados et al. 2002]

It is unclear how the LRIG analysis has taken into account placebo patients receiving early escape open-label adalimumab, as the majority of patients randomised to placebo went on to receive early escape open-label adalimumab between weeks 12 and 24.

Given the relative short-term nature of the trials, it is recommended to consider long-term observational data sources in order to assess whether AS patients can spontaneously resolve without anti-TNF therapy. Data from the Outcome in Ankylosing Spondylitis International Study (OASIS) observational study, as employed in the Abbott model adopted by the LRIG model for the estimation of AS-related costs, do not provide evidence of spontaneous resolution of patients’ symptoms and disease activity (as measured by the evolution in the BASDAI score, BASFI score and EuroQOL score for individual patients over four years).

The natural history of AS has also been investigated by Brophy and colleagues². Using the Bath Ankylosing Spondylitis Radiology Index (BASRI-total), this study showed AS to be a linearly progressive disease with about a 35% change every 10 years with no evidence at all of spontaneous resolution.
Given the preponderance of subjective outcome measures for this disease, it is perhaps useful to consider more stringent efficacy criteria such as ASAS Partial Remission, changes in C-reactive protein (CRP) and magnetic resonance imaging (MRI) assessments.

CRP is a well-established, sensitive, and objective marker of inflammation. In the adalimumab trials, the CRP level remained constant over 24 weeks (mean change over 24 weeks = -0.2mg/dL [-0.48,0.09] for the placebo group. In contrast the adalimumab arm was associated with a mean change of -1.17 mg/dL [95% -1.45, -0.90]), which does not support the concept that placebo patients may improve spontaneously.

MRI has been used to demonstrate reduction in inflammatory spine lesions in AS patients. MRI assessments clearly demonstrate statistically significant reductions in inflammation in both the spine and sacroiliac joints of AS patients when treated with adalimumab compared to placebo after 12 weeks, and that this effect is sustained through 52 weeks of continuous adalimumab treatment.

Finally, a low placebo response was demonstrated for the ASAS Partial Remission measure whereby only 5.6% of placebo patients achieved partial remission versus 22.1% of adalimumab patients at 24 weeks (p<0.001). Partial Remission is a low disease state that was also maintained for 52 weeks on continuous adalimumab treatment.

Impact of issue on economic modelling approach:

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The overall evidence base does not support the hypothesis of spontaneous resolution of disease for conventional therapy and therefore this assumption should be removed from the LRIG economic model.
**Intermittent therapy with anti-TNF agents in AS leads to rapid relapse**

As highlighted above, the evidence base does not support spontaneous resolution and Abbott considers that there is no rationale for intermittent therapy for anti-TNF agents. This position is supported by the BSR guidelines for the use of anti-TNF agents in AS which recommend continuous treatment for patients with severe active disease. Abbott therefore adopted this approach in modelling continuous adalimumab therapy in the submitted model.

It is likely that the inflammatory process inherent in AS is ongoing and can lead to changes in the spine, which can continue in the absence of symptoms. Given the chronic nature of the disease and the consequences of progression of spinal changes, any therapy for AS should be given on a continuous basis to reduce or prevent spinal inflammation and progression of the disease.

The evidence indicates that withdrawal from anti-TNF agents in AS leads to rapid relapse. Baraliakos and colleagues\(^7\) have demonstrated that discontinuation of infliximab after 3 years of infliximab infusion led to a worsening in the condition of patients. In this study, 97.6% had to be retreated with infliximab due to a relapse in disease activity (BASDAI \(\geq 4\)). The mean time to relapse was 17.5 weeks, with 10 patients (24%) demonstrating a relapse within 12 weeks. Re-treatment with infliximab led to a state similar to that before treatment was stopped, thereby supporting the conclusion that continuous therapy with infliximab would prevent relapse of disease. This is further supported by clinical studies for etanercept. Brandt and colleagues\(^8\) reported that after discontinuation of etanercept, 75% of the patients experienced a relapse after a mean of 6 weeks.

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The evidence base supports the need for continuous therapy for AS and therefore anti-TNF treatment should be modelled as continuous therapy, as per the existing base case from the LRIG economic model.
**Disease progression and long-term benefit on anti-TNF agents in AS**

Disease progression and long-term benefit of anti-TNF agents in AS can be analysed using a number of outcome measures.

Evidence from MRI studies demonstrates that acute inflammatory lesions in the spine and sacro-iliac joints can be effectively suppressed, suggesting that bony destruction and proliferation can be prevented with anti-TNF therapy. Braun and colleagues have demonstrated that patients receiving infliximab were associated with a decrease in spinal inflammation on MRI whereas those on placebo showed persistent inflammatory spondylitis. MRI improvements for patients receiving adalimumab have been noted as part of an open-label study and also in the larger M03-606 adalimumab trial which demonstrated a significant reduction at one year in both spinal and sacroiliac inflammation in patients receiving adalimumab compared to those receiving placebo. The ability of anti-TNF agents to suppress disease activity over the long term in AS (up to 5 years) has been confirmed.

The long-term benefits of anti-TNF agents in suppressing inflammation are supported by their mechanism of action. Histological analysis of synovial tissue from AS patients treated with infliximab demonstrated reduction in thickness and inflammatory cell infiltrate. Etanercept has been shown to exert a beneficial effect on articular cartilage biomarkers of degradation and turnover in patients with AS. Similarly, adalimumab has shown a statistically significant reduction in both matrix metalloproteinase –3 and urinary CTX-II level compared to placebo.

Overall, by demonstrating long-term suppression of inflammation it is argued that maintenance of functional ability in AS can be achieved in the long term with the use of anti-TNF therapy.

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The evidence base suggests that anti-TNF agents can reduce inflammation in AS over the long term and that BASFI progression in AS should be set at 0 BASFI points per year for anti-TNF agents and 0.07 BASFI points per year for conventional therapy within the LRIG economic model. It should be noted that the assumption in the model submitted by Abbott has a more conservative rate of BASFI progression of 0.05 BASFI points per year for patients on conventional therapy. The cost-effectiveness of anti-TNF agents in AS appears to be more sensitive to the long-term suppression of disease symptoms rather than inhibition of radiographic progression as highlighted by the LRIG model.
The long-term discontinuation rate of anti-TNF agents in AS

In line with other economic analyses of anti-TNF agents, the model submitted by Abbott used a 10% long-term annual discontinuation rate. It should be noted that this is a conservative assumption compared to the 4% long-term discontinuation rate used by Boonen and colleagues. The 4% rate was estimated using expert opinion from rheumatologists with experience of treating AS patients with anti-TNF agents. Kobelt and colleagues highlighted the problem with using open-label extensions to trials for estimating the long-term discontinuation rate. As patients in a trial are not subject to discontinuation at three months as per BSR guidelines for AS, it is likely that these non-responding patients will stop treatment at a later time point in the trial. Therefore using open-label extension data may artificially inflate the long-term discontinuation rate in clinical practice in the UK. For this reason, it is not possible to provide an accurate estimate of long-term discontinuation using the data for the 48-week open-label extension to the adalimumab trials.

It is argued that observational data may provide the best estimate of the long-term discontinuation rate. Long-term discontinuation rates are likely to be lower for AS than for rheumatoid arthritis as there are limited treatment options for patients stopping anti-TNF agents for AS. This is supported by recent evidence from observational data on the use of anti-TNF agents, which indicates that discontinuation rates are significantly lower for AS compared to rheumatoid arthritis.

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The long-term discontinuation rate for the LRIG model should not be estimated from open-label continuation trials, but should be based on a systematic review of discontinuation rates from biologic registries.
Importance of costs incurred outside the healthcare system in ankylosing spondylitis

In considering the cost-effectiveness of anti-TNF agents for the treatment of ankylosing spondylitis (AS) it should be remembered that patients typically present in their late 20s, and successful treatment is likely to avert significant lost work productivity. This view is acknowledged in the assessment report:

‘The total cost of treating patients with AS is dominated by indirect costs. If an analyst were to take a healthcare provider perspective only, a significant proportion of relevant costs would be overlooked [Page 59 of the assessment report].

Further, published evidence on the economic burden of the disease demonstrates that there are other substantial costs incurred outside the healthcare system in the form of expenditure incurred by patients and caregivers. The impact of non-healthcare costs on the results of the economic model submitted by Abbott has been examined. The base case cost per QALY for adalimumab including only NHS costs is £23,097. In comparison, when indirect (work productivity) costs and other costs incurred by patients and carers are included, the cost per QALY improves to £5,093. These results indicate that adalimumab is cost-effective for the treatment of AS and using a narrower focus of NHS costs (whilst still demonstrating cost-effectiveness) does not reflect the true cost-effectiveness of these agents. The low cost per QALY for anti-TNF agents for AS when indirect costs are included is noted in the assessment report:

‘A discussion of an analysis that incorporates costs other than those faced by the NHS, in particular the cost associated with informal care and days off work for working age individuals, is not pursued since infliximab is clearly cost-effective under all reasonable values under these circumstances [Page 94 of the assessment report].

The disability with AS is also associated with significant state financial support and it is likely that a number of patients eligible for treatment with anti-TNF agents will currently be in receipt of disability living allowance or an attendance allowance. A study by Bhogal and Kay in Newcastle has provided evidence of a strong relationship between AS disability and receipt of disability benefits. This survey indicated that a BASFI score of greater than 4 is associated with the receipt of disability benefits. Therefore, effective control of disease (as measured by reduction in BASFI score) through the use of anti-TNF agents could reduce the cost of financial benefit payments for persons with AS.

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Although the reference case for cost-effectiveness analyses submitted by consultees to NICE specifies the healthcare perspective, given the significant burden of indirect and other costs for this particular disease, it is important for the LRIG economic model to consider a non-reference case approach.
Relationship between BASDAI, BASFI scores and utility

The LRIG model uses the utility model developed by Schering-Plough, drawing on a regression analysis based on a cross-sectional postal survey of AS patients. The utility regression model submitted by Abbott uses data on the Health Utility Index (HUI III) measured directly from patients receiving adalimumab or conventional therapy in the phase III clinical trials. The analyses submitted by Abbott have been criticised for the exclusion of age from the regression model. However, during model development, age was not determined to be a significant predictor of utility and was therefore excluded from the final regression model. Further, it is noted that the coefficient for age in the regression model adopted by the Assessment Group is very small (0.0016809 QALY per year of age) suggesting that after 30 years, the average utility of a subject would decrease by about 0.05 QALY due to age alone.

It is therefore argued that the utility model submitted by Abbott is the optimal source from the available evidence for the relationship between BASDAI, BASFI scores and utility for patients with AS treated with adalimumab.

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The utility-regression model submitted by Abbott is based on measured utility, BASDAI and BASFI evidence on the same patients within the framework of randomised controlled trials and should be used for the LRIG model.
**Other issues**

- **Treatment of patients according to BSR guidelines for AS**

To ensure the cost-effectiveness of agents in AS, it is important to target patients with active severe disease. The BSR guidelines for anti-TNF agents ensure that therapy is offered only to patients with sustained active disease for at least four weeks and who have failed to respond to NSAID therapy. Patients are eligible for anti-TNF therapy according to the BSR guidelines if:

- The patients’ disease satisfies the modified New York criteria for a diagnosis of AS
- Ankylosing spondylitis is active with active spinal disease defined as
  - BASDAI ≥ 4 cms
  - And spinal pain VAS (last week) ≥ 4cms
  - Both on two occasions at least four weeks apart without any change of treatment
- Failure of conventional treatment with 2 or more NSAIDs each taken sequentially at maximum tolerated/recommended dosage for 4 weeks.

It should be noted that the model submitted by Abbott considered the cost-effectiveness of anti-TNF agents when targeted to patients with sustained active disease as defined by the BSR guidelines for treatment with anti-TNF agents in AS.

- **Discounting of future costs and benefits in AS**

Data provided in table 7-12b in the addendum to the assessment report highlight the impact of using a 6% discount rate for future costs and 1.5% for future benefits in the health economic modeling. Using these rates yields a lower cost per QALY in the LRIG model compared to NICE’s currently recommended rates of 3.5% for costs and benefits. The equity impact of using different discount rates for decision making in AS compared to the earlier rheumatoid arthritis assessment (which used 6% and 1.5% discount rates) should be considered in this appraisal.

- **Impact of treatment on mortality**

AS is associated with a 50% increased mortality compared to the general population\(^{23}\).

‘*Should even modest survival benefits be identified in future, there is no doubt that the cost-effectiveness of anti-TNF agents in treating AS would be markedly improved*’ [Page 105 of the assessment report].

As noted in the assessment report, there are a number of plausible pathways by which anti-TNF agents could reduce mortality. Spinal osteoporosis frequently occurs in severe AS. Osteoporosis may contribute to spinal fractures and progressive spinal deformity (i.e. lead to complications which can contribute to morbidity and mortality)\(^{24}\). Anti-TNF blockers have been reported to be effective in restoring bone mineral density\(^{25}\). Therefore by improving bone density, osteoporosis, a key complication of AS, can be reduced, minimising associated morbidity and mortality. Amyloidosis can also occur as a complication of AS and may contribute to the increased mortality. A study has shown anti-TNF therapy may be useful in amyloidosis secondary to inflammatory arthropathies\(^{26}\). Anti-TNF therapy also improves the cardiovascular risk profile of patients with rheumatoid arthritis by improving the lipid profile (higher HDL-cholesterol and decreased LDL:HDL ratio) and decreasing inflammation\(^{27}\).

A study of mortality among RA patients treated with TNF inhibitors has also been conducted in the US using the National Data Bank for Rheumatic Diseases (63,811 patient years of follow up)\(^{28}\). This study indicated that the use of TNF inhibitors was associated with a reduction in the mortality risk (Hazard Ratio 0.72, 95% CI 0.62 to 0.84). TNF inhibitor therapy was most strongly associated with reduced cardiovascular mortality (0.55 to 0.69).
Response to criticisms of the model submitted by Abbott

The assessment report criticises the decision to re-specify patient characteristics after 48 weeks in the Abbott model. The rationale for selecting the same age for all patients in the simulation is that the demographic profile of the patients in the adalimumab clinical trials was slightly different for patients receiving adalimumab compared to patients on placebo. Patients receiving adalimumab were slightly younger than patients receiving placebo. Since age is a factor affecting survival in the model, one concern was that a small difference in age between model arms could lead to a biased estimate of cost-effectiveness for adalimumab, by affecting the survival component of the QALY calculation.

For analogous reasons, the racial composition of patients was standardised between the adalimumab and placebo arms in the model due to the potential impact on quality of life estimates (Caucasian race was associated with lower utility estimates). Therefore, it is argued that resetting the demographic characteristics of patients from 48 weeks onwards is a conservative approach. Similarly the BASDAI, BASFI and spinal pain VAS scores were adjusted at baseline to reflect slight differences in the baseline values observed in the adalimumab trials. The scores of patients receiving adalimumab were increased at all time points in the model by a fixed value equal to the average difference in scores between adalimumab and placebo patients at baseline in the trials. This adjustment was necessary to reduce a potentially biased estimation of the cost effectiveness of adalimumab versus conventional therapy in favour of adalimumab. It should be noted that in sensitivity analyses, removing all adjustments to trial data had a minor impact on the cost per QALY estimates for adalimumab versus conventional therapy (30-year analysis = £23,330).

The assessment report also criticised the handling of disease scores in patients withdrawing from adalimumab therapy. By assuming that patients who discontinued therapy were assigned the average BASDAI and BASFI scores of the placebo group, the model submitted by Abbott is conservative as it means that patients discontinuing adalimumab would be as similar as possible in outcomes as the patients in the placebo group.
### Summary of modelling assumptions

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Overall, on consideration of the evidence base, Abbott considers that adalimumab is a highly clinically and cost-effective chronic therapy for the treatment of severe active AS for patients who have failed conventional therapy.
References


15 Maksymowycz WP et al. Adalimumab suppresses biomarkers of cartilage degradation in active ankylosing spondylitis-results of the Canadian AS study. American College of


Bhogal R, Kay LJ. Patients with ankylosing spondylitis and psoriatic arthritis with a BASFI score of 4 or higher are likely to receive financial benefits. BSR conference 2006, Abstract 336


