Adalimumab

(HUMIRA®)

National Institute for Health and Clinical Excellence (NICE)

Health Technology Appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying anti-rheumatic drugs and after the failure of conventional disease-modifying anti-rheumatic drugs only

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Executive Summary to Submission by AbbVie

abbvie

Executive Summary

The main goal of treatment in Rheumatoid Arthritis is sustained remission. However, this is often only possible if an optimal treatment strategy is initiated as early as possible after symptom onset and diagnosis. Historically in the UK, patients who have failed treatment with conventional DMARDs and initiate an anti-TNF have generally had RA for at least 11 years, received a large number of prior DMARDs and have already had extensive irreversible joint damage. Although data from the UK BSRBR show that characteristics such as disease duration and number of previous DMARDs prior to initiating an anti-TNF are decreasing year on year, even recent estimates are still much higher than those reported in other countries. Indeed, Hyrich et al. showed that from 2001 to 2008, the mean disease duration in RA patients in the BSRBR starting an anti-TNF went from an average of 15.0 years in 2001 to 11.4 years in 2008; and the mean number of DMARDs prior to initiating an anti-TNF went from 5.0 DMARDs in 2001 to 3.2 in 2008.

If the recommendations of NICE Clinical Guideline 79 for RA are followed, it is likely that the disease duration, number of prior DMARDs and HAQ at time of starting a biologic will be reduced over time. However, data are available showing that few patients receive an initial DMARD combination as their first line therapy. It is hoped that compliance with the recommendations of NICE CG79 would be improved with the development of the RA Quality Standard as it is known that early aggressive disease control will improve outcomes for patients with RA.

Since the last NICE Multiple Technology Appraisal of anti TNF agents in RA (TA130), there has been a change in clinical support in the UK for use of anti-TNF therapy in patients with DAS28<5.1, based on an increasing body of evidence showing the benefits of treating patients with moderate disease activity with anti-TNFs. Indeed, as a result of this increasing evidence, the British Society for Rheumatology (BSR) treatment guidelines for anti-TNFs changed to broaden the eligibility criteria to treat patients with active RA as measured by DAS28 from >5.1 to DAS28 >3.2 and with > 3 tender and swollen joints who have undergone trials of two DMARDs including methotrexate (MTX; unless contraindicated), bringing UK practice in line with EULAR and ACR guidelines.

Data from the Early Rheumatoid Arthritis Network (ERAN), the Early Rheumatoid Arthritis Study (ERAS), the British Rheumatoid Outcome Study (BROSG), and the Yorkshire Early Arthritis Register show that patients with persistent moderate disease activity experienced significant functional impairment (measured by HAQ and Larsen Score) and impact on their work status at three and five years since diagnosis. The conclusion from these analyses was that the majority of RA patients with a DAS28 of 3.2 - 5.1 at 3 years have only marginally better functional, radiological and orthopaedic outcomes at 5 years when compared with those with a DAS28 >5.1 who continue to receive non-biologic DMARDs. These results suggest that current DAS thresholds for eligibility to commence anti-TNF therapy may not differentiate between groups in terms of functional, radiological, orthopaedic and occupational outcomes, and consequently patients with a lower DAS28 should be eligible for anti-TNF therapy if they are not showing satisfactory response to conventional DMARDs.

NICE guidance TA130 currently stipulates that patients eligible for treatment with an anti-TNF must have failed at least two conventional DMARDs and have high disease activity (DAS28>5.1). Furthermore, in order to remain on treatment, patients need to achieve >1.2 improvement in their DAS28 score from baseline at the 6 month assessment. Whilst this is an appropriate level of improvement for patients with severe disease activity, if the eligibility criteria is expanded to include patients with moderate disease activity this will no longer be the case.

Data from the DE019 pivotal randomised controlled trial of adalimumab in patients who were inadequate responders to methotrexate support the value of treating patients with a DAS28 >3.2 after failure of methotrexate. Patients with moderate disease activity at baseline experienced similar improvements in their disease as patients with high disease activity at baseline. Furthermore, the proportion of patients with moderate disease activity in remission was higher than those patients who had a DAS28 score >5.1 at baseline; suggesting that the likelihood of reaching remission as a treatment goal, and achieving all the benefits associated with it, is greater if adalimumab is administered before patients reach a high disease activity state. Results from the large observational

study ReAct support the findings observed in DE019 that a higher proportion of patients with moderate disease activity treated with adalimumab achieve a EULAR good response, low disease activity state, or remission compared to patients with severe disease activity. Nevertheless, the data indicate that patients with DAS>5.1 at baseline achieve a significant benefit in terms of absolute DAS improvement and highlight the importance of having a response criterion which includes either the magnitude of improvement or the on-going level of disease activity, as is the case with the EULAR criteria.

The combination of adalimumab and methotrexate reduces the risk of joint damage onset or progression and improves physical function more effectively than methotrexate alone. These benefits are thought to result partly from a more rapid and intense inhibition of inflammation with combination therapy than with methotrexate alone. However, patients treated with combination therapy tend to have minimal or no progression of joint damage regardless of inflammatory activity; whereas the level of joint damage tends to reflect the extent of inflammation in methotrexate-treated patients suggesting that combination therapy may inhibit joint damage through mechanisms that are independent of inflammatory activity. Alternatively, the TNF cytokine may cause joint damage only after it exceeds some threshold that is greater than that required to cause inflammation.

The prevention of radiographic progression has become an important clinical outcome for patients with rheumatoid arthritis in recent years. This is because there is an increasing amount of literature providing evidence for the links between joint damage and disability in RA. Furthermore, studies have demonstrated that inhibition of radiographic progression has a meaningful impact on patients' lives in terms of both HAQ scores and employment status.

A Bayesian mixed treatment comparison incorporating a meta regression was conducted to inform the economic model. Given the range of treatments and subpopulations of interest (that the patient population defined in the scope is very broad in that it includes both DMARD naïve and DMARD experienced patients with RA), a comprehensive MTC is unlikely to satisfy the exchangeability assumption. Meta-regression holds the potential to explicitly model for sources of heterogeneity between studies, thus potentially satisfying the strong assumptions of MTC while still providing useful evidence for this technology appraisal. A random coefficients ordered logistic meta-regression was used to adjust for observed characteristics of studies and study arms thought to potentially contribute to treatment-effect heterogeneity as well as for unobservable factors that manifested themselves as variations in baseline risk from trial to trial. It is important to consider the effect that different trial designs, statistical analysis methods, severity of patient populations, prior treatment failures, early escape options, concomitant treatment dosing and other unobserved differences can have on efficacy outcomes in RA. These factors are not always clearly and consistently reported in RCT publications to allow appropriate adjustment.

The overall effect of adjusting for baseline risk was as expected, with studies having greater propensity for ACR-20 response on the baseline arm being likely to have lower relative effectiveness. This association was most pronounced for etanercept and certolizumab and least pronounced for infliximab. For the MTX-experienced patient population, biologics in combination with MTX or other DMARDs, median posterior simulated ACR20 responses for the 6 month estimates are highest for etanercept and lowest for golimumab. The interquartile ranges are tighter for the three older anti-TNFs, adalimumab, etanercept and infliximab, as well as abatacept than for golimumab and certolizumab. Median posterior simulated ACR50 responses are highest for etanercept and lowest for infliximab, while ACR70 responses are highest for adalimumab and certolizumab and lowest for abatacept and infliximab. Estimated responses get tighter the higher the level of ACR response.

AbbVie has developed a cost-utility model for adalimumab. The results are derived for different population subgroups, according to the scope set for the appraisal by NICE, and show that adalimumab in combination with methotrexate is a cost-effective option for moderate to severe RA patients. The main results from the cost-utility model are:

- In the methotrexate-experienced patient population with severe disease activity (DAS28 > 5.1), adalimumab in combination with methotrexate is considered cost-effective, with a lifetime incremental cost per quality-adjusted life year (QALY) gained with respect to conventional DMARDs of £16,650. This is very similar to the estimated cost per QALY of etanercept (£16,571) and certolizumab (£17,071), both taken in combination with methotrexate.

- In the methotrexate-experienced patient population with moderate disease activity (3.2 < DAS28 ≤ 5.1), adalimumab in combination with methotrexate is considered cost-effective, with a lifetime incremental cost per quality-adjusted life year (QALY) gained with respect to conventional DMARDs of £18,792. This is very similar to the estimated cost per QALY of etanercept (£18,721) certolizumab (£19,217) and golimumab (£19,784), all taken in combination with methotrexate.

In conclusion, this submission demonstrates that adalimumab in combination with methotrexate represents a clinical and cost-effective option for the treatment of RA patients with moderate and severe disease activity, for the NHS in England and Wales.