National Institute for Health and Clinical Excellence

Health Technology Appraisal

Adalimumab, Etanercept, Infliximab, Rituximab and Abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of TA36, review of TA126 and 141)

The British Health Professionals in Rheumatology (BHPR) are a group of health professionals currently in practice caring for people with inflammatory arthritis. BHPR members work in a variety of hospital and community settings and promote patient and allied health professional interests on a wide range of issues by working closely with the Department of Health and other national and European professional bodies and voluntary organisations.

Treatment of RA in current practice

The main goal of treatment of RA is the induction and maintenance of remission, improvement of quality of life, and the prevention and reduction of joint damage. Treatments usually consist of non steroidal anti-inflammatory drugs (NSAIDs) that reduce pain and stiffness, disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate which slow the disease process and reduce joint damage. Biologic agents (primarily the anti-TNFα drugs) that have been available for the last 10 years for these patients have proved to be the most beneficial for reducing joint damage and improving quality of life. Patients with moderate to severe RA are treated aggressively with DMARDs and are moved to biologic drugs if their disease does not come under control with the traditional DMARDs according to previous NICE appraisals (TA130).

There is geographical variation in practice due to funding issues in various PCTs around England and Wales, and it has not been unusual for patients to contact their local MP in order to access the newer biologic treatments – even though NICE guidance has been issued.

Current alternatives to therapy are DMARDs – methotrexate, leflunomide, azathioprine, sulphsalazine and hydroxychloroquine. Evidence has shown that although DMARDs are helpful, especially when used in combination they are not as effective as the combination of methotrexate and biologic therapy for sustaining remission or stopping joint damage (Grigor et al., Klareskog et al.).

Population

Patients with high inflammatory markers, high titres of anti-CCP antibodies and high rheumatoid factor tend to have a worse prognosis, however, there is a cohort of patients who are sero-negative for rheumatoid factor who also do badly and do not respond to the biologic B cell depleter rituximab (often used as salvage therapy in biologic failure). These particular patients need to have

access to more than one biologic drug in order to gain or maintain control of their disease.

Occasionally patients do not respond to a biologic therapy (primary non responder) and sometimes they respond in the first instance but lose response after a period of time (secondary non responder). However, the evidence is that patients can respond to a second Anti-TNFα agent and gain control of their disease (see references below too numerous to mention!!).

Advantages and disadvantages of the technology

The current alternative to biologic therapy is combination therapy using methotrexate and other DMARDs, the evidence is whilst this is effective to some degree it is not as effective as using biologic therapy. Patients expect to be treated with a drug therapy that will help them to regain their former lifestyle, remain in the workplace and contribute to the greater economy of the country. They expect to have access to the same treatments that are available elsewhere in Europe and the world, by curtailing access to treatments health professionals have to deal with the psychological distress of managing patient expectations.

Intolerance to the chosen Anti-TNFα agent (usually adalimumab or etanercept), is a comparatively rare but significant adverse reaction. The differing pharmaceutical presentation of the products can cause difficult with manipulation and subsequent injection site trauma. Our anecdotal clinical experiences show a variation in patient acceptability to each product, which often involves a switch to a more suitable formulation. This patient-driven acceptability is of utmost importance and is a key driver of compliance. Whilst this is not true pharmacological treatment failure, it is still an important issue that requires careful negotiation between HCP and patient. The ability to change products following treatment failure of any type is a clear driver of positive patient outcome.

Being able to offer modification of an alternative pharmacological pathway early on in biologic treatment failure is a sound therapeutic option. We realise that the evidence to back up this assumption will be difficult to find, as the finance required to generate such date is prohibitive to all but the large pharmaceutical companies. As most product licenses are secured on the basis of a minimally acceptable therapeutic outcome, it is unlikely that this body of evidence will ever be synthesised. Therefore a pragmatic position would be to rely on a sensible understanding of structure-activity relationships when considering switching of agents. It therefore follows that a change from a fusion protein to a fully human model or to a T or B cell modulator in some sort of ordered sequence could be an advantageous therapeutic strategy in some patients.

Implementation Issues

Biologic therapies are currently used throughout the UK and therefore it is unlikely there will be any implementation issues.

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