The National Institute for Health and Clinical Excellence (NICE) has recommended, in a final appraisal, the use of rituximab, adalimumab, etanercept, infliximab and abatacept as possible treatment options for rheumatoid arthritis (RA) after treatment with a TNF inhibitor has failed.

The appraisal evaluates adalimumab use after the failure of at least one TNF inhibitor, and combines this evaluation with reviews of previous NICE guidance on the use of adalimumab, etanercept, infliximab, rituximab and abatacept.

According to the NICE report, there are an estimated 580,000 people in England and Wales who suffer with rheumatoid arthritis, and according to Carole Longson, Director, Health Technology Evaluation center at NICE “approximately 15% of these or 87,000 people have a severe form of the disease”.

As RA is a progressive disease it can become a moderate disability for many vastly affecting their quality of life if the treatment available does not have the desired effect. Treatments are individually tailored but do not suit everybody, some provide inadequate response or do not have sustained efficacy, whilst others are simply not tolerated by the patient.

Longson explained that “Different people respond in different ways to treatment and the committee heard from clinical experts and patients about the importance of having multiple options available”.

Rituximab (MabThera, Roche Products), in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other disease-modifying antirheumatic drugs (DMARDs), including at least one TNF inhibitor. Treatment can only continue if an adequate response is achieved (by improving the disease activity score (DAS28) of 1.2 points or more.

Longson commented “The focus of this appraisal was to look at treatment options when a TNF inhibitor has not worked or when it has lost its effect. The evidence suggests that rituximab works in this context and is a cost-effective treatment option”.

NICE also recommends adalimumab (Humira, Abbott Laboratories), etanercept (Enbrel, Wyeth Pharmaceuticals) and infliximab (Remicade, Schering-Plough) for the treatment of severe rheumatoid arthritis in patients who have responded inadequately to other DMARDs, including treatment with a TNF inhibitor or who have an intolerance of other DMARDs, a contraindication to rituximab or methotrexate or if they experience and adverse effect to these. Again treatment should only be continued if there is an adequate response after 6 months.

This advice comes in addition to the previous NICE recommendation of adalimumab, etanercept and infliximab as possible treatment options for RA in those whom DMARDs have failed.

Longson hopes that “This wider choice of options will mean that people will be able to manage their rheumatoid arthritis more effectively”.

The report suggests that future treatment prospects could come from comparing adalimumab, etanercept and infliximab’s clinical effectiveness when used sequentially after failure of treatment with a TNF inhibitor with the clinical effectiveness of treatment strategies such as DMARDs.
Erythropoiesis gene expression signatures and pathogenesis in systemic juvenile idiopathic arthritis

Recent research has determined that an erythropoiesis signature in active systemic juvenile idiopathic arthritis (sJIA) is associated with the expansion of CD34+ cells, indicating infection may be an indicator of ineffective erythropoiesis and hemophagocytosis due to hypercytokinemia.

Previously published studies had suggested that sJIA is associated with a prominent erythropoiesis gene expression signature. The aim of this research led by Hinze et al from Division of Rheumatology, Cincinnati Children’s Hospital Medical Center, was to determine whether this signature was associated with peripheral blood mononuclear cells (PMBCs) and their relevant subpopulations and its specificity for sJIA.

Isolated PMBCs from 199 patients, 23 with sJIA, 176 non-sJIA and 38 controls were examined with reference to their surface antigens and gene profiles. The proportion of the PMBC subpopulations were compared with the sJIA, non-sJIA patients and the controls. Dr Hinze and colleagues found that this correlated strongly with the erythropoiesis signature. Gene-expression data were also compared with patients with familial hemophagocytic lymphohistiocytosis (FHLH) and a cohort of sJIA patients to establish whether the signature was present.

The study details that expansion of immature cells was seen more prominently in patients with sJIA and anemia, whilst patients with non-sJIA and anemia did not exhibit the erythropoiesis signature. The erythropoiesis signature association was found to be prominent in patients with FHLH and in a published cohort of patients with active sJIA, but not in patients with inactive sJIA.

These results could mean that infection may be an indicator of ineffective erythropoiesis and hemophagocytosis due to hypercytokinemia as the study documents; however, further research will be required.


About the Bulletin Board
The Bulletin Board highlights some of the most important events and research in the field of rheumatology. If you have newsworthy information, please contact: Christine Forder, Commissioning Editor, International Journal of Clinical Rheumatology, Future Medicine Ltd, Unitec House, 2 Albert Place, London N3 1QB, UK Tel.: +44 (0)20 8371 6090; Fax: +44 (0)20 8343 2313; c.forder@futuremedicine.com

in brief...
The study investigates the risk of clinical outcomes across the gastrointestinal tract and whether this was greater with selective drugs than with non-selective drugs, in particular celecoxib versus diclofenac slow release plus omeprazole. A double-blind randomized trial was undertaken in patients with osteoarthritis or rheumatoid arthritis with increased gastrointestinal risk. Patients were negative for the presence of Helicobacter pylori and had previous gastroduodenal ulceration.

The patients were assigned in a 1:1 ratio to receive celecoxib 200 mg twice a day or diclofenac slow release 75 mg twice a day plus omeprazole 20 mg once a day. A primary endpoint was determined as the development of significant upper or lower gastrointestinal events. A total of 4,484 patients were randomly allocated to treatment (2,238 celecoxib, 2,246 diclofenac plus omeprazole). A total of 20 (0.9%) patients receiving celecoxib and 81 (3.8%) receiving diclofenac plus omeprazole met criteria for the primary endpoint. In addition, 114 (6%) patients taking celecoxib versus 167 (8%) taking diclofenac plus omeprazole withdrew early because of gastrointestinal adverse events. The risk of clinical outcomes throughout the gastrointestinal tract was lowest in patients who were treated with a COX-2-selective NSAID than in those receiving a non-selective NSAID plus a PPI.

A genome-wide association study meta-analysis was conducted of 5539 rheumatoid arthritis patients and 20,169 controls. This was then followed by a replication in an independent set of 6768 rheumatoid arthritis cases and another 8806 controls. A total of 34 single nucleotide polymorphisms (SNPs) were selected for replication, seven new rheumatoid arthritis risk alleles were identified at genome-wide significance when analyzing all 41,282 samples. Stahl and colleagues, refined associations of two established rheumatoid arthritis risk loci (L2RA and CCL21) and confirmed an association at AFF3. The seven new associations bring the numbers of confirmed rheumatoid arthritis risk loci to 31 among individuals of European descent. A total of 11 additional SNPs, of which some are validated autoimmune risk alleles, suggest that those identified are genuine risk alleles for the development of rheumatoid arthritis.
Therapeutic tolerogenic dendritic cells for the treatment of rheumatoid arthritis

Researchers from The Institute of Cellular Medicine at Newcastle University have generated and characterized therapeutic tolerogenic dendritic cells (tolDCs) as a ‘promising experimental treatment’ for rheumatoid arthritis (RA).

TolDCs are experimental treatments that are able to target autoreactive T cells in autoimmune diseases. The goal of this line of research at Newcastle University aims to bring tolDC therapy for RA to the clinical setting. Translational issues related to the manufacturing of tolDCs from RA patients, manufacturing practice, the stability of tolDCs, and control markers for selection were addressed by the study.

The team, lead by Dr Harry et al., generated human monocyte-derived tolDCs from RA patients and healthy controls using the immunosuppressive drugs dexamethasone and vitamin D(3), and the cGMP-grade immunomodulator, monophosphoryl lipid A, in the cGMP-compliant medium, CellGroDC. The functionality of the tolDCs and the tolDC-modulated autologous CD4 T cells was determined by the researchers using flow cytometry, [(3)H] thymidine incorporation and ELISA.

“The results of this study have shown that tolDCs can be established from RA patients and that they are comparative to healthy donors, and can be ‘quality controlled’ by looking for the marker TLR-2. The study concludes that “tolDCs are a promising cellular therapeutic for tailored immunomodulation in the treatment of RA’.


Tocilizumab demonstrates encouraging results in treating childhood arthritis

New research from the TENDER trial, a Phase III study, has shown that tocilizumab appears to be effective at reducing symptoms in children suffering from systemic onset juvenile idiopathic arthritis (JIA).

The TENDER trial was carried out in approximately 70 centers in 20 countries and aimed to investigate the efficacy and safety of tocilizumab in 112 patients with systemic onset JIA. Systemic JIA affects up to 2500 children under 16 years of age in the UK, with a peak age of onset between 18 months and 2 years. Symptoms of the disease include swollen, painful and stiff joints as well as fever, rash, fatigue, swollen glands and weight loss.

The cause of systemic JIA is unknown; however research has shown that patients suffering from the disease have high levels of IL-6 in their blood and joints.

The results of the study showed that a 90% improvement was observed in over a third of patients. Furthermore, significantly more patients in the tocilizumab group achieved a JIA ACR30 response along with absence of fever at week 12 in comparison to the placebo group (85 vs 24%, p<0.0001). It should be noted that these results are still quite preliminary and the trial is expected to continue over a 5-year period to assess the long-term effects of tocilizumab treatment in this population.

Adverse events were reported in three patients in the tocilizumab group. These included angioedema and hives (urticaria), varicella (chicken pox) and bacterial arthritis, all of which resolved quite easily. No adverse events were reported in the placebo group.

Patricia Woo, Professor of Paediatric Rheumatology at Great Ormond Street Hospital commented on the significance of these results: “This is a major advance for these young people. Children with systemic JIA remain a group with a high unmet medical need, and those at the more severe end of the disease spectrum have significant morbidity throughout their lives as well as a higher rate of mortality than other types of JIA. As a notoriously difficult disease to treat, we need new treatments like tocilizumab to help combat systemic JIA. This condition can seriously disrupt the child’s development and the day to day life of the family. Without effective treatment up to half of the affected children develop chronic and persistent arthritis and a majority of these children can be left with significant disability.”

Tocilizumab is not yet licensed for the treatment of systemic JIA however a license application will be submitted toward the end of 2010.