NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Tocilizumab for the treatment of juvenile idiopathic arthritis

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: Royal College of Pathologists

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify) **a specialist in the mechanism of the condition (immunology/autoimmune problems) and therefore in assessing the evidence that support the use of the technology for this condition**

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The course of JIA is highly variable, some patients achieve spontaneous resolution whilst others sustain significant joint contractures, eye problems, growth retardation and permanent disability. In patients who develop joint contractures multiple surgical interventions, including joint replacements, may be required.
The prognosis generally depends on the subtype of JIA, its severity, how early therapy begins and the adequacy of treatment. Patients with polyarticular or SoJIA tend to have a worse prognosis and more severe disability. Up to 50% of children continue to have an active disease in their adulthood, in spite of having had treatment.

Early aggressive therapy is recommended, and because it is not known on presentation who and what kind of patient will need treatment escalation, patients should be followed closely.

Tocilizumab was effective in a fashion similar to the other approved biologic agents when compared with placebo. The randomized controlled trials reviewed show the benefit of Tocilizumab in SoJIA at the approved dose of 4–8 mg/kg every four weeks with or without combination MTX/DMARDs. The benefit of having a drug

administered monthly as opposed to weekly or biweekly is an attractive option for patients and clinicians.

It will be difficult to know which biologic is superior for a patient with refractory disease without head-to-head trials comparing the different agents. Tocilizumab has efficacy comparable with other biologics, and will be an option for those who fail the current recommended treatment.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

One phase III study and two phase II studies have demonstrated high rates of clinical improvement with Tocilizumab in a group of SoJIA patients refractory to conventional treatment, according to accepted measures of response. (*Yokota S et al. Lancet 2008;371:998-1006. Woo P et al. Arthritis Res Ther 2005;7:R1281-8. Yokota S, et al. Arthritis Rheum. 2008; 58(9)Supplement:S631.)*

A long-term extension study has demonstrated a sustained clinical improvement and a favourable risk-benefit profile with tocilizumab in this patient group. Only a single unpublished non-comparative study provides evidence for the efficacy of tocilizumab in patients with polyarticular JIA.*(http://clinicaltrials.gov/show/NCT00642460. www.bi.adisinsight.com)*

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There are no direct comparisons of tocilizumab with other biological agents for the treatment of JIA such as etanercept and adalimumab.
An advantage over TNF inhibitors is that tuberculosis does not seem to be a safety issue because IL6 does not have an effect on granuloma formation.

IL-6 is thought to play a causative role in atherosclerosis, IL-6 blockade may decrease the incidence of cardiovascular events. (Coronary artery disease is a well-known extra-articular feature of rheumatoid arthritis).

Tocilizumab induces a significant reduction of peripheral pre- and post-switch memory B cells and serum immunoglobulin levels. The most common adverse events reported in the open-label extension were nasopharyngitis 55%, URTIs 34%, gastroenteritis 29%, and bronchitis 25%. Increases in liver enzymes occurred in 18 - 29%. Headache and skin reactions were the most commonly reported events within the first 24 hours of infusion.

None of the studies have shown direct evidence of the effects of tocilizumab on joint destruction, a major disease manifestation and a significant determinant of future disability.
The long term effects of tocilizumab in paediatric patients, with therapy extending into adolescence or adulthood, are not known.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

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Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

All patients receiving Tocilizumab should be registered with the British Society for Paediatric and Adolescent Rheumatology (BSPAR) Biologics Registry.

Appropriate advice should be available to families of children taking Tocilizumab on the following:
-Immunisations
-Foreign travel
-Opportunist infection
-Management of contact with chickenpox or shingles

Equality

Are there any issues that require special attention in light of the NICE's duties to have due regard to the need to eliminate unlawful discrimination and promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others?