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:
British Society of Paediatric and Adolescent Rheumatology (BSPAR)

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- 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.)? **YES: I am a board member (but not employee) of the charity BSPAR, which represents health professionals caring for children with systemic JIA in UK and Ireland**
- other? (please specify)

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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?

My understanding (from working in 3 UK centres and conversations with other centres) is that there is broad agreement for initial stages of management of systemic JIA (sJIA): namely high dose NSAIDs, steroids - usually initially IV methylprednisolone 30mg/kg/day for 3 days, except when very mild, then oral prednisolone with boosts of IV as needed. Where disease activity persists after e.g. 4 weeks, unable to successfully wean steroids or if disease severe initially: methotrexate is used (generally at around 15mg/m^2/week and often by SC injection).

If intolerant of this regime or not adequately treated then there is less clear agreement of the next steps (especially of the order to try).
Subsequent options include:

- **anti-TNF alpha therapy: (infliximab infusions or etanercept SC especially)**
- **steroid joint injections if arthritis main concerns, to reduce systemic steroid dose needed**
- **high dose intravenous immunoglobulin: regular need, expensive and pressures on use**
- **oral ciclosporin: side effect profile and renal monitoring needed**
- **anakinra: daily SC injection, need to use a part of a new vial each day**
- **tocilizumab is already used in several centres (including my own)**
- **oral thalidomide: complicated to access, risk peripheral neuropathy and obvious anxiety relating to pregnancy**
- **autologous stem cell rescue after marrow ablation (autologous bone marrow 'transplant')**
- **cyclophosphamide: toxic side effect profile**

Tocilizumab requires hospital day-case attendance for infusion, but most patients require frequent review and blood tests anyway. Main advantage of tocilizumab is that it helps many individual resistant to all / most of described above. There are no comparative trials, but results for tocilizumab (the Roche trials central to this assessment) are more impressive than anti-TNFalpha therapy when analysed for the sJIA subtype. The advantages of better control of sJIA on lower dose steroids are very wide ranging and produce lifelong benefits including:

- **fewer steroid side effects that are well known (especially growth restriction, vulnerability to infection, osteoporosis)**
- **reduce risk of long-term joint damage / need for joint replacement**

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- **less pain, better energy: with obvious benefits to school attendance, education, relationships with peers and social development**
- **reduce risk of developing amyloidosis**
- **reduce the increased risk of cardiovascular disease associated with persistent inflammation**
- **reduce disruption to family including sibling development and parent / carer employment. The families description of transformation of life of child and all family members in response to tocilizumab is a very compelling argument. I think it is very disappointing that non-NHS cost implications (e.g. parents ability to maintain employment, pay taxes!) are not considered.**

My experience (of using in 6 patients) is of rapid resolution (often after first dose) of fever, rash and raised inflammatory markers. Abnormal FBC indices normalise within weeks. However arthritis takes longer to come under sustained remission, although I have found it responds well to steroid joint injections.

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?
Systemic JIA typically has 3 patterns:

- **approx 11% follow a one-off (monocyclic) course, within good response and withdrawal of NSAIDs and steroids possible over a few months, with no return of disease activity**
- **polycyclic course in 34%: relapsing / remitting course**
- **55% have unremitting course with difficulty achieving any significant remission**

I think tocilizumab's place is in the management of the last 2 groups, so (unless severe activity or only partial response to steroids) tocilizumab use should be reserved to see if remission develops soon, suggesting monocyclic course.
I am not sure whether tocilizumab should always wait until after methotrexate (intolerance or failed). Methotrexate does help some children with sJIA, as do many of the alternatives listed above, but my impression is that reponse rates are not as impressive as for the published tocilizumab trials.

In addition, although there will only be case report supporting evidence as very rare situation, I think there is a role for acute use of tocilizumab to treat macrophage activation syndrome (secondary HLH) triggered by sJIA activity.

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)?
I strongly believe that all children with systemic JIA should be looked after by or in conjunction with a tertiary paediatric rheumatology centre. Tocilizumab

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for children with sJIA needs to be given on a paediatric ward with appropriate guidelines, experienced nurses and paediatricians able to look after anaphylactic reactions. Blood test monitoring needed.

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?
Already available. I think there is large variation in UK of when tocilizumab is used in hierarchy of management of resistant sJIA and not used in all UK centres.

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.

No established UK clinical guidelines. I am currently developing some for BSPAR, mainly around advice on administration and monitoring, with overview of evidence. Not intending to advise place of tocilizumab in management of sJIA, but if becomes NICE approved likely to be used much more widely.

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?

I think for active systemic JIA when frequent review and blood tests are needed, the inconvenience of attending a hospital day-case unit, typically every 2 weeks initially is not a great problem. Often preferred to subcutaneous injections (especially the daily injections of anakinra).
No extra clinical requirements, but should be mandatory to be given by or in conjunction with a tertiary paediatric rheumatology service.
Have used in conjunction with methotrexate, but as already mentioned not clear if needed and I note one of the main trials does not use this.
As discussed previously the better evidence of benefit is the main advantage.

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.

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Not aware of any evidence guiding when / how to stop tocilizumab when induces and maintains remission. In Leeds if there is good response to first 4 doses (2 weeks apart) we have increased interval to every 4 weeks, as typically used in treatment of rheumatoid arthritis. We have not seen any relapses, but small numbers.

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?

TENDER UK trial representative of population discussed here. Trials published earlier too are for same disease, mainly in Japanese popluation. Not aware of any significant differences between population of children with sJIA in Japan (or other countries) from those in UK.
CORE outcome variables (includes inflammatory markers), prednisolone dose, fever, school / nursery days missed and parents' ability to work are the most important outcome variables for me. Data on last 2 not recorded as far as I am aware.

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?

Screening before starting for any infection including mycobacterial. Monitoring blood tests (easily taken with each IV infusion) essential especially to look for neutropenia, raised liver enzymes and cholesterol / lipid abnormalities.
Not aware of any recurrent side effects from routine practice not described in trials.

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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.

Not aware of any extra evidence regarding tocilizumab which is not accessible from Roche or literature search. My experience of using tocilizumab as above.

Information re etanercept vs sJIA in Lovell's papers and also information from etanercept registries may be useful: Prof Tauny Southwood in Birmingham may be able to release unpublished information for the UK registry. Germany has etanercept registry and has published data.

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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.

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)?

NICE guidance recommending toclizimab would allow greater access to this therapy. The opposite result would severely limit accessibility, through difficulty obtaining funding.
No extra training.
Protocol / guidance for administration needed and BSPAR developing.

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?

As long as guidelines followed in all regions, not aware of any.