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National Institute for Health and Clinical Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester M1 4BD

1st September 2011

Dear [redacted],

Comments on the August 2011 Appraisal consultation document regarding tolizumab for the treatment of systemic juvenile idiopathic arthritis technology appraisal: on behalf of BSPAR

Overall comments:

We believe published evidence and our experience shows clear and very significant benefit in the management of resistant systemic JIA. Tocilizumab has revolutionised the treatment of sJIA, delivering outcomes and steroid sparing in resistant cases far in excess of other available treatments. The TENDER trial was a robust international randomised controlled trial utilising a design consistent with previous trials of biologic agents in JIA.
If systemic JIA is uncontrolled the burden of disease and associated steroid toxicity is enormous on patients and families. The disease may be life threatening in some cases, often due to associated macrophage activation syndrome, pleural or cardiac disease. The economic impact on working parents who may lose employment whilst caring for a child with sJIA must be recognised, as must cost savings to the NHS in the short terms by reducing the need for hospital treatments as well as the long term outcome of allowing these children to become independent adults in the workplace. .

The review requests an economic model based on absolute level of health status (as measured by CHAQ), however as with most trials of treatments for JIA, the key TENDER trial assesses improvement in a series of core outcome variables, to reflect damage from previous disease and many other factors eg what help is given will mean different CHAQ scores for the same level of disease activity. It is not possible to use an absolute CHAQ score to define health status, nor to use scores to define eg health state requiring hospitalisation. We believe that ability to reduce corticosteroid dose is also an extremely important outcome measure. Other important outcomes are growth, school attendance, ability to make and maintain peer relationships and ultimately independent adult function.

There are great difficulties in estimating costs involved in treating uncontrolled systemic JIA which is a rare disease, also most centres use tocilizumab as current practice for management of resistant sJIA, so we are not seeing the problems we used to as frequently. If this is an ultimate sticking point then further objective information on this should be sought from a review of sJIA patients in our community or using information from UK biologics registry. Could NICE recommend cost effectiveness of tocilizumab when annual treatment is or is expected to be over a certain level, to get around the uncertainty of these very critical costing estimates? There is a significant cost implication of various treatments including admissions for intravenous methylprednisolone, steroid joint injections under GA, immunosuppressive doses if IV immunoglobulins, other biologics and Autologous Stem Cell Rescue Therapy (Autologous “Bone Marrow Transplant”). Without access to tocilizumab a number of children with sJIA will progress to Autologous Stem Cell Rescue Therapy (typically requiring a 4 month admission to one of 2 NSCAG funded transplant centres (Great Ormond Street and Newcastle). This therapy was being used increasingly frequently, prior to tocilizumab, but now is hardly used at all.

The majority of work towards the economic model must come from the manufacturer's economists as these area are out of our expertise.

We have consulted widely within the BSPAR community and the overwhelming majority view of consultant paediatric rheumatologists is that tocilizumab is highly effective in the majority of sJIA patients and has revolutionised the treatment of this disease. A consequence of NICE not approving this treatment would be that future children in the same situation as children currently benefiting from tocilizumab will be denied access to this treatment.

We believe a review of all biologic treatments for all subtypes of JIA by NICE would make sense for the NHS as a whole, when these decisions are being discussed with PCTs across the UK already, with a huge amount of repetition of work. Agreed pathways of management akin to those developed for the management of rheumatoid arthritis would benefit patients, PCTs and clinicians.

Regarding preliminary recommendations:

1.1

We note that the European Commission and FDA have recently approved tocilizumab for the treatment of active sJIA in patients two years of age and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs and systemic corticosteroids, can information be gained from their processes that may help the NICE review process

1.2

As discussed above there are difficulties associated with the objective health states requested as the basis of cost analysis.
Most systemic JIA presents before 5 years and it is likely that the median age when sJIA patients will be identified as resistant to NSAIDs, corticosteroids and methotrexate is likely to be under 5 years.
As already mentioned impact of corticosteroid load is large and so ability to reduce corticosteroid dose is important when comparing different treatments.

There is variation in current UK treatment of systemic JIA resistant to NSAIDs, corticosteroids and methotrexate. The majority of UK centres prefer tocilizumab, second choice usually anakinra and third anti-TNF alpha inhibitors (with etanercept or infliximab used most widely). Prior to the availability of tocilizumab many centres would treat sJIA with infliximab (possibly requiring doses greater than that required for polyarticular JIA) over etanercept. It should be noted again that some children with systemic JIA meet criteria from the NICE Technology Appraisal Guidance no.35 (March 2002, but not reviewed) but we highlight there is an extremely limited evidence base for the use of any anti TNF agent in sJIA, and no RCT data.

The evidence of benefit of resistant sJIA is much clearer to toclizimab than to anakinra or any anti-TNF alpha agent.

1.3
Data on radiographic evidence of progression of joint damage would be interesting, but I doubt this data is available and certainly not available from alternative agents on a scale that would allow comparison. We think it is fair to assume that reduced sJIA activity translates to reduced joint damage.

3.11
The main studies looking at etanercept for all subtypes of JIA (including sJIA patients) do not seem to be covered

Eg

-Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Giannini EH et al Arthritis & Rheumatism. Volume 60, Issue 9, pages 2794–2804, September 2009

- Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Lovell DJ et al. Arthritis Rheum. 2008 May;58(5):1496-504.

3.14

We are not sure that an adjustment factor in one study is translatable to other studied populations, althought accept it is a crude way to derive to gain some 'ballpark'information where studies are limited

3.16

I don't really understand the Markov modelling, but as discussed at the meeting in July we believe children can move between ACR response lines.

3.20 and 3.30

Assumptions of cost of managing disease at different levels of CHAQ score will be very different between patients and are very subjective estimates. More accurate information may be available from the UK biologics registry. Uncontrolled sJIA with a significant 'systemic features' can require frequent infusions of IV high dose methylprednisolone (30+ per year is not unheard of) and lengthy inpatient stays.

4.2

Many UK Paediatric Rheumatology centres currently use tocilizumab if sJIA does not respond to NSAIDs, corticosteroids and methotrexate. If tocilizumab was unavailable most would use anakinra. Etanercept, adalimumab or infliximab are options, particularly for arthritis symptoms and most centres have experience of these being effective, but less commonly than anakinra or tocilizumab. Tocilizumab has largely superceded anti TNF agents in sJIA.

4.4

Increasing the interval between tocilizumab infusions when remission is sustained does not yet have an evidence base, but experience suggests that this can be done without deterioration much sooner than 18 months, perhaps at 6 months, thus reducing the cost of tocilizumab.

In response to the specific questions:

Has all of the relevant evidence been taken into account?

Etanercept trials as above. Data from UK registry re costings may be helpful.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

We are convinced that there is clinical and cost effectiveness. Concerns with desire for estimated costs associated with absolute CHAQ levels and ignoring the improvement of core outcome variables as reflecting improvement of sJIA activity which is the hallmark of trials in this area.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

We cannot support the guidance not to recommend tocilizumab for specific situations of children with resistant sJIA, being fully aware of the health and cost implications of this situation.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?

No issues

We hope these comments are useful. We are keen to attend the meeting on 14th September.

Yours sincerely,

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1st September 2011