14.10.14

Dear NICE

Re: Multiple Technology Appraisal (MTA), MTA UC - revTA140, revTA262, golimumab (2nd line) [ID695] - Appraisal Consultation Document

Please find a response on behalf of the British Society of Paediatric Gastroenterology, Hepatology & Nutrition (BSPGHAN) in our role as a registered stakeholder and following on from a formal request from NICE for comments following publication of the consultation document recently.

The IBD working group of BSPGHAN have reviewed the document and wish to provide written feedback to NICE on the MTA. We are extremely disappointed in the initial recommendations and think they will unfairly deny access to infliximab in children with chronic active Ulcerative Colitis (UC) as outlined below:

"1.2 Infliximab is not recommended within its marketing authorisation for treating children and adolescents aged 6 to 17 years who have severely active ulcerative colitis that has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies."

We fully support the document submitted by the British Society of Gastroenterology (BSG) highlighting the reasons why severely restricting access for adults with chronic active UC is also misguided and as such will not seek to repeat these points but will merely restrict our comments to those most pertinent to children.

- Has all of the relevant evidence been taken into account?

The IBD WG believe that not all of the specific evidence relating to paediatrics has been indeed been considered. There is a lack of recognition that paediatric UC is different and that models applied in adults cannot be translated into making assumptions about care of paediatric patients. There is no recognition of the different phenotype of UC in children with significantly higher rates of pancolitis seen in children compared to adults.(1) This directly impacts on disease behaviour with higher admission rates for acute severe colitis and higher colectomy rates.(2) The colectomy rate in children is double the equivalent rate in adults after the same time period from diagnosis.(1)

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

The group does not believe that the interpretations take all of the relevant factors into account. As stated in the previous section, translation of annual colectomy rates from the IBSEN cohort into a model for colectomy rates in UK children is not valid. Using a 15 year old to model for all paediatric patients also is inaccurate:

4.73 "The Committee discussed the cost-effectiveness of infliximab in children and adolescents. It noted that the Assessment Group presented a scenario analysis in this population which differed from the analysis in adults only in that the starting age of patients in the model was set to 15 years. In the analysis that compared infliximab with conventional therapy only (that is, when colectomy is not an option), the ICER was £68,400 per QALY gained. The Committee was aware that the company's submission for infliximab did not include a separate analysis in children and adolescents. Given the ICER estimated by the Assessment Group, the Committee concluded that infliximab could not be considered a cost effective use of NHS resources for treating children and adolescents with severely active ulcerative colitis that has responded inadequately to conventional therapy."

The model offered no weight for the patient so the costing calculations cannot be worked out accurately in the base case provided. Given the mg/kg dosing of infliximab, different costing calculations would need to made at different ages due to the massive weight differential and subsequent cost differential between the ages of 6 and 17 – a one age fits all is neither appropriate nor accurate. The failure to consider the unique nature of childhood and adolescence is also not addressed. The delaying of colectomy by using infliximab in children with UC has been demonstrated in previous paediatric studies.(3) The benefit of giving an adolescent in education the chance to undertake their examinations with use of an anti-tnf even if this is only delaying surgery to a later and more appropriate time has a profound impact on the young person's future education and earning potential. This has not been factored into any modelling. This clearly challenges the validity of the conclusion "There are no specific groups of people for whom the technology is particularly cost effective."

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

The current recommendations are not, in their present form suitable, and as such if implemented they will have a profound and significant impact on all paediatric gastroenterology teams treating children with UC in the NHS. There will be no other option for these children but to have a colectomy. The suggestion that these children could be maintained on "conventional" therapy is incorrect especially as anti-tnf therapy is considered only when they are failing this treatment. Surgery does not provide a cure and there are significant complications and consequences both acute and longer term. The psychological impact of the disease is most profound in this age group and there is no recognition of the negative impact of having a stoma (even if temporary) in a child or

teenager. In addition, the longer term impact of surgery on fecundity is not considered or it would seem costed.

The recommendation as is would put the UK paediatric IBD care significantly outside the care offered in other European countries and would be against the recommendations of the European guidelines for the care of children with UC.(4)

The recognition that the price of this treatment dropping significantly with the launch of biosimilar infliximab in February 2015 in the UK has also not been factored in. The failure to consider optimising treatment response by trough level and antibody measurement means the guidance is not really reflective of current UK practice. The fact that there are so few medical options for this group of patients who have more extensive and severe disease makes this proposed guidance all the more challenging. Of note the recent licence of Vedolizumab for adults in the UK is not likely to be translated to a paediatric licence for around 7 years based on previous time lags between adult and paediatric trials for other biologics and in keeping with the companies currently proposed paediatric investigational plan.(5;6) This decision would therefore condemn a generation of children with UC to higher rates of ill health and colectomy given the lack of any new therapies on the horizon.

In conclusion, the current guidance does not accurately or fairly summarise all of the relevant evidence, the assumptions used to model the costings are flawed and it does not reflect current UK paediatric practice. We would suggest children be allowed access to an induction course of infliximab for chronic active UC with the option for responders only to carry on treatment with reassessment at one year in line with the current NICE guidance on infliximab for paediatric Crohn's disease.

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The BSPGHAN IBD working group is a representative multidisciplinary body from the paediatric community from across the whole of the UK.

Reference List

(1) Van Limbergen J, Russell RK, Drummond HE *et al*. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology* 2008;**135**(4):1114-22.

(2) Turner D, Walsh CM, Benchimol EI *et al*. Severe paediatric ulcerative colitis: incidence, outcomes and optimal timing for second-line therapy. *Gut* 2008;**57**(3):331-8.

(3) Hyams JS, Lerer T, Griffiths A *et al*. Outcome Following Infliximab Therapy in Children With Ulcerative Colitis. *American Journal of Gastroenterology* 2010;**105**(6):1430-6.

(4) Turner D, Levine A, Escher JC *et al*. Management of Pediatric Ulcerative Colitis: Joint ECCO and ESPGHAN Evidence-based Consensus Guidelines. *Journal of Pediatric Gastroenterology and Nutrition* 2012;**55**(3):340-61.

(5) Hanauer SB, Feagan BG, LICHTENSTEIN GR *et al*. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**(9317):1541-9.

(6) Hyams J, Crandall W, Kugathasan S *et al*. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 2007;**132**(3):863-73.