National Institute for Health and Care Excellence

Ulcerative colitis (moderate, severe) - infliximab (review TA140), adalimumab (review TA262) & golimumab (2nd line) [ID695] ACD Consultation

Royal College of Nursing

Introduction

The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for **Ulcerative colitis (moderate, severe) - infliximab (review TA140), adalimumab (review TA262) & golimumab (2nd line) [ID695].**

Nurses caring for people with Ulcerative Colitis reviewed the documents on behalf of the RCN.

Appraisal Consultation Document – RCN Response

The Royal College of Nursing (RCN) welcomes the opportunity to review the Appraisal Consultation Document of this appraisal. Comments and recommendations have been submitted by the RCN IBD (Inflammatory Bowel Disease); Adult patients, British Society of Paediatric Gastroenterology, Hepatology & Nutrition (BSPGHAN); Paediatric IBD, British Society of Gastroenterology (BSG) and the RCN Gastrointestinal (GI) Nurse Forums on behalf of the Royal College of Nursing

i) **Has the relevant evidence been taken into account?**

We fully support the comments submitted by the forum highlighting the reasons why access for adults with chronic active UC is misguided as indicated in this response and as such will not seek to repeat these points here but will merely restrict comments to those most pertinent to children.

The response to the above question is no, relevant evidence has not been taken into account as 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)

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

No they are not. As stated, 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 inappropriate.

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."

No consideration of patient weight was taken in these models. Paediatric patients are dosed using a 'mg/kg' dose. Clearly, there is a significant difference in the weight of a 6yr old and a 15yr old (as used in the NICE model) and this would obviously have a subsequent effect on costings. A 'one age fits all' approach is neither appropriate nor accurate. In addition, the failure to consider the unique nature of

childhood and adolescence is also not addressed. Delaying colectomy through the use of infliximab in children with UC has been demonstrated in previous paediatric studies. (3) The benefit of giving a young person 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. In particular, this challenges the conclusion that "There are no specific groups of people for whom the technology is particularly cost effective."

We feel this appraisal has not fully explored the direct and indirect costs such as loss of earnings, loss of education and the longer term socioecomic effects of these; and it may have underestimated the impact of poorly treated disease on health. Additionally, as healthcare professionals who have significant contact with people diagnosed with Inflammatory Bowel Disease (IBD) we have identified that patients with Ulcerative Colitis (UC) feel their treatment options are unequal to those with Crohns disease (CD).

We are concerned that the current Appraisal Consultation Document does not address medical options after failure of conventional therapy. It appears to assume that patients will respond to a re-trial of medications to which they have previously been refractory. Clinical experience tells us this is not the case. Therefore the current document does not provide options for patients' refractory to conventional therapy that are unsuitable for, or unwilling to have, surgery.
It is likely that this cohort will require management with on-going steroids. The overarching aim of ulcerative colitis management is steroid-free remission. Repeated or long-term exposure to steroids is associated with potentially irreversible complications including osteoporosis, diabetes, hypertension, increased susceptibility to serious infection, adrenal insufficiency and hepatic and ophthalmologic effects.

We are not clear that the economic models used have taken these factors, and costs treating them, into account. The modelling tool also does not appear to have considered the financial impact when patients are unwell such as the loss of earnings, lack of productivity, loss of education and general impact on family life. People with chronically

active disease may be unable to work, or work full time due to severity of symptoms, such as urgency, faecal incontinence or fatigue.
Patients with ulcerative colitis are at an increased risk of colorectal cancer. That risk increases with duration, anatomical extent and activity of disease. Therefore people who have chronically active, poorly controlled disease are at significantly increased risk of developing bowel cancer. These are a group who may require annual surveillance colonoscopies with associated costs, impact on service and, importantly, morbidity.

We also have concerns regarding the lack of weight given to the effects of pelvic surgery on fertility. The economic model made the presumption that 47.3% and 5% of patients going to colectomy will develop transient or chronic post-surgical complications respectively. With regards to colectomy and Ileo-anal pouch procedure (IAAP), the British Society of Gastroenterology Guidelines (2011) state that complication rates can be significant and pouchitis remains a persistent and difficult problem following surgery, therefore incurring on-going costs through complex medical and often surgical management and follow-up. The ACD goes further to state fecundity of young women may be reduced by 40-50% following IAPP, probably as a result of pelvic surgery and subsequent pelvic adhesion and that an exploration of alternative medical or surgical options should be undertaken in women of childbearing potential before IAPP. The European evidenced-based consensus on reproduction in inflammatory bowel disease (2010) report that pelvic surgery may lead to impotence or ejaculatory problems in men and that those who undergo ileoanal pouch surgery for UC, may experience retrograde ejaculation and erectile dysfunction.
Pelvic surgery for IBD increases the incidence of subfertility in females and previous systematic reviews including the ECCO guidelines (2010), conclude that the fertility of women with UC was reduced after restorative proctocolectomy. A meta-analysis found that ileal pouch-anal anastomosis (IPAA) conferred a three-fold increased risk of infertility compared to medical management.
It is essential for this to be considered in greater depth within the appraisal as the long-term effects of colectomy and IAAP must be considered against the use of Anti-TNF treatment for prevention of hospital admission and colectomy.

The draft ACD states that "conventional therapy was an on-going option throughout the treatment pathway for moderately to severely active ulcerative colitis because most patients are unlikely to consider surgery until later (unless the patient has acute disease, which is not covered by this appraisal)". The European evidenced-based consensus on reproduction in inflammatory bowel disease (2010) state there are no data to support the approach of subtotal colectomy with rectal stump and ileostomy during childbearing years and then creating an IPAA later in life to help reduce infertility rates. They note the drawbacks of the latter procedure include ileostomy complications during pregnancy such as obstruction and stoma related problems.

The aims of IBD management is to significantly improve the quality of life for patients, eliminate or reduce costs associated with emergency admissions, repeated endoscopies, conditions associated with the use of long term steroids, major surgery and follow-up care.

In our experience, the provision of anti-TNF (infliximab) therapy in appropriate patients:

- Impacts on disease prevention by reducing the risk of complications and co-morbidities associated with severe ulcerative colitis
- Impacts on health inequalities through equitable treatment access (to people with CD)
- Improves outcomes, quality and/or safety
- reduces the risk of complications and co-morbidities associated with severe ulcerative colitis
- Improves patient experience. The treatment can potentially reduce the need for repeated hospital admissions for the patient group in question, thereby improving quality of life and allowing them to be managed in an outpatient setting
- Improves cost efficiency by reducing admissions, in -patient care, reducing diagnostic endoscopies and avoiding surgery

Surgery may require a 3-stage procedure: a sub total colectomy, followed by a second operation at 6 months for stoma and pouch formation and a third operation at 12 months for stoma reversal. There is a 40% risk of pouchitis which requires further intensive intervention and monitoring. These are all factors which should be considered within the economic modelling.

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

No. This 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 particularly if it has failed before. 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 developing 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 also means the guidance is not reflective of current UK practice. The fact that there are so few medical options for this group of patients who have extensive and severe disease makes this proposed guidance all the more challenging. 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.

There is a psychological risk to patients who reluctantly have a colectomy if they feel they have no other choice. People often wish to exhaust all possible medical option before contemplating major surgery.The idea of an ileostomy to some is unthinkable and can impact on the ability to form and maintain relationships.
Patients are increasingly aware of variations in treatments for their UC across the country and internationally. It is unacceptable to patients with UC that patients with Colonic Crohns disease can access Anti-TNF,

yet patients with Ulcerative Colitis cannot, despite the similarities between the two diseases.
We note that the draft guidance does highlight that there are patients who require biological therapy for a period of time before surgery. The advantage of this is to decrease/stop the steroids as well as allowing the patient to mentally be prepared for surgery. These two things have a positive effect on the surgical outcome.
Surgery is not always the most appropriate course of action, particularly in patients who have received high dose corticosteroids, such as those with acute exacerbations of refractory ulcerative colitis. Corticosteroids steroids give more potential risk of post-operative complications. First-stage surgery for refractory ulcerative colitis is a sub total colectomy and ileostomy. According to national guidelines, a large proportion of patients with moderate to severe active UC patients have left sided disease. While the draft guidelines explain that surgery in proctitis is not considered due to disease distribution, the same must be said of left sided disease. Following initial stage of surgery, patients are left with a rectal stump in preparation for the second stage and pouch formation. There are variations of the stump size depending on the surgical findings and individual surgeons. Post-surgical complication of diversion proctitis and inflammation of the rectal stump can occur. This may be a contraindication for the final completion stage of the pouch, as described in the draft guidelines but can have on-going costs associated with further surgical intervention, medical management and patient distress and quality of life issues.

We also express great concern over 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

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.

iv) **Are there any aspects of the recommendations that need particular consideration to ensure that NICE avoids unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

General Comments

The emphasis of the use of anti-TNF therapy in UC has been placed on the patient with severe disease requiring hospitalisation. We would suggest that in the current climate where the role of the specialist nurse is to reduce admission rates and length of stays for patients with IBD, as a result patients with moderate/ severe disease are being kept out of hospital for longer periods than previously with regular reviews in outpatients. The proposed guidance does not support this practice and has the potential to increase hospitalisations to provide patients with access to these therapies.

We believe there are other exceptional circumstances that need to be highlighted. For example, we see at least 5 patients per year who are hospitalised on their first presentation of ulcerative colitis and who historically would have undergo a colectomy during this period of hospitalisation. The availability of biologic therapies in this scenario is invaluable, in that patients are given time to absorb their diagnosis and the implications of diagnosis which although may only delay surgery gives patients the time and opportunity to psychologically adjust to their change in health and longer term are more accepting of surgery. Throughout the document there is reference to Ulcerative Proctitis, this is one of the most challenging presentations of UC to manage in that only 40% of the dose of oral medical therapies are able to promote healing within this affected this area. We would suggest that a substantial number of patients require immunomodulating therapy and this is a mainstay of treatment of this patient group beyond the implied topical steroids advocated in the document.

This group of patients have immense problems after colectomy in that their retained rectal stumps/ mucus fistula remains problematic with rectal bleeding and loss of mucus remaining a problem. This longer term influences surgical management.

Conclusion

In light of the comments and recommendations above the Royal College of Nursing do not support recommendations provided within the ACD of the above appraisal.

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References

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