NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal (MTA)

"Ulcerative colitis (moderate, severe) - infliximab (review TA140), adalimumab (review TA262) & golimumab (2nd line).

Infliximab biosimilar (Remsima™)

Celltrion Healthcare

5th August 2014

Celltrion Healthcare

Celltrion Healthcare (CTHC) is the manufacturer of Remsima™, the first biosimilar monoclonal antibody approved by the European Medicines Agency (EMA)[1].

Please note that throughout the Assessment Group report the company has been referred to as Celltrion, we would, respectfully, like to point out that this should read Celltrion Healthcare.

CTHC made a manufacturer's submission as part of the ongoing multiple technology appraisal: "Ulcerative colitis (moderate, severe) - infliximab (review TA140), adalimumab (review TA262) & golimumab (2nd line)".

We have some issues which we would like to address relating to the publication of the ScHARR Assessment Group's report on the ongoing multiple technology appraisal: Ulcerative colitis (moderate, severe) - infliximab (review TA140), adalimumab (review TA262) & golimumab (2nd line).

Colectomy: not the ideal solution for all patients

The Assessment Group acknowledges the substantial burden that ulcerative colitis has upon the NHS. The burden to patients and carers is also substantial and the importance of tailoring the treatment to individual patients is crucial for the best outcomes.

One of the objectives of this assessment was stated as:

- To estimate the expected net budget impact associated with implementing each intervention

We note that the assessment group have chosen to compare anti-TNF treatment to surgery even though the accepted conventional treatment in the UK is to avoid surgery if at all possible. There are suggestions throughout the assessment report that patients may prefer the surgical option to other treatments, however colectomy is not the ideal solution for all patients. We would like to understand what evidence exists for this assumption. There are a number of possible complications with surgery and the outcomes are variable between NHS centres. The costs of complications may have been underestimated by the Assessment Group. The considerable variation is not only defined by the centre and surgeon but also by the individual patient's needs and is dependent on a number of factors which could include:

- post-operative care (e.g. pain management, rehabilitation, prevention of DVT)
- length of stay or bed days (this is highly variable between centres and for individual patients,
- infections, (post-surgical, both hospital related (direct or acquired) or in the community)
- ongoing care following discharge from hospital, (e.g. district nurse and GP care)
- re-admission for complications. (e.g. pain, infections)
- Follow-up appointments both in secondary and primary care
- stoma care costs, (cost of equipment and the psychological cost for patient and family)
- loss of earnings, (for both patient and carer)

All of these costs could also be influenced by whether the surgery is elective or emergency and whether or not the patient has had any medical pre-treatment, but there have been no

distinctions made within the report. The impact of surgery for patients and their carers therefore seems to have been underestimated. In addition there has been no significant consideration to the affects that surgery has on the psycho-social and quality of life issues, for example for those patients facing management of a lifelong ileostomy.

We also found that the cost effectiveness of infliximab therapy in UC patients has been demonstrated in another study based on cost estimations for the treatment of patients in NHS England and Wales in 2006/7[3]. Infliximab when compared to standard of care had an estimated incremental cost per QALY gained of £19,696. This is lower than that suggested by the Assessment group.

Evidence supporting CTHC claim on colectomy

We should like to draw your attention to the following:

1. NICE has published a Clinical Guideline on Ulcerative Colitis guideline CG166[4] in which it clearly describes the rational and circumstance for surgery that it is recommended if **no** response to drug treatment is seen:

> *"Current medical approaches focus on treating active disease to address symptoms, to improve quality of life, and thereafter to maintain remission. The long-term benefits of achieving mucosal healing remain unclear. The treatment chosen for active disease is likely to depend on clinical severity, extent of disease and the person's preference, and may include the use of amino-salicylates, corticosteroids or biological drugs. These drugs can be oral or topical (into the rectum), and corticosteroids may be administered intravenously in people with acute severe disease.* ***Surgery may be considered as emergency treatment for severe ulcerative colitis that does not respond to drug treatment. People may also choose to have elective surgery for unresponsive or frequently relapsing disease that is affecting their quality of life****".*

2. The Assessment Group appears to suggest that surgery is the "best option" and standard of care, even though patients reading the below section of the NHS Choices website[5] would not have the same impression.

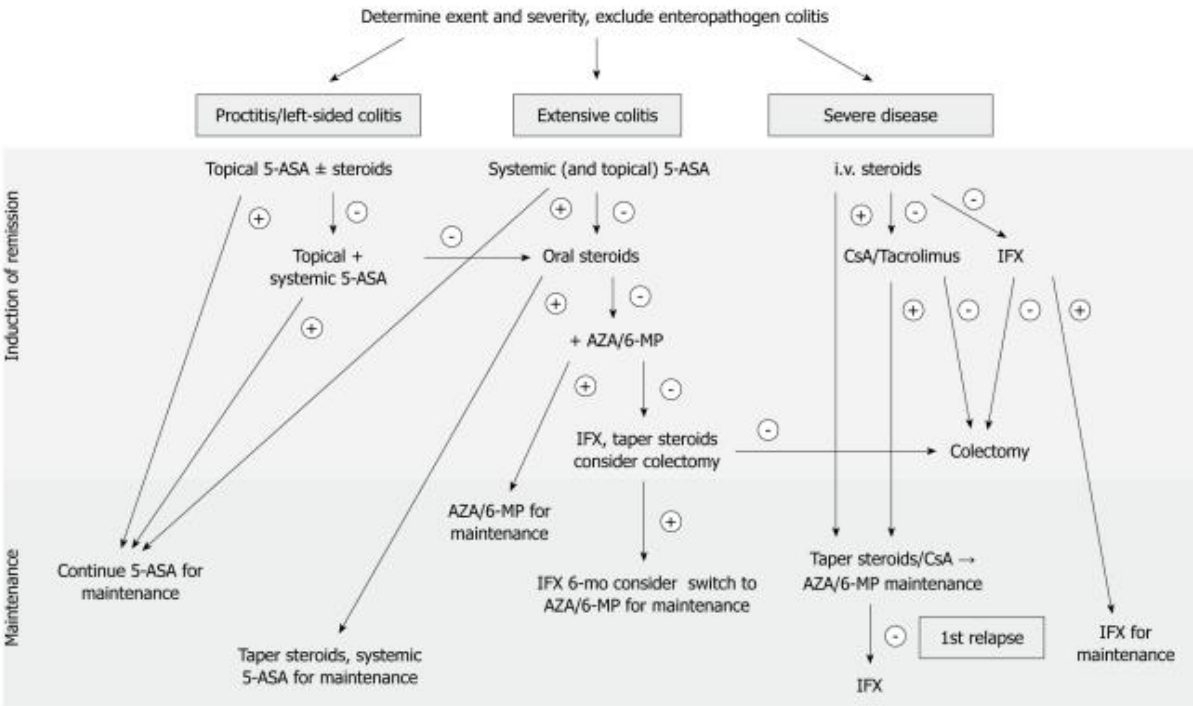
> ***"The main aims of treatment are to:***
>
> ***•reduce symptoms, known as inducing remission (a period without symptoms)***
>
> ***•maintain remission***
>
> ***This will usually involve taking various types of medication, although surgery may sometimes be an option.***
>
> *Surgery*
>
> *If you have frequent flare-ups that have a significant effect on your quality of life, or you have a particularly severe flare-up that isn't responding to medication, surgery may be an option.*
>
> *Surgery for ulcerative colitis involves permanently removing the colon (known as a colectomy).*
>
> *During the operation, your small intestine will be used to pass waste products out of your body instead of your colon. This can be achieved by creating:*
>
> *•an ileostomy – where the small intestine is diverted out of a hole made in your abdomen. Special bags are placed over this opening, to collect waste materials after the operation*
>
> *•an ileo-anal pouch – where part of the small intestine is used to create an internal pouch that is then connected to your anus, allowing you to pass stools normally*
>
> *Ileo-anal pouches are increasingly used because an external bag to collect waste products is not required.*

3. *As the colon is removed, ulcerative colitis cannot recur after surgery.* ***However, it's important to consider the risks of surgery and the impact of having a permanent ileostomy or ileo-anal pouch****".*Colectomy although an established treatment option is not generally considered to be the routine first-line treatment. A number of publications

suggest that the treatment should be tailored to the individual and the goals of treatment are to induce steroid free remissions. This has been explored by Meier and Sturm[6] who state that:

"*The goal of treatment is to induce a steroid free remission while at the same time preventing complications of the disease itself and its treatment. The choice of treatment depends on severity, localization and the course of the disease."*

The algorithm below[6] is more reflective of current treatment methods than might be suggested by the Assessment group. Surgery is clearly an option but is reserved for patients who are refractory to other treatments.



Treatment algorithm for ulcerative colitis. 5-ASA: 5-Aminosalicylic acid; AZA: Azathioprine; CsA: Cyclosporine A; IFX: infliximab; 6-MP: 6-Mercaptopurine.

Furthermore, the roles of infliximab and surgery in the management of UC were reviewed by Rizzo et al[7]. Although the authors conclude that more research is needed to assess the long-term risk of colectomy, there is broad support for the use of infliximab to induce and maintain clinical and endoscopic remission.

"IFX has demonstrated efficacy in inducing and maintaining clinical and endoscopic remission in the long run. IFX can also avoid urgent colectomy in patients with severe acute UC refractory to intravenous steroids. The real impact of biological therapy on the natural history of UC is still controversial, whereas it is not clear if it allows avoidance of colectomy or rather than a delay. The median colectomy risk for UC patients treated with IFX is about 10%-20% in both RCTs and observational studies, with higher rate for patients with severe acute attack. Data from RCTs support the efficacy of IFX in reducing the risk of surgeries in the long-term, but none was designed to assess IFX effects on surgeries".

The use of surgery is also discussed and reviewed in the ECCO guidelines[8]. The recommendations are that surgery should be used where appropriate and the use of medicines is recognised as an alternative for some patients. In their summary on the use of anti-TNFs, the authors quote two published papers to show that induction and maintenance

infliximab achieves steroid free remission in 21% of patients at 7 months and 26% at 12 months.[9] Further analysis of the ACT 1 and 2 trial data reported a cumulative incidence of colectomy at 54 weeks of 10% for infliximab and 17% for placebo (p=0.02; absolute risk reduction 7%).[10] Compared with placebo, fewer ulcerative colitis-related hospitalisations and surgeries/procedures per 100 patient-years of treatment occurred with infliximab therapy: 40 vs 20 (P = .003) and 34 vs 21 (P = .03), respectively. Infliximab offers patients the option of a non-surgical approach to their disease management.

This finding is supported by a retrospective study[11] on 50 patients with steroid-refractory ulcerative colitis (SRUC) requiring medical rescue underwent treatment with first-line cyclosporine A (n=20) or infliximab (Remicade, Centocor Inc.; n=30) between January 2005 and December 2011. Treatment with infliximab and cyclosporine A appear to yield comparable short- and long-term efficacy in preventing colectomy in patients with steroid-refractory ulcerative colitis (SRUC), although patients with CsA treatment may be more likely to require a switch to another medication.

A recent Canadian study[12] found that the incidence rate of colectomy for medically refractory ulcerative colitis has declined in parallel with increasing anti-TNF use. Colectomy rates from 1998 to 2005 were compared to those from 2005-2011.

- During 1998–2011, 481 patients with ulcerative colitis underwent a colectomy for medically refractory disease.
- There was negligible change in the total colectomy incidence rate from 1998 to 2005, with an annual percent change of 4.4% (95% confidence interval (CI): -1.12% to 10.16%).
- From 2005-2011, following the approval and increasing use of anti-TNF therapy (infliximab was approved in 2005), the total colectomy incidence rate decreased by 16.1% (95% CI: -21.32% to -10.54%) every year to 0.9 per 100 ulcerative colitis patients in 2011.

Whilst we recognise the importance that surgery plays for some patients the use of anti-TNFs has led to marked changes in the way in which patients with UC are managed, and we would encourage the committee to consider any recommendations which could lead to an undue emphasis being placed on surgery.

Remsima should be considered in the incremental analysis of the ICERs in the Assessment Report

In addition to the above, CTHC would like to point out a few other corrections to be made for the Assessment Report with regard to the status of biosimilar infliximab, Remsima.

Not only has Remsima been approved[1] with the same INN as the originator infliximab, it is licensed for the same eight indications including ulcerative colitis in adults and children as the originator infliximab. The EMA used the data from the two studies to grant the licence for Remsima, Planet RA [13](in Rheumatoid Arthritis as detailed in the CTHC submission) and Planet AS[14] (in Ankylosing Spondylitis). This data along with the robust physiochemical and biological comparison demonstrated pharmacokinetic and therapeutic equivalence in rheumatic conditions, allowing extrapolation to all of the same eight indications as the originator infliximab including UC[1]. The clinical data used in the Summary of Product Characteristics[2] also includes that from the originator infliximab where the EMA has extrapolated the evidence to all of the indications. Therefore we would like to request for

consistencies on the references to Remsima to read “biosimilar to Remicade” throughout the report.

The assessment group stated that biosimilars to Remicade were considered as part of the evidence base for infliximab as part of this assessment. This recognises the fact that Remsima has been licensed by the EMA for the same INN and the same indications as the originator infliximab. We request that the inconsistent reference used in the Assessment Report –in particular in the Section 5.2.3.6 *Biosimilar to infliximab* would be corrected. Furthermore, we therefore request that the description of infliximab in the Section 3.4.3 *Marketing Licence and administration method* to include the manufacturer details of biosimilar infliximab in the heading next to infliximab.

The NHS is aware of the impending arrival of biosimilar infliximab to the UK market when the originator infliximab patent expires on February 24th 2015. The NHS would therefore welcome advice and guidance from NICE on the use of biosimilars. In particular medicines optimisation pharmacists will find the guidance invaluable as the lower costs of using biosimilar infliximab will impact hugely on budgets. We therefore suggest that Remsima should be considered in the incremental analysis of the ICERs in the Assessment Report.

The potential cost savings that Remsima might offer the NHS should be included in conclusions of the report

The health related quality of life and outcome data available to CTHC in this assessed indication (UC) should be exactly the same as that for the originator. The only difference between biosimilar infliximab and originator infliximab would therefore be the acquisition cost. Thus the most reasonable option considered by CTHC would have been to produce a cost minimisation model. However, given that this methodology is not preferred by NICE and knowing that assessment groups have rejected these in the past, a health economic model was not submitted by CTHC.

The Assessment Group has however built its own *de novo* health economic model, but has not included the lower cost of biosimilar infliximab as an option. (Table 4, page19).

Given the strong interest within the NHS with regard to cost saving, we are concerned and disappointed to read that biosimilar infliximab, in particular Remsima has been excluded from any health economic analysis in the Assessment Report.

Whilst we realise that this may be partly due to the fact that a price for Remsima was not submitted at this time, this is because no NHS price has been agreed with the Department of Health yet, and hence it is not publically available.

We suggest that even though a price has not yet been agreed with the Department of Health and is therefore not in the public domain; it would have been possible for the Assessment Group to have carried out a sensitivity analysis around the cost of the originator infliximab ranging from, for example, 10 % - 30% lower than the originator NHS list price (Table 4). (Analysts and horizon scanning groups in the UK have already highlighted and estimated lower prices for the biosimilars discounted by 10 to 30% below that of the originator; all of which is in the public domain). This would have an impact on the ICER for biosimilar infliximab and may influence the overall recommendations for the treatment of ulcerative colitis. Therefore the conclusions in the assessment report fail to address the potential cost savings that biosimilar infliximab (Remsima) might offer the NHS.

Remsima's budget impact analysis

We would encourage the Assessment Group to explore this prior to the first committee meeting. The results of this sensitivity analysis are likely to have an impact on the evidence and conclusions presented by the assessment group to the committee. Using the assessment group's executable model, drug acquisition costs for infliximab were varied in the range of 10 – 30% lower than the originator cost keeping all other parameters constant. The PSA (probabilistic sensitivity analysis) for 500 iterations was run and the results are as shown in the table below:

Option	0% discount		10% discount		20% discount		30% discount	
	Qaly	Cost	Qaly	Cost	Qaly	Cost	Qaly	Cost
Conventional treatment	10.66	£71,833	10.66	£71,833	10.66	£71,833	10.66	£71,833
Infliximab	11.01	£95,002	11.01	£92,880	11.01	£90,757	11.01	£88,634
Adalimumab	11.02	£89,998	11.02	£89,998	11.02	£89,998	11.02	£89,998
Golimumab	10.82	£88,236	10.82	£88,236	10.82	£88,236	10.82	£88,236
Colectomy	14.93	£42,228	14.93	£42,228	14.93	£42,228	14.93	£42,228

It has been also possible to produce the ICER table presented below with the same discounting scenario, 10 – 30%.

ICERs compared to conventional treatment			
	10% discount	20% discount	30% discount
Infliximab	£61,155	£54,987	£48,818
Adalimumab	£50,341	£50,341	£50,341
Golimumab	£104,455	£104,455	£104,455

As shown above, the ICERs for biosimilar infliximab (Remsima) are lower than the ones published in the report for other treatments and further preliminary values indicate a lower or similar cost effectiveness to adalimumab when compared to surgery or conventional treatment. The Assessment Group quote £50600 for adalimumab vs conventional treatment our own estimates are approximately £48800 for biosimilar infliximab (Remsima) with offering 30% discount lower than the originator (Remicade) cost.

Suggested actions

CTHC would welcome the opportunity to hold a discussion with NICE as soon as possible and preferably before the first appraisal committee to address the issues raised above.

We should also like to know how we can help provide the Assessment Group with the information it needs to carry out the proposed economic analyses, described above, so that NICE can provide prescribers, pharmacists, NHS England and NHS Wales with clear and unconfused guidance.

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