Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including review of TA140 and TA262)

Crohn's and Colitis UK

Crohn's and Colitis UK is the major UK charity offering information and support to anyone in the UK affected by these conditions. Established in 1979 as a partnership between patients, their families and the health professionals caring for them, the charity's services include four information and support services, a website, a wide range of accredited information sheets and booklets and a nationwide network of locally-based groups. The charity also raises awareness of these conditions, campaigns for improved health and social provision for patients, and funds vital research. Crohn's and Colitis UK is the working name of the National Association for Colitis and Crohn's Disease and currently has nearly 31,000 members UK-wide.

Impact of IBD on quality of life

Education, employment, personal relationships and social and family life may all be disrupted by the unpredictable occurrence of IBD flare-ups. The frequent and urgent need for the toilet, together with loss of sleep and the invisible symptoms of pain and continual or profound fatigue, can severely affect self-esteem and social functioning, particularly among the young and newly-diagnosed. These lifelong conditions most commonly first present in the teens and twenties, as a critical juncture in young people's lives, as they prepare for employment, take the first steps in their careers and form significant long-term relationships. For understandable reasons, a proportion of people with IBD may normalise an unnecessarily limited pattern of life, as a result of inadequate control of symptoms from poor medical management or anxiety about loss of bowel control if they venture too far from familiar environments.

Treatment for Ulcerative Colitis

Conventional therapies for Ulcerative Colitis are suboptimal and 30% of patients continue to experience flares or chronic symptoms as well as the adverse effects of nonspecific anti-inflammatory agents such as corticosteroids. Biological treatments offer hope to these individuals not only that surgery may be avoided, but that they can resume their lives. The UK-wide IBD Biological Therapies Audit 2013 found that "biological therapies [infliximab and adalimumab] are effective treatments for patients with IBD with 62% of adult patients entering clinical remission with corresponding improvements in patient-reported quality of life scores (https://www.rcplondon.ac.uk/projects/biologics). The 2014 report will be available from 25th September and will provide significant new data on biologics for Ulcerative Colitis, in terms of outcomes and current practice in relation to prescribing, including for moderate to severe disease.

Currently, access to these treatments is very limited for Ulcerative Colitis, unless patients are able to secure exceptional funding through their clinical commissioning group. This is at odds with access for those with Crohn's Disease, despite the fact that there is often an overlap between the conditions and an individual's diagnosis can change from one to the other. This can leave patients facing a postcode lottery until their condition becomes so severe that they are hospitalised and may then require emergency surgery.

Additionally, since the NICE guidance for infliximab for moderate to severe UC was produced in 2008, there has been a significant amount of new data demonstrating the value of infliximab, adalimumab and golimumab as maintenance therapy for Ulcerative Colitis, with similar efficacy to that for Crohn's Disease (E.g. Reinisch et al, Long-term infliximab maintenance therapy for ulcerative colitis: the ACT-1 and -2 extension studies, *Inflamm Bowel Dis*. 2012; Sandborn et al. Adalimumab induces and maintains clinical remission in patients with moderate to severe ulcerative colitis. *Gastroenterology*, 2012; Sandborn et al, Subcutaneous golimumab induces clinical response and remission in patients with moderate to severe ulcerative colitis. *Gastroenterology*, 2014.)

For example, low colectomy rates have been shown at up to four years and it has been concluded that infliximab *"rapidly controls symptoms, induces and sustains steroid-free remission, stimulates mucosal healing and reduces serious complications. Although infliximab tends to be reserved for patients with severe disease, it may be even more beneficial for moderate disease earlier in the disease course*." (Recommendations for the treatment of ulcerative colitis with infliximab: a gastroenterology expert group consensus. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22325181. Furthermore, as a patient's risk of colon cancer develops significantly after 8 to 10 years of active disease, effective biological therapy could decrease this risk.

Cost-effectiveness

While biological therapies are expensive compared to conventional treatments, audit data suggests that the high acquisition costs for these drugs may be offset by reductions in costs for other services. There are strong arguments, both clinically and economically, for ensuring optimal outpatient management of disease flare-ups and effective maintenance of remission. Biological therapies clearly have an important role to play in this and it is hoped that this appraisal process will now provide the opportunity for their potential to be realised for those with Ulcerative Colitis at least to bring guidance in line with that for Crohn's Disease.

Crohn's and Colitis UK believes that NICE should give a positive recommendation for NHS funding to be available for infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy.

Patient experiences

"I'm on Humira for my Ankylosing Spondylitis but it also takes care of my Colitis. I had a flare during a stressful time last year, but since then it's killed them off before they've gotten anywhere. I know it works because I can feel the flare coming sometimes a couple of days before I take my shot, and a couple of days after it's back to normal. Pain of injections is irrelevant. Its 12 seconds of horror compared to a lifetime."

"Infliximab is the only drug that has worked for me. I had severely active UC in 2012-13. After 5 months of a severe flare prior to diagnosis, I was successfully treated with mesalazine and steroids (bleeding stopped). However, 2 weeks later I developed myocarditis which put me in hospital. It was unclear whether this was the mesalazine or because I was so run down and anaemic that I had simply contracted a virus. To be safe the mesalazine was stopped and I began to taper off the steroids. The myocarditis was treated with strong iv antibiotics.

Sadly, 2 or 3 weeks later the symptoms of UC returned, possibly because of the antibiotic treatment and, despite immediate intervention with steroids, it became a very severe flare. I was admitted to hospital again and given iv steroids. When this didn't work I was put on iv ciclosporin and later ciclosporin and azathioprine tablets.

This did not fully control my symptoms so a couple of months later I washed out the ciclosporin and went onto infliximab (as well as aza). It was a wonder drug for me. I had it at 2 week intervals and after 3 infusions stopped bleeding. By August 13 after my first 8 week wait I considered myself in remission. This was fully confirmed by a colonoscopy in April which showed just a tiny amount of scarring. I now have infusions every 8 weeks and haven't had a flare since (although I still have diarrhoea 1-2 times a day).

I was extremely close to having surgery and am so happy I didn't need it. I am pretty much back to full strength and lead a much more fulfilling daily life. I am a teacher and this school year I only had 1 day off sick which feels close to a miracle after 6 weeks off and needing to work part time for the remainder of the previous year.

Being so ill was a really traumatising experience and I think I can only really appreciate how normal I feel when I reflect on what I coped with 2 years ago and even last summer. I think surgery would have been even more traumatising and even with i-pouch reversal I know I would be on the loo up to 8 times a day. I feel very grateful that I am not.

I am indebted to my consultant for fighting the case for my funding. NICE need to make biologics accessible as a long term treatment for UC."

"I was granted exceptional case funding by my local CCG in August last year to continue treatment with infliximab for my UC. I am currently waiting for a decision as to whether I will continue to receive funding and I live in constant fear of my treatment being brought to an end for funding reasons.

I was diagnosed with UC in 2011 and although I responded to steroids I quickly became steroid dependent and I was in need of maintenance treatment. After a year-long moderate flare I had run out of options and I was initially advised that I was not ill enough for infliximab and that my only option was to take part in a twelve week clinical trial for humira. After the twelve weeks the treatment would have to be stopped as there would be no funding.

I failed screening for the humira trial twice due to infections which meant that for a number of weeks my UC was effectively untreated. Eventually it was agreed that I could have infliximab, but only three doses, following which my team would need to apply for special funding from my CCG. I had to be admitted to hospital via A and E for my first infusion, which I had to wait for 12 hours. I did not need admission, but the NICE guidelines provide that the first infusion has to be given as an inpatient. This is the first problem with the guidelines as they stand.

Infliximab worked immediately for me and it was a real revelation after trying many treatments that had not worked during the previous year. I am continuing to feel better and better with each infusion.

After my second dose, it was decided that an application for exceptional case funding would be made for maintenance doses since these are not recommended by NICE for UC. This was at the time when CCGs were new and no one was clear as to who was responsible for what. By the time that my first maintenance dose was due, I had no decision on funding and I was told by my team at the hospital that they would not treat me. I spent a week fighting with them about this decision, and chasing my CCG. If I had not had the initiative and strength to fight then I would not have accessed treatment.

After putting me through a number of additional tests my hospital finally agreed to fund a compassionate dose of infliximab pending my CCG's decision. I was only told this three days before my infusion was due. That week was the most stressful time of my life. Effectively I was being told that they knew which treatment I needed but that I could not have it because it's too expensive. It is actually quite terrifying to be told as a patient that you might be denied the treatment that you need.

My CCG eventually made a decision to fund my treatment, five months after the application was made. I am told that I am one of the lucky ones since many patients wait for over a year for a decision. I was also told that if I had lived in one of the neighbouring boroughs then I would not have been successful. There is a real postcode lottery.

I have been informed that if I stop responding to infliximab then humira would be considered however it is even more difficult to access funding for this and it is not NICE approved at all for UC at the moment. Infliximab and humira are approved as maintenance treatments for UC by the European Medicines Agency. Infliximab has enabled me to continue working and avoid repeated hospital admissions and surgery.

I am in touch with a number of other patients on forums and my impression is that there is complete discrepancy in accessing these treatments throughout the country."

"I had Infliximab as a rescue therapy as my 2nd UC flare was more severe than my first. It was either Infliximab or the removal of my colon. Lucky for me it worked. Now I am on Humira for Crohn's."

"Hoping to start infliximab later this year, kept getting refused it when I had severe UC but now I also have Crohn's it is more readily available, why is this if there is any chance of a drug helping someone it needs to be an available."

For further information, please contact [redacted], Crohn's and Colitis UK, [redacted] [redacted]