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A prospective study of infliximab withdrawal after 12 months of treatment in patients with Crohn's disease: how will NICE guidance affect patient care?

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ABSTRACT– Infliximab is a biological agent that is licensed for the treatment of severe Crohn's disease. The annual cost of infliximab treatment is approximately £16,456 (excl VAT). In May 2010, the National Institute for Health and Clinical Excellence (NICE) recommended that patients should receive biological agents as a planned course of treatment only until treatment failure or until 12 months after the start of treatment, whichever is shorter. Patients should then have their disease reassessed to determine whether they still have active disease and whether ongoing therapy is still appropriate. We assessed the impact of the new NICE guidance on patient care by prospectively auditing patients who had been receiving infliximab for 12 months or more. The audit provided the opportunity for full disease reassessment and, for patients who were in clinical remission, the option to stop treatment. Disease was reassessed in 21 patients; a further 13 patients refused consent. Four patients were in deep clinical remission and discontinued infliximab. Implementation of the NICE recommendations on the use of infliximab in Crohn's disease is likely to be challenging in the face of significant resistance from patients who have an understandable fear of relapse. It might be more appropriate to discuss treatment withdrawal when high-quality evidence is available to support this management option.

KEYWORDS: Crohn's disease, biological agents, infliximab, inflammatory bowel disease

Introduction

Crohn's disease is a chronic inflammatory and destructive disease of the gastrointestinal tract. Diseased areas become inflamed and ulcerated, resulting in a spectrum of clinical features, which vary depending on the severity of the inflammation and the area of the gastrointestinal tract that is most affected. Clinical features include weight loss, diarrhoea, abdominal pain, lethargy and anorexia. Crohn's disease has a prevalence of 100–150 per 100,000 people in the UK and has the greatest incidence in young people.[1] The disease tends to follow a relapsing and remitting course, with patients suffering from acute flares followed by periods of partial or complete remission. Over time, Crohn's disease can be complicated by fibro-stenotic, penetrating or fistulating disease, which often requires surgical intervention. Approximately 70% of people with ileal Crohn's disease will need some form of surgical intervention within ten years of diagnosis.[2,3]

Although Crohn's disease is not yet curable, several medical therapies, such as steroids, liquid diets, antibiotics, thiopurines, methotrexate and biological agents (infliximab and adalimumab), can be used to treat its symptoms.[4,5] The aim of therapy with these agents should be to induce mucosal healing, improve quality of life and reduce long-term complications. A recent, randomised controlled trial suggested that early, aggressive medical treatment of inflammatory Crohn's disease with a combination of a thiopurine and infliximab resulted in clinical remission and mucosal healing in the majority of patients with acute, moderate to severe Crohn's disease within one year of commencing treatment.[6] Biological agents are, however, expensive and have the potential to cause significant side effects, such as serious infections and possibly an increased risk of malignancy.[7,8]

In 2007, NICE was asked to appraise the clinical and cost effectiveness of biological agents within their licensed indications for Crohn's disease. In May 2010, a technology appraisal (TA187)[9] was published that made recommendations on the use of infliximab or adalimumab in patients with Crohn's disease. On the basis of uncontrolled data from an abstract and a small retrospective case series, NICE recommended that all patients with Crohn's should have their disease reassessed one year after commencing treatment with infliximab or adalimumab. If a patient is deemed to be in clinical remission, as determined by clinical features, biological markers, or endoscopic or radiological studies, NICE recommend that treatment with biological agents be withdrawn (while the patient should continue to take either a thiopurine or methotrexate). Treatment also had to be withdrawn in the event of treatment failure. Given the current economic climate, NHS reforms and savings, it is likely that the use of biological agents will be carefully scrutinised by primary care trusts and commissioning boards to ensure adherence to the NICE recommendations.

We decided to perform a prospective study in our cohort of patients with Crohn's disease who were receiving infliximab as a maintenance treatment to identify patients who had received at

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least 12 months of treatment and to offer them a full reassessment of their disease activity. If they were found to be in clinical remission, they were offered the chance to stop infliximab treatment.

Methods

The Kent and Sussex Hospital (now relocated and renamed The Tunbridge Wells Hospital in Pembury) is an acute district general hospital serving a population of about 250,000 people living in south-west Kent and north-east Sussex. The case notes of all patients with Crohn's disease receiving treatment with infliximab were reviewed to determine the duration of treatment. Those who had received 12 or more months of treatment were sent a letter informing them of the latest NICE recommendations and the need to reassess their disease activity before continuing treatment with infliximab. Patients were subsequently seen at the Day Care Unit that they attended for their treatments for a full clinical review including determination of Harvey–Bradshaw index (Table 1).

Blood tests and endoscopic and/or radiological assessment were arranged for patients who consented to possible treatment withdrawal and were in *clinical* remission (Harvey Bradshaw Index ⩽3) (Table 1). *Deep clinical* remission, for the purposes of this study, was defined as complete clinical, biochemical and endoscopic or radiological remission (Table 2). These criteria are based on data from the STORI (infliximab diSconTinuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressors) trial, which suggested that infliximab could be safely discontinued in patients with stable disease.[10] The study identified several predictive factors for relapse:

- Crohn's Disease Endoscopic Index of Severity score ⩾ 2
- ultrasensitive C-reactive protein (CRP) > 5 mg/dl
- haemoglobin < 14.5 g/dl
- white blood cell count ⩾ 6.0×10^9/l
- faecal calprotectin > 300 μg/g
- infliximab trough levels ⩾ 2 μg/ml.

Male gender and the absence of previous surgical resection were also predictive factors for relapse. Those patients who were in deep clinical remission stopped treatment with infliximab and, if there were no contraindications, restarted treatment with thiopurine or methotrexate. They were then offered six-monthly review in clinic and advised to contact the gastroenterology department or their GP immediately if they felt their symptoms were returning. They were all reassured that treatment with biological agents could be restarted in the event of a relapse, if clinically appropriate.

Table 1. Harvey Bradshaw Index. Based on symptoms in past 24 hours. A score of ⩽3 strongly suggests remission; a score of ⩾7 suggests severe active disease.

General well-being: 0 = very well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible
Abdominal pain: 0 = none, 1 = mild, 2 = moderate, 3 = severe
Number of liquid stools per day: (score 1 for each)
Abdominal mass: 0 = none, 1 = dubious, 2 = definite, 3 = definite and tender
Complications: arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissure, new fistula, abscess, fever in the past week **(Score 1 for each)**

Table 2. Deep clinical remission. This was achieved when patients had complete clinical, biochemical and endoscopic or radiological remission.

Clinical remission (Harvey Bradshaw Index ⩽ 3)
CRP < 5mg/dl
Haemoglobin > 14.5g/dl
Endoscopic mucosal healing: Crohn's Disease Endoscopic Index of Severity < 2
OR
Radiological: No radiological evidence of ongoing inflammation

Results

A total of 27 patients at our hospital were receiving treatment with infliximab (5 mg/kg infusions every eight weeks). Their mean age was 37 years (range 20 to 81 years). The mean duration of therapy was 35.4 months (range 1 to 94 months). Six patients on infliximab who had received less than 12 months of treatment were excluded from the study. These patients were, however, advised that their disease activity would be reassessed one year after starting this drug.

Of the 21 patients who had received infliximab for 12 months or more, only eight (38%) consented to reassessment of their disease to investigate potential treatment withdrawal. For various reasons, 13 (62%) patients entirely refused reassessment of their Crohn's disease activity. Some were not feeling entirely well when they were seen and did not want to '*rock the boat*'. Others were very fearful about a relapse and the associated implications in terms of how this would affect their general health and whether they might need surgery. They felt that infliximab had '*changed my life*'. One patient was self-employed and anxious about the potential financial implications of becoming seriously unwell, as he had been prior to starting infliximab treatment. Those who were interested in withdrawal of infliximab were keen to avoid the potential side effects of the drugs, including a possible increased risk of lymphoma, infections or even demyelinating disease.

Of the eight patients who agreed to reassessment, six were found to be in clinical remission (Harvey–Bradshaw Index <3). The remaining two patients were excluded from further reassessment on the basis of a Harvey–Bradshaw Index of eight, indicating ongoing disease activity and high risk of relapse. Those in clinical remission went on to have blood tests, including full blood count, urea and electrolytes and CRP. Biochemical remission was confirmed in all six patients, who went on to have colonoscopy if their disease was known to be ileo-colonic or an

MRI scan of the small bowel if they were known to have had small bowel Crohn's. Of the six patients who underwent endoscopic or radiological assessment, four were found to be in deep clinical remission and discontinued infliximab treatment; they will be reassessed in six months. Two were found to have ongoing active Crohn's disease and continued with their infliximab treatments (Fig 1).

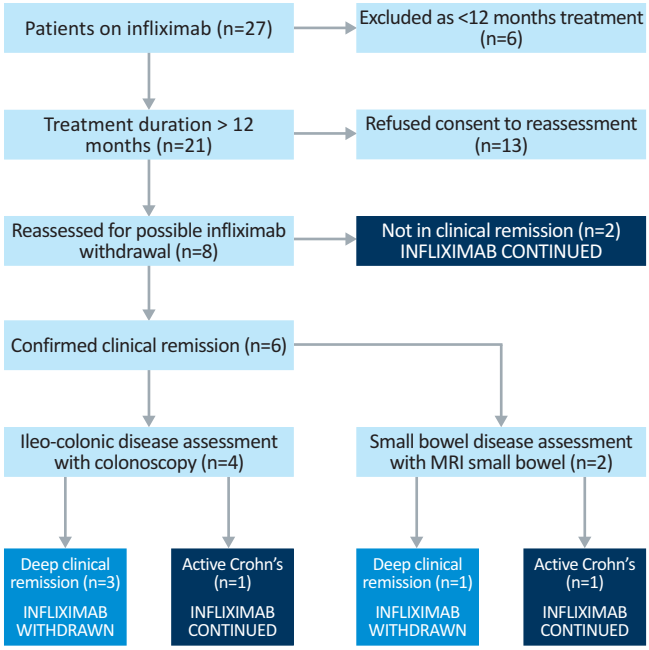

Fig 1. Results of patients assessed for possible infliximab withdrawal.

Discussion

Implementation of the latest NICE recommendations on the use of biological agents as a 'planned course of treatment' for patients with Crohn's disease for more than 12 months is likely to be challenging. We found that patients whose disease status has improved in response to biological agents after failure to respond to conventional therapy have an understandable fear of relapse if treatment is withdrawn. Even though they understand that treatment with biological agents could be restarted in the event of a relapse, they are not prepared to accept the risk of secondary loss of response or infusion reactions if antibodies to the drugs have formed. Often therefore, patients are reluctant to discuss the potential withdrawal of biological agents.

When compared with other available treatments, biological agents have greater positive impact on mucosal healing and, when used early, they have the potential to change the natural history of Crohn's disease.[11,12] These findings are supported by good evidence from large randomised controlled trials, which can be discussed with patients during the informed consent process when treatment with biological agents is initiated. There is also good evidence to suggest that biological agents are relatively safe when continued in the long-term.[13] No such high-quality evidence exists, however, to support withdrawal of these agents after a 12 month period. The NICE recommendations regarding treatment withdrawal are based on only two abstracts. In one, a small retrospective Italian series showed that mucosal healing predicted sustained remission after withdrawal of biological agents in patients with ulcerative colitis and Crohn's disease.[14] This study was based on uncontrolled, retrospective data that were not specific to Crohn's disease. The second abstract was from the GETAID group and presented prospective data from the STORI trial. In this trial, 115 patients on a combination of infliximab and an immunomodulator in stable steroid-free remission for six months had infliximab treatment withdrawn. After a median follow-up of 12 months, 45 (39%) suffered clinical relapse. Both studies suggest that mucosal healing is the major factor that must be evaluated when considering withdrawal of biological agents. However, neither of the studies nor the NICE guidelines clarify the optimal investigation pathway that should be used to assess clinical remission prior to treatment withdrawal.

Since publication of the NICE guidelines, one follow-up study has been published, providing further data from the STORI trial. The 115 patients whose infliximab treatment was stopped were followed up for a median period of 28 months after treatment withdrawal. They demonstrated a relapse rate at one year after infliximab withdrawal of 43.9% ± 5.0% (n=52). In those with two or fewer risk factors for relapse, however, the one-year relapse rate was only 15%. Retreatment with infliximab was effective and well-tolerated in 88% of patients who suffered a relapse.[15] The study acknowledges, however, that there are limitations in the interpretation of their results. First, the study cohort was small and was not matched by a control group in whom infliximab therapy was continued. Second, the patients were highly selected and had a median disease duration of 7.8 years, so it is very difficult to know whether these results would be reproducible in patients with early Crohn's disease. Third, the study is limited by a relatively short period of follow-up, with no data for longer-term outcomes. There was also disagreement between the investigators and the analysts about whether or not patients were in relapse in at least 11 cases, which raises concerns about the consistency of assessment. This could have led to an underestimation of the relapse rate. The study authors acknowledge that no recommendation regarding the withdrawal of infliximab should therefore be made until data from controlled studies are available.

No randomised controlled studies have been performed to support treatment withdrawal as a management option in patients with Crohn's disease severe enough to warrant biological therapy. The lack of evidence to support any treatment withdrawal strategy creates a significant dilemma for inflammatory bowel disease specialists contemplating how best to adhere to the new NICE guidance.[16,17]

In our experience, the perception amongst patients with whom treatment withdrawal was discussed is that the overriding reason for considering cessation of therapy is one of cost-efficacy, rather than of clinical best interests. It is very difficult to

alter this notion when evidence to support withdrawal of treatment is lacking. Patients with Crohn's disease on biological agents are often a very well-informed group, who wish to be actively involved in decisions regarding their treatment. We feel that more robust, high-quality data are needed to help inform patient decisions regarding withdrawal of treatment.

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