Safety of infliximab in 10 years of clinical practice
Sarah O'Donnell, Stephen Murphy, Malik M. Anwar, Maria O'Sullivan, Niall Breslin, Humphrey J. O'Connor, Barbara M. Ryan and Colm A. O'Morain

Assessment of the long-term safety of anti-tumour necrosis factor therapies is vital for the safe treatment of inflammatory bowel disease, a disease affecting a young cohort of patients.

Aims The aim of this retrospective study was to assess the safety and long-term outcome of infliximab use in clinical practice in our institution on an intention to treat basis over the 10-year period from December 1998 to 31 December 2008.

Methods All cases receiving infliximab for ulcerative colitis or Crohn's disease over a 10-year period were identified from hospital pharmacy records. The study was based on a single centre cohort, with an unselected patient group.

Results A total of 271 patients were identified as receiving infliximab for either Crohn's disease or ulcerative colitis over the 10-year study period. In total, 2169 infusions were given to the patient cohort. Fifty adverse events led to discontinuation of infliximab therapy in 47 cases. Two patients stopped due to neurological complications. There were six malignancies diagnosed within the cohort during the study period. Four of these were diagnosed while the individual was receiving Infliximab and two occurred at an interval of 21–52 months post their final infliximab infusion. A total of five deaths (1.5%) were observed during the study period.

Conclusion Infliximab therapy seems to be safe and efficacious in the long term. Although the development of malignancy remains a concern, we have not seen an increased risk of serious infection within our cohort.

Keywords: adverse events, Crohn's disease, inflammatory bowel disease, infliximab, safety, ulcerative colitis

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Received 21 October 2010 Accepted 7 April 2011

Introduction
Infliximab, a mouse–human chimeric monoclonal antibody to tumour necrosis factor (TNF)-α has been in use in clinical practice for more than 10 years. In gastroenterology, it was initially used in the treatment of Crohn’s disease and then ulcerative colitis. The randomized controlled trials designed to assess efficacy and safety did not reveal an excess of serious adverse events in the short term [1–4]. However, concern remains over its safety profile in routine clinical practice. Commonly reported adverse events include acute infusion reactions, delayed hypersensitivity, and infection including reactivation of tuberculosis [5–7]. Anti-TNF agents have also been associated with demyelinating disease [8], drug-induced lupus [9], and more recently T cell lymphoma [10]. Initially, anti-TNF therapies were reserved for those with medically refractory disease, but with recent evidence suggesting a benefit to top down treatment strategies, a larger percent of people with inflammatory bowel disease (IBD) will be exposed to anti-TNF therapies, many at a young age. The assessment of the long-term safety of anti-TNF therapies is therefore vital for the safe treatment of these chronic diseases affecting a young cohort of patients.

The aim of this study was to assess the safety and long-term outcome of infliximab use in clinical practice in our institution on an intention to treat basis over the 10-year period from December 1998 to 31 December 2008.

Methods
All patients receiving infliximab for ulcerative colitis or Crohn’s disease over a 10-year period were identified from hospital pharmacy records. The retrospective study was based on a single-centre cohort, with an unselected patient group. Each case was reviewed to determine the short-term and long-term safety profiles of infliximab. Charts were reviewed for patient profile, concomitant immunosuppressant, duration and nature of infliximab therapy, adverse events, and reason for discontinuation. Minor adverse events leading to temporary discontinuation of infliximab were outside the scope of this study.

Results
A total of 271 patients were identified as receiving infliximab for either Crohn’s disease or ulcerative colitis over the 10-year study period. In total, 2169 infusions were given to the patient cohort. There were 122 male and 149 female patients. The median age of the group at

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DOI: 10.1097/MEG.0b013e3283479125
first infusion was 33 years (interquartile range: 26–45 years). The majority of patients were receiving infliximab for the treatment of Crohn’s disease (n = 201, 74%). Seventy patients received infliximab for ulcerative colitis. Of the patients receiving infliximab for Crohn’s disease, 87 had inflammatory-type disease, 61 strictureing, and 53 internal fistulizing diseases. A total of 104 had ileocolonic involvement, 67 colonic, and 30 had isolated small bowel involvement. Nineteen patients had upper gastrointestinal tract involvement. Forty-six of these patients (23%) had surgery for Crohn’s disease before infliximab therapy (Table 1).

Patients received an average of eight infusions, with 43 (16%) receiving more than 15 infusions. Patients receiving treatment for Crohn’s disease received an average of nine infusions versus six for the treatment of ulcerative colitis, (P = 0.019; confidence interval: 0.43–4.795). Infliximab was prescribed in a step-up manner, with patients initially being treated with mesalazine, and if requiring steroids an immunosuppressant was introduced followed by the addition of infliximab. Sixty-two percent (n = 175) of patients were receiving a concomitant immunosuppressant. Intolerance to immunosuppressant such as azathioprine is not uncommon. A total of 78 patients received episodic therapy, 157 received maintenance therapy, and 36 initially received episodic followed by maintenance therapy. In our centre, patients receiving maintenance therapy received an infusion every 8 weeks after an induction regimen, whereas patients receiving episodic therapy received an infusion only when a symptomatic recurrence warranted it. Most patients who received episodic treatment were receiving therapy during the earlier years of infliximab use reflecting patterns of clinical practice. The median follow-up period was 58.8 months (interquartile range: 30–87 months).

At the end of the study period, 54 (20%) patients remained on maintenance therapy with infliximab at our institution. Four patients had transferred their care to other institutions while receiving infliximab and therefore follow-up data were not available. Some patients (68, 25%) had stopped due to a primary nonresponse to infliximab, 41 (15%) stopped due to secondary nonresponse. Thirty-four patients (13%) discontinued therapy because they had entered remission, and 17 (6%) had achieved fistula closure. In 16 patients (6%), infliximab therapy had been used as bridging therapy while commencing an immunosuppressant. Therapy was discontinued in 36 (13%) due to an adverse event. Fifty-five of the patients were retreated with infliximab after a drug holiday. Of these 15 patients (27%) who were successfully retreated, seven continued on infliximab to the end of the study period. Fourteen (25%) had adverse events including eight infusion reactions.

Adverse events (50) led to discontinuation of infliximab therapy in 47 patients. Three patients were retreated at an interval and experience a second adverse event. Twenty-five of these patients experienced an acute infusion reaction. Sixteen of these occurred in patients being treated with infliximab for the first time; one reaction for every 122 infusions. Nine infusion reactions occurred among those retreated after a drug holiday; one reaction for every 36 infusions.

Infliximab was discontinued due to infection in five patients. There was one case of extrapulmonary tuberculosis; this patient was later successfully treated with a second-line anti-TNF after antimycobacterial treatment. Three patients stopped due to recurrent mild-to-moderate infections. Two patients discontinued due to herpes zoster infection. Both of these were later retreated without recurrence of the herpes zoster. Two patients stopped due to neurological complications, one patient had confirmed demyelination on MRI, and one patient was undergoing investigation for paresthesia at the end of the study period. Nine patients developed a serum sickness such as delayed reaction; including skin reactions in four, myalgia in three, and nausea in two patients. Four patients discontinued infliximab due to the diagnosis of a malignancy. Other reasons for discontinuation included a colonic perforation leading to colectomy in one patient. Development of alveolitis was seen in one patient and has been described elsewhere [11]. The development of a subdeltoid bursitis early in treatment led to discontinuation in another patient [12] and a retinal vein thrombosis occurred in one patient [13].

There were six malignancies diagnosed within the cohort during the study period. Four of these were diagnosed while the individual was receiving infliximab, and two occurred at an interval of 21–52 months post their final infliximab infusion. Two were diagnosed with squamous cell carcinomas of the lung; both of these individuals were smokers. A colitis-associated colonic neoplasia was diagnosed in one case leading to colectomy. This patient had received infliximab 21 months before this diagnosis but had had no response. Two small bowel malignancies were diagnosed, one adenocarcinoma and one lymphoma, both in patients with Crohn’s disease (Table 2). All six patients were on concomitant immunosuppressant therapy.
A total of five deaths were observed during the study period. The median age at death was 64 years. This occurred at a mean of 14 months post last infliximab infusion (range: 1–52 months). Only two of these deaths were felt to have a possible link to infliximab therapy; a small bowel lymphoma and a pancreatic malignancy. There were two further deaths from lung cancers, both in long-term smokers, aged 75 and 62 years. One death occurred after a variceal bleed, this patient had primary sclerosing cholangitis complicating ulcerative colitis.

**Discussion**

Randomized controlled trials have demonstrated infliximab to be safe and efficacious in the treatment of IBD. [1–4] However, concerns remain about its long-term safety. To date, few studies have examined the long-term safety of infliximab in clinical practice, in which unlike in clinical trials all-comers are included on an intention to treat basis without stringent inclusion and exclusion criteria. This study has examined the safety over a 10-year period with an almost 5-year average follow-up period (58.8 months). A total of 271 individuals received more than 2000 infusions, with 16% receiving more than 15 infusions. Twenty-five percent experienced a primary nonresponse to infliximab and 15% a secondary nonresponse. This was a retrospective analysis and as such minor adverse events leading to temporary discontinuation of infliximab were outside the scope of this study. Overall, we observed adverse events leading to discontinuation of therapy in 16.2% of patients.

**Infusion reactions**

Infusion reactions were the most commonly encountered adverse event. The rate of infusion reaction is low in comparison with some reports with only 9% experiencing infusion reaction. However, published rates vary depending on whether investigators are reporting only on serious reactions or report on every mild reaction, which may not require discontinuation of infliximab therapy. Rates of 3.8–17% have been reported elsewhere [5,14–16]. It was the practice at our institution until 2007 that all patients were pretreated with hydrocortisone and infusions administered for more than 2 h. Ongoing studies are being used to determine the optimal infusion time and need for premedication and therefore protocols have varied in recent years. Variability in discontinuation after infusion reaction reflects different practices at different centers.

**Malignancy**

There were six malignancies diagnosed within the cohort during the study period. Four of these were diagnosed while the patients were receiving infliximab and two at an interval. A recent study including 734 patients in Belgium found that 13% experienced a severe adverse event [14]. Twenty-one patients (2.8%) developed a malignancy in this group. Similar rates of malignancy have been seen in other studies [5,15,17]. The development of malignancy is a major concern with the long-term use of infliximab. Placebo-controlled trials have not shown an increased incidence of malignancy, but follow-up has been short [2–4]. The Treat registry with 15 000 patient-year follow-up did not show an increased rate of malignancy [18]. However, this registry must be viewed with caution due to potential selection bias of included patients as registration of adverse events was at the physician’s own discretion. Two studies have assessed the risk of malignancy in a case-controlled manner in patients with IBD treated with infliximab compared with the patients with IBD not exposed to anti-TNF therapies [14,17]. Neither study showed an increased incidence of malignancy in the infliximab group. Within our cohort, six malignancies were diagnosed. Two were diagnosed with squamous cell carcinomas of the lung; both of these individuals were smokers and aged more than 60 years. It has been suggested that anti-TNF therapy may be associated with an increased risk of the development of lung cancers; however, a definite causative link is hard to prove given the presence of confounding factors. Lees et al. [15] report three cases of lung cancer in their Scottish cohort. All three were once again smokers and aged more than 65 years. They suggest that anti-TNF exposure may cause an accelerated course in susceptible people. A trial of infliximab in the chronic obstructive pulmonary disease had a high rate of lung malignancy, once again a group of susceptible individuals, mainly older than 65-years of age with a smoking history [19]. Although this increase was not statistically significant, it certainly warrants further evaluation. A colitis-associated colonic neoplasm was diagnosed in one patient leading to colectomy. This was picked up on surveillance colonoscopy. This patient had received infliximab 21 months before this diagnosis, but had had no response. Infliximab has been shown to improve mucosal-healing rates [2,4]. The risk factors for the development of colitis-associated neoplasia include the extent of inflammation and severity of inflammation. Therefore, it could be hypothesized that it was the lack of a response to infliximab rather than the infliximab therapy itself that led to this malignancy. Two small bowel malignancies were diagnosed; one adenocarcinoma and one lymphoma both in patients with Crohn’s disease. The lymphoma was diagnosed at emergency surgery at

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<td>Patients developing a malignancy</td>
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<td>Squamous cell lung</td>
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Sclerosing cholangitis complicating ulcerative colitis.

**Squamous cell lung carcinoma**

**Pancreatic adenocarcinoma**

**Colitis-associated adenocarcinoma**

**Small bowel lymphoma**

**Small bowel adenocarcinoma**

**Malignancy**

There were two further deaths from lung cancers, both in long-term smokers, aged 75 and 62 years. One death occurred after a variceal bleed, this patient had primary sclerosing cholangitis complicating ulcerative colitis.
the point of a perforation. These two malignancies were felt to have a possible link to infliximab therapy.

**Demyelination**

There were two patients with possible demyelination among the cohort. The development of demyelination after infliximab therapy has been described [8,14,15,20]. Symptoms often resolve with discontinuation of therapy. Many population-based studies have shown a clustering of other autoimmune conditions including multiple sclerosis with IBD [21–23]. Therefore, although infliximab therapy cannot always be blamed for the development of demyelination in patients with IBD if there is a temporal association, the infliximab should be discontinued as symptoms may resolve with termination of therapy.

**Mortality**

A total of five deaths (1.5%) were observed during the study period. Overall mortality rates of 1.6–4% have been reported elsewhere [5,14–16]. Only two of these deaths were felt to have a possible link to infliximab therapy, a small bowel lymphoma and a pancreatic malignancy. There were two further deaths from lung cancers, both in long-term smokers, aged 77 and 64 years. As discussed above, there may be a slight increased risk of lung cancer with infliximab therapy but age and smoking history are likely confounders and therefore no strong link can be made. One death occurred after variceal bleed, this patient had primary sclerosing cholangitis complicating ulcerative colitis. This was felt to be unrelated to infliximab therapy. One study found that the age was the only positive predictor for death [14]. Most deaths occurring in patients treated with infliximab occur in the setting of malignancy where causality cannot always be determined, with deaths rarely occurring as a result of serious infection [5,14]. A large Belgian study examining the risk of serious infection with infliximab therapy found that the excess risk of infection was related to concomitant steroid use [14]. Therefore, concomitant medications must be taken into account when examining the risk of serious infection and anti-TNF therapies.

**Conclusion**

Infliximab therapy seems to be safe and efficacious in the long term. Severe adverse events can occur and patients should be carefully selected and monitored during therapy. Although the development of malignancy remains a concern, we have not seen an increased risk of serious infection within our cohort. Longer follow-up is still necessary.

**Acknowledgement**

Declaration of personal interest: Colm O'Morain is on the international advisory board of Abbott, Schering Plough, and Shire pharmaceutical companies. He has unrestricted educational grants from Abbott and Schering Plough.

Conflicts of interest: none declared.

**References**