

Infliximab therapy in Crohn's disease: a pragmatic approach?

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SUMMARY

Background

Infliximab is recognized as an effective therapy in unresponsive luminal and fistulating Crohn's disease. The use of maintenance or 'on demand' therapy thereafter is controversial.

Aim

To assess the need for maintenance infliximab therapy in a clinical setting where immunomodulatory agents are widely used and where episodic therapy is used in preference to maintenance therapy.

Methods

Ninety-three patients with Crohn's disease receiving infliximab; 72 with unresponsive luminal disease and 21 with fistulous disease. Data collected included disease site and duration, surgical and smoking history, initial response rates, duration of response maintenance and concomitant medications.

Results

Fifty-six of 72 (78%) patients with luminal disease and 11 of 21 (52%) with fistulous disease achieved an initial response. Ten of 67 responders required conversion to maintenance infliximab infusions, while 31 remain in remission. Patients with luminal disease and those who had not taken previous surgery had higher response rates to infliximab. Younger patients and those with small bowel disease had higher relapse rates following initial response. Three patients developed allergic reactions to infliximab and one patient died of progressive pulmonary disease 6 weeks after their first infusion.

Conclusions

Many patients with Crohn's disease can be maintained successfully with an episodic infliximab regimen.

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INTRODUCTION

Infliximab is a chimeric monoclonal antibody, which binds tumour necrosis factor (TNF)- α with high affinity and neutralizes its biological activity.¹ The ACCENT I and ACCENT II studies demonstrated its efficacy in Crohn's disease unresponsive to conventional treatment.^{2, 3} Because of high relapse rates in these studies it is generally recommended that patients receive regular maintenance infusions. Remission is associated with better mucosal healing, reduced hospitalizations, fewer repeat operations and better quality of life.^{4, 5} However, the basis on which maintenance infliximab therapy is recommended is open to question. The early studies using infliximab in Crohn's disease were notable for the low use of concomitant immunomodulatory drugs.^{2, 3} Baert *et al.* have shown that the addition of immunomodulatory agents is associated with fewer antibodies to infliximab while at the same time showing longer remissions and less infusion reactions.⁶ There is no clear consensus on the optimum strategy for anti-TNF- α therapy in Crohn's disease.

The aim of this study was to assess the need for maintenance infliximab therapy in Crohn's disease in a unit where immunomodulatory drugs are widely used and where episodic treatment is the only initial regime employed. The secondary aim was to analyse what factors, if any, were associated with initial response to infliximab and subsequent relapse following discontinuation.

METHODS

Patients

This study included 93 consecutive patients (median age 29 years; 56 female) receiving infliximab infusions for Crohn's disease in a single gastroenterology unit with a special interest in inflammatory bowel disease. This represents 11% of patients attending St Vincent's University Hospital with Crohn's disease ($n = 822$). All 93 patients in the study had either failed steroid therapy or were steroid-dependent and, where possible, were receiving immunomodulatory agents. Azathioprine was prescribed at a dose of 2 mg/kg/day and mercaptopurine (6-mercaptopurine) at 50 mg/day. These dosages were not changed when infliximab was commenced. All patients had a normal chest radiograph prior to infliximab treatment. No patient had clinical

evidence of sepsis or of symptomatic stricturing disease at the time of their first infusion. Demographic, clinical and endoscopic data were retrieved from a prospective database. Patients were followed up regularly in specialist inflammatory bowel disease clinics and also contacted by telephone to determine clinical status. Median follow-up time in those not relapsing was 66 weeks (range: 1–221).

Infliximab infusions were given at a dose of 5 mg/kg over 3 h. Individuals in the luminal disease group received a single infusion at week 0 and those who achieved an initial response were offered repeat infusions on relapse. Those achieving a partial response had a further infusion 8 weeks later and were subsequently re-evaluated. Patients who had no response to an initial infusion were not retreated. Patients with fistulating disease received a series of three infusions at week 0, 2 and 6. Again, responders were offered repeat infusions in an episodic manner.

Response to infliximab for patients with luminal disease was defined as complete resolution of Crohn's related symptoms. Response in fistulating disease was defined as closure of all fistulae. Remission was defined as continuing response in patients who required not more than 5 mg prednisolone daily. For the purpose of this study, remission commenced from the point of complete response, i.e. after the patient's first infusion for those responding initially or after their last infusion if they required more than one to achieve remission. Likewise, remission for patients with fistulating disease commenced only after their 6-week infusion. Relapse was defined as the need for further infliximab infusions or other biological response modifiers, surgical resection or the need for >5 mg prednisolone per day. Patients receiving infliximab more than 14 weeks following a previous infusion were pre-treated with 200 mg of hydrocortisone intravenously.⁷ Antibodies to infliximab were not measured.

Statistical analysis

Continuous data are presented as medians and inter-quartile ranges and differences between groups were assessed using Wilcoxon's rank sum test. Categorical data were analysed using the chi-square test. For survival analyses, Kaplan–Meier curves were constructed and differences in outcome between groups were assessed by the log-rank test. Multivariate outcome analyses were performed with the Cox proportional

hazards model using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA). Two-sided *P*-values of <0.05 were considered significant in all analyses.

RESULTS

Patient population

Table 1 shows demographic and clinical details along with disease site and the types of fistulae at the time of starting infliximab. Sixty-four patients (69%) were receiving a stable dose of an immunomodulator for at least 3 months prior to commencing infliximab (56 on azathioprine, four on mercaptopurine, three on mycophenylate and one on methotrexate) and a further 19 (20%) were successfully commenced on immu-

nomodulators at the time of their first infliximab infusion (15 on azathioprine, three on mycophenylate and one on mercaptopurine).

Initial response to infliximab

Figure 1 shows the clinical course of the patient population throughout the study period. Overall, 67 patients (72%) responded to infliximab, 11 with fistulating disease and 56 with luminal disease. Forty-seven patients with luminal disease (84%) responded after a single infusion, five after two infusions and three after three infusions. A single patient, who had been unwell for the previous 10 years and had nine operations including bowel resections over that time, felt so improved during infliximab therapy that she asked to continue treatment for a total of five infusions. She stopped inf-

Table 1. Demographic, clinical and biochemical features of 93 patients with Crohn's disease prior to receiving infliximab

Patient age at first infusion [years (range)]	29 (17–82)
Gender	
Female	56 (60)
Male	37 (37)
Disease site	
Large bowel only	49 (53)*
Small and large bowel	32 (35)
Small bowel only	12 (13)
Time from diagnosis to first infusion [years (range)]	5.0 (0.1–33.5)
Follow-up time in patients not relapsing [weeks (range)]	66 (1–221)
Symptoms in 72 patients with luminal disease	
Diarrhoea	57 (79)†
Abdominal pain	46 (64)
Weight loss	23 (32)
PR bleeding	14 (19)
Other symptoms‡	20 (28)
Fistula type in 21 patients with fistulating disease	
Perianal	9 (43)
Enterocutaneous	7 (33)
Rectovaginal	3 (14)
Peristomal	1 (5)
Enterovesical	1 (5)
C-reactive protein prior to first infusion [median (range)]	25 (3–334)
Immunomodulatory medications	
Commenced prior to infliximab	64
Successfully commenced at first infusion	19
Intolerant	10

Values are expressed as *n* (%).

* Percentages do not total 100% because of rounding.

† Percentages do not total 100% as some patients had multiple symptoms.

‡ Other symptoms included abdominal distention, fatigue, nausea/vomiting, mouth ulcers, uveitis, erythema nodosum, pyoderma gangrenosum.

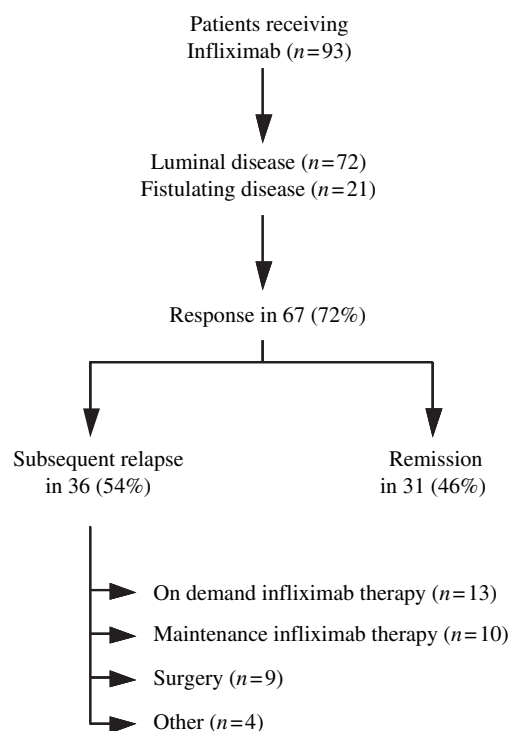


Figure 1. Flow diagram of 93 patients receiving infliximab for Crohn's disease. 'Other' includes two patients enrolled in trials of anti-tumour necrosis factor (TNF) α , one patient with a prolonged response to a course of oral steroids and one starting maintenance treatment with adalimumab ($n = 1$).

liximab after the fifth infusion and remains well 9 months later on azathioprine alone. All 11 patients with fistulating disease who responded to infliximab did so after a standard course of three infusions. The factors associated with treatment response are shown in Table 2. Patients with luminal disease and those without previous resection surgery had significantly better response rates but neither smoking at the time of initial infusion nor C-reactive protein (CRP) were associated with response rate. Response rates between those 64 patients on immunomodulatory drugs prior to infusion and the 29 patients either not on these agents or starting them after infliximab infusion were similar ($P = 0.15$).

Relapse following infliximab

Relapse-free survival of all 67 responders is illustrated in Figure 2. Estimated relapse-free survival after initial response was 55% after 1 year and 38%, 33%

and 29% after 2, 3 and 4 years respectively. Table 3 and Figure 3 show factors associated with relapse and indicate that young patients and those with small bowel disease had higher relapse rates after stopping infliximab. Both variables were confirmed as independent predictors of relapse in a multivariate regression analysis (Table 4). Relapse was unrelated either to concomitant treatment with immunomodulatory drugs either in those patients receiving these medications before infusion therapy ($P = 0.29$), or in the 'immunomodulatory group' as a whole ($P = 0.66$).

Treatment

Thirty-one of the 67 responders (46%) have remained in remission during their cumulative 617-month follow-up period (mean follow-up 20 months; range: 1–51), while 36 (54%) relapsed after stopping treatment (Figure 1). A single patient in the former group remains on low-dose prednisolone (2.5 mg daily). Nine of the latter group underwent subsequent surgery, including five who had an ileocaecal resection for symptomatic stricturing disease and a further two with proximal colonic disease who had a colectomy with ileorectal anastomosis, one in preference to further infliximab therapy and the other because of an allergic reaction to infliximab. A single patient had a left hemicolectomy following an acute haemorrhage while the final patient had an abdomino-perineal resection for recurrent fistulous disease.

Twenty-three patients who relapsed required 'on-demand' infliximab infusions. Ten of these were subsequently converted to maintenance infusions every 2 months. The mean time from initial response to initiation of maintenance therapy was 17 months (range: 8–43). These 10 patients required a total of 17 infusions (median one infusion per patient; range: 0–4) prior to initiation of maintenance therapy, corresponding to one infusion per patient every 10 months. Furthermore, 13 patients required only intermittent infusions following relapse and none have lost their response to the drug. Overall, a total of 14 infusions were given to these patients over a cumulative follow-up period of 237 months, corresponding to one infusion per patient every 17 months. Finally, after initial relapse, four other patients were either enrolled in trials of anti-TNF α ($n = 2$), had a prolonged response to a single course of oral steroids ($n = 1$) or commenced maintenance treatment with adalimumab ($n = 1$).

Table 2. Response to infliximab in 93 patients with Crohn's disease in relation to clinical features

Variable	Response (<i>n</i> = 67)	No response (<i>n</i> = 26)	<i>P</i> -value
Gender			
Male	23 (62)	14 (38)	0.08*
Female	44 (79)	12 (21)	
Age at first infusion [year; median (IQ range)]	29 (23–39)	33 (21–46)	0.44†
Disease onset to first infusion [year; median (IQ range)]	5.0 (1.0–9.8)	5.1 (1.6–9.9)	0.64†
Disease type			
Luminal disease	56 (78)	16 (22)	0.02*
Fistulating disease	11 (52)	10 (48)	
Disease site			
Large bowel only	38 (78)	11 (22)	0.21*
Small bowel	29 (66)	15 (34)	
Previous bowel resection			
No	49 (83)	10 (17)	0.002*
Yes	18 (53)	16 (47)	
Immunomodulatory treatment prior to first infusion			
No	18 (62)	11 (38)	0.15†
Yes	49 (77)	15 (33)	
CRP at first infusion [mg/L; median (IQ range)]	26 (5–45)	23 (10–83)	0.69†
Smoking at first infusion			
No	34 (71)	14 (29)	0.79*
Yes	33 (73)	12 (27)	

Values are expressed as *n* (%).

* Chi-square test.

† Wilcoxon's rank sum test (Mann–Whitney *U*-test).

IQ, interquartile; CRP, C-reactive protein.

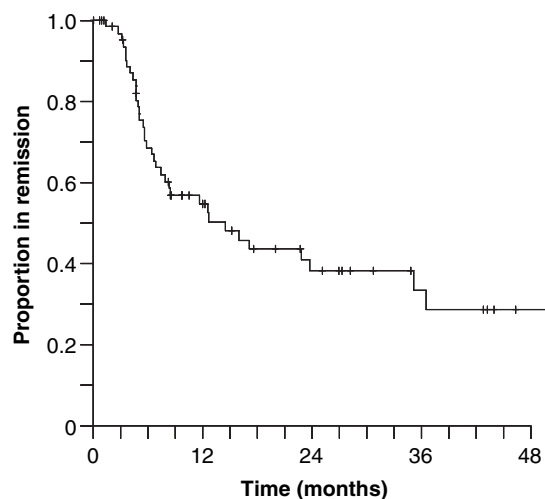
**Figure 2.** Relapse-free survival following discontinuation of infliximab in 67 patients responding to treatment.

Table 5 shows the outcome for the 10 patients who were not receiving immunomodulatory agents. Seven responded to infliximab and four remain in remission.

Four have required surgery, two for recurrent disease and one is lost to follow-up.

Complications

A single patient, an 82-year-old female, died 6 weeks after her first infliximab infusion. She had an immediate therapeutic response, but developed progressive pulmonary disease 2 weeks later and died after 3 weeks from respiratory failure. Opportunistic organisms were not isolated and a postmortem examination indicated adult respiratory distress syndrome. Three patients developed hypersensitivity reactions to infliximab (two type I and one type III), two of whom were receiving immunomodulatory drugs at the time: none required hospital admission. One patient experienced a severe serum sickness reaction following a single infliximab infusion. This patient had commenced azathioprine at the same time. A single patient was found to have moderate cervical dysplasia (CIN II) early in the course of her treatment. She had been

Table 3. Relapse-free survival following discontinuation of infliximab in 67 patients responding to treatment in relation to clinical features

Variable	Two year relapse-free survival (%)	P-value
Gender		
Male	49.7	0.10
Female	31.3	
Age at first infusion (years)		
<35	27.2	0.05
≥35	60.8	
Disease onset to first infusion (years)		
<5	35.5	0.80
≥5	41.7	
Disease type		
Luminal disease	40.8	0.61
Fistulating disease	33.3	
Disease site		
Large bowel only	46.0	0.01
Small bowel	29.3	
Previous bowel resection		
No	37.5	0.96
Yes	43.6	
C-reactive protein at first infusion (mg/L)		
<25	25.0	0.18
≥25	47.1	
Smoking at first infusion		
No	40.4	0.66
Yes	35.6	

commenced on azathioprine 3 months prior to infusion. One patient with severe anorectal disease had rectal carcinoma diagnosed 7 months after failed therapy. A colonoscopy 2 months prior to treatment had shown severe rectal inflammation, but a discrete mass was not seen. Azathioprine had been commenced at the time of infusion but the patient had been receiving Methotrexate for arthritis over the 2 years prior to infliximab. Neither of these latter events was considered to be infliximab related.

DISCUSSION

Crohn's disease, unresponsive to conventional treatment and not readily amenable to surgery, presents clinicians with difficult decisions. The introduction of anti-TNF α therapy appears to have greatly improved the outlook for patients as evidenced by double-blind trials that have shown superiority of regular infliximab infusions over placebo in terms of clinical and histo-

logical remission.^{2, 3} A logical conclusion of these studies is that patients commencing infliximab should receive regular infusions, possibly for many years. However, this concept is not universally accepted and others have argued that the concomitant use of drugs, such as azathioprine or mercaptopurine might facilitate episodic regimes.^{6, 8} The purpose of our study was to determine if episodic use of infliximab, along with immunomodulatory treatment where possible, is feasible in clinical practice. The response rate of 72% to infliximab in our series is similar to what one would expect from previous randomized-controlled trials. However, it is perhaps surprising that over two-thirds of our patients did respond, given that these were all patients in whom we were unable to maintain remission using conventional therapies, including surgery. Of further interest is the relatively high rate of remission 1, 2 and 3 years after discontinuation of infliximab, even though most patients received only a single infusion. The reason for this is not clear, but it may at least partially relate to the high percentage of patients receiving immunomodulatory drugs. Our results are supported by data from the United Kingdom and the US showing significantly higher response rates and longer remission rates for those patients established on immunosuppressive treatments.^{9, 10} In contrast, however, a report from Seattle on the use of infliximab in 122 patients failed to find any value in the use of concomitant immunosuppressives.¹¹ As almost 90% of our patients were on immunomodulatory drugs the study did not have the statistical power to determine any formal association between such medications and either response or relapse in patients receiving infliximab. In our report only luminal disease and the absence of previous resection surgery predicted a favourable initial response, although it should be remembered that our study was not specifically designed or powered to identify all potential variables associated either with response or relapse.

A little over one half of all responders in our study relapsed. Nine subsequently underwent surgery, two of whom chose this option rather than a further infliximab infusion. The ACCENT I and II studies have shown that a proportion of patients receiving maintenance treatment will require surgery, while previous reports indicate that surgery may be more common in those patients receiving episodic infliximab therapy or placebo.^{4, 5} We noted, at the time of surgery that the adjacent colonic disease was quiescent in two of the three patients who required an ileal resection, indica-

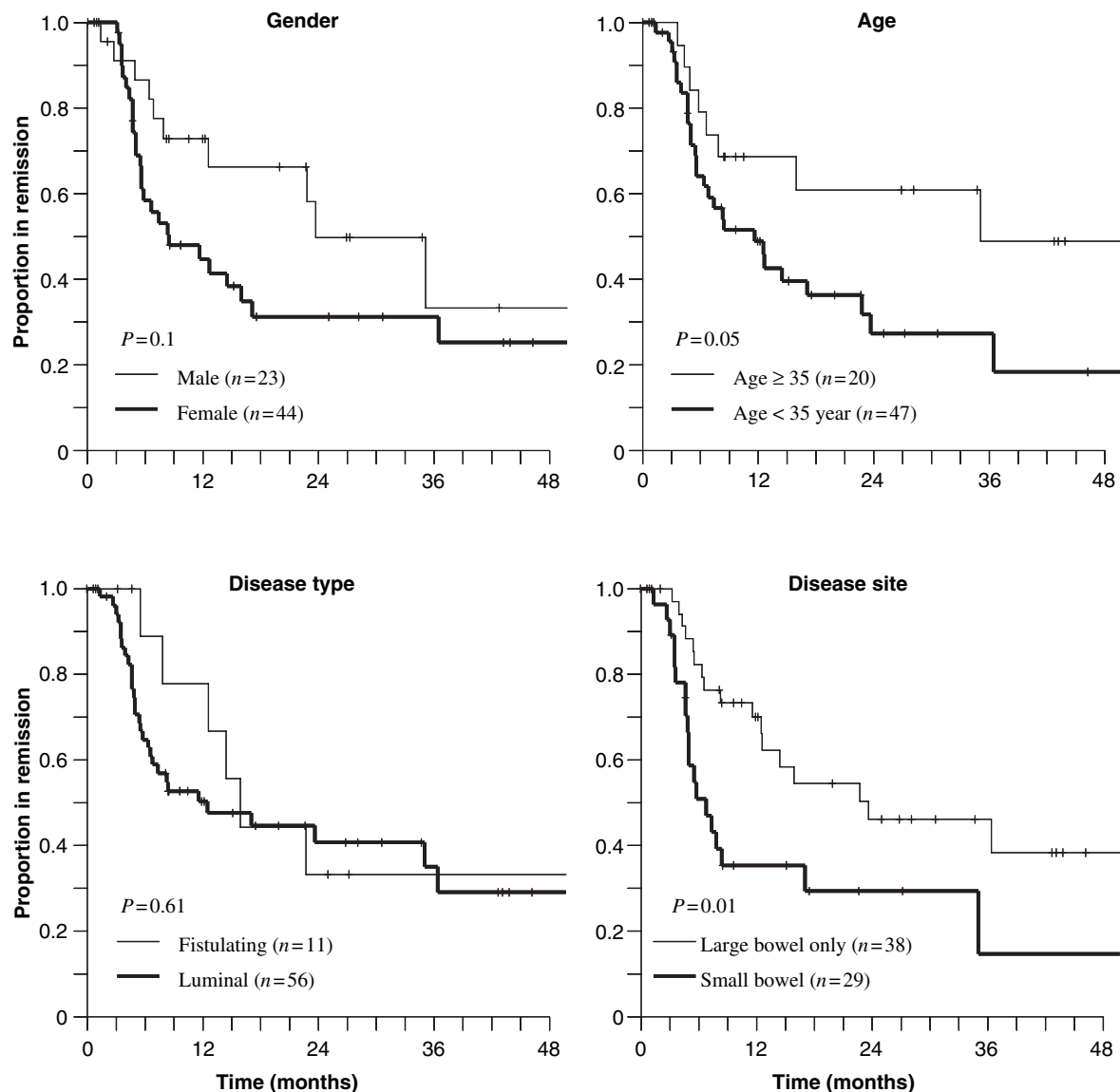


Figure 3. Relapse-free survival following discontinuation of infliximab in 67 patients responding to treatment stratified by gender, age at first infliximab infusion, disease type and disease site.

Table 4. Final regression analysis model of factors associated with subsequent relapse in 67 patients responding to infliximab therapy

Variable	β	S.E. β	Relative risk (95% CI)	P-value
Age*	-0.05	0.02	0.96 (0.92-0.99)	0.01
Small bowel disease	0.81	0.34	2.3 (1.2-4.4)	0.02

S.E., standard error; CI, confidence intervals.

* Age entered as a continuous variable.

ting healing of colonic disease in the absence of a significant small bowel response. Indeed, the presence of small bowel disease was one of only two independent indicators of relapse in the patient population. In addition to the nine patients undergoing surgery, 23 further patients were converted to either on-demand or scheduled treatment. However, none of these patients lost their response to infliximab treatment and it may be that pre-treatment with intravenous hydrocortisone, as recommended by Farrell *et al.*,⁷ prevented unwanted side-effects. The widespread use of immunomodulatory agents may also have benefited our patients, because

Table 5. Demographic, clinical and follow-up data relating to 10 patients not receiving immunomodulatory agents

Case	Age /sex	Indication for infliximab	Infusions	Comments	Immunomodulatory drugs
1	32/F	Perianal fistula	3	Response, no recurrence	Intolerant
2	34/F	Rectovaginal fistula	3	Response, no recurrence	Intolerant
3	26/F	Enterocutaneous fistula	3	Surgery for recurrence	Intolerant
4	28/F	Enterocutaneous fistula/rectal disease	3	Surgery for recurrence	Intolerant
5	33/M	Enterocutaneous fistula/duodenal, ileal disease	3	No response, surgery	Not given
6	26/M	Active gastric, ileal, colonic disease	1	Response, no recurrence	Refused
7	33/F	Active ileal, colonic disease	1	Response, no recurrence	Intolerant
8	24/F	Active ileal, colonic disease	1	Response	Lost to follow-up before azathioprine started
9	42/F	Active ileal, colonic disease	1	No response, surgery	Not given
10	59/M	Active colonic disease	1	No response	Intolerant

Baert *et al.* have clearly shown that immunosuppressive therapy decreases the size of the immunogenic response.⁶ As noted above, small bowel involvement and younger age were the only independent factors predicting relapse following initial remission. The harmful effects of active cigarette smoking on the course of Crohn's disease are well documented⁹⁻¹¹ but we did not find any association between smoking and either initial response to infliximab or subsequent relapse. This finding may indicate that active smoking affects disease severity *per se* rather than modifies a particular patient's response to treatment.

Safety and cost are important aspects of all drug usage. Safety is a major concern when considering the use of biological therapies, but there is little evidence at present to suggest that episodic treatment is any safer than maintenance treatment. Colombel *et al.* reported a 6% incidence of serious adverse events attributable to infliximab in 500 consecutively treated patients.¹² They found that the risk of infectious complications rose as the number of infusions increased. However, it should be noted that the five deaths attributed to infliximab occurred in individuals receiving three or less infusions. A recent Swedish population-based study also recorded a significant number of fatal adverse events,¹³ but again noted that five of six deaths attributed to infliximab occurred after a single infusion and mostly in elderly patients. Our data are similar in so far as the only death in our report was seen after a single treatment in an 82-year-old female. With regard to costs, an episodic regime might reduce

expenditure overall; however, there are many other factors, such as surgery and bed costs in ill patients that must also be taken into account. Jewell *et al.* have attempted to answer this question in the past and showed that infliximab is probably cost-effective when all factors are considered.¹⁴ Drug costs tend to decrease with time and competition and thus should not be used as a major reason for opting for an episodic regime.

What is the value of a clinical outcomes study such as this? The study is uncontrolled and there are potential biases inherent in all observational reports. However, it should be noted that the study was not performed to compare one method of infliximab administration to another, but merely to determine if episodic treatment is feasible. In relation to decision-making within the clinic, we did not use any recognized disease activity score to determine the need for infliximab, initial response to treatment, or relapse following discontinuation. In a clinical trial situation, an objective scoring system is an important aspect of the study, but such systems are actually rarely used for making decisions in clinical practice. This study provides information on the effectiveness of therapy in day-to-day clinical management that might not be extrapolated from tightly structured controlled trials. Overall, the report highlights the effectiveness of infliximab in Crohn's disease given on an episodic basis. It may also help identify individuals who will need infrequent infusions to maintain good health. Such an approach may reduce costs and avoid long-term com-

plications and it seems sensible to incorporate episodic treatment arms into future controlled studies of anti-TNF α therapy in Crohn's disease.

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