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Efficacy, tolerability, and predictors of response to infliximab therapy for Crohn's disease: A large single centre experience

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KEYWORDS
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Abstract

Background: Infliximab is licenced for use in Crohn's disease (CD). Trial data demonstrate that infliximab is effective for inducing remission of active CD, healing fistulising CD, and preventing relapse once in remission. However, long-term data regarding efficacy, safety, and predictors of response are still emerging.
Aim: To examine these issues in a large cohort of patients who received infliximab for CD.
Methods: A retrospective analysis of prospectively collected data was performed for 210 patients receiving infliximab for luminal or fistulising CD. Response to infliximab induction therapy, and sustained clinical benefit, were assessed by a decrease in Harvey–Bradshaw Index (HBI) of $\geq$2 points. Remission was defined as an HBI $\leq$ 4. Physician's global assessment was used where HBI could not be obtained. Demographic and disease factors that may predict response to therapy were analysed by Kaplan–Meier plots and univariate and multivariate analyses.
Results: Overall, 173 (82.4%) patients responded to infliximab induction, with 114 (65.9%) achieving sustained clinical benefit. Almost 40% of the study cohort had an HBI $\leq$ 4, indicating remission, at last point of follow-up (median 24 months). Concomitant immunosuppression predicted sustained clinical benefit in the first 6 months of therapy (P = 0.03). An inflammatory disease phenotype (P = 0.04 univariate analysis, P = 0.03 Kaplan Meier analysis) and male gender (P = 0.03) also predicted sustained clinical benefit. Episodic therapy was associated with an increased likelihood of secondary non-response. Adverse events, including malignancies, were few.
Conclusion: In this single centre study, infliximab was efficacious and well-tolerated in CD.

Abbreviations CRP, C-reactive protein; CD, Crohn's disease; HBI, Harvey–Bradshaw index; IBD, Inflammatory bowel disease; IBS, Irritable bowel syndrome; IQR, Interquartile range.

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1. Introduction

Infliximab (Remicade®, Centocor Ortho Biotech Inc, Pennsylvania, USA) is a monoclonal IgG_1 antibody against tumour necrosis factor alpha, and is licenced for the treatment of severe luminal and fistulising Crohn's disease (CD). Studies have demonstrated that infliximab is more effective than placebo at inducing remission of active CD, healing fistulising CD, and preventing relapse once remission is achieved.[1–3] Several studies have also demonstrated that infliximab therapy decreases hospitalisation and surgery for CD patients,[4–6] and may, despite its relative expense, reduce the costs of care associated with the disease.[6]

Long-term clinical data from large patient cohorts, with regard to continued efficacy, remission, and tolerability are scarce,[7,8] as are studies reporting patient factors that may predict response to infliximab therapy. Data concerning the long-term safety of biological therapies, particularly in the context of combined immunosuppression, are also limited, with few studies reporting safety data out to several years of therapy.[9–11] This is an important issue as the recent SONIC study has demonstrated that patients receiving infliximab with concomitant immunomodulators are more likely to respond to induction therapy, and to be maintained in remission at 26 weeks, compared with infliximab given as monotherapy.[12]

In our tertiary referral centre for inflammatory bowel diseases (IBD), over 200 patients have received infliximab therapy for either luminal or fistulising CD. Due to prospective collection of data for each patient at commencement of infliximab, and during continued long-term therapy thereafter, we are able to accurately estimate the efficacy, tolerability, and safety of infliximab therapy, as well as examine factors that may predict response, in a large cohort of CD patients.

2. Materials and methods

2.1. Participants and setting

The IBD Clinic at the Leeds General Infirmary, Leeds, UK has been treating CD patients with infliximab therapy since 2000. This is a large teaching hospital in a city in the North of England, with a population of approximately 800,000, which also receives tertiary referrals from other centres. Once patients are initiated on treatment they are monitored at regular intervals during therapy by a team of specialist inflammatory bowel disease nurses.

Patients included in this study received infliximab therapy either episodically, or as scheduled maintenance therapy. Episodic therapy was defined as a single infusion of infliximab at induction, followed by further infusions if necessary, upon recurrence of symptoms. Scheduled therapy with infliximab was defined as a three-dose infliximab induction regimen at 0, 2, and 6 weeks, followed by regular 8-weekly infusions thereafter. Patients who were not receiving concomitant immunomodulators were routinely pre-medicated with intravenous hydrocortisone with each infliximab infusion. During the follow-up period of the study, some patients were switched from one treatment regimen to the other.

During the initial induction phase, patients received either a single-dose or three-dose induction of infliximab, administered by an IBD nurse specialist at the Leeds Immune Mediated Inflammatory Diseases Unit. Patients were assessed by the attending physician at a subsequent outpatient visit to determine whether infliximab was to be continued, and which treatment regimen to follow.

2.2. Data collection

All data were collected prospectively and analysed retrospectively by the authors. Demographic data included: sex, disease duration prior to infliximab therapy, smoking status, Montreal classification (age at diagnosis of CD, disease location and phenotype, presence of fistulae and type of fistula), and a history of major abdominal surgery (defined as any intestinal resection related to CD). On commencement of infliximab therapy, data concerning the type of induction regimen used, Harvey Bradshaw indices (HBI), C-reactive protein (CRP) levels, concomitant immunomodulator or corticosteroid use, dose escalation of infliximab to 10 mg/kg, or reduction in interval of dosing to 6 weekly infusions to help maintain or recapture response, requirement for subsequent surgery, and adverse events, including infusion reactions, delayed hypersensitivity to infliximab, opportunistic infections, and mortality were recorded.

2.3. Definitions of response and remission

Response to infliximab was determined following the three-dose induction (i.e. following week 6 of therapy) for the patients on scheduled therapy, and within 6 weeks post-infusion following single-dose induction. Response was defined by a decrease in HBI of $\geq$2 points from baseline, with remission defined using an HBI of $\leq$4, or using a physician's global assessment in those patients where HBI could not be recorded due to the presence of a stoma, or where data were incomplete or unavailable. Primary non-response to infliximab therapy was defined as failure to achieve a $\geq$2 point decrease in HBI, or satisfy a physician's global assessment that response had been achieved, following induction therapy as described above. Infliximab was discontinued in all primary non-responders. Sustained clinical benefit with infliximab during continuing therapy, was also defined using a decrease in HBI $\geq$2 points from baseline, or satisfying a physician's global assessment that continued benefit was achieved, where HBI data were not available. Remission was defined as an HBI of $\leq$4 at the last point of follow-up. Secondary non-response to infliximab therapy was defined according to a physician's global assessment of relapse of disease activity, including the need for rescue therapy with corticosteroids or an alternative biological therapy, or surgery, during continued treatment in all patients who had responded to initial infliximab induction therapy.

2.4. Statistical analysis

Continuous data were analysed using medians with an interquartile range (IQR). All categorical data were compared between groups of patients using the Pearson χ^2 statistic. The proportion of patients experiencing response

after single or three-dose infliximab induction therapy, and sustained clinical benefit with either episodic or 8-weekly infusions at last point of follow-up were calculated. The association between demographic data, lifestyle factors, disease characteristics, concomitant medications, and the likelihood of achieving response or sustained clinical benefit were explored with univariate and multivariate analyses using Cox regression, and Kaplan Meier survival analysis with comparison of hazard ratios using the LogRank test. Factors influencing time to loss of response to infliximab therapy were analysed using the Fisher exact test with calculation of odds ratios with 95% confidence intervals (CI). All statistical analyses were performed using SPSS for Windows version 14.0 (SPSS Inc, Chicago, Illinois, USA).

3. Results

In total, 210 patients received infliximab therapy, between the years 2000 and 2010, with a median follow-up of 24 months (IQR 7–48 months). This represents approximately 10% of the entire cohort of CD patients under follow-up in our centre. Individual patient characteristics are provided in Table 1. Twenty-two patients had a stoma at the time of infliximab commencement, and therefore did not have HBI data recorded. Forty-seven (22.4%) patients received a single-dose of infliximab as induction therapy with episodic infusions thereafter, with a median duration of follow-up of 52 months (IQR 28–79.5 months), and 163 patients commenced infliximab as scheduled 8-weekly therapy following three-dose induction, with a median duration of follow-up of 17 months (IQR 5–37 months). There were a total of 3165 infliximab infusions administered with a median of 12 infusions (IQR 4–22 infusions) per patient.

Table 1 Characteristics of 210 involved individuals on commencement of infliximab.

Female sex (%)	124 (59.0)
Median age at diagnosis in years (IQR)	23 (19–32.75)
Median duration of disease pre infliximab in months (IQR)	72 (36–156)
Principal indication for therapy (%)	
Luminal	135 (64.3)
Fistulising	75 (35.7)
Montreal classification (%)	
A1	37 (17.6)
A2	141 (67.2)
A3	32 (15.2)
B1	149 (71.0)
B2	40 (19.0)
B3	21 (10.0)
L1	31 (14.7)
L2	72 (34.3)
L3	107 (51.0)
L4 modifier	5 (2.4)
P modifier	70 (33.3)
Current smoker (%)	55 (26.2)
Previous Crohn's-related surgery (%)	131 (62.4)
Major abdominal surgery (%)	99 (47.1)
Examination under anaesthesia (%)	43 (20.5)
>1 surgical intervention (%)	70 (33.3)

Of the 47 patients who received a single infusion of infliximab as induction therapy, five (10.6%) discontinued therapy during the induction phase. Of these, two were primary non-responders, two experienced intolerable adverse events, and one discontinued for other reasons. The remaining 42 patients had a response to single-dose infliximab induction. Of these, only five (10.6%) patients continued with episodic therapy throughout the entire study period, receiving a total of 73 infusions (median 11 (IQR 8–19) infusions per patient). The other 37 (78.7%) patients who had a response to single-dose infliximab induction were switched to scheduled 8-weekly therapy in an attempt to achieve or maintain sustained clinical benefit, receiving a total of 903 infusions (median 22 (IQR 16–37) infusions per patient).

Of the 163 patients that received three-dose induction therapy, 32 (19.6%) discontinued during the induction phase. Of these, 16 were primary non-responders, eight experienced intolerable adverse events, and eight discontinued for other reasons.

Five (3.1%) of the 131 patients who had successful three-dose induction (3.1%) switched to episodic therapy, receiving a total of 106 infusions, (median 23 (IQR 14–27) infusions per patient). The remaining 126 (77.3%) patients went on to receive scheduled 8-weekly therapy throughout the study period, receiving a total of 1988 infusions, (median 13 (IQR 7–23) infusions per patient).

3.1. Response to infliximab induction therapy

One hundred and seventy-three (82.4%) patients had a response to induction therapy with infliximab, as determined by HBI and/or a physician's global assessment (Fig. 1). Harvey–Bradshaw indices were available in 104 (60.1%) of these 173 responders, both at baseline and following infliximab induction therapy. Data were unavailable for 49 patients, and HBI were not appropriate in a further 20 patients due to the presence of a stoma. Median HBI pre-infliximab in responders was 8.0 (IQR 6.0–11.75), compared with 3.5 (IQR 2.0–5.0) following induction therapy ($P \leq 0.001$). C-reactive protein levels were also available in 136 (78.6%) responders both at baseline and following induction therapy with infliximab, with a median CRP of 18.4 mg/l (IQR 2.5–47.0) pre-infliximab compared with 2.5 mg/l (IQR 2.5–8.2) after induction ($P \leq 0.001$). Ninety-nine (57.2%) patients had an elevated CRP (defined as $\geq$5 mg/l at baseline), and 65 (65.7%) of these had normalisation of the CRP following induction therapy. Univariate and multivariate analysis of factors influencing response to infliximab induction are provided in Table 2. In multivariate analyses, there was a significantly higher likelihood of failure to respond to infliximab induction if treated with three-dose induction therapy ($P = 0.02$), and a significantly lower likelihood of failure with an inflammatory phenotype ($P = 0.03$), and in patients of male gender ($P = 0.006$).

There were a total of 18 (8.6%) patients who were primary non-responders to infliximab therapy (following a median of 2 infusions per patient). These patients discontinued infliximab therapy. Outcomes in these patients included

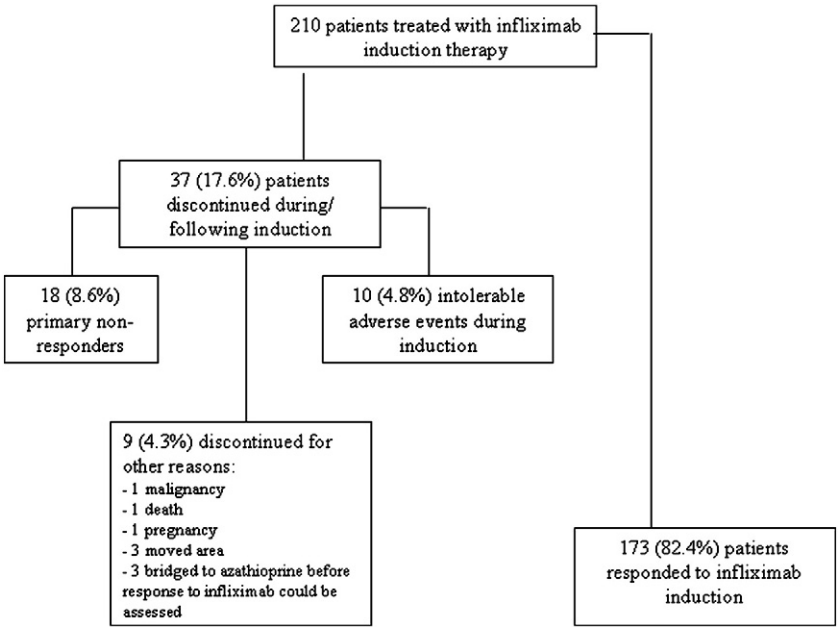

Figure 1 Response to infliximab induction therapy.

switching to a second biologic (adalimumab) in seven (38.9%), intestinal resection in six (33.3%), recommencement of previous therapy in four (22.2%) and switching to methotrexate in one. Harvey–Bradshaw indices were available in 15 primary non-responders, both at baseline and following induction therapy, with a median HBI of 7 (IQR 5.5–13) pre-infliximab and 9 (IQR 4.5–14) post-induction therapy (P=0.93). C-reactive protein levels were obtained in all 18 primary non-responders at baseline and following induction therapy, with a median CRP of 13.1 mg/l (IQR 2.5–29.0) pre-infliximab and 11.3 mg/l (IQR 2.5–58) post (P=0.46). A further 10 (4.8%) patients discontinued infliximab therapy during induction due to intolerable adverse events, and could not be classified as responders or non-responders. Five (50%) of these patients subsequently received adalimumab therapy, four (40%) were observed, and one (10%) required intestinal resection. Finally, nine patients discontinued infliximab following induction therapy for other reasons, which included three receiving induction therapy as a bridge to azathioprine, three moving out of the area, one patient being diagnosed with malignancy, one death (unrelated to infliximab), and one pregnancy.

3.2. Sustained clinical benefit with infliximab

At the last point of follow-up in August 2010, 114 (54.3%) of 210 patients had experienced sustained clinical benefit with infliximab as determined by HBI, or a physician's global assessment of continued improvement in symptoms (Fig. 2). Median duration of follow-up for patients with sustained clinical benefit was 33.5 months (IQR 17–57). Fifteen (8.7%) of these patients were no longer receiving infliximab therapy, but were in clinical remission following cessation of the drug, and were classed as having experienced sustained benefit with infliximab. Twelve of these patients were subsequently maintained successfully with azathioprine. Univariate and multivariate analyses of factors influencing sustained clinical benefit, according to patient characteristics, are provided in Table 3, and out to 60 months of therapy by Kaplan Meier survival analyses (Fig. 3). There was a significantly lower likelihood of failure to achieve sustained clinical benefit to infliximab in patients of male gender (P=0.03 for multivariate analysis), and with an inflammatory phenotype (P=0.04 for univariate analysis, and P=0.03 LogRank test with Kaplan Meier survival analysis).

Harvey–Bradshaw indices were available at the last point of follow-up in 99 patients with sustained clinical benefit, as 15 patients had a stoma, with a median HBI of 3 (IQR 2–5). Of these 99 patients, 74 (74.7%) had a score of ≤4, indicating clinical remission (median follow-up of 31.50, IQR 15.25–52.0). Therefore of the total cohort, of 188 patients where HBI could be recorded, 39.4% had an HBI ≤4 at the last point of follow-up. Eighteen (18.1%) of the 99 patients still receiving infliximab required a reduction in the infusion interval, and a further three required a single dose escalation of infliximab to 10 mg/kg, to maintain a sustained clinical benefit.

There were 32 (15.2%) patients who received infliximab therapy within the first 12 months of diagnosis with CD, with a median follow-up of 17.5 months (IQR 5–43 months). There was less likelihood of failing to achieve a sustained clinical benefit if infliximab was commenced within the first 12 months of diagnosis (Hazard ratio 0.81), however this did not reach statistical significance (P=0.22, LogRank test).

3.3. Discontinuation of infliximab therapy

Fifty-nine (34.1%) patients who had initially responded to infliximab induction subsequently discontinued therapy (Fig. 2). Of these, 41 (25.2%) of 163 patients who had received scheduled 8-weekly infliximab therapy as the initial regimen

Table 2 Factors predicting failure to respond to infliximab therapy.

Characteristic	Univariate			Multivariate		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Main indication						
Luminal	1.0					
Fistulising	0.68	0.32–1.36	0.26	1.07	0.48–2.41	0.86
Disease duration pre-infliximab						
≤3 yr	1.0					
>3 yr	0.77	0.39–1.49	0.43	0.64	0.30–1.33	0.23
Disease phenotype						
Stricturing/penetrating	1.0					
Inflammatory	0.55	0.28–1.06	0.07	0.42	0.20–0.90	0.03
Infliximab induction regimen						
Single-dose	1.0					
Scheduled three-dose	9.7	1.33–70.90	0.03	10.76	1.47–78.58	0.02
Concomitant immunomodulator						
No	1.0					
Yes	0.73	0.38–1.42	0.35	0.76	0.39–1.49	0.43
Concomitant corticosteroids						
No	1.0					
Yes	1.67	0.87–3.19	0.12	1.67	0.82–3.41	0.16
Previous major abdominal surgery						
No	1.0					
Yes	1.05	0.55–2.01	0.87	0.72	0.33–1.58	0.42
Smoker						
No	1.0					
Yes	0.49	0.23–1.07	0.08	0.57	0.47–1.13	0.12
Gender						
Female	1.0					
Male	0.37	0.17–0.80	0.01	0.34	0.15–0.74	0.006
CRP						
<5	1.0					
≥5	0.70	0.36–1.39	0.31	0.71	0.03–1.62	0.98

discontinued therapy, compared with 18 (38.3%) of 47 patients who received episodic therapy initially (P=0.08). There were 32 (18.5%) secondary non-responders to therapy. Of these, 14 had received infliximab episodically initially, and 18 received 8-weekly scheduled therapy. A reduction in the infusion interval was attempted in 10 (31.3%), and a dose escalation in seven (21.9%) of these secondary non-responders to try and recapture response, but these measures were unsuccessful. The remaining 15 (46.9%) patients with secondary non-response were either given corticosteroids, an alternative biological therapy, or underwent surgery. Outcomes in the 32 secondary non-responders included switching to a second biologic (adalimumab) in 15 (46.9%), intestinal resection in 13 (40.6%), and recommencement of previous therapy in four (12.5%). Of the remaining 27 patients, 18 (10.4%) experienced intolerable adverse events requiring discontinuation of infliximab therapy, and nine (5.2%) patients discontinued therapy for other reasons including a diagnosis of malignancy, opportunistic infection, and moving out of the area.

Patients were significantly more likely to experience secondary non-response to infliximab if treated with single-dose at induction and subsequent episodic therapy (OR 3.14, 95% CI 1.41 to 7.01, P=0.01) and the time to loss of response occurred sooner if the patient had a stricturing or penetrating disease phenotype, compared with an inflammatory phenotype (median of 2 months (IQR 1–19.5 months) versus 22 months (IQR 4.5–47 months), P=0.007). Other patient characteristics, such as sex, age at diagnosis, duration of disease pre-infliximab, smoking history, and history of previous surgery did not appear to influence the time to loss of response.

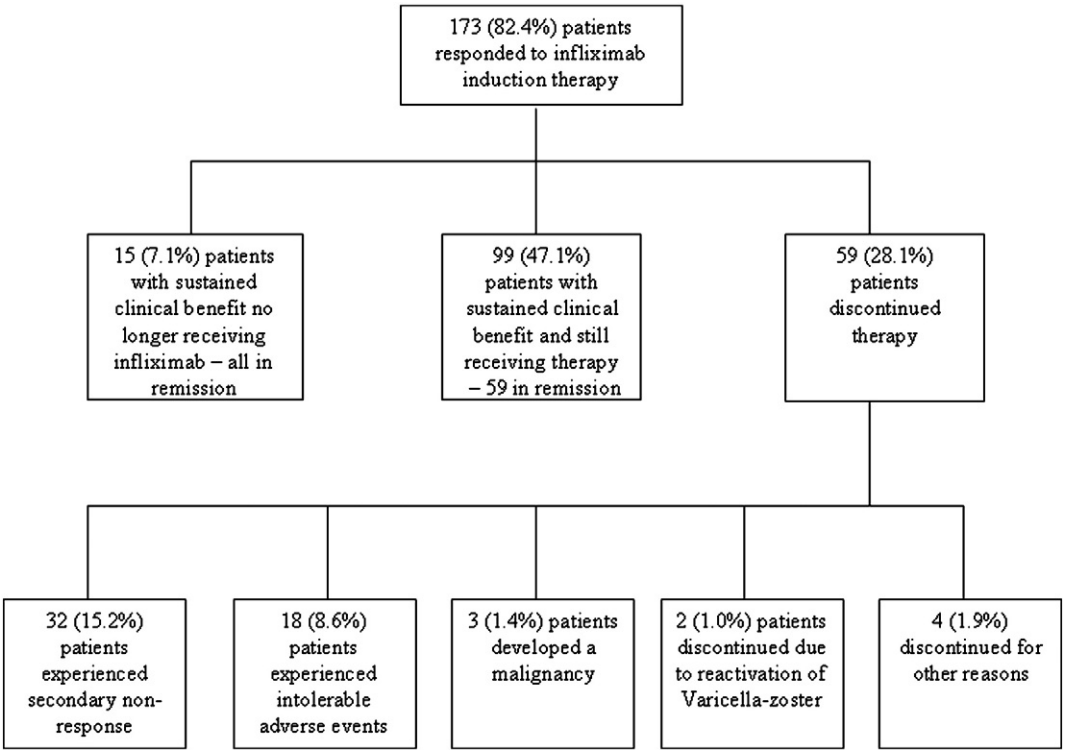

Figure 2 Sustained clinical benefit with infliximab.

3.4. Concomitant immunomodulator therapy

One hundred and forty-six (69.5%) patients were receiving concomitant immunomodulator therapy on commencement of infliximab: 114 azathioprine, 26 methotrexate, four mercaptopurine, and two mycophenolate mofetil. Overall, there was no significant difference in sustained clinical benefit between the patient groups receiving concomitant immunomodulator therapy, compared with those not taking immunomodulators ($P=0.19$ LogRank test). However, in the first 6 months of infliximab therapy, patients were significantly more likely to have sustained clinical benefit with infliximab if taking concomitant immunomodulator therapy ($P=0.03$ LogRank test), an effect that appeared to attenuate with time (Fig. 4).

3.5. Corticosteroid-sparing effects of infliximab

Eighty-seven (41.4%) patients were receiving corticosteroids upon commencement of infliximab therapy. Sixty-six (75.9%) of these individuals were no longer receiving corticosteroid therapy at the last point of follow-up. There was no difference in the ability to discontinue corticosteroids between scheduled and episodic groups ($P=0.68$). Receiving corticosteroids at commencement of infliximab therapy had no significant effect on likelihood of sustained clinical benefit.

3.6. Adverse events during treatment with infliximab

Overall, 59 (28.1%) patients experienced an adverse event associated with infliximab therapy during either infliximab induction or during continuing therapy. Of these, 33 patients permanently discontinued infliximab. Thirty-five (16.7%) patients experienced an infusion or hypersensitivity reaction to infliximab. Twenty-three patients had a reaction during the infusion, with eight discontinuing therapy as a result. Of the remaining patients who suffered reactions during the infliximab infusion that did not require cessation of therapy, the symptoms included, breathlessness and wheezing, maculopapular skin rashes, headaches, and hypotension. In all cases, infliximab was temporarily suspended and recommenced at a slower infusion rate during the same visit, with careful monitoring. Twelve patients experienced hypersensitivity reactions to infliximab, all of them discontinuing therapy, and seven (3.3%) patients discontinued therapy due to the development of various psoriatiform skin rashes.

Opportunistic infections were rare. Fourteen (6.7%) infections were attributed to infliximab therapy, seven of which were reactivation of *Varicella zoster* in patients who had all previously been exposed to the virus. One UK-born White Caucasian male patient developed pulmonary tuberculosis (TB). He had not previously had TB exposure, infection, or contacts and had a clear chest X-ray on commencement of therapy. In this case infliximab was discontinued and the patient received 6 months of anti-tuberculous therapy. Other opportunistic infections included gastroenteritis secondary to cryptosporidium, recurrent chest infection, and cutaneous abscess formation.

There were two deaths during the follow-up period. One was due to a spindle cell myxoma, with other clinical features suggestive of lymphoma, and was therefore considered to be attributable to infliximab therapy. The patient received a total of 13 infusions over a 20 month period. The other death was due to a cerebral haemorrhage, which occurred following

Table 3 Factors predicting failure to achieve sustained clinical benefit to infliximab therapy.

Characteristic	Univariate			Multivariate		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Main indication						
Luminal	1.0					
Fistulising	0.94	0.61–1.44	0.76	1.2	0.68–2.13	0.52
Disease duration pre-infliximab						
≤3 yr	1.0					
>3 yr	1.06	0.68–1.67	0.79	0.94	0.49–1.79	0.85
Disease phenotype						
Stricturing/penetrating	1.0					
Inflammatory	0.63	0.41–0.97	0.04	0.69	0.48–1.06	0.09
Infliximab regimen						
Episodic	1.0					
Scheduled 8-weekly	1.52	0.90–2.57	0.12	1.05	0.57–1.94	0.87
Concomitant immunomodulator						
No	1.0					
Yes	0.75	0.49–1.16	0.20	0.78	0.44–1.38	0.39
Concomitant corticosteroids						
No	1.0					
Yes	1.25	0.83–1.91	0.29	1.28	0.70–2.35	0.43
Previous major abdominal surgery						
No	1.0					
Yes	1.21	0.8–1.84	0.36	1.22	0.66–2.25	0.52
Smoker						
No	1.0					
Yes	0.88	0.57–1.36	0.56	1.25	0.70–2.24	0.45
Gender						
Female	1.0					
Male	0.47	0.30–0.74	0.001	0.49	0.31–0.78	0.03
CRP						
<5	1.0					
≥5	0.88	0.55–1.40	0.58	0.84	0.49–1.53	0.57

a head injury, and was therefore not attributable to infliximab therapy. A further two cancers were also diagnosed, one a mucinous adenocarcinoma in an entero-vaginal fistula diagnosed after just two infliximab infusions, and therefore likely to have been present prior to commencement of infliximab, despite a negative biopsy prior to therapy, and secondly a renal cell carcinoma, diagnosed after 27 infusions during a 42 month period. The patient successfully underwent partial nephrectomy of the right kidney.

Overall, 26 (44.1%) patients who experienced an adverse event to infliximab were receiving concomitant immunomodulator therapy at the time of the event. Patients were significantly more likely to experience an adverse event if not on concomitant immunosuppression ($P<0.001$, OR 4.91, 95% CI 2.58–9.36). There was no significant difference in adverse events when comparing episodic versus scheduled therapy ($P=0.62$).

4. Discussion

Real-life data with regard to clinical efficacy of infliximab, and predictors of long term sustained benefit, are still emerging. In this single centre study, we have demonstrated an initial response to infliximab induction therapy in more than 80%, and a sustained clinical benefit in approximately 50% of patients. In addition, almost 40% achieved an HBI ≤4 at the last point of follow-up, indicating remission. Corticosteroid-sparing effects of infliximab were also apparent, with 75% of the study cohort who were receiving corticosteroids at the time infliximab was

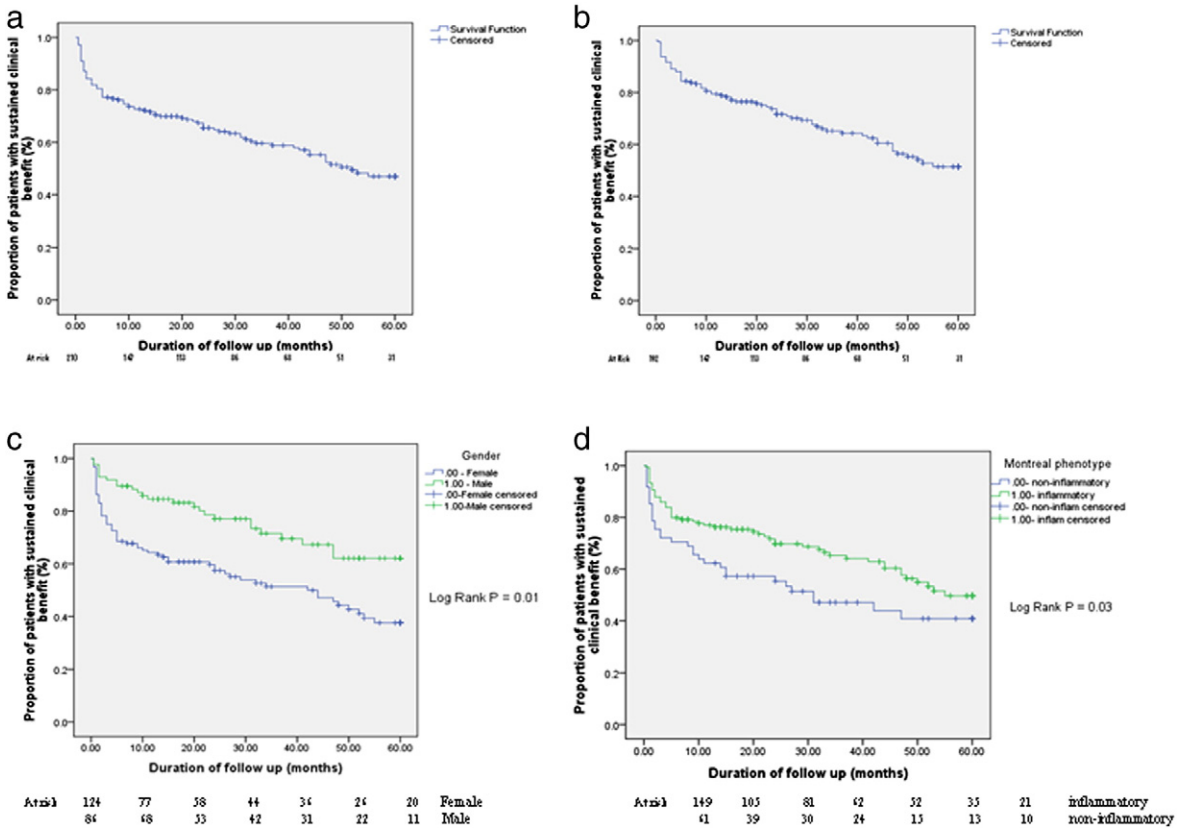

Figure 3 Kaplan Meier survival plots showing sustained clinical benefit to infliximab according to patient characteristics; (a) sustained clinical benefit: entire cohort (b) sustained clinical benefit excluding primary non-response (c) sustained clinical benefit according to gender (d) sustained clinical benefit according to Montreal disease phenotype.

commenced being able to discontinue these at the last point of follow-up. Intolerable adverse events were experienced by approximately 16% of the study cohort, and there was one malignancy leading to death, which may have been attributable to infliximab therapy.

We identified some predictors of long-term sustained clinical benefit among our cohort of patients. All of the 210 patients included in the study, had their disease phenotype recorded according to the Montreal classification,[13] and patients with inflammatory disease did significantly better, with regard to sustained clinical benefit, than those with stricturing or penetrating disease in both the univariate and Kaplan Meier analyses. Although, intuitively, this is not surprising, it perhaps indicates that patients with less inflammation may need consideration of alternative treatment options, such as surgery or endoscopic dilatation, prior to the initiation of infliximab, and that routine recording of the Montreal classification could help to guide this decision.

It is unclear why males had a significantly lower likelihood of both failure to respond to infliximab induction therapy and failure to achieve sustained clinical benefit. The majority of females who discontinued therapy, did so within the first 6 months following infliximab initiation, and the number of cases that discontinued each year subsequent to this, were similar for both males and females. This may represent incorrect patient selection at the time of commencement of infliximab, or reflect the fact that functional disorders, such as irritable bowel syndrome (IBS), which may mimic ongoing activity in CD,[14] are more prevalent in the female population in general.[15,16] However, as data concerning IBS-type symptoms were not collected as part of this study, this is speculative.

With regard to immunomodulator drugs, there were significantly higher rates of sustained clinical benefit in patients receiving concomitant immunosuppression upon commencement of infliximab, although this effect was only observed up to 6 months of therapy. Data from a recent randomised controlled trial[17] demonstrated that withdrawal of immunosuppression at 6 months in patients receiving combined biological and immunosuppressive therapy did not appear to affect efficacy of biological therapy at 2 years of follow-up, and our data support this. As combination therapy with both immunomodulators and biologics may be associated with the development of hepatosplenic T-cell lymphoma,[18] the ability to withdraw immunosuppression without affecting efficacy of biological therapy is an important issue.

There was also a significantly higher likelihood of failure to respond to infliximab induction if treated with three-dose induction, rather than single-dose induction. This may relate to patients with more severe disease activity receiving three-dose, rather than single-dose, induction prior to standardised induction therapy in our centre, although this initial difference in response did not translate into a significant difference in rates of sustained clinical benefit. In addition, the majority of the episodically treated patients subsequently required a switch to scheduled 8-weekly therapy to maintain a sustained clinical benefit with

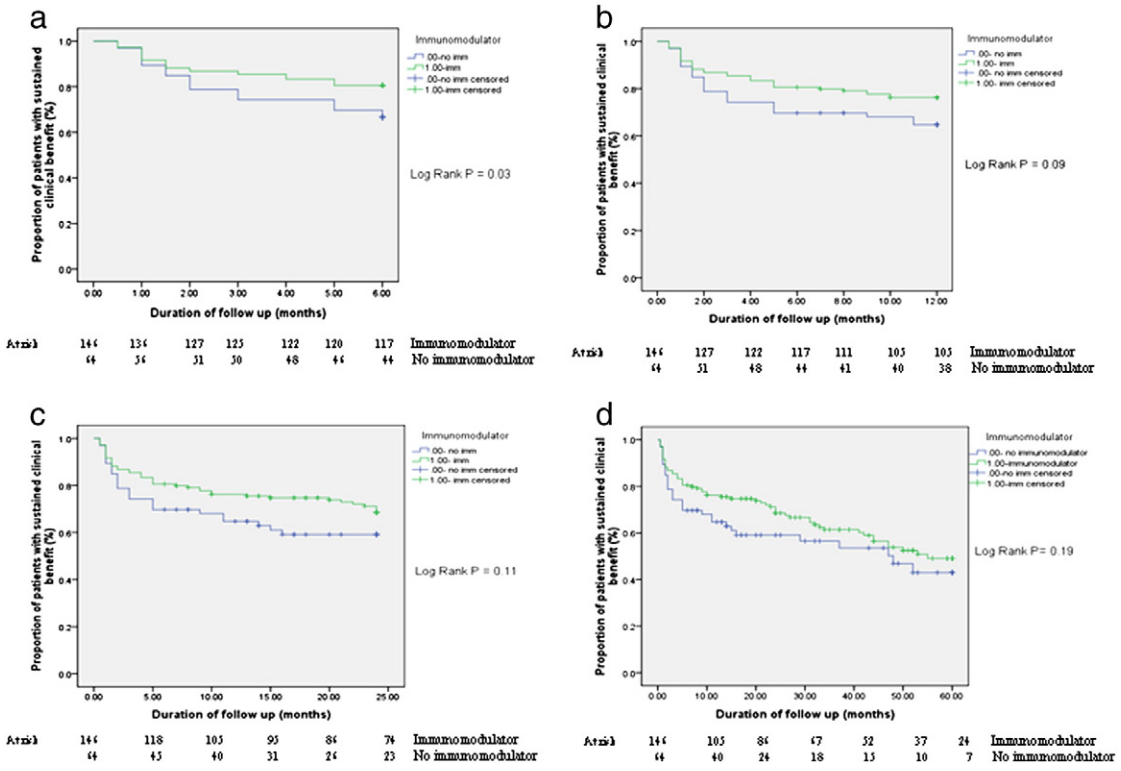

Figure 4 Sustained clinical benefit according to infliximab according to duration of immunomodulator therapy; (a) at 6 months (b) at 12 months (c) at 24 months (d) at 60 months.

infliximab, and were ultimately more likely to experience secondary non-response to infliximab, arguing against this as an effective therapeutic regimen.

Strengths of this study include prospective data collection, with the inclusion of a large number of patients from a single centre tertiary referral centre. The median duration of follow-up was 24 months for the entire study cohort, and 33.5 months for patients with sustained clinical benefit, and data were collected from over 200 patients treated with infliximab, making this study the largest UK experience, to date, in terms of patient numbers and duration of follow-up. The collection of HBI scores at baseline, following induction therapy, and at the last point of follow-up augments the validity of the physician's global assessment and is therefore a further study strength. Weaknesses include the fact the study was conducted entirely in a tertiary referral centre, meaning that the results may not be generalisable to patients receiving infliximab in the secondary care setting. Despite prospective data collection, the retrospective nature of the study meant that we were unable to collect HBI data for some patients during follow-up, and due to the broad characteristics of the patient population, which included individuals with isolated small bowel and peri-anal Crohn's disease, mucosal healing was not assessed routinely. Finally, as the clinician's utilisation of biological therapy has evolved over the years, particularly with respect to initiating therapy in a scheduled regimen as opposed to episodically, and earlier and more aggressive patient selection for biological therapy, the characteristics of the patient cohort may have altered over time due to the long duration of data collection.

There are other published studies, including the large observational cohort from Leuven, that describe the long-term benefits of infliximab in adult CD patients.[8,19–24] However, the majority of these are limited by relatively modest numbers of study participants, retrospective data collection, no analysis of potential predictors of response, and no objective assessment of either response or remission. In other studies that have evaluated predictors of response to infliximab therapy it is interesting to note that there are similarities to the data presented here. For instance, we have reported that patients are more likely to experience secondary non-response to infliximab if treated episodically, with Gonzaga et al.[20] also demonstrating that patients were significantly more likely to discontinue therapy if treated episodically. Concomitant immunomodulator therapy has also been shown, in clinical cohorts, to be associated with maintaining a longer response to infliximab.[19,22]

The data from this study are important, particularly with respect to considering when to stop infliximab therapy. Recent guidance in the UK from the National Institute for Health and Clinical Excellence,[25] has recommended that all new patients receiving biological therapy should have the efficacy of treatment reviewed after 12 months of therapy and that, if clinical remission has been achieved, withdrawal of therapy should be considered. We have demonstrated that the efficacy of infliximab is much more durable than 12 months, which raises the possibility that withdrawal of infliximab at this time point may be too soon. Indeed, the majority of patients who received infliximab episodically, who were effectively having infliximab therapy withdrawn after each infusion, required a switch to

scheduled 8-weekly therapy to help prevent relapse and achieve, or maintain, a clinical response. Furthermore, a recent study has demonstrated that 50% of patients had a disease relapse within 500 days following cessation of infliximab therapy.[7] Reintroduction of infliximab therapy upon relapse may be successful in recapturing response or remission, at least in the short-term,[26] but long-term data regarding this strategy are still emerging.

Overall, we have demonstrated an excellent response to induction therapy and sustained clinical benefit with infliximab therapy in a large tertiary referral centre mirroring real-life clinical practise. We have highlighted that the majority of patients who commenced infliximab episodically required escalation to scheduled therapy to maintain response or achieve sustained clinical benefit, and that these patients were ultimately more likely to experience secondary non-response to infliximab. Patients were more likely to achieve sustained clinical benefit if they had inflammatory disease upon commencement of infliximab therapy, and also appeared to do better if concomitant immunomodulator therapy was used. We have also demonstrated a good safety profile with infliximab, even in patients receiving concomitant immunosuppression. Decisions regarding withdrawal of biological therapy need further evaluation, in particular the clinical consequences of such strategies in the longer-term management of CD patients.

Competing interests

Dr John Hamlin has participated on advisory boards for Schering-Plough/MSD pharmaceuticals.

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