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Efficacy and safety of short-term adalimumab treatment in patients with active Crohn's disease who lost response or showed intolerance to infliximab: a prospective, open-label, multicentre trial

J. HINOJOSA*, F. GOMOLLÓN†, S. GARCÍA‡, G. BASTIDA§, J. L. CABRIADA¶, C. SARO**, D. CEBALLOS††, M. PEÑATE‡‡ & M. A. GASSULL§§ ON BEHALF OF GETECCU GRUPO ESPAÑOL DE TRABAJO PARA EL ESTUDIO DE E. CROHN Y COLITIS ULCEROSA (SPANISH SCIENTIFIC GROUP ON CROHN'S DISEASE AND ULCERATIVE COLITIS)

*Hospital de Sagunto, Valencia; †Hospital Clínico Lozano Blesa, Zaragoza; ‡Hospital Miguel Servet, Zaragoza; §Hospital La Fe de Valencia, Valencia; ¶Hospital de Galdakao, Vizcaya; **Hospital de Cabueñes, Gijón; ††Hospital de G Canaria Dr Negrín, Las Palmas; ‡‡Hospital Insular, Las Palmas; §§Hospital German Trías y Pujol, Badalona, Spain

Correspondence to:
Dr J. Hinojosa, Gastroenterology Unit (Coloproctology Clinic), Hospital de Sagunto, Puerto de Sagunto, 46520 Sagunto, Valencia, Spain.
E-mail: jhinojosad@gmail.com

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SUMMARY

Background
The use of tumour necrosis factor antagonists has changed the therapeutic approach to Crohn's disease.

Aim
To determine response and remission rates associated with the 4-week induction phase of adalimumab treatment in patients with luminal and/or fistulizing Crohn's disease, who have lost response to or become intolerant of infliximab.

Methods
In this multicentre, prospective, open-label, observational, 52-week study, 50 adults received an induction dose of adalimumab (160 mg at baseline followed by 80 mg at week 2).

Results
Of the 36 patients with luminal Crohn's disease, 83% achieved clinical response [≥70-point reduction in the Crohn's Disease Activity Index (CDAI) score] and 42% achieved clinical remission (CDAI score <150) at week 4. Of the 22 patients with fistulizing disease, five (23%) experienced fistula remission (complete closure of all fistulas that were draining at baseline), and nine (41%) experienced fistula improvement (≥50% decrease in the number of fistulas that were draining at baseline) at week 4. Of the 19 adverse events, most [13 (68%)] were mild, and no serious or infectious adverse events occurred.

Conclusions
Adalimumab may be an effective alternative in patients with luminal and/or fistulizing Crohn's disease who have lost response to or become intolerant of infliximab.

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Table 1. Baseline demographic and clinical characteristics

Characteristic	All patients ($n = 50$)	Fistulizing Crohn's disease* ($n = 22$)	Luminal Crohn's disease† (CDAI ≥220; $n = 36$)
Age (years, mean ± s.d.)	37.4 ± 10.4	36.3 ± 9.1	37.8 ± 11.0
Disease duration (years, mean ± s.d.)	9.9 ± 5.7	9.7 ± 6.5	9.7 ± 5.2
Baseline CDAI score (mean ± s.d.)	268 ± 101	205 ± 97.2	314 ± 65.5
Sex, *n* (%)			
Females	32 (64)	14 (64)	25 (69)
Males	18 (36)	8 (36)	11 (31)
Smoking status, *n* (%)			
Smokers	21 (42)	9 (41)	14 (39)
Former smokers	17 (34)	6 (27)	14 (39)
Non-smokers	12 (24)	7 (32)	8 (22)
Prior Crohn's-related surgery, *n* (%)	30 (60)	14 (64)	20 (56)
Location of disease (>1 location possible), *n* (%)			
Ileum	8 (16)	4 (18)	7 (19)
Ileocolon	29 (58)	11 (50)	21 (58)
Colon	17 (34)	11 (50)	13 (36)
Gastroduodenal	1 (2)	0	1 (3)
Other	8 (16)	4 (18)	3 (8)
Crohn's-related concomitant medications, *n* (%)			
Azathioprine	30 (60)	17 (77)	20 (56)
Glucocorticoids	26 (52)	9 (41)	23 (64)
Mercaptopurine	2 (4)	1 (4)	1 (3)
Methotrexate	1 (2)	0 (0)	1 (3)
Reason for discontinuing infliximab, *n* (%)			
Intolerance	32 (64)	17 (77)	21 (58)
Loss of response	18 (36)	5 (23)	15 (42)

* Includes 12 patients with pure fistulizing Crohn's disease and 10 patients with luminal and fistulizing Crohn's disease.
† Includes 26 patients with pure luminal Crohn's disease and 10 patients with luminal and fistulizing Crohn's disease.
CDAI, Crohn's Disease Activity Index.

INTRODUCTION

Crohn's disease (CD) begins as a chronic transmural inflammation of the gastrointestinal tract that typically evolves over time into an obstructive or fistulizing pattern of disease.[1, 2] The overall incidence of CD is 5.6/100 000 persons in Europe, with recent data suggesting that the incidence in southern Europe is approaching the incidence reported for northern countries.[3–5] CD has a tremendous impact on quality of life, and the associated socioeconomic burden is high.[6] Because there is no medical or surgical cure for CD, the goal of therapy is to induce and maintain remission.[7]

Genetic and environmental factors, particularly cigarette smoking, may affect disease activity.[8, 9] An imbalance in the immune response to protein antigens normally present in the intestinal microbial flora may lead to various immune defects in a genetically susceptible host.[8] An excessive proinflammatory response from type-1 helper T cells results in increased production of proinflammatory cytokines, including interferon-γ, interleukins and tumour necrosis factor (TNF).[8] TNF is believed to play a key role in the pathogenesis of CD.[8]

The use of TNF antagonists has changed the therapeutic approach to CD, particularly in patients with severe and refractory disease. Infliximab is a chimaeric IgG_1 monoclonal antibody to TNF that has been demonstrated to induce and maintain clinical response and remission in a significant proportion of both patients with active inflammatory disease and patients with fistulizing disease.[10–15] During long-term treatment with infliximab, however, the development of anti-infliximab antibodies may contribute to the loss of drug efficacy and/or

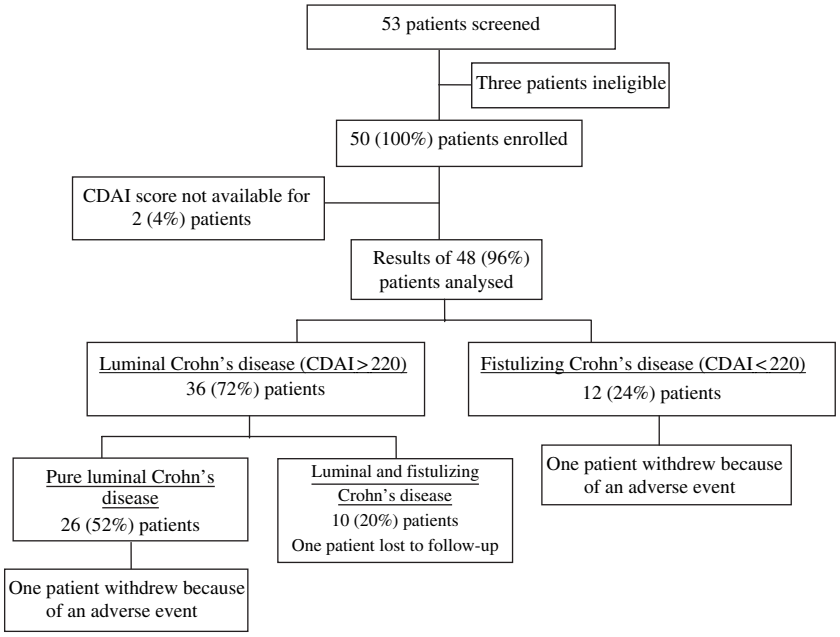

Figure 1. Patient distribution and disposition through week 4. CDAI, Crohn's Disease Activity Index.

development of intolerance experienced by some patients.[16–18]

Adalimumab is a fully human IgG_1 monoclonal antibody to TNF that has also been shown to induce and maintain clinical response or remission in patients with active inflammatory CD.[19–21] Preliminary evidence indicates that adalimumab is clinically beneficial in some patients with CD who have lost response to or became intolerant of infliximab.[22–26] Based on these data, we designed a compassionate-use study to evaluate the long-term safety and effectiveness of adalimumab in adults with CD who lost response to or were intolerant of infliximab. The objective of this paper is to present the 4-week safety and effectiveness results from the induction phase of our study.

PATIENTS AND METHODS

Study design

This 52-week, multicentre, prospective, open-label, observational study investigated the safety and therapeutic effectiveness of adalimumab in patients with luminal or fistulizing CD who lost response to or were intolerant of infliximab treatment. Analyses of the short-term (4-week) results are reported. All patients received an initial dose of adalimumab 160 mg at the baseline visit followed by 80 mg at week 2. This induction regimen was based on preliminary data reported for the Clinical assessment of Adalimumab Safety and efficacy Studied as Induction therapy in CD study (CLASSIC-I)[27] assuming that patients with refractory disease would receive treatment. Patients self-injected adalimumab, which was provided as commercially available prefilled syringes containing 0.8 mL (40 mg) of adalimumab (Abbott Laboratories, Abbott Park, IL, USA).

Ethics

Permission for compassionate use of adalimumab was obtained according to the regulations of Spanish Ministry of Health and Consumption (Madrid, Spain). The study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki (2004 revision), and all patients voluntarily provided written, informed consent. The Ethics Committee of the leading hospital (Hospital de Sagunto, Valencia, Spain) approved the study protocol.

Patients

Patients were adults age >18 years with a diagnosis of CD (confirmed by radiology or endoscopy evaluation) at least 3 months before enrollment. Additional inclusion criteria were: a baseline Crohn's Disease Activity Index (CDAI) score >220[27] and/or the presence of active draining perianal fistulas; a previous clinical response to infliximab with subsequent loss of response

Table 2. Clinical response and remission at week 4 and Crohn's Disease Activity Index scores over time

Measure of effectiveness	Pure luminal Crohn's disease (CDAI ≥ 220; $n = 26$)*†	Luminal and fistulizing Crohn's disease (CDAI ≥ 220; $n = 10$)	Pure fistulizing Crohn's disease (CDAI < 220; $n = 12$)*	Luminal Crohn's disease (CDAI ≥ 220; $n = 36$)‡	Fistulizing Crohn's disease ($n = 22$)‡§
Week 4 remission, *n* (%)	8 (31)	7 (70)	9 (75)¶	15 (42)	5 (23)
Week 4 CDAI 100-point response, *n* (%)	18 (69)	9 (90)	0	27 (75)	9 (41)
Week 4 CDAI 70-point response, *n* (%)	20 (77)	10 (100)	2 (17)	30 (83)	12 (55)
Baseline CDAI scores (mean ± s.d.)	322 ± 67.5	293 ± 57.6	132 ± 50.3	314 ± 65.5	205 ± 97.2
Week 2 CDAI scores (mean ± s.d.)	180 ± 77.8	179 ± 73.2	115 ± 49.0	180 ± 75.5	146 ± 68.5
Week 4 CDAI scores (mean ± s.d.)	185 ± 103	138 ± 58.3	105 ± 38.6	171 ± 94.2	121 ± 50.7

* Includes patients who had only luminal disease; patients with fistulizing disease were excluded.
† One patient from each group discontinued because of an adverse event before the week 4 visit.
‡ One patient lost to follow-up before week 2.
§ Includes 12 patients with pure fistulizing Crohn's disease and 10 patients with luminal and fistulizing Crohn's disease.
¶ Of the nine patients who had a week 4 CDAI score < 150, seven had a baseline CDAI < 150. Of the four patients with a baseline CDAI > 150, two achieved remission and two did not.
CDAI, Crohn's Disease Activity Index.

and/or intolerance because of acute or late reactions, as judged by the investigator; and normal cardiac, hepatic and renal function. Loss of response to infliximab was defined as no clinical improvement despite use of high-dose infliximab (10 mg/kg) or as requiring a reduced interval (<6 weeks) between two consecutive doses. All patients were screened for tuberculosis using a protein purified derivative skin test and chest radiograph. Patients with evidence of a previous tuberculosis infection required a documented history of prophylaxis or initiation of prophylaxis at least 1 month before receiving the first dose of adalimumab.

Patients with a history of primary non-response to infliximab were excluded from participation. Additional exclusion criteria included symptomatic obstructive stricture or an intestinal resection ≤2 weeks before or planned within 4 weeks after the baseline visit; active infection or a history of listeriosis or untreated tuberculosis; and a history of cancer or lymphoproliferative disease, with the exception of successfully treated basal or squamous cell carcinoma. In patients with perianal disease, the presence of an abscess was excluded by clinical examination and endorectal ultrasonography and/or pelvic magnetic resonance imaging before inclusion in the study.

Measures

In patients with active luminal disease, CDAI was used for evaluation of response. Clinical response was defined by the CDAI 70-point response (a reduction of ≥70 points from baseline) and the CDAI 100-point response (a reduction of ≥100 points from baseline). These definitions of clinical response were used to allow comparison of results with previous studies of TNF antagonists for the treatment of CD. Remission was defined as a CDAI score <150.[28] In patients with fistulizing disease, response was defined as ≥50% decrease in the number of perianal fistulas that were draining at baseline during at least two consecutive treatment visits. Fistula remission was defined as the complete closure of all perianal fistulas that were draining at baseline during at least two consecutive treatment visits.

Additional measurements were erythrocyte sedimentation rate (ESR; mm/first hour) and C-reactive protein (CRP) concentrations (mg/dL) in all patients at every clinic visit and the Perianal Disease Activity Index (PDAI) score in patients with perianal disease.[29] Safety assessments included physical examinations, measurement of vital signs and measurement of haematology

Table 3. Fistula improvement and remission and Perianal Disease Activity Index scores over time in patients with fistulizing disease

Measure of effectiveness	Luminal and fistulizing Crohn's disease (CDAI ≥ 220; $n = 10$)	Pure fistulizing Crohn's disease (CDAI < 220; $n = 12$)*	Fistulizing Crohn's disease ($n = 22$)*†
Patients with fistulas, *n* (%)			
Baseline	10 (100)	12 (100)	22 (100)
Week 2	9 (90)	11 (92)	20 (91)
Week 4	7 (70)	9 (75)	16 (73)
Number of fistulas (mean ± s.d.)			
Baseline	3.8 ± 5.5	2.5 ± 1.2	3.1 ± 3.8
Week 2	1.2 ± 1.2	1.7 ± 1.4	1.5 ± 1.3
Week 4	1.0 ± 1.2	0.6 ± 0.8	0.8 ± 1.0
Closed at week 4	2.8 ± 5.8	1.9 ± 1.2	2.3 ± 4.0
Fistula remission at week 4, *n* (%)	3 (30)	2 (17)	5 (23)
Fistula improvement at week 4, *n* (%)	4 (40)	5 (42)	9 (41)
Baseline PDAI scores (mean ± s.d.)	9.6 ± 2.1	11.3 ± 3.2	10.5 ± 2.8
Week 2 PDAI scores (mean ± s.d.)	6.7 ± 3.3	7.6 ± 4.3	7.2 ± 3.8
Week 4 PDAI scores (mean ± s.d.)	4.7 ± 2.2	6.1 ± 3.6	5.4 ± 3.0

* One patient discontinued because of an adverse event before the week 4 visit.
† Includes 12 patients with pure fistulizing Crohn's disease and 10 patients with luminal and fistulizing Crohn's disease.
CDAI, Crohn's Disease Activity Index; PDAI, Perianal Disease Activity Index.

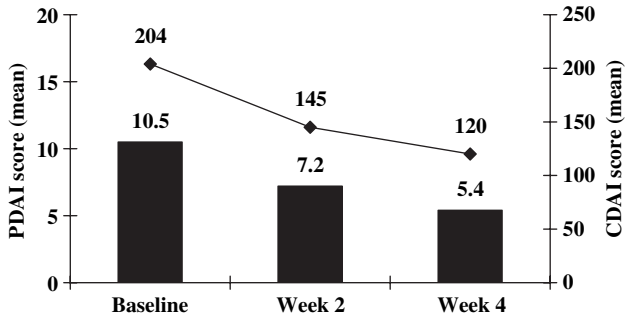

Figure 2. Change in Perianal Disease Activity Index (PDAI) and Crohn's Disease Activity Index (CDAI) scores over time for patients with fistulizing Crohn's disease ($n = 22$). The maximum PDAI score is 20 units; there is no maximum CDAI score.

values at every visit. Adverse events were assessed throughout the study.

Statistical analyses

Because this investigation was an observational, compassionate-use study, no formal sample size calculation was performed. The population for both safety and effectiveness evaluations included all patients who received at least one dose of adalimumab. Drug effectiveness was analysed separately for patients with luminal disease and for patients with fistulizing disease. For patients with luminal CD (CDAI ≥220), the primary efficacy outcome was the percentage of patients who experienced induction of remission (CDAI <150) at week 4 based on an intention-to-treat (ITT) analysis. Secondary efficacy analyses included the percentage of patients who achieved the CDAI 70-point response and the percentage who achieved the CDAI 100-point response based on an ITT analysis. Subgroup analyses for patients with luminal CD included an ITT analysis of remission, response criteria for patients with luminal CD only, and response criteria for patients with luminal and fistulizing CD.

For patients with fistulizing CD, mean changes from baseline to weeks 2 and 4 are summarized descriptively for PDAI scores and the number of draining perianal fistulas. An ITT analysis was completed to determine the percentage of patients who achieved fistula improvement and the percentage who achieved fistula remission. Subgroup analyses of patients with fistulizing CD included analysis of the change in PDAI scores, the change in the number of draining perianal fistulas, and achievement of improvement and remission criteria as described earlier for patients with fistu-

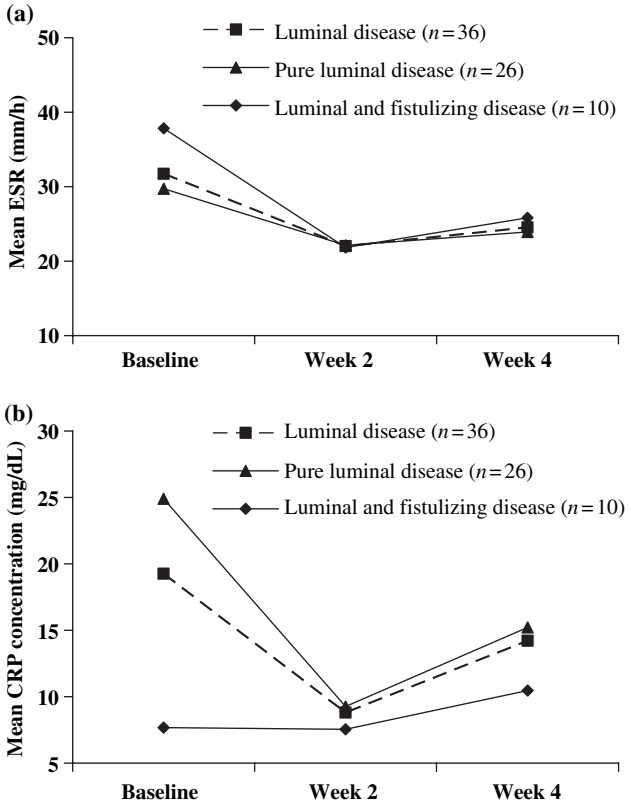

Figure 3. (a) Mean erythrocyte sedimentation rates (ESR) and (b) mean C-reactive protein (CRP) concentrations over time for patients with luminal Crohn's disease.

lizing CD only and for patients with luminal and fistulizing CD.

Changes in ESR and CRP concentrations were summarized descriptively (e.g. mean ± s.d., median, interquartile ranges) and qualitatively. Mean CDAI scores over time are summarized according to smoking status (i.e. non-smokers, smokers, former smokers). Adverse events are summarized descriptively; no formal statistical analysis of adverse events was completed.

RESULTS

Fifty patients were enrolled from September 2004 to July 2005 at 30 centres in Spain. Baseline clinical and demographic variables are summarized in Table 1. The mean age of patients was 37.4 ± 10.4 years (mean ± s.d.) with a mean duration of CD of 9.9 ± 5.7 years. Sixty-four percent of the patients were female, and 42% were current smokers. Sixty percent of patients had prior surgery for CD. The intestinal areas most commonly affected by CD were the ileocolon (58% of patients) and the colon (34% of patients). In addition to adalimumab, 66% of patients were receiving immunomodulators (60% azathioprine, 4% mercaptopurine and 2% methotrexate); and 52% were receiving glucocorticoid treatment. Reasons for previously discontinuing infliximab treatment (intolerance or loss of response) are presented in Table 1 for patients with luminal CD and for all patients with fistulizing CD. Of 26 patients with pure luminal CD, 50% had discontinued infliximab because of loss of response and 50% had discontinued because of intolerance. In contrast, most of the patients with fistulizing CD (75% in the group with pure fistulizing CD and 80% in the group with luminal and fistulizing CD) had discontinued infliximab because of intolerance.

Baseline CDAI scores were not available for two of the 50 enrolled patients. The remaining 48 patients were grouped according to baseline CDAI scores and/or presence of fistulae (Figure 1). Of the 50 patients enrolled, 36 (72%) had luminal CD (mean CDAI score, 314 ± 65.5). Of these 50 patients, 26 patients (52%) had luminal disease only, with a mean CDAI score of 322 ± 67.5, and 10 patients (20%) had luminal and fistulizing disease (mean CDAI score, 293 ± 57.6). Twelve of 50 patients (24%) had only fistulizing CD (mean baseline CDAI score, 132 ± 50.3; mean baseline PDAI score, 11.3 ± 3.2). One patient with luminal CD and one patient with fistulizing CD withdrew from the study before the week 4 visit because of an adverse event (see Figure 1).

Clinical remission and response rates, as defined by CDAI scores, are summarized in Table 2. Of the 36 patients with luminal CD, the ITT analysis indicated that a 4-week course of adalimumab induced remission (CDAI score <150) in 15 patients (42%) and induced response defined as CDAI 100-point response in 27 patients (75%) and CDAI 70-point response in 30 patients (83%). The results of detailed subgroup analyses are summarized in Table 2.

The clinical response rates for patients with fistulizing CD are summarized in Table 3. Nine of the 22 patients with fistulizing disease (41%) showed significant improvement (response, as defined in Patients and methods) in fistulas during the first 4 weeks of adalimumab treatment and complete remission was achieved in five of 22 patients (23%). In all patients with fistulizing disease, an improvement in PDAI scores and a reduction in the number of fistulas from baseline to week 4 were observed (see Table 3). The magnitude of reduction in PDAI scores paralleled the

Table 4. Adalimumab efficacy at week 4 by reason for discontinuing infliximab

	Pure luminal Crohn's disease		Luminal and fistulizing Crohn's disease		Pure fistulizing Crohn's disease	
Reason for discontinuing infliximab	Loss of response	Intolerance	Loss of response	Intolerance	Loss of response	Intolerance
n	13	12	2	8	3	8
Remission (CDAI < 150, %)	39	23	50	75	100	75
CDAI 100-point response (%)	77	62	100	88	0	0
CDAI 70-point response (%)	85	69	100	100	67	0
Change in PDAI score (mean)*	N/A	N/A	−6.5	−4.5	−4.3	−5.3

* For patients with perianal fistulas.
CDAI, Crohn's Disease Activity Index; N/A, not applicable; PDAI, Perianal Disease Activity Index.

magnitude of reduction in CDAI scores over time for this group of patients (Figure 2). Results for the detailed analyses for subgroups of patients with fistulizing CD are shown in Table 3.

The changes in acute phase reactants over time are illustrated in Figure 3a (mean ESR) and b (mean CRP concentration). The maximum response was evident at week 2.

When analysing adalimumab response by smoking status for patients with luminal CD, although smokers had a higher mean baseline CDAI score (340 ± 63.9) than non-smokers (308 ± 77.9) and former smokers (284 ± 47.5), there were no differences in response between these groups. Similarly, when analysing data according to previous infliximab history, we did not find any differences in the response to adalimumab between patients with previous loss of response and intolerance to infliximab (Table 4).

During the first 4 weeks of adalimumab treatment, 17 patients reported 19 adverse events. Most adverse events [13 (68%)] were mild, five were moderate, and one was considered severe (pruritic erythema). Of the 10 adverse events that were categorized as possibly related to study medication, the investigators noted that possible alternative causalities included concomitant medications for two adverse events and CD or comorbid disorders for eight adverse events. No serious and no infectious adverse events were reported (Table 5).

DISCUSSION

Adalimumab treatment was associated with clinical response in 83% and remission in 42% of the 36 patients with luminal CD who previously lost response to or were intolerant of infliximab. The induction of clinical remission in patients with luminal CD was rapid, with evidence of remission apparent by week 2. This remission rate is similar to the remission rate of 36% in infliximab-naive patients with active CD who were receiving the same dosage regimen of adalimumab in the CLASSIC-I study.[20] In fact, although differences in populations and

Table 5. Adverse events during study period

Event	Intensity
Nausea/dizziness	Mild
Diarrhoea	Mild
Erythema (pruritic)	Moderate
Metrorrhagia*	Mild
Erythema (non-pruritic)	Mild
Erythema (pruritic)‡	Severe
Muscle pain	Mild
Vomiting	Moderate
Fatigue/pain in lower limbs†	Moderate
Fatigue	Moderate
Short-term weakness	Mild
Arthralgia	Mild
Fever‡	Mild
Erythema (pruritic)*	Moderate
Cough/expectoration	Mild
Nausea/vomiting	Mild
Erythema†	Mild
Nausea/dizziness	Mild
Dysphagia	Mild

* Same patient.
† Same patient.
‡ Patients withdrew from study.

concomitant treatments make comparisons difficult, the response and remission rates demonstrated herein are higher than those reported 4 weeks after a single dose of infliximab in patients with severe CD, with 65% of infliximab patients experiencing a clinical response (≥70-point reduction on CDAI) and 33% achieving remission (CDAI <150).[10] Clinical response in patients with luminal CD was paralleled by a decrease in biological activity as measured by CRP concentrations and ESR.

The response to adalimumab in the 22 patients with fistulizing disease was also rapid, with 23% of patients experiencing fistula remission and 41% experiencing fistula improvement at week 4. The percentage of patients experiencing fistula improvement was similar to the percentage reported in a short-term, placebo-controlled study of infliximab in patients who were naive to TNF antagonist treatment, in which the difference between the rates of fistula improvement in placebo- and infliximab-treated patients was 42% for the 5 mg/kg dose of infliximab.[12] It is worth noting that infliximab treatment failed for the patients in the current study and that a lower rate of fistula improvement might be expected compared with TNF antagonist-naive patients. In the present study, more patients (30%) with luminal and fistulizing CD (CDAI ≥220) achieved remission of fistulas than did patients with only fistulizing CD (17%). These data confirm the importance of controlling disease activity in patients with associated perianal disease. The long-term maintenance phase of this study will determine the durability of adalimumab response and remission for both the luminal and fistulizing components of CD.

The findings in this study are consistent with published reports demonstrating that adalimumab induces remission and response in patients with CD who were intolerant of or who experienced an attenuated response to infliximab. However, a direct comparison of remission and response rates is difficult because of differences in adalimumab dosage regimens and different definitions of clinical response in the published literature.[22–24] The CLASSIC-I trial demonstrated that an adalimumab induction dose of 160/80 mg is the optimal induction treatment regimen for TNF antagonist-naive patients with moderate to severe CD.[20] The current study is the first open-label, prospective study to analyse the induction of response to adalimumab in patients with active luminal or fistulizing CD using an induction regimen of 160/80 mg. With the exception of the CLASSIC-I trial, the adalimumab dosage used in most studies of patients with CD is lower than that used in the current study.

This study has certain limitations, the most important being an open-label study with a small number of patients. In addition, these data should be confirmed in other populations. Of note, however, is that this study population was patients with refractory and active luminal and/or fistulizing CD despite conventional immunomodulatory treatment and that infliximab treatment had failed in these patients. Data in this study suggest that adalimumab could be an effective alternative for treatment of these difficult-to-treat patients, at least in the short-term, and confirm the need for further data.

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STATEMENT OF INTERESTS

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