Journal of Crohn's and Colitis, 2016, 812–820
doi:10.1093/ecco-jcc/jjw032
Advance Access publication January 27, 2016
Original Article

Original Article

Safety and Efficacy of Granulocyte/Monocyte Apheresis in Steroid-Dependent Active Ulcerative Colitis with Insufficient Response or Intolerance to Immunosuppressants and/or Biologics [the ART Trial]: 12-week Interim Results

Axel Dignass,[a] Ayesha Akbar,[b] Ailsa Hart,[b] Sreedhar Subramanian,[c] Gilles Bommelaer,[d] Daniel C. Baumgart,[e] Jean-Charles Grimaud,[f] Guillaume Cadiot,[g] Richard Makins,[h] Syed Hoque,[i] Guillaume Bouguen,[j] Bruno Bonaz[k]

[a]Department of Gastroenterology, Hepatology, Oncology and Metabolic Diseases, Markus-Krankenhaus, Frankfurt/Main, Germany [b]IBD Unit, St Mark's Hospital and Academic Institute, London, UK [c]Department of Gastroenterology, Royal Liverpool University Hospital, Liverpool, UK [d]Service Hépatologie-Gastroentérologie, CHU Clermont-Ferrand, Clermont-Ferrand, France [e]Department of Medicine, Division of Gastroenterology and Hepatology, Charité Medical Center - Virchow Hospital, Humboldt-University of Berlin, Germany [f]Assistance Publique Hôpitaux de Marseille, Marseille, France [g]Service d'Hépato-gastro-entérologie, CHU du Reims, Hôpital Robert Debré, Reims, France [h]Cheltenham General Hospital, Cheltenham, UK [i]Barts Health NHS Trust, Whipps Cross University Hospital, London, UK [j]Service des Maladies de l'Appareil Digestif et CIC1414, University Hospital of Rennes, Pontchaillou, France [k]Clinique Universitaire d'Hépato-Gastroentérologie, CHU Grenoble, Grenoble, France

Corresponding author: Axel Dignass, Department of Medicine 1, Agaplesion Markus Hospital, Wilhelm-Epstein-Str. 4, D-60431 Frankfurt/Main, Germany. Tel: +49 69 95332201; email: axel.dignass@fdk.info

Abstract

Background and Aims: Patients with active, steroid-dependent ulcerative colitis with insufficient response or intolerance to immunosuppressants and/or biologic therapies have limited treatment options. Adacolumn, a granulocyte/monocyte adsorptive apheresis device, has shown clinical benefit in these patients. This study aimed to provide additional clinical data regarding the safety and efficacy of Adacolumn in this patient subgroup.

Methods: This single-arm, open-label, multicentre trial [ART] was conducted at 18 centres across the UK, France, and Germany. Eligible patients were 18–75 years old with moderate-to-severe, steroid-dependent active ulcerative colitis with insufficient response or intolerance to immunosuppressants and/or biologics. Patients received ≥ 5 weekly apheresis sessions with Adacolumn. The primary endpoint was clinical remission rate [clinical activity index ≤ 4] at Week 12.

Results: In all, 86 patients were enrolled. At Week 12, 33/84 [39.3%] of patients in the intention-to-treat population achieved clinical remission, with 47/84 [56.0%] achieving a clinical response [clinical activity index reduction of ≥ 3]. Clinical remission was achieved in 30.0% of patients with previous immunosuppressant and biologic failure; steroid-free clinical remission and response were observed in 22.6% and 35.7% of these patients, respectively. Quality of life [Short Health

Scale] significantly improved at Week 12 [$p < 0.0001$]. The majority of adverse events were of mild/moderate intensity.

Conclusions: At Week 12, Adacolumn provided significant clinical benefit in a large cohort of steroid-dependent ulcerative colitis patients with previous failure to immunosuppressant and/or biologic treatment, with a favourable safety profile. These results are consistent with previous studies and support Adacolumn use in this difficult-to-treat patient subgroup.

Key Words: Ulcerative colitis; apheresis; adacolumn

1. Introduction

Ulcerative colitis [UC] is a chronic relapsing and remitting inflammatory condition of the colon affecting between 1 and 20 people per 100 000 population per year.[1,2] Relapses present with symptoms such as abdominal pain, bloody diarrhoea, weight loss, and anaemia, all of which have a significant impact on quality of life.[2]

The therapeutic goal of UC treatments is to induce steroid-free clinical remission,[3] with remission defined as the complete resolution of symptoms; a response to treatment is defined as clinical improvement.[2] Treatment typically follows an escalation or step-up approach whereby additional therapies are added in order to induce and maintain remission. Common therapeutic agents used to control disease activity include 5-aminosalicylate [5-ASA] compounds, steroids, immunosuppressants [thiopurines], calcineurin inhibitors [cyclosporine, tacrolimus], and biologic agents such as anti-tumour necrosis factor alpha [TNF-α] antibodies [infliximab, adalimumab] and the anti-adhesion molecule vedolizumab.[3,4,5] There is, however, an urgent need for therapies for steroid-dependent and steroid-refractory moderate-to-severely active UC patients due to side effects, patient intolerance to existing treatments, and failure of previous treatments. After the failure of existing therapies, surgery is often the only remaining option for these patients.[3]

In this context, granulocyte and monocyte adsorptive [GMA] apheresis [Adacolumn®, Otsuka Pharmaceuticals] and granulocytapheresis [GCAP; Cellsorba®, Asahi Medical] have emerged as non-pharmacological treatments with few side effects.[6,7,8] The mechanism of action of GMA apheresis consists of the selective removal of the cell populations involved in the induction and perpetuation of bowel inflammation from the peripheral blood [neutrophils, monocytes, and platelets] without affecting other cells such as lymphocytes and erythrocytes.[9] GMA has also been shown to modulate levels of proinflammatory cytokines such as TNF-α, interleukin [IL]-1β, IL-6, and IL-8, and reduces cell-surface levels of L-selectin, a molecule that plays a key role in initiating leukocyte adhesion to the vascular endothelium.[10,11]

The clinical efficacy of GMA apheresis has been demonstrated in several studies, with clinical remission and response rates comparable to those seen with conventional therapies.[12,13,14] Registry data have shown that in clinical practice, apheresis leads to long-term steroid-free clinical remission in up to one-third of steroid-dependent UC patients.[15] An open-label multicentre study of 39 patients with steroid-refractory chronic active UC found that five apheresis sessions with Adacolumn resulted in a 37.1% clinical remission rate at Week 6, with 28.6% of patients achieving endoscopic remission. The median total dose of systemic steroids decreased from 20.0 mg/day at baseline to 15.0 mg/day at Week 6 [$p < 0.05$]. Quality of life as measured by the Inflammatory Bowel Disease Questionnaire [IBDQ] increased significantly by 24 points [$p < 0.01$].[16]

Further clinical data on Adacolumn in difficult-to-treat UC patients are, however, required in order to fully explore the role of this device in the management of patients for whom clinical guidelines do not provide additional guidance due to limited treatment options.

The ART study was designed to further evaluate the effectiveness and safety of Adacolumn in patients with moderate-to-severe UC who had an inadequate response to, or lost response to, or were intolerant to immunosuppressants and/or a biologic therapy. We report here the 12-week interim results of the 96-week ART study.

2. Methods

2.1. Study design

The ART [Adacolumn in Refractory UC Patients Trial] study is a single-arm, open-label, multicentre, post-marketing device study [NCT01481142] conducted at 18 centres across the UK, France, and Germany in accordance with the guidelines established in the Declaration of Helsinki. ART is a 96-week study, consisting of a 5-week treatment period and an additional optional 5-week treatment period, with study evaluations at Weeks 12, 24, and 48, and an additional telephone contact at Week 96 [Figure 1a].

2.2 Patient population

Eligible patients were 18 to 75 years old with moderate-to-severe, steroid-dependent, refractory active UC with insufficient response or intolerance to immunosuppressants and/or biologic agents. Insufficient response was defined as clinical activity index [CAI] ≥ 6 after 3 months of treatment with 2.5 mg/kg azathioprine or 1.5 mg/kg 6-mercaptopurine or after 14 weeks of starting anti-TNF-α therapy. Intolerance to previous therapies was defined as an allergic reaction, pancreatitis, severe immunosuppression, a psychotic disorder, or any contraindication according the manufacturer's package insert.

UC was documented by clinical symptoms, endoscopic findings, and histology. Disease severity and steroid dependence were defined according to the ECCO guidelines.[2] Key inclusion criteria were UC CAI ≥ 6 and endoscopic activity index [EAI] ≥ 4,[17] and adequate peripheral venous access for the completion of apheresis.

Exclusion criteria included history of hypercoagulation disorder, hypersensitivity or intolerance to apheresis procedures, heparin allergy, or previous heparin-induced thrombocytopenia.

Patients were required to give written informed consent before undergoing any study procedures.

2.3. Study procedures

Endoscopy was performed at screening to evaluate EAI. Patients were treated with once-weekly Adacolumn apheresis over 5 consecutive weeks; this could be extended for up to 10 once-weekly treatments dependent upon treatment response, at the discretion of the investigator. The treatment schedule followed the typical clinical approach for administering Adacolumn apheresis in patients with UC.[18] Each apheresis session was performed at a 30 ml/min flow rate

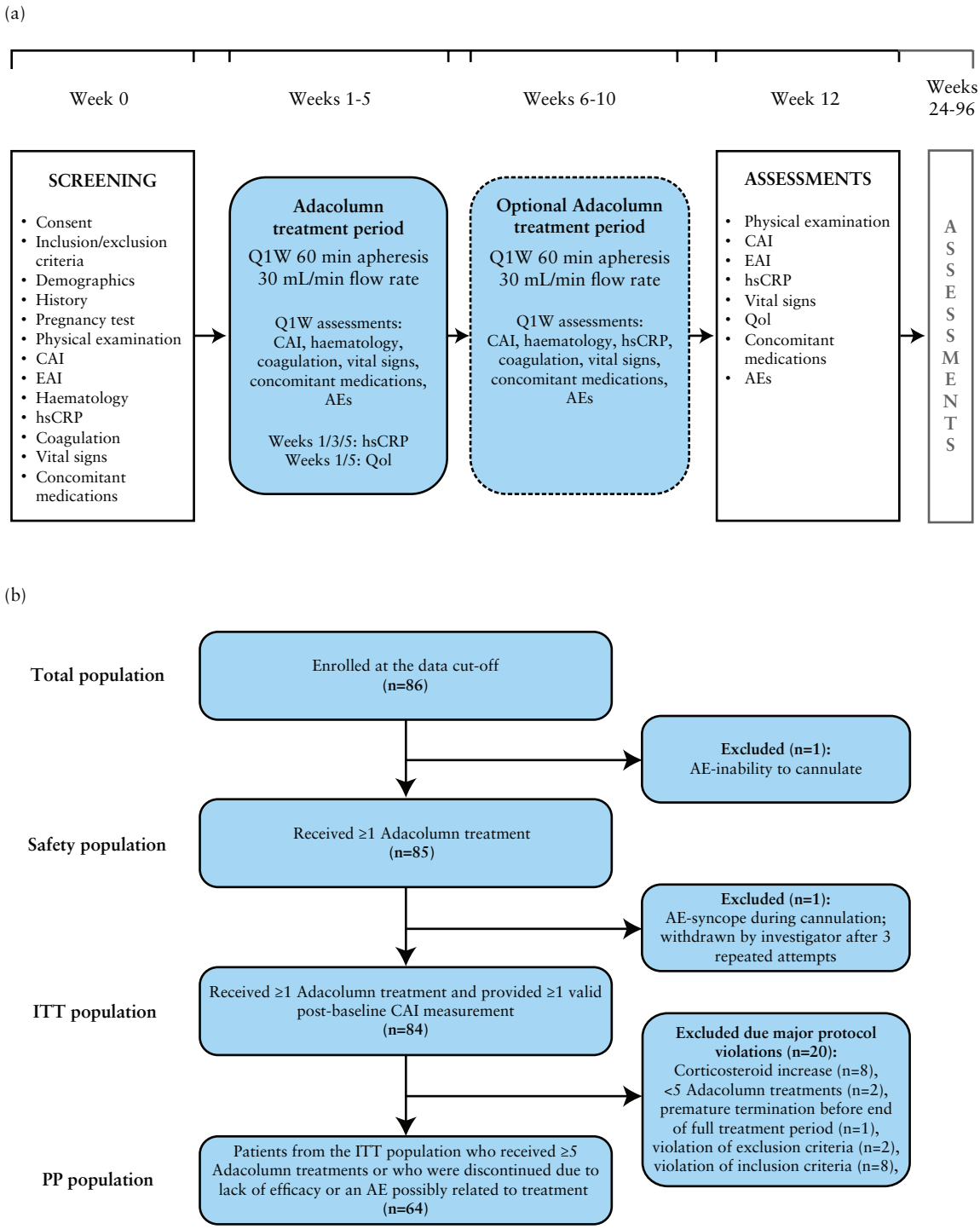

Figure 1. Study design [a] and participant flow [b]. AE, adverse event; CAI, clinical activity index; EAI, endoscopic activity index; hsCRP, high sensitivity C-reactive protein; ITT, intention-to-treat; PP, per protocol; QoL, quality of life; Q1W, every week.

for 60 min, with a final volume of 1.8 l of peripheral venous blood processed per session. Any eventual interruptions of apheresis were not to be included in the 60 min apheresis time period. A decrease in the dose of concomitant steroids was allowed during the study, if tapered down in suitable steps, at the discretion of the investigator.

2.4. Study objectives and outcomes

The primary objective of this study was to assess device efficacy, as measured by the primary endpoint of UC remission rate at Week 12, with remission defined as achieving a CAI score of ≤ 4. The secondary objectives were to observe and document device efficacy as measured by: UC response rate at Week 12, with response defined as a reduction in CAI of ≥ 3; steroid-free remission and response rates at Week 12; time to remission and response; time to steroid-free remission and response; change from baseline in CAI and EAI at Week 12; quality of life change at Week 12, as measured by the Short Health Scale for UC[19]; high-sensitivity C-reactive protein [hsCRP] levels at Week 12; and calprotectin levels at Week 12.

Additional secondary objectives were to observe and document device safety as measured by: adverse events [AEs] and vital signs at each study visit; laboratory safety parameter changes [haemoglobin, red blood cell counts, white blood cell counts, platelets and coagulation parameters] at screening, baseline, and every treatment visit; and physical examination findings at baseline and Week 12.

2.5. Statistical analysis

This interim analysis was performed on all patients enrolled in the ART study who had a baseline visit at least 12 weeks before the data cut-off of 1 July 2013. Only data collected until the end of the 12-week follow-up period were included. Descriptive summaries were generated where appropriate for each of the primary and secondary outcomes. The summary for the primary efficacy variable includes absolute frequencies, rates [percentages], and exact 95% confidence intervals [CIs] for the rates [Pearson–Clopper intervals].

Efficacy endpoints were assessed in the intention-to-treat [ITT] population [defined as all patients with ≥1 treatment and ≥ 1 valid post-baseline CAI measurement] and the per-protocol [PP] population [defined as all patients from the ITT population who received ≥ 5 treatments or who discontinued due to lack of efficacy or due to an AE with at least possible relation to the study device or treatment]. Remission rate at Week 12 was estimated within the ITT and PP populations, calculated by dividing the number of patients with remission by the total number of patients; all missing values were analysed as not showing remission. Time to remission and response and time to steroid-free remission and response were summarised using Kaplan–Meier estimates. The reference range for central calprotectin testing was 0–50 mg/kg. In addition, a 200 mg/kg clinical cut-off level was also used to assess the effects of GMA on calprotectin levels in this interim analysis, as it is generally appreciated that in IBD patients a cut-off level for calprotectin of 50 mg/kg is not appropriate and may not reflect relevant inflammatory activity. The proportions of patients above and below the cut-off of 200 mg/kg were analysed using McNemar's test. Safety endpoints were assessed in the safety population, defined as all patients with ≥ 1 treatment.

All analyses were performed using SAS® Software Version 9.1.3 or later.

3. Results

3.1. Patient disposition

Patients were enrolled from 12 October 2011. As of the data cut-off date of 1 July 2013, 86 patients were enrolled and signed informed consent, and were included in the total population [Figure 1b]. The safety population included 85/86 [98.8%] patients who initiated ≥ 1 Adacolumn apheresis treatment. Included in the ITT population were the 84/86 [97.7%] patients who received ≥ 1 treatment and provided ≥ 1 valid post-baseline CAI measurement; 1 patient was excluded due to an AE [syncope during cannulation] and was withdrawn by the investigator; 64/86 [74.4%] patients received ≥ 5 treatments or were discontinued due to lack of efficacy or an AE, and were included in the PP population; the remaining 20 [23.8%] patients were excluded from the PP population due to protocol violations [Figure 1b]. In the safety population, 79/85 patients [92.9%] received 5 apheresis treatments; 59/85 [69.4%] received 6 or more treatments.

Of the total population, 72/86 [83.7%] patients completed Week 12; 5/86 [5.8%] did not complete the mandatory treatment period; and 9/86 [10.5%] withdrew after this period but before Week 12. Of the patients who did not complete Week 12, 4/84 [4.7%] of patients withdrew due to an AE, 2/84 [2.3%] withdrew consent, and 4/84 [4.7%] were withdrawn at investigator's discretion, due to worsening colitis or venous access problems.

3.2. Patient demographics and baseline characteristics

Patient demographics and baseline characteristics of the safety population are shown in Table 1. A majority of patients [63.5%] were male, with a mean age of 44.8 years; 37 patients had left-sided disease and 42 had pancolitis; only one patient had proctitis [1.2% of all patients]. The majority of patients [71.8%] had moderate UC, and one-fifth [20.0%] had severe UC. Nearly two-thirds

Table 1. Summary of patient demographics and baseline characteristics [safety population].

Characteristic	*N* = 85
Age, years	
Mean [SD]	44.8 [14.2]
Weight, kg	
Mean [SD]	76.5 [18.9][a]
Sex, *n* [%]	
Male	54 [63.5]
Female	31 [36.5]
Ulcerative colitis severity, *n* [%]	
Mild	7 [8.2]
Moderate	61 [71.8]
Severe	17 [20.0]
Localisation of disease, *n* [%][2,28]	
Left-sided	37 [43.5]
Proctitis	1 [1.2]
Pancolitis	42 [49.4]
Other	5 [5.9]
Number of previous hospital admissions related to ulcerative colitis, *n* [%]	
0	25 [29.4]
1	22 [25.9]
2	12 [14.1]
3	8 [9.4]
≥ 4	18 [21.2]
Number of ulcerative colitis episodes in the past 12 months, *n* [%]	
0	12 [14.1]
1	10 [11.8]
2	11 [12.9]
Chronic active	52 [61.2]
Time since first diagnosis, months	
Mean [SD]	106.3 [108.9]
Median [lower quartile, upper quartile]	70.0 [29.0, 123.0]
Incidence of insufficient response[b] or intolerance[c] to medications, *n* [%]	
Any insufficient response or intolerance	85 [100.0]
Immunosuppressant medication	83 [97.6]
Anti-TNF-α treatment	37 [42.4]
Immunosuppressants and anti-TNF-α treatment	30 [35.2]

SD, standard deviation; TNF-α, tumour necrosis factor alpha.

[a]*N* = 84.

[b]Clinical activity index ≥ 6 after 3 months of treatment with 2.5 mg/kg azathioprine or 1.5 mg/kg 6-mercaptopurine or after 14 weeks from starting anti-TNF-α therapy.

[c]Allergic reaction, pancreatitis, severe immunosuppression, a psychotic disorder, or any contraindication according the manufacturer's package insert.

of patients [61.2%] had chronic active UC in the past 12 months. Nearly all patients [98.8%] used concomitant medications during the 12 weeks, with 67.1% using glucocorticoids; 97.6% and 42.4% of patients had previously failed on immunosuppressants or anti-TNF-α therapies, respectively, and 35.2% had failed on both.

3.3. Ulcerative colitis remission rate

After Adacolumn treatment, 33/84 (39.3% [95% CI 28.8, 50.6]) and 24/64 37.5% [95% CI 25.7, 50.5]) of patients in the ITT and PP populations, respectively, achieved remission [primary endpoint; Table 2].

Remission rates were also analysed for the subgroups of patients who previously failed on other medications. Remission was achieved at Week 12 by 31/77 (40.3% [95% CI 29.2, 52.1]) of patients who failed on immunosuppressants, 10/36 (27.8% [95% CI 14.2, 45.2]) of patients who failed on anti-TNF-α treatment, and 9/30 (30.0% [95% CI 14.7, 49.4]) of patients who failed on both immunosuppressants and anti-TNF-α treatment.

3.4. Ulcerative colitis response rate

After Adacolumn treatment, 47/84 (56.0% [95% CI 44.7, 66.8]) and 34/64 (53.1% [95% CI 40.2, 65.7]) of patients in the ITT and PP populations, respectively, achieved a clinical response [Table 2].

When analysed by subgroups, 44/77 (57.1% [95% CI 45.4, 68.4]), 14/36 (38.9% [95% CI 23.1, 56.5]), and 12/30 (40.0% [95% CI 22.7, 59.4]) of patients who failed on immunosuppressants, anti-TNF-α treatment, or both therapies, respectively, achieved a response.

The Kaplan–Meier plots shows the time to remission [Figure 2a] and response [Figure 2b] for the ITT population; median estimates of time to remission and response were 43 days [95% CI 29, 63] and 24 days [95% CI 20, 34], respectively. Kaplan–Meier estimates of patients in remission and response at any time point were 52/84 [61.9%] and 66/84 [78.6%], respectively. Results were similar for the PP population.

Table 2. Summary of efficacy outcomes at Week 12.

Outcome	ITT population [*N* = 84]	PP population [*N* = 64]
Remission [CAI of ≤ 4]		
n [%]	33 [39.3]	24 [37.5]
95% CI	28.8, 50.6	25.7, 50.5
Response [CAI reduction ≥ 3]		
n [%]	47 [56.0]	34 [53.1]
95% CI	44.7, 66.8	40.2, 65.7
Steroid-free remission		
n [%]	19 [22.6]	15 [23.4]
95% CI	14.2, 33.1	13.8, 35.7
Steroid-free response		
n [%]	30 [35.7]	23 [35.9]
95% CI	25.6, 46.9	24.3, 48.9
CAI score change from baseline		
N	70	52
Mean [SD]	-3.4 [3.6]	-3.4 [3.7]
Minimum, maximum	-11.0, 4.0	-11.0, 4.0
95% CI	-4.3, -2.6	-4.5, -2.4
EAI score change from baseline		
N	64	52
Mean [SD]	-2.2 [3.5]	-2.4 [3.2]
Min, max	-10, 6.0	-10.0, 4.0
95% CI	-3.0, -1.3	-3.3, -1.5

CAI, clinical activity index; CI, confidence interval; EAI, endoscopic activity index; ITT, intention-to-treat; PP, per protocol; SD, standard deviation.

3.5. Additional secondary efficacy outcomes

Other secondary outcomes at Week 12 included steroid-free remission and response, and CAI and EAI change from baseline [Table 2]. Adacolumn treatment resulted in 22.6% and 35.7% of patients in the ITT population achieving steroid-free remission and response, respectively, at Week 12. These patients also experienced mean reductions in CAI and EAI of 3.4 and 2.2, respectively, at Week 12. Results were similar between the ITT and PP populations [Table 2].

Time to steroid-free remission and response for the ITT population is shown in Figure 3; at any time point, 28/84 [33.3%] and 36/84 [42.9%] of patients were in steroid-free remission or response.

A continued reduction in steroid use was observed during the study, with 32/84 [38.1%] patients steroid-free at Week 1 compared with 39/71 [54.9%] at Week 12. Mean steroid dose equivalent also decreased, from 14.7 mg at Week 1 to 9.5 mg at Week 12. Similar results were observed for the PP population.

Inflammatory activity at enrolment was confirmed in the ITT population by the median baseline hsCRP of 8.4 mg/l, with 51.8% of patients formally above the reference range. Median hsCRP decreased throughout the study to 5.3 mg/l at Week 12, with 36.2% formally above the reference range; however, this change was not statistically significant [p = 0.4303]. Similar results were observed for the PP population. Calprotectin levels numerically decreased relative to baseline; in the ITT population, median levels were 771.5 mg/kg at Week 1 with 94.6% of patients formally above the reference range, and 499 mg/kg at Week 12 with 86.6% of patients formally above the reference range. Correspondingly, the percentages of patients above the 200 mg/kg cut-off value decreased from 89.0% at baseline to 75.0% at Week 12. McNemar's test of paired proportions found that the percentage of patients below the cut-off increased significantly from baseline to Week 12 [p = 0.0325].

Quality of life improved from baseline to Week 12 [Table 3], with reductions in all four parameters of the Short Health Scale. The largest reduction was observed for the 'bowel disease affecting daily activities' parameter, with a mean 22.2% reduction from baseline to Week 12. The results of a repeated measures analysis of covariance model indicated a significant effect in change from baseline for all four parameters [p < 0.0001]. Similar results were observed for the PP population.

3.6. Safety evaluation

The majority of AEs experienced by patients were mild or moderate. Overall, 61/85 [71.8%] patients in the safety population experienced ≥ 1 AE during the treatment-emergent period [from study start-up to 2 weeks after the last treatment], and 8/72 [11.1%] experienced ≥ 1 AE during the follow-up period until Week 12 [Table 4]. No deaths occurred during the study. 6/85 [7.1%] patients experienced a serious adverse event [SAE]: UC, 4/85 [4.7%]; anal abscess, 1/85 [1.2%]; cytomegalovirus infection, 1/85 [1.2%]. None of these SAEs were considered related to study treatment according to the study investigators. The most frequent treatment-emergent adverse events [TEAEs] by MedDRA preferred term were headache [20.0%], colitis ulcerative [11.8%], and poor venous access [10.6%] [Table 5].

Mean changes in haemoglobin from baseline through Week 10 ranged from -0.21 to -0.44 g/dl; however, no clinically significant changes were observed at Week 12 compared with baseline. The number of platelets decreased from baseline at every visit, not

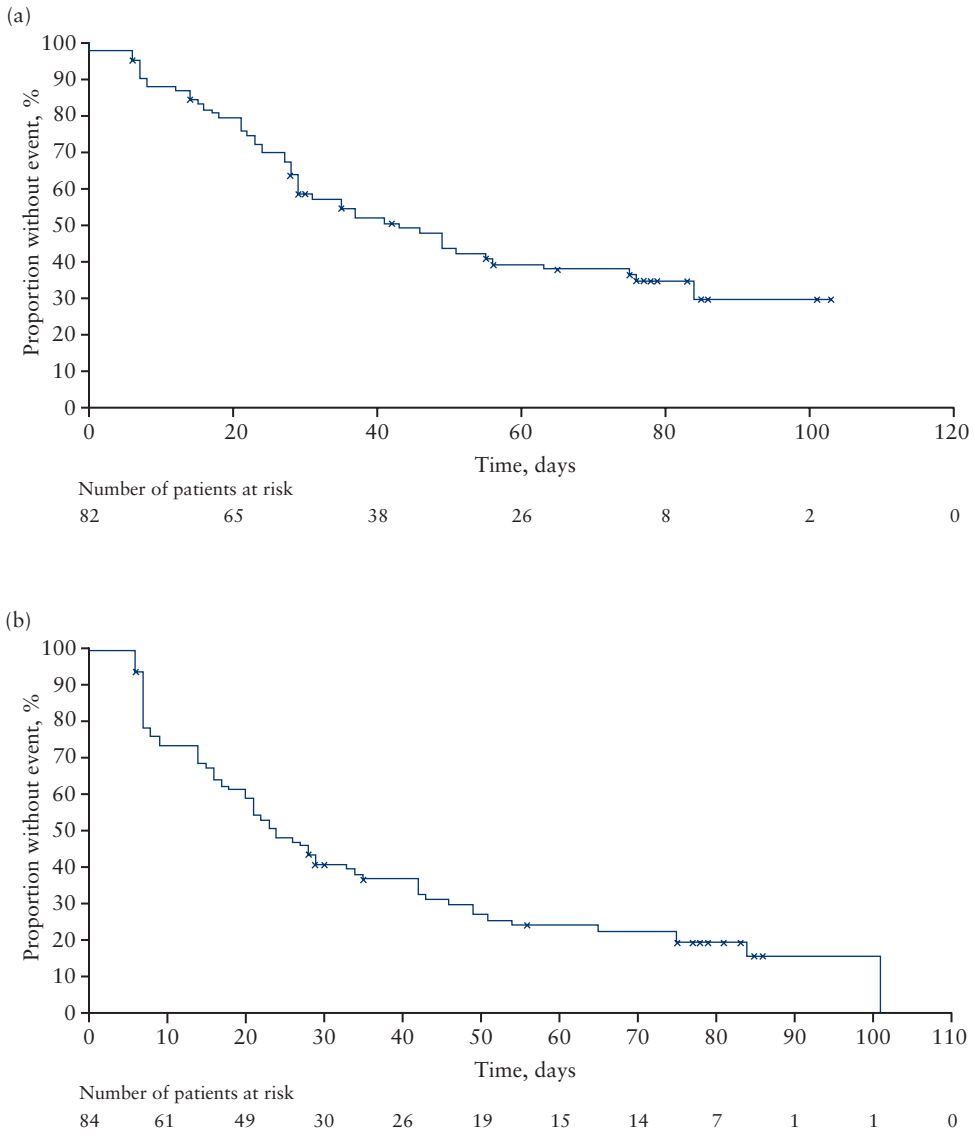

Figure 2. Time to [a] remission and [b] response for the ITT population. ITT, intention-to treat.

exceeding a maximum change of -28.8 x 10^9/l at Week 7. There were no clinically significant shifts in other laboratory parameters or in vital signs. There were no colectomies during the treatment-emergent period and there was one during the follow-up period.

5.4. Discussion

UC is a debilitating chronic disease that often affects young patients. Not all patients respond to biologic therapy, which can be associated with significant side effects. Our 12-week interim results from a large cohort of such UC patients show a treatment benefit with Adacolumn in UC patients with limited other therapeutic options. Nearly 40% of the patients in this trial achieved remission at Week 12 and over half achieved a response; furthermore, 23% of patients achieved steroid-free remission, with 36% achieving steroid-free response. Additional outcomes such as quality of life, CAI, and EAI also improved at Week 12 relative to baseline. The levels of calprotectin, which serve as a marker of inflammation,[20] also decreased over the course of the study. The majority of AEs were of mild or moderate intensity, and no new safety signals were observed.

The results of this interim analysis are consistent with previous studies; a pooled meta-analysis of seven randomised controlled trials showed that response or remission was achieved more often in UC patients treated with GMA [risk reduction 1.41; p = 0.01] than in patients treated with conventional therapy, and that after 12 weeks significantly higher remission rates were observed (risk reduction 1.22 [95% CI 1.04, 1.43]).[12] Another meta-analysis demonstrated a significantly improved response rate (odds ratio 2.88 [95% CI 1.60, 5.18]) and remission rate (odds ratio 2.04 [95% CI 1.36, 3.07]) as a result of GMA apheresis compared with conventional pharmacotherapy in patients with active moderate-to-severe UC.[14] In a systematic review of the clinical trial literature, it was shown that GMA apheresis appears to be of some benefit in moderate-to-severe UC,[13] suggesting further randomised controlled trials are required in patients with active disease. In a randomised controlled trial enrolling a moderate-to-severe steroid-dependent/refractory UC population, the non-inferiority of 5 and 10 Adacolumn treatments was established after 12 weeks, with clinical remission observed in 44% and 40% of patients, respectively.[21] These data are in contrast to a randomised trial of Adacolumn, in which patients with

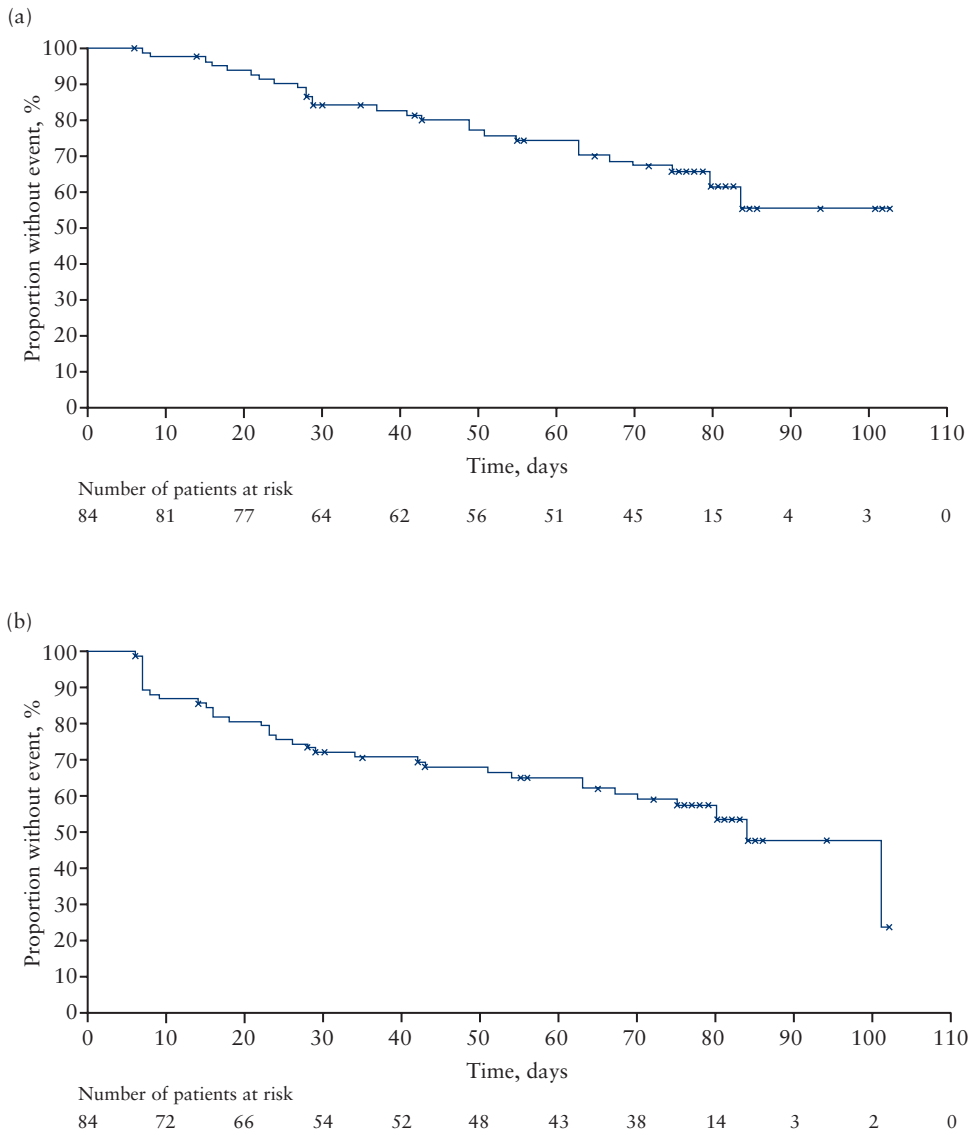

Figure 3. Time to [a] steroid-free remission and [b] steroid-free response for the ITT population. ITT, intention-to-treat.

Table 3. Quality of life change from baseline to Week 12 in the ITT population [*N* = 85].

Parameter	*n*	Mean [SD]	Min, max	95% CI
Symptoms from bowel disease	65	-19.0 [33.7]	-80.0, 93.0	-27.4, -10.7
Bowel disease affecting daily activities	65	-22.2 [33.9]	-87.0, 90.0	-30.6, -13.8
Bowel disease causing worry	65	-11.7 [29.7]	-70.0, 90.0	-19.1, -4.4
General well-being	65	-15.0 [33.0]	-98.0, 62.0	-23.2, -6.8

CI, confidence interval; ITT, intention-to-treat; SD, standard deviation; min, minimum; max, maximum.

Table 4. Summary of adverse events experienced in the study.

n [%]	Treatment-emergent period [*N* = 85]	Follow-up period [*N* = 72]
Patients with ≥ 1 AE	61 [71.8]	8 [11.1]
Patients with ≥ 1 SAE	6 [7.1]	0 [0]
Patients with ≥ 1 possibly treatment-related AE	27 [31.8]	0 [0]
Patients with ≥ 1 treatment-related SAE	0 [0]	0 [0]
Patients with ≥ 1 treatment-related AE leading to discontinuation of study treatment	16 [18.8]	0 [0]
Deaths	0 [0]	0 [0]

AE, adverse event; SAE, serious adverse event.

moderate-to-severe active UC received either Adacolumn or sham apheresis for 9 weeks. Clinical response was observed in 44% of Adacolumn-treated patients and 39% of sham-treated patients, a difference that was not statistically significant. However, a *post hoc* analysis found significant differences in clinical remission and response in patients with modified Riley scores of 7, denoting histologically active disease with erosions or ulcerations.[22] This suggests

Table 5. Most frequent treatment-emergent adverse events in the safety population [*N* = 85] by preferred term [> 5.0%].

MedDRA preferred term, *n* [%]	TEAE	Follow-up AE
Headache	17 [20.0]	0 [0]
Colitis ulcerative	10 [11.8]	3 [4.2]
Poor venous access	9 [10.6]	0 [0]
C-reactive protein increased	7 [8.2]	0 [0]
Vascular access complication[a]	7 [8.2]	0 [0]
Vascular procedure complication	6 [7.1]	0 [0]
Abdominal pain	5 [5.9]	0 [0]
Fatigue	5 [5.9]	0 [0]
Haemoglobin decreased	5 [5.9]	0 [0]

AE, adverse event; TEAE, treatment-emergent adverse event.
[a]Inability to cannulate or no flow

that the effect of apheresis is more apparent in UC patients with active disease.[23]

Since other therapies such as anti-TNF-α are associated with risk of serious infections, lymphoma, and associated mortality,[3,24,25] the favourable safety profile of Adacolumn as observed in the past and in present studies may therefore be of benefit in these patients. Common fears of patients with ulcerative colitis include adverse events associated with medications, which can affect adherence to treatments.[26,27] GMA itself is not without adverse events; in previous studies, shivering, nausea, headaches, 'flushing', and fever have been reported in 5–33% of treated patients.[7] The most common treatment-emergent adverse event observed in the present study was headache. Due to the nature of GMA, vascular access adverse events pose a potential problem for treatment administration; in this study, 8.2% of patients experienced vascular access complications, defined as the inability to cannulate or no flow. The events observed in this study were however mild-to-moderate; a non-drug therapy such as Adacolumn with this safety profile may be an attractive option for patients.

The ART population was composed of patients who are difficult to treat and for whom the current clinical guidelines are of less use due to a paucity of therapeutic options. A limitation of this study was the single-arm design, meaning that statistical comparisons could not be performed. A placebo control would have been included under ideal circumstances, but the clinical setting of the patient population provided the rationale for the ART study design, due to the difficulty of performing randomised trials in patients with urgent medical need. Positive data have been produced from clinical trials of anti-TNF-α therapies, with long-term steroid-free remission rates of 26% and 13.3% at 12 months,[3] and vedolizumab every 8 weeks in patients with moderate-to-severe UC which resulted in 12-month remission and steroid-free remission rates of 42% and 31%, respectively.[5] However, despite these data there still exists a sizeable population of patients that require effective treatment because of a lack of response to these drugs; results from the full 96-week ART study will provide insight into the long-term effectiveness of Adacolumn treatment.

In conclusion, Adacolumn treatment provided a positive and safe clinical benefit in terms of UC remission and response after 12 weeks in a difficult-to-treat patient subgroup who have limited effective treatment options.

Funding

This work was supported by Otsuka Pharmaceuticals Ltd. Medical writing assistance was provided by Jon Viney, PhD, of Succinct Medical Communications, funded by Otsuka Pharmaceuticals Ltd.

Conflict of Interest

AD received travel support and provision of writing assistance, medicines, equipment, or administrative support from ECCO relating to the submitted work. He has also received consultancy fees, speaker fees, or presentation development fees from Abbott, MSD, Ferring, UCB, Otsuka, Roche/Genentech, Takeda, Pharmacosmos, Holy Stone Biotech, Dr Falk, Sandoz, Hospira, Mundipharma, Vifor, Immundiagnostik, and Kompetenznetz CED, outside the submitted work. The Frankfurt Institute of Welfare and the Living With Cancer Foundation have provided grants to his institution. AA's institution received payment for the running of the study, including investigator fees and nurse time. She also has received advisory board and speaker fees outside the submitted work. AH received an advisory board fee outside the submitted work. SS received board membership and lectureship fees from Abbvie, Dr Falk, Boehringer Ingelheim, Vifor, Jenssen, MSD, Actavis, and Shire, payment for the development of educational presentations from MSD and Abbvie, and meeting expenses from MSD, Abbvie, and Actavis, outside the submitted work; his institution received a fee per patient for recruitment to the ART study. DB received consultancy and lectureship fees from Otsuka outside the submitted work. GC received a grant from Otsuka relating to the submitted work, and board membership, lectureship, and meeting expenses from Ipsen, Novartis, Keocyt, Pfizer, Abbvie, and Ferring, outside the submitted work. RM received travel support from Otsuka related to the submitted work. SH received travel support from Otsuka related to the submitted work, and a grant and consulting fee from Otsuka paid to his institution related to the submitted work. GB received board membership, consultancy, and lectureship fees from Abbvie, MSD, Ferring, and Norgine, outside the submitted work. BB reports no conflict of interest relating to the submitted work; he has received consultancy fees from MSD, Abbvie, Ferring, Biogaran, and Takeda, outside the submitted work. GB and J-CG report no conflicts of interest.

Author Contributions

All authors were involved in the conduct of the study and the development of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

The authors would like to express their thanks to all investigators of the ART trial: Dr Purushothaman Premchand, Clinical Diagnostic Unit, Queens Hospital, Romford, UK; Dr Anton Gillessen, Herz-Jesu-Krankenhaus Hiltrup GmbH, Münster, Germany; Dr Phil Matthews, Department of Medicine, University Hospital of North Durham, Durham, UK; Dr Christophe Michiels, CHU Le Bocage, Service Hepato-Gastro-Enterologie, Dijon, France; Dr Jacques Moreau, Hôpital Rangueil, Pôle Digestif, Toulouse, France; Dr Wolfgang Ramlow, Clinic for Nephrology, Dialysis and Apheresis, Rostock, Germany; Dr Stefan Schanz, Kreisklinikum Siegan, Siegan, Germany; Dr Christian von Tirpitz, Medizinische Klinik – Gastroenterologie, Kreisklinik Biberach-Ochsenhausen-Laupheim-Riedlingen, Biberach, Germany.

References

1. Danese S, Fiocchi C. Ulcerative colitis. *N Engl J Med* 2011;**365**:1713–25.
2. Dignass A, Eliakim R, Magro F, *et al*. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 1: Definitions and diagnosis. *J Crohns Colitis* 2012;**6**:965–90.
3. Dignass A, Lindsay JO, Sturm A, *et al*. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012;**6**:991–1030.
4. Bär F, Sina C, Fellermann K. Thiopurines in inflammatory bowel disease revisited. *World J Gastroenterol* 2013;**19** 1699–706.
5. Feagan BG, Rutgeerts P, Sands BE, *et al*. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;**369**:699–710.
6. Saniabadi AR, Tanaka T, Ohmori T, Sawada K, Yamamoto T, Hanai H. Treating inflammatory bowel disease by adsorptive leucocytapheresis: a desire to treat without drugs. *World J Gastroenterol* 2014;**20**:9699–715.
7. Vecchi M, Vernia P, Riegler G, D'Incà R, Annese V, Bagnoli S. Therapeutic landscape for ulcerative colitis: where is the Adacolumn[®] system and where should it be? *Clin Exp Gastroenterol* 2013;**6**:1–7.

8. Matsumoto T, Andoh A, Okawa K, *et al*. Multivariate analysis for factors predicting rapid response of leukocytapheresis in patients with steroid-resistant ulcerative colitis: a multicenter prospective open-label study. *Ther Apher Dial* 2008;**12**:484–90.
9. Hanai H, Takeda Y, Eberhardson M, *et al*. The mode of actions of the Adacolumn therapeutic leucocytapheresis in patients with inflammatory bowel disease: a concise review. *Clin Exp Immunol* 2011;**163**:50–8.
10. Kashiwagi N, Hirata I, Kasukawa R. A role for granulocyte and monocyte apheresis in the treatment of rheumatoid arthritis. *Ther Apher Dial* 1998;**2**:134–41.
11. Saniabadi AR, Hanai H, Takeuchi K, *et al*. Adacolumn, an adsorptive carrier based granulocyte and monocyte apheresis device for the treatment of inflammatory and refractory diseases associated with leukocytes. *Ther Apher Dial* 2003;**7**:48–59.
12. Habermalz B, Sauerland S. Clinical effectiveness of selective granulocyte, monocyte adsorptive apheresis with the Adacolumn device in ulcerative colitis. *Dig Dis Sci* 2010;**55**:1421–8.
13. Thanaraj S, Hamlin PJ, Ford AC. Systematic review: granulocyte/monocyte adsorptive apheresis for ulcerative colitis. *Aliment Pharmacol Ther* 2010;**32**:1297–306.
14. Zhu M, Xu X, Nie F, Tong J, Xiao S, Ran Z. The efficacy and safety of selective leukocytapheresis in the treatment of ulcerative colitis: a meta-analysis. *Int J Colorectal Dis* 2011;**26**:999–1007.
15. Cabriada JL, Domènech E, Ibargoyen N, *et al*. Leukocytapheresis for steroid-dependent ulcerative colitis in clinical practice: results of a nationwide Spanish registry. *J Gastroenterol* 2012;**47**:359–65.
16. Kruis W, Dignass A, Steinhagen-Thiessen E, *et al*. Open label trial of granulocyte apheresis suggests therapeutic efficacy in chronically active steroid refractory ulcerative colitis. *World J Gastroenterol* 2005;**11**:7001–6.
17. Rachmilewitz D. Coated mesalazine [5-aminosalicylic acid] versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. *BMJ* 1989;**298**:82–6.
18. Yamamato T, Umegae S, Matsumoto K. Safety and clinical efficacy of granulocyte and monocyte adsorptive apheresis therapy for ulcerative colitis. *World J Gastroenterol* 2006;**12**:520–5.
19. Hjortswang H, Järnerot G, Curman B, *et al*. The Short Health Scale: a valid measure of subjective health in ulcerative colitis. *Scand J Gastroenterol* 2006;**41**:1196–203
20. Lehmann FS, Burri E, Beglinger C. The role and utility of faecal markers in inflammatory bowel disease. *Ther Adv Gastroenterol* 2015;**8**:23–36.
21. Dignass AU, Eriksson A, Kilander A, Pukitis A, Rhodes JM, Vavricka S. Clinical trial: five or ten cycles of granulocyte-monocyte apheresis show equivalent efficacy and safety in ulcerative colitis. *Aliment Pharmacol Ther* 2010;**31**:1286–95.
22. Sands BE, Sandborn WJ, Feagan B, *et al*. A randomized, double-blind, sham-controlled study of granulocyte/monocyte apheresis for active ulcerative colitis. *Gastroenterology* 2008;**135**:400–9.
23. Kruis W, Nguyen P, Morgenstern J. Granulocyte/Monocyte Adsorptive Apheresis in Moderate to Severe Ulcerative Colitis Effective or Not? *Digestion* 2015;**92**:39–44.
24. Rahier JF, Ben-Horin S, Chowers Y, *et al*. European Evidence-based Consensus on the prevention, diagnosis, and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009;**3**:47–91.
25. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2009;**7**:874–81.
26. Kane SV, Brixner D, Rubin DT, Sewitch MJ. The challenge of compliance and persistence: focus on ulcerative colitis. *J Manag Care Pharm* 2008;**14**[1 Suppl A]:s2–12; quiz s13–5.
27. Irvine EJ. Patients' fears and unmet needs in inflammatory bowel disease. *Aliment Pharmacol Ther* 2004;**20**:54–9.
28. Satsangi J, Silverberg MS, Vermeire S, Colombel J. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;**55**:749–53.