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Anti-CD3 antibody visilizumab is not effective in patients with intravenous corticosteroid-refractory ulcerative colitis

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► Additional appendix is published online only. To view these files please visit the journal online (<http://gut.bmj.com>).

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ABSTRACT

Background and aims Pilot studies with visilizumab, a humanised monoclonal antibody to CD3, suggest efficacy for corticosteroid-refractory ulcerative colitis (UC). A placebo-controlled trial was warranted.

Methods A randomised, double-blind, placebo-controlled study evaluated the efficacy of visilizumab induction treatment in 127 patients with severely active UC despite treatment with ≥ 5 days of intravenous corticosteroids. Patients received placebo or visilizumab 5 μ g/kg intravenously on days 1 and 2. Corticosteroids were tapered according to disease activity. Patients were followed up for 90 days. The primary end point was induction of response at day 45. Secondary end points included remission and mucosal healing at day 45, symptomatic response at day 15 and colectomy.

Results Response at day 45 occurred in 55% of patients receiving visilizumab compared with 47% of those who received placebo ($p=0.475$). Remission at day 45 occurred in 8% of patients receiving visilizumab compared with 9% of those who received placebo ($p=0.704$). Mucosal healing at day 45 occurred in 29% of patients receiving visilizumab compared with 26% of those who received placebo ($p=0.799$). Symptomatic response at day 15 occurred in 82% of patients receiving visilizumab compared with 74% of those who received placebo ($p=0.244$). Colectomy was performed in 18% of patients receiving visilizumab compared with 7% of those who received placebo ($p=0.130$). Cardiac disorders and vascular disorders occurred more frequently in the patients who received visilizumab.

Conclusion Visilizumab at a dose of 5 μ g/kg for two consecutive days was not effective for severe, corticosteroid-refractory UC and was associated with increased cardiac and vascular adverse events. (Registered at <http://www.clinicaltrials.gov> NCT00279422/).

INTRODUCTION

Severe ulcerative colitis is defined by the Truelove and Witts criteria as 6 or more stools per day with frequent blood and signs of systemic toxicity.¹ Approximately 15–20% of all patients with ulcerative colitis will develop a severe flare at some point in their disease course.² In patients with severe colitis, initial treatment consists of the Oxford treatment regimen described by Truelove and Jewell—namely, intravenous fluids, electrolyte supplements, bowel rest, transfusion if indicated, intravenous corticosteroids and rectal cortico-

Significance of this study

What is already known about this subject?

- Medical treatments for intravenous corticosteroid-refractory ulcerative colitis are limited.
- Previous uncontrolled trials reported that visilizumab, a humanised IgG2 monoclonal antibody to CD3, might be effective for intravenous corticosteroid-refractory ulcerative colitis.
- Previous studies with visilizumab primarily used the modified Truelove and Witts Severity Index (MTWSI, also known as the Lichtiger Index) to assess efficacy.
- The MTWSI was also used in previous studies to demonstrate that ciclosporin was effective for intravenous corticosteroid-refractory ulcerative colitis.

What are the new findings?

- Visilizumab resulted in transient almost complete T-cell depletion.
- Visilizumab was not effective for the treatment of intravenous corticosteroid-refractory ulcerative colitis.
- The response and remission rates as measured by the MTWSI were much higher than the response and remission rates measure by the Mayo Score.
- Visilizumab was associated with increased rates of infections, cytokine release syndrome, cardiac disorders and vascular disorders.

How might they impact on clinical practice in the foreseeable future?

- Treatments that are broadly directed against T cells may not be effective for ulcerative colitis.
- The MTWSI score correlates poorly with the Mayo score and with endoscopic healing and may not be measuring a clinically meaningful effect.
- Additional validation of instruments to assess efficacy of medical treatments in patients with intravenous corticosteroid-refractory ulcerative colitis is needed.

steroids.³ Sixty per cent of patients treated with this regimen will be symptom free by the end of 5 days, 15% will have significant improvement and 25% will not improve and require salvage medical treatment or colectomy.^{4 5} Salvage medical

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treatments for patients who fail to improve include ciclosporin, tacrolimus and infliximab.^{6–12} The controlled data supporting these salvage treatments are limited by small sample size, and longer-term follow-up studies with ciclosporin have reported high rates of subsequent colectomy and treatment-associated mortality of 2–3%.^{13–15} A recent meta-analysis reported that the colectomy rate in patients with severe ulcerative colitis requiring treatment with intravenous corticosteroids has not changed in the past 30 years.¹⁶ New treatments for patients with severe intravenous corticosteroid-refractory ulcerative colitis are needed.

T cells have an important role in the pathogenesis of ulcerative colitis and targeting T-cell surface receptors such as CD3 is a potential therapeutic strategy for this disease.^{17–18} Visilizumab (HuM291, Nuvion) is a humanised IgG2 monoclonal antibody to the invariant CD3 chain of the T-cell receptor CD3.¹⁹ Visilizumab was engineered to reduce FcR binding, thus diminishing cytokine release syndrome, complement fixation and activation of resting T cells while at the same time selectively inducing apoptosis in active T cells.^{19–20} Visilizumab has previously been evaluated for the treatment of renal allograft rejection and graft versus host disease.^{21–23} Open label phase I and IIa trials of visilizumab in patients with severe intravenous corticosteroid-refractory ulcerative colitis have shown evidence of efficacy and indicated that a dose of 5 µg/kg administered on two consecutive days is an appropriate clinical dose.^{24–25}

We conducted a 90 day placebo-controlled trial of visilizumab in patients with severe intravenous corticosteroid-refractory ulcerative colitis.

PATIENTS AND METHODS

Patients

This multicentre, randomised, double-blind, placebo-controlled study was conducted globally at 75 sites in 14 countries (Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Hungary, Israel, Netherlands, Norway, Slovakia, Ukraine, United States) between February 2006 and November 2007. The institutional review board or ethics committee at each site approved the protocol. All patients gave written informed consent.

Eligible patients included men or women at least 18 years of age with a diagnosis of ulcerative colitis for whom oral corticosteroid treatment had failed or who were newly diagnosed and hospitalised and who currently had severely active intravenous corticosteroid-refractory disease. Severely active intravenous corticosteroid-refractory ulcerative colitis was defined by a modified Truelove and Witts Severity Index score (MTWSI, also known as the Lichtiger score)^{6–26} ≥ 10 points on or after the fifth consecutive day of intravenous corticosteroids (methylprednisolone ≥ 40 mg/day or equivalent) and within 1 day before randomisation. In addition, patients were required to have a Mayo score^{26–27} of ≥ 10 points and a Mayo sigmoidoscopy subscore of ≥ 2 points. The Mayo score was calculated on the day of sigmoidoscopy by a blinded gastroenterologist, after a minimum of three consecutive days (ie, on or after the fourth consecutive day) of intravenous corticosteroids. In addition to intravenous corticosteroids, patients could be receiving mesalamine, azathioprine, 6-mercaptopurine, or methotrexate.

Patients were excluded from study participation if they had an ileostomy, proctocolectomy or subtotal colectomy with ileorectal anastomosis, or required immediate surgical, endoscopic, or radiological intervention for massive haemorrhage, perforation, sepsis, intra-abdominal or perianal abscess, or toxic megacolon.

Patients were also excluded if they had had a positive *Clostridium difficile* test within 10 days before the first dose of study drug, active medically significant infections (particularly those of viral aetiology such as cytomegalovirus colitis), any medically significant opportunistic infection within the past 12 months, vaccination with a live virus within 6 weeks, or were seropositive for human immunodeficiency virus, hepatitis B virus surface antigen, or hepatitis C virus antibody. Additional exclusion criteria included significant renal, liver, central nervous system, pulmonary, vascular, gastrointestinal, or endocrine conditions or laboratory abnormalities (eg, white blood cell count $<2.5 \times 10^3/\mu\text{L}$; platelet count $<150 \times 10^3/\mu\text{L}$; haemoglobin concentration <8 g/dl; creatinine ≥ 1.6 mg/dl; alanine aminotransferase or aspartate aminotransferase ≥ 2 times the upper limit of normal; alkaline phosphatase ≥ 1.5 times the upper limit of normal); a non-therapeutic level of a chronic anti-convulsant drug within 4 days, or medically significant cardiac conditions, including a history of myocardial infarction, coronary artery disease, congestive heart failure, or arrhythmias within 6 months. Patients were also excluded if they had a history of lymphoproliferative disorder or malignancy within the past 5 years (except for non-melanoma skin cancer or carcinoma in situ of the cervix). Patients who had received the first dose of infliximab, or another anti-tumour necrosis factor drug within 4 weeks of randomisation or a subsequent dose within 2 weeks of randomisation, ciclosporin or tacrolimus (FK506) within 2 weeks, or any investigational treatment within 60 days, were excluded. Pregnant and/or lactating women were also excluded from study participation.

Design of the study

Eligible patients were randomised (in a 2:1 ratio) to receive intravenous infusions of visilizumab (Nuvion, PDL BioPharma, Redwood City, California, USA) at a dose of 5 µg/kg or placebo on days 1 and 2. Ondansetron, acetaminophen and diphenhydramine were administered within 1 h before each dose of study drug and as needed after dosing for treatment of cytokine release syndrome symptoms. Patients were also hydrated with at least 1 litre of intravenous fluids before receiving study drug and hydration was continued after dosing. Meperidine or morphine sulphate were used for treatment of chills. Patients were followed up through day 90. The study employed central randomisation with adaptive treatment allocation stratified according to: (1) prior treatment with infliximab within 8 weeks and (2) investigational site.

Mesalamine was permitted at a stable dose throughout the trial. Azathioprine, 6-mercaptopurine and methotrexate were discontinued at the screening visit. Intravenous corticosteroids were converted to oral prednisone 40 mg at day 3. Beginning on day 9, patients with a baseline MTWSI score <16 points and a stable or improved day 9 MTWSI score tapered their prednisone dose by 5 mg/week until discontinuation. Patients with a baseline MTWSI score >16 points were managed at the investigator's discretion until day 15 and then tapered their prednisone dose by 5 mg/week until discontinuation. Patients who had an increase from baseline in their MTWSI score ≥ 3 points during the study could increase their prednisone dose by up to 20 mg/day to a maximum daily dose of 40 mg/day. After day 45, patients could resume or initiate azathioprine at a dose of 2.0 mg/kg/day.

Efficacy evaluations

The MTWSI score (table 1) was determined at baseline and at days 1, 2, 4, 8, 11, 15, 22, 30, 45, 60 and 90. Symptomatic

Table 1 Modified Truelove and Witts Severity Index (MTWSI) also known as the Lichtiger Index

Variable	Scores				
	0	1	2	3	4 5
Diarrhoea (number of daily stools)	0–2	3 or 4	5 or 6	7–9	≥10
Nocturnal diarrhoea	No	Yes			
Visible blood in stool (% of movements)	0	<50	≥50	100	
Fecal incontinence	No	Yes			
Abdominal pain or cramping	None	Mild	Moderate	Severe	
General wellbeing	Perfect	Very good	Good	Average	Poor Terrible
Abdominal tenderness	No	Mild and localised	Mild to moderate and diffuse	Severe or rebound	
Need for antidiarrhoeal drugs	No	Yes			

The MTWSI score ranges from 0 to 21 with higher scores indicating more severe disease. Reprinted with permission from: **Lichtiger S**, Present DH. Preliminary report: cyclosporine in treatment of severe active ulcerative colitis. *Lancet* 1990;**336**:16–19.

response was defined as a MTWSI score of ≤9 points, with a reduction of ≥3 points from baseline. Symptomatic response was assessed at day 15. The Mayo score (table 2) was determined at baseline and day 45. The partial Mayo score was a 10 point score (0–9 points) comprising stool frequency, rectal bleeding and physician's global assessment domains from the total Mayo score. Response was defined as a decrease from baseline in the total Mayo score ≥3 points with an accompanying decrease in rectal bleeding subscore ≥1 point or an absolute rectal bleeding subscore of 0 or 1. Remission was defined as a total Mayo score of <3 points, with no individual subscore >1 point. Mucosal healing was defined as an absolute endoscopy subscore of ≤1 point. Response, remission and mucosal healing were assessed at day 45. Central reading of the endoscopy findings was not employed.

Safety evaluations

At each visit, adverse events and concomitant drugs were recorded. Blood was collected for C-reactive protein (CRP), T-cell counts, Epstein–Barr virus (EBV) DNA and liver function test values and other routine laboratory safety assessments. Assays for anti-visilizumab antibodies were not performed.

Statistical methods

The primary end point was response at day 45. Secondary end points were remission at day 45, mucosal healing at day 45, symptomatic response at day 15, time to symptomatic response, time to disease progression (defined as a need for salvage treatment—that is, the administration of ciclosporin, tacrolimus, infliximab, re-treatment on another visilizumab protocol, or colectomy), time to colectomy, ability to taper prednisone dose to 0 mg/day for at least seven consecutive days and time to prednisone dose of 0 mg/day in patients who were able to achieve this. Patients who took prohibited medication, who experienced disease progression before day 45, or who underwent a colectomy were not considered to be in response. In addition, patients with insufficient data for response assessment were not considered to be in response.

A two-sided 0.05 level Cochran–Mantel–Haenszel χ^2 test, stratified by treatment with infliximab within 8 weeks and study site region was used to compare dichotomous end points (ie, response, remission, mucosal healing, symptomatic response, or ability to taper prednisone dose to 0 mg/day for at least 7 consecutive days). The median time to disease progression and the median time to colectomy were estimated using the Kaplan–Meier product-limit method. Continuous variables, such as age, CRP, CD4+ T-cell count, EBV titre and MTWSI score were analysed using a three-way analysis of variance at 5% significance level, with effects for treatment group, treatment

with infliximab within 8 weeks and study site region. Adverse events were analysed using Fisher's exact test. All efficacy analyses used intention-to-treat methods.

Assuming a response rate of 15% in the placebo group and a two-sided test at the 0.05 level, a sample size of 100 patients in the visilizumab group and 50 patients in the placebo group provides power of 0.90 to detect an improvement in the response rate to 40% with visilizumab.

Table 2 Mayo scoring system for assessment of ulcerative colitis activity

Stool frequency*
0=Normal number of stools for this for this patient
1=1–2 stools more than normal
2=3–4 stools more than normal
3=5 or more stools more than normal
*Each patient served as his or her own control to establish the degree of abnormality of the stool frequency.
Rectal bleeding†
0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passed
†The daily bleeding score represented the most severe day of bleeding.
Findings of flexible proctosigmoidoscopy
0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, mild friability)
2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)
Physician's global assessment‡
0 = Normal (there are no symptoms of colitis, the patient feels well and the flexible proctosigmoidoscopy score is 0) (stool frequency = 0, rectal bleeding = 0, patient's functional assessment = 0, flexible proctosigmoidoscopy findings = 0)
1 = Mild disease (mild symptoms and proctoscopic findings that were mildly abnormal) (the subscores should be mostly 1s: stool frequency = 0 or 1; rectal bleeding = 0 or 1; patient's functional assessment = 0 or 1; sigmoidoscopy findings = 0 or 1)
2 = Moderate disease (more serious abnormalities and proctosigmoidoscopic and symptom scores of 1 to 2) (the subscores should be mostly 2's: stool frequency = 1 or 2; rectal bleeding = 1 or 2; patient's functional assessment = 1 or 2; sigmoidoscopy findings = 1 or 2)
3 = Severe disease (the proctosigmoidoscopic and symptom scores are 2–3 and the patient probably requires corticosteroid treatment and possibly hospitalisation) (the subscores should be mostly 3s: stool frequency = 2 or 3; rectal bleeding = 2 or 3; patient's functional assessment = 2 or 3; sigmoidoscopy findings = 2 or 3)
‡The physician's global assessment acknowledged the three other criteria, the patient's daily record of abdominal discomfort and general sense of wellbeing and other observations, such as physical findings and the patient's performance status. Patient's functional assessment (this variable is not included in the 12-point index calculation but is considered as a measure of general sense of wellbeing when determining the physician's global assessment score)
0 = Generally well
1 = Fair
2 = Poor
3 = Terrible

The Mayo score ranges from 0 to 12 with higher scores indicating more severe disease. Reprinted with permission from: **Schroeder KW**, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid treatment for mildly to moderately active ulcerative colitis. *N Engl J Med* 1987;**317**:1625–9.

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RESULTS

Patient disposition, baseline characteristics and baseline concomitant drugs

The enrolment and treatment of patients in the trial is shown in figure 1. On 24 August 2007 an independent Data Safety Monitoring Board reviewed the interim efficacy and safety data on 91 patients and recommended that the trial be stopped because of insufficient efficacy and an inferior safety profile for visilizumab compared with placebo. The trial was stopped on 28 August 2007, at which time 127 of the planned 150 patients had already been randomised and treated. These patients were followed up out to day 90 according to the protocol. Of the 127 patients, 84 were randomised to visilizumab and 43 to placebo. The baseline characteristics including concomitant drugs were generally similar in the two groups (table 3).

Efficacy

At day 45, there were no significant differences between the treatment groups in the rates of response (figure 2A), remission (figure 2B), or mucosal healing (figure 2C). Similarly, at day 15 there were no significant differences between the treatment groups in the rates of symptomatic response (figure 3A). The median (95% CI) time to symptomatic response was 11 (8 to 15) days in the visilizumab group and 11 (8 to 30) days in the placebo group. The mean MTWSI scores over time are shown in figure 3B. The correlations between the MTWSI score and the total Mayo score and the partial Mayo score at day 45 were 0.6476 and 0.6476, respectively. Disease progression occurred in 26% (22 of 84) of patients in the visilizumab group and 33% (14 of 43) of patients in the placebo group. Of these patients, 19 in the visilizumab group (23%) and 11 in the placebo group (26%) received salvage treatment with an anti-tumour necrosis factor agent (infliximab or adalimumab). The median time to disease progression could not be calculated in the visilizumab and placebo groups ($p=0.372$; figure 3C). The proportions (95% CI) of patients who underwent colectomy were 18% (10% to 28%; 15 of 84 patients) in the visilizumab group and 7% (2% to 19%; 3 of 43 patients) in

Table 3 Summary of demographic and baseline disease characteristics

Subjects randomised	Placebo 43	Visilizumab 5 µg/kg 84
Male, n (%)	28 (65)	52 (62)
Caucasian, n (%)	40 (93)	78 (93)
Age (years)		
Mean (SD)	40.8 (13.5)	40.4 (12.9)
Body weight (kg)		
Mean (SD)	74.8 (16.8)	75.5 (17.3)
Disease duration (years)		
Mean (SD)	6.4 (6.8)	6.8 (7.1)
Involved colonic area, n		
Less than splenic flexure, n (%)	11 (25.6)	27 (32.1)
Less than hepatic flexure, n (%)	10 (23.3)	14 (16.7)
Pancolitis, n (%)	20 (46.5)	42 (50.0)
Missing, n (%)	2 (4.7)	1 (1.2)
Mayo score		
Mean (SD)	10.7 (0.8)	10.7 (0.9)
MTWSI score		
Mean (SD)	13.0 (2.1)	13.5 (2.2)
C-reactive protein (mg/l)		
Mean (SD)	37 (44)	30 (49)
Median (range)	23 (0–200)	10 (0–265)
CD4+ T-cell count (µl)		
Mean (SD)	415 (287)	637 (420)
EBV (≥5000 copies/ml), n (%)	15 (34.9)	24 (28.6)
Current medication, n (%)		
Aminosalicylates	11 (25.6)	30 (35.7)
Corticosteroids	43 (100)	84 (100)
Immunomodulators		
Azathioprine	8 (18.6)	10 (11.9)
6-MP	1 (2.3)	0 (0)
Methotrexate	3 (7.0)	1 (1.2)
Ciclosporin	1 (2.3)	0 (0)
Anti-TNF agent within 8 weeks	6 (14.0)	10 (11.9)
Anti-TNF agent within 2 weeks	4 (9.3)	4 (4.8)
Past medication, n (%)		
Aminosalicylates	38 (88.4)	75 (89.3)
Corticosteroids	38 (88.4)	76 (90.5)
Immunomodulators		
Azathioprine	23 (53.5)	44 (52.4)
6-MP	7 (16.3)	13 (15.5)
Methotrexate	6 (14.0)	10 (11.9)
Ciclosporin	4 (9.3)	8 (9.5)
Anti-TNF agent	14 (32.6)	30 (35.7)
Smoking status, n (%)		
Non-smoker	25 (58.1)	38 (45.2)
Previous smoker	12 (27.9)	42 (50.0)
Current smoker	6 (14.0)	4 (4.8)

EBV, Epstein-Barr virus; 6-MP, 6-mercaptopurine; MTWSI, modified Truelove and Witts Severity Index; TF, tumour necrosis factor.

Figure 1 Enrolment and treatment of patients. Forty-three patients with severe intravenous steroid-refractory ulcerative colitis were randomised to receive intravenous treatment with placebo and 84 were randomised to receive visilizumab 5 µg/kg on days 1 and 2. The efficacy and safety populations through day 90 comprise all 127 randomised patients.

the placebo group. The median time to colectomy could not be calculated in the visilizumab and placebo groups ($p=0.130$). The proportions (95% CI) of patients who tapered prednisone to 0 mg for at least 7 days were 14% (7% to 24%; 12 of 84 patients) in the visilizumab group and 21% (10% to 36%; 9 of 43 patients) in the placebo group ($p=0.255$). The median time to prednisone dose of 0 mg/day could not be calculated in the visilizumab and placebo groups.

CRP, CD4+ T-CELL COUNTS AND EBV REACTIVATION

The baseline mean and median CRP concentrations for the two treatment groups are shown in table 3. The mean CRP concentrations over time are shown in figure 4A.

Figure 2 The proportions of patients at day 45 with response (A), remission (B) and mucosal healing (C).

The administration of visilizumab resulted in a rapid reduction of CD4+ T-cells in all patients (figure 4B). The CD4+ T-cell counts were reduced from a mean (SD) value of 637 (420) cells/ μ l at baseline to a nadir value of 10 (16) cells/ μ l. The CD4+ T-cell decreases were reversible with a median (min, max) time to recovery of 15 (2, 157) days. Eighty-eight per cent of patients recovered their CD4+ T-cell counts by day 90 (recovery defined as CD4+ T-cell cell count ≥ 200 cells/ μ l or $\geq 80\%$ of the patient's baseline value). Similar results were observed for CD3+, CD3+CD4+, CD3+CD8+, CD3-CD16/56 T-cell counts and to a lesser degree CD3-CD19+ T-cell counts (data not shown).

At baseline, 35% of patients in the placebo group and 29% of patients in the visilizumab group were EBV positive (defined as ≥ 5000 copies/ml). After administration of visilizumab, the whole-blood EBV DNA levels increased in 16% of patients in the visilizumab group (increase defined as EBV concentrations >0.5 log of the baseline value) as compared with 7% in the placebo group. The increase in EBV DNA was transient with a median (min, max) time to recovery (defined as EBV levels $\leq 10^{0.5} \times$ subject's baseline level) of 30 (28, 121) days.

Safety

Adverse events occurred in 77% of patients in the placebo group and 96% of patients in the visilizumab group (table 4). Grades 2, 3 and 4 adverse events occurred more frequently in the visilizumab group. The proportions of patients with serious adverse events were similar in the placebo and visilizumab groups. One patient in the visilizumab group developed hepatic focal nodular hyperplasia. No patient developed cancer and no patient died.

The incidence of infections was slightly lower in the placebo group than in the visilizumab group (table 4). Serious infections occurred in three patients (7%) in the placebo group and four patients (5%) in the visilizumab groups. Infectious adverse events of interest included herpes simplex (2%), oral fungal

infection (2%) and sepsis (2%) in the placebo group and herpes zoster (2%), cytomegalovirus (1%), fungal infection (1%), fungal oesophagitis (1%) and oral candidiasis (1%) in the visilizumab group.

Cardiac disorders, vascular disorders and cytokine release syndrome all occurred more frequently in patients who received visilizumab. Many of the cardiac and vascular disorder adverse events overlapped with the adverse events that contributed to cytokine release syndrome. Cardiac disorders occurred in 5% of patients in the placebo group and 12% of patients in the visilizumab group (table 4). Cardiac disorders of interest include angina pectoris (1%), cardiomyopathy (1%) and myocardial ischaemia (1%), all in the visilizumab group. Vascular disorders occurred in 5% of patients in the placebo group and 23% of patients in the visilizumab group (table 4). Vascular disorders of interest included phlebitis (2%), superficial thrombophlebitis (2%), deep venous thrombosis (1%) and vasculitis (1%), all in the visilizumab group. Cytokine release syndrome occurred in 19% of patients in the placebo group and 70% of patients in the visilizumab group (table 4).

An increase from baseline in liver transaminases (alanine aminotransferase (ALT), aspartate amino transferase (AST) and γ -glutamyltransferase (GGT)) was seen in about half of the patients receiving visilizumab. The proportion of patients with increases in liver function tests during the study that were 1.5-fold above the upper limit of normal or 1.5-fold above the patient's baseline concentration were as follows: ALT, 12% placebo, 51% visilizumab; AST, 2% placebo, 37% visilizumab; and GGT, 14% placebo, 63% visilizumab. In contrast, the proportion of patients with increases in alkaline phosphatase and total bilirubin were minimal (5% placebo, 6% visilizumab and 2% placebo, 7% visilizumab, respectively). These increases in transaminases were transient (usually lasting <2 weeks), were not associated with clinical sequelae and resolved in nearly all patients by day 90.

Figure 3 The proportions of patients at day 15 with symptomatic response (A), mean modified Truelove and Witts Severity Index (MTWSI) scores over time (B) and the time to disease progression (C).

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Figure 4 The mean C-reactive protein (CRP) concentrations (A) and CD4+ T-cell counts (B) over time. D, day; H, hour; M, minute.

DISCUSSION

The results of our study show that visilizumab administered at a dose of 5 µg/kg for two consecutive days is not effective in achieving symptomatic response at day 15; response, remission, or mucosal healing at day 45; prolongation of time to disease progression; or corticosteroid discontinuation in patients with severe intravenous corticosteroid-refractory ulcerative colitis. The patients who received visilizumab had a trend towards a greater rate of colectomy and were more likely to experience signs and symptoms of cytokine release, including cardiac and vascular disorders, some of which were severe and/or serious. Based on this unfavourable benefit to risk profile identified during an interim analysis, the trial was discontinued prematurely.

There are a variety of potential explanations for the lack of successes of visilizumab. In the preceding phase I and I/II trials, response (as measured by the Mayo score) was defined as a decrease from baseline ≥ 3 points, without a requirement for reduction in the rectal bleeding score ≥ 1 point or an absolute rectal bleeding score of 0 or 1 point. This may have overestimated clinically meaningful rates of response.^{24 25} In this study, similar to previous studies with infliximab,²⁸ a more rigorous definition of response was used that required BOTH a decrease from baseline ≥ 3 points AND a reduction in the rectal bleeding score ≥ 1 point or an absolute rectal bleeding score of 0 or 1 point. This more rigorous definition might have led to a somewhat lower response rate of 55%. In addition, the placebo response rate of 47% was considerably higher than expected. It should be emphasised that no validated instrument exists for assessing disease activity in patients with severe, intravenous corticosteroid-refractory ulcerative colitis and few clinical trial data with any agent exist for this patient population.

The rate of symptomatic response at day 15 (as measured by the MTWSI) was high in this study, although similar to the rates of symptomatic response reported in the previous phase I and I/II trials with visilizumab.^{24 25} Interestingly, the placebo response rate of 74% (as measured by the MTWSI) was much higher than expected and much higher than reported previously in a much smaller study where the placebo response rate was 0%.⁶ In contrast with the day 15 results, the rates of response, remission and healing at day 45 (as measured by the Mayo score) were considerably lower. The correlations between the MTWSI score and both the total Mayo score and the partial Mayo score were low at baseline and moderate at day 45. The MTWSI was developed empirically for use in several small studies.^{6 29} It has never been validated. It appears that symptomatic response measured by the MTWSI may not be a clinically important effect.

The entry criteria for our study required that a minimum of 5 days of intravenous steroids should have failed for patients. Paradoxically, this might have led to higher than expected rates

of placebo response, owing to a delayed carry over anti-inflammatory effect of intravenous steroids. It is possible that a requirement for a longer course of intravenous steroids to fail might reduce placebo response rates.⁶ Alternatively, recruiting patients who fail to respond to intravenous steroids over a shorter (3 day) period using other criteria, might also reduce the placebo effect.³⁰ It should also be noted that there were few treatment-naïve patients in the trial; approximately 90% of patients had previously received a course of steroids, 60% had received azathioprine or 6-mercaptopurine, 30% had received infliximab or adalimumab and 10% had received ciclosporin. It should also be noted that our patient population with severe ulcerative colitis had more severe disease than the outpatients enrolled in the ACT 1 and 2 trials of infliximab²⁸ and the inpatients in the Jarnerot trial.¹⁰ More research is needed to identify the optimal selection criteria and duration of intravenous steroid treatment for trials of drugs in patients with severe, intravenous corticosteroid-refractory ulcerative colitis.

The rates of colectomy observed in the placebo and visilizumab treatment groups (7% and 18%, respectively) are relatively low. By comparison, a meta-analysis of patients with severe ulcerative colitis reported a mean colectomy rate of 27%¹⁶ and a placebo-controlled trial of infliximab in severe ulcerative colitis reported a 90-day colectomy rate of 67% in the placebo group.¹⁰ It should be noted that 23% of patients in the visilizumab group and 26% of patients in the placebo group received salvage treatment with an anti-tumour necrosis factor agent (infliximab or adalimumab). Salvage treatment may have had the effect of lowering the colectomy rate.

The visilizumab dose of 5 µg/kg was established in open label phase I and I/II trials, which demonstrated that there was no difference in response rates for doses ranging from 5.0 to 12.5 µg/kg.^{24 25} A dose ≥ 15 µg/kg was associated with greater efficacy but also more severe cytokine release syndrome.²⁴ In our study, the 5 µg/kg dose led to a rapid and almost complete, transient depletion of CD4+ T cells in nearly all patients, suggesting that short-term, higher doses of visilizumab that are also tolerable are unlikely to be more effective. This finding also suggests the more general conclusion that transient T-cell depletion may not be an effective treatment strategy in patients with severe, intravenous corticosteroid-refractory ulcerative colitis.

Signs and symptoms of cytokine release syndrome occurred in 70% of patients treated with visilizumab and included cardiac and vascular events. Specific cardiac and vascular disorders of interest in patients treated with visilizumab include angina pectoris, cardiomyopathy, myocardial ischaemia, phlebitis, superficial thrombophlebitis, deep venous thrombosis and vasculitis. Whether these adverse events occurred as a result of cytokine release syndrome or were directly caused by visilizumab is unclear. Visilizumab also resulted in a transient

Table 4 Summary of safety analyses for all randomised patients

	Placebo (N=43)	Visilizumab 5 µg/kg (N=84)	p Value
Patients who reported adverse events, n (%)	33 (77)	81 (96)	0.0011
Related, n (%)	9 (21)	68 (81)	<0.0001
Adverse events reported	192	596	
Patients who reported serious adverse events, n (%)	7 (16)	14 (17)	1.0000
Related, n (%)	0 (0)	4 (5)	0.2990
Serious adverse events reported*	10	20	
Toxicity grade of adverse events			
Grade 4, n (%)	1 (2)	0 (0)	0.3386
Grade 3, n (%)	5 (12)	16 (19)	0.3254
Grade 2, n (%)	14 (33)	47 (56)	0.0150
Grade 1, n (%)	13 (30)	18 (21)	0.2838
Deaths	0 (0)	0 (0)	1.0000
Adverse events occurring at frequency of ≥10% in any treatment group, n (%)			
Cardiac disorders	2 (5)	10 (12)	0.3357
Tachycardia	0 (0)	7 (8)	0.0943
Angina pectoris	0 (0)	1 (1)	1.0000
Cardiomyopathy	0 (0)	1 (1)	1.0000
Myocardial ischaemia	0 (0)	1 (1)	1.0000
Palpitations	0 (0)	1 (1)	1.0000
Sinus bradycardia	1 (2)	0 (0)	0.3386
Sinus tachycardia	1 (2)	0 (0)	0.3386
Nausea	2 (5)	17 (20)	0.0194
Abdominal pain	5 (12)	9 (11)	1.0000
Vomiting	0 (0)	12 (14)	0.0081
Pyrexia	6 (14)	36 (43)	0.0013
Chills	3 (7)	30 (36)	0.0005
Fatigue	7 (16)	16 (19)	0.8102
Arthralgia	5 (12)	13 (16)	0.7886
Back pain	1 (2)	11 (13)	0.0968
Myalgia	0 (0)	10 (12)	0.0159
Headache	9 (21)	31 (37)	0.0730
Insomnia	1 (2)	8 (10)	0.2712
Pharyngolaryngeal pain	5 (12)	4 (5)	0.1654
Acne	6 (14)	3 (4)	0.0606
Vascular disorders	2 (5)	19 (23)	0.0107
Hypotension	2 (5)	5 (6)	1.0000
Flushing	0 (0)	3 (4)	0.5504
Hypertension	0 (0)	3 (4)	0.5504
Hot flush	0 (0)	2 (2)	0.5486
Phlebitis	0 (0)	2 (2)	0.5486
Thrombophlebitis	0 (0)	2 (2)	0.5486
Superficial thrombophlebitis	0 (0)	2 (2)	0.5486
Deep venous thrombosis	0 (0)	1 (1)	1.0000
Vasculitis	0 (0)	1 (1)	1.0000
Adverse events of interest, n (%)			
Herpes zoster	1 (2)	2 (2)	1.0000
Cytomegalovirus	0 (0)	1 (1)	1.0000
Fungal infection	0 (0)	1 (1)	1.0000
Fungal oesophagitis	0 (0)	1 (1)	1.0000
Oral candidiasis	0 (0)	1 (1)	1.0000
Oral fungal infection	1 (2)	0 (0)	0.3386
Sepsis	1 (2)	0 (0)	0.3386
Hepatic focal nodular hyperplasia	0 (0)	1 (1)	1.0000
One or more infections, n (%)	13 (30)	29 (35)	0.6930
Patients with serious infections, n (%)	3 (7)	4 (5)	0.6880
Specific types of serious infections, n (%)			
Herpes zoster	1 (2)	1 (1)	1.0000
Abdominal abscess	0 (0)	1 (1)	1.0000
Cytomegalovirus infection	0 (0)	1 (1)	1.0000
Infected cyst	1 (2)	0 (1)	0.3386

Continued

Table 4 Continued

	Placebo (N=43)	Visilizumab 5 µg/kg (N=84)	p Value
Perirectal abscess	0 (0)	1 (1)	1.0000
Pilonidal cyst	0 (0)	1 (1)	1.0000
Sepsis	1 (2)	0 (0)	0.3386
Patients with cytokine release syndrome, n (%)	8 (19)	59 (70)	0.0001
Specific types of cytokine release symptoms, n (%)			
Nausea	0 (0)	12 (14)	0.0081
Abdominal pain	2 (5)	5 (6)	1.0000
Vomiting	0 (0)	6 (7)	0.0955
Upper abdominal pain	0 (0)	2 (2)	0.5486
Diarrhoea	1 (2)	1 (1)	1.0000
Pyrexia	2 (5)	32 (38)	0.0001
Chills	2 (5)	29 (35)	0.0059
Fatigue	4 (9)	11 (13)	0.7722
Arthralgia	2 (5)	8 (10)	0.4928
Back pain	0 (0)	9 (11)	0.0278
Musculoskeletal discomfort	0 (0)	3 (4)	0.5504
Headache	5 (12)	27 (32)	0.0165
Dizziness	2 (5)	2 (2)	0.6035
Dyspnoea	1 (2)	1 (1)	1.0000
Exertional dyspnoea	0 (0)	1 (1)	1.0000
Hypotension	1 (2)	4 (5)	0.6616

*A total of 30 serious adverse events (SAEs) (10 placebo, 20 visilizumab) occurred in this study: 21 patients had SAEs—14 (17%) in the visilizumab group and 7 (16%) in the placebo group. The SAEs that occurred in the placebo group included leucopenia (2%), abdominal pain (7%), diarrhoea (2%), intestinal obstruction (2%), malaise (1%), herpes zoster (2%), infected cyst (2%) and sepsis (2%). The SAEs that occurred in the visilizumab group included anaemia (1%), neutropenia (1%), cardiomyopathy (1%), abdominal pain (1%), inguinal hernia (1%), small intestine obstruction (1%), pyrexia (1%), hepatitis cholestasis (1%), herpes zoster (1%), abdominal abscess (1%), cytomegalovirus (1%), perirectal abscess (1%), pilonidal cyst (1%), open wound (1%), dehydration (1%), migraine (1%), deep vein thrombosis (1%) and superficial thrombophlebitis superficial (1%).

increase in liver transaminases. We have reported this phenomenon in patients with Crohn's disease treated with visilizumab.³¹ Interestingly, the observed cardiac and vascular events, as well as the transient elevations of hepatic enzymes, have not been reported with other humanised anti-CD3 antibodies in other autoimmune diseases such as type I diabetes.³² The rates of EBV reactivation in our study were lower than those reported in previous studies of visilizumab in patients with severe ulcerative colitis.^{24–25} This is probably owing to a change in definitions. In previous studies we reported that any patient with an EBV concentration above the limit of measurement (≥250 copies per ml) were classed as positive and any increase from baseline was considered to be an increase. In this study, only EBV concentrations ≥ 5000 copies/ml were reported as positive and an increase from baseline was defined as EBV concentrations >0.5 log of the baseline value.

At the dosing regimen tested, visilizumab was neither safe nor effective in treating severe, intravenous corticosteroid-refractory ulcerative colitis. These findings challenge our current understanding of the pathophysiology of ulcerative colitis.

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Competing interests WS, JFC, DH, LM, ST, SRT, GV and STa have served as consultants and received research support from PDL BioPharma. PS and DCB have received research support from PDL BioPharma, MF and JNL are former employees of PDL BioPharma.

Ethics approval This multicentre study was conducted globally at 75 sites in 14 countries (Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Hungary, Israel, Netherlands, Norway, Slovakia, Ukraine, United States). The institutional review board or ethics committee at each site approved the protocol. All patients gave written informed consent.

Inflammatory bowel disease

Contributors WS, JFC, DH, LM, ST, SRT, GVA and STa were members of the steering committee and were also study investigators for this clinical trial. They contributed to the conception and design of the trial, data interpretation, drafting and critical revision of the manuscript. PS and DCB were study investigators for this clinical trial who contributed to the data interpretation, drafting and critical revision of the manuscript. MF and JNL were the medical monitors for this trial, who contributed to the conception and design of the trial, data interpretation, drafting and critical revision of the manuscript.

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REFERENCES

1. **Truelove SC**, Witts LJ. Cortisone in ulcerative colitis. Final report on a therapeutic trial. *BMJ* 1955;**2**:1041–8.
2. **Edwards FC**, Truelove SC. The course and prognosis of ulcerative colitis. Part I. Short-term prognosis. *Gut* 1963;**4**:299–308.
3. **Truelove SC**, Jewell DP. Intensive intravenous regimen for severe attacks of ulcerative colitis. *Lancet* 1974;**1**:1067–70.
4. **Jarnerot G**, Rolny P, Sandberg-Gertzen H. Intensive intravenous treatment of ulcerative colitis. *Gastroenterol* 1985;**89**:1005–13.
5. **Allison J**, Herrinton LJ, Liu L, et al. Natural history of severe ulcerative colitis in a community-based health plan. *Clin Gastroenterol Hepatol* 2008;**6**:999–1003.
6. **Lichtiger S**, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994;**330**:1841–5.
7. **D'Haens G**, Lemmens L, Geboes K, et al. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. *Gastroenterol* 2001;**120**:1323–9.
8. **Van Assche G**, D'Haens G, Noman M, et al. Randomised, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis.[see comment]. *Gastroenterol* 2003;**125**:1025–31.
9. **Sands BE**, Tremaine WJ, Sandborn WJ, et al. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: a pilot study. *Inflamm Bowel Dis* 2001;**7**:83–8.
10. **Jarnerot G**, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomised, placebo-controlled study. *Gastroenterol* 2005;**128**:1805–11.
11. **Ogata H**, Matsui T, Nakamura M, et al. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. see comment. *Gut* 2006;**55**:1255–62.
12. **Baumgart DC**, Macdonald JK, Feagan B. Tacrolimus (FK506) for induction of remission in refractory ulcerative colitis. *Cochrane Database Syst Rev* 2008: CD007216.
13. **Campbell S**, Travis S, Jewell D. Ciclosporin use in acute ulcerative colitis: a long-term experience. *European Journal of Gastroenterology & Hepatology* 2005;**17**:79–84.
14. **Moskovitz DN**, Van Assche G, Maenhout B, et al. Incidence of Colectomy During Long-term Follow-up After Cyclosporine-Induced Remission of Severe Ulcerative Colitis. *Clin Gastroenterol Hepatol* 2006;**4**:760–5.
15. **Sternthal MB**, Murphy SJ, George J, et al. Adverse events associated with the use of cyclosporine in patients with inflammatory bowel disease. *Am J Gastroenterol* 2008;**103**:937–43.
16. **Turner D**, Walsh CM, Steinhart AH, et al. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clinical Gastroenterology & Hepatology* 2007;**5**:103–10.
17. **Targan SR**, Karp LC. Defects in mucosal immunity leading to ulcerative colitis. *Immunological Reviews* 2005;**206**:296–305.
18. **Baumgart DC**, Carding SR. Inflammatory bowel disease: cause and immunobiology. *Lancet* 2007;**369**:1627–40.
19. **Cole MS**, Stellrecht KE, Shi JD, et al. HuM291, a humanized anti-CD3 antibody, is immunosuppressive to T cells while exhibiting reduced mitogenicity in vitro. *Transplantation* 1999;**68**:563–71.
20. **Chau LA**, Tso JY, Melrose J, et al. HuM291(Nuvion), a humanized Fc receptor-nonbinding antibody against CD3, anergizes peripheral blood T cells as partial agonist of the T cell receptor. *Transplantation* 2001;**71**:941–50.
21. **Norman DJ**, Vincenti F, de Mattos AM, et al. Phase I trial of HuM291, a humanized anti-CD3 antibody, in patients receiving renal allografts from living donors. *Transplantation* 2000;**70**:1707–12.
22. **Carpenter PA**, Appelbaum FR, Corey L, et al. A humanized non-FcR-binding anti-CD3 antibody, visilizumab, for treatment of steroid-refractory acute graft-versus-host disease. *Blood* 2002;**99**:2712–9.
23. **Carpenter PA**, Lowder J, Johnston L, et al. A phase II multicenter study of visilizumab, humanized anti-CD3 antibody, to treat steroid-refractory acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2005;**11**:465–71.
24. **Plevy S**, Salzberg B, Van Assche G, et al. A phase I study of visilizumab, a humanized anti-CD3 monoclonal antibody, in severe steroid-refractory ulcerative colitis. *Gastroenterol* 2007;**133**:1414–22.
25. **Baumgart DC**, Targan SR, Dignass AU, et al. Prospective randomised open-label multicenter phase I/II dose escalation trial of visilizumab (HuM291) in severe steroid-refractory ulcerative colitis. *Inflamm Bowel Dis* 2010;**16**:620–9.
26. **D'Haens G**, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterol* 2007;**132**:763–86.
27. **Schroeder KW**, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomised study. *N Engl J Med* 1987;**317**:1625–9.
28. **Rutgeerts P**, Sandborn WJ, Feagan BG, et al. Infliximab induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;**353**:2462–76.
29. **Lichtiger S**, Present DH. Preliminary report: cyclosporin in treatment of severe active ulcerative colitis.[see comment]. *Lancet* 1990;**336**:16–19.
30. **Travis SPL**, Farrant JM, Ricketts C, et al. Predicting the outcome in severe ulcerative colitis. *Gut* 1996;**38**:905–10.
31. **Baumgart DC**, Lowder JN, Targan SR, et al. Transient cytokine-induced liver injury following administration of the humanized anti-CD3 antibody visilizumab (HuM291) in Crohn's disease. *Am J Gastroenterol* 2009;**104**:868–76.
32. **Keymeulen B**, Vandemeulebroucke E, Ziegler AG, et al. Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes. *N Engl J Med* 2005;**352**:2598–608.

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