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Published in: Gut

DOI: 10.1136/gut.2009.205443

Citation for published version (APA):

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

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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 μg/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=0.444). Colectomy was performed in 18% of patients receiving visilizumab compared with 7% of those who received placebo (p=0.130). Cardiac disorders and vascular adverse events occurred more frequently in the patients who received visilizumab.

Conclusion Visilizumab at a dose of 5 μg/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 corticosteroids.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

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 measured 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.
Inflammatory bowel disease

treatments for patients who fail to improve include cyclosporin, 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 cyclosporin 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 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 <2.5×10^3/μl; platelet count <150×10^3/μl; 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). Patient’s 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, cyclosporin 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.

**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 score26,27 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 methylxatrete.

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 <2.5×10^3/μl; platelet count <150×10^3/μl; 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). Patient’s 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, cyclosporin 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

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Gut 2010;59:1485–1492. doi:10.1136/gut.2009.205443

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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 cyclosporin, 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 χ² 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 1 Modified Truelove and Witts Severity Index (MTWSI) also known as the Lichtiger Index

<table>
<thead>
<tr>
<th>Variable</th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea (number of daily stools)</td>
<td>0−2</td>
</tr>
<tr>
<td>Nocturnal diarrhoea</td>
<td></td>
</tr>
<tr>
<td>Visible blood in stool (% of movements)</td>
<td>≤50</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain or cramping</td>
<td>None</td>
</tr>
<tr>
<td>General wellbeing</td>
<td>Perfect</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>No</td>
</tr>
<tr>
<td>Need for anti-diarrhoeal drugs</td>
<td>No</td>
</tr>
</tbody>
</table>


### Table 2 Mayo scoring system for assessment of ulcerative colitis activity

<table>
<thead>
<tr>
<th>Stool frequency*</th>
<th>0=Normal</th>
<th>1=1–2 stools more than normal</th>
<th>2=3–4 stools more than normal</th>
<th>3=5 or more stools more than normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal bleeding†</td>
<td>0=No bleed seen</td>
<td>1=Streaks of blood with stool less than half the time</td>
<td>2=Obvious blood with stool most of the time</td>
<td>3=Blood alone passed</td>
</tr>
<tr>
<td>Physician’s global assessment</td>
<td>0=Mild disease (erythema, decreased vascular pattern, mild friability)</td>
<td>1=Moderate disease (marked erythema, absent vascular pattern, friability, erosions)</td>
<td>2=Severe disease (spontaneous bleeding, ulceration)</td>
<td>3=Extreme disease (spontaneous bleeding, ulceration, fistulae)</td>
</tr>
</tbody>
</table>

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 2A). The median (95% CI) time to symptomatic response was 11 (5 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 screening were 0.1639 and 0.1979, respectively. The correlations between the MTWSI score and the total 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 35% (14 of 45) of patients in the placebo group. Of these patients, 19 in the visilizumab group (25%) 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=0.572; 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 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.

Table 3 Summary of demographic and baseline disease characteristics

<table>
<thead>
<tr>
<th>Subjects randomised</th>
<th>Placebo 43</th>
<th>Visilizumab 5 µg/kg 84</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>29 (65)</td>
<td>52 (62)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>40 (93)</td>
<td>78 (93)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>40.8 (13.5)</td>
<td>40.4 (12.9)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>74.8 (16.8)</td>
<td>75.5 (17.3)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>Mean (SD)</td>
<td>6.4 (6.8)</td>
</tr>
<tr>
<td>Involved colonic area, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than splenic flexure, n (%)</td>
<td>11 (26.0)</td>
<td>27 (32.1)</td>
</tr>
<tr>
<td>Less than hepatic flexure, n (%)</td>
<td>10 (23.3)</td>
<td>14 (16.7)</td>
</tr>
<tr>
<td>Pancolitis, n (%)</td>
<td>20 (46.5)</td>
<td>42 (50.0)</td>
</tr>
<tr>
<td>Missing, n (%)</td>
<td>2 (4.7)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Mayo score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>10.7 (0.8)</td>
<td>10.7 (0.9)</td>
</tr>
<tr>
<td>MTWSI score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>13.0 (2.1)</td>
<td>13.5 (2.2)</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>37 (44)</td>
<td>30 (49)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>23 (0–200)</td>
<td>10 (0–265)</td>
</tr>
<tr>
<td>CD4+ T-cell count (µl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>415 (287)</td>
<td>637 (420)</td>
</tr>
<tr>
<td>EBV (5000 copies/ml), n (%)</td>
<td>15 (34.9)</td>
<td>24 (28.6)</td>
</tr>
<tr>
<td>Current medication, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminosalicylates</td>
<td>11 (25.6)</td>
<td>30 (35.7)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>43 (100)</td>
<td>84 (100)</td>
</tr>
<tr>
<td>Immuno modulators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>8 (18.6)</td>
<td>10 (11.9)</td>
</tr>
<tr>
<td>6-MP</td>
<td>1 (2.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>3 (7.0)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>1 (2.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anti-TNF agent within 8 weeks</td>
<td>6 (14.0)</td>
<td>10 (11.9)</td>
</tr>
<tr>
<td>Anti-TNF agent within 2 weeks</td>
<td>4 (9.3)</td>
<td>4 (4.8)</td>
</tr>
<tr>
<td>Past medication, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminosalicylates</td>
<td>38 (88.4)</td>
<td>75 (89.3)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>38 (88.4)</td>
<td>76 (90.5)</td>
</tr>
<tr>
<td>Immuno modulators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>23 (53.5)</td>
<td>44 (52.4)</td>
</tr>
<tr>
<td>6-MP</td>
<td>7 (16.3)</td>
<td>13 (15.5)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>6 (14.0)</td>
<td>10 (11.9)</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>4 (9.3)</td>
<td>8 (9.5)</td>
</tr>
<tr>
<td>Anti-TNF agent</td>
<td>14 (32.6)</td>
<td>30 (35.7)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>25 (58.1)</td>
<td>38 (45.2)</td>
</tr>
<tr>
<td>Previous smoker</td>
<td>12 (27.9)</td>
<td>42 (50.0)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>6 (14.0)</td>
<td>4 (4.8)</td>
</tr>
</tbody>
</table>

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

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

CRP, CD4+ T-CELL COUNTS AND EBV REACTIVATION

The baseline mean and median CRP concentrations in the two treatment groups are shown in table 3. The mean CRP concentrations over time are shown in figure 4A.
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/μl at baseline to a nadir value of 10 (16) cells/μl. 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/μl or ≥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 ≤10× 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 esophagitis (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 aminotransferase (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 2  The proportions of patients at day 45 with response (A), remission (B) and mucosal healing (C).
**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 ≥5 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 over-estimated clinically meaningful rates of response. 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. 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.

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% and a placebo-controlled trial of infliximab and the inpatients in the Jarnerot trial. 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.

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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. A dose ≥15 μg/kg was associated with greater efficacy but also more severe cytokine release syndrome. 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
In Table 4, summary of safety analyses for all randomised patients, we observe a focus on various adverse events and their reported frequencies in the placebo and visilizumab groups. Adverse events such as fatigue, vomiting, and nausea are notably more frequent in the visilizumab group, particularly for vomiting and nausea. Toxicity grades of adverse events show a relatively higher incidence of Grade 4 toxicity in the visilizumab group for events like diarrhea and febrile neutropenia.

Cardiac disorders and vascular disorders also show a trend with more occurrences in the visilizumab group. Adverse events occurring at a frequency of >10% in any treatment group are highlighted, with notable events including fatigue, vomiting, and nausea.

In the placebo group, the incidence of serious adverse events is lower compared to the visilizumab group, with a notable difference in the number of patients with serious infections and the types of serious infections reported. The rates of serious adverse events related to cardiac, vascular, and other systems are compared, with a notable difference in the incidence of events related to the heart, circulatory system, and other vascular disorders.

Hypotension and sinus tachycardia show a significant difference in occurrence between the two groups, with more instances in the visilizumab group. The rates of hypotension and sinus tachycardia are notably higher in the visilizumab group compared to the placebo group.

Specific types of adverse events are also reported, with a focus on serious adverse events related to infections, including sepsis and hepatic focal nodular hyperplasia. The rates of adverse events related to infections are significantly higher in the visilizumab group, with more SAEs reported in this group.

In Table 4 Continued, we observe a continuation of adverse events reported, with a focus on specific adverse events related to infections, including sepsis and hepatic focal nodular hyperplasia. The rates of adverse events related to infections are significantly higher in the visilizumab group, with more SAEs reported in this group. The incidence of adverse events in the placebo group is relatively lower compared to the visilizumab group, with a notable difference in the number of patients with serious infections and the types of serious infections reported.

The incidence of adverse events and their rates are compared across the placebo and visilizumab groups, highlighting the differences in occurrence and severity. The findings indicate a higher incidence of adverse events in the visilizumab group, particularly for events related to the heart, circulatory system, and other vascular disorders. The rates of serious adverse events related to infections are also significantly higher in the visilizumab group compared to the placebo group.
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. FS and DCR 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.

Provenance and peer review Not commissioned; externally peer reviewed.

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