Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial

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Summary

Background Etrolizumab is a humanised monoclonal antibody that selectively binds the β7 subunit of the heterodimeric integrins α4β7 and αEβ7. We aimed to assess etrolizumab in patients with moderately-to-severely active ulcerative colitis.

Methods In this double-blind, placebo-controlled, randomised, phase 2 study, patients with moderately-to-severely active ulcerative colitis who had not responded to conventional therapy were recruited from 40 referral centres in 11 countries. Eligible patients (aged 18–75 years; Mayo Clinic Score [MCS] of 5 of higher [or ≥6 in USA]; and disease extending 25 cm or more from anal verge) were randomised (1:1:1) to one of two dose levels of subcutaneous etrolizumab (100 mg at weeks 0, 4, and 8, with placebo at week 2; or 420 mg loading dose [LD] at week 0 followed by 300 mg at weeks 2, 4, and 8), or matching placebo. The primary endpoint was clinical remission at week 10, defined as MCS of 2 or less (with no individual subscore of >1), analysed in the modified intention-to-treat population (mITT; all randomly assigned patients who had received at least one dose of study drug, had at least one post-baseline disease-activity assessment, and had a centrally read screening endoscopic subscore of ≥2). This study is registered with ClinicalTrials.gov, number NCT01336465.

Findings Between Sept 2, 2011, and July 11, 2012, 124 patients were randomly assigned, of whom five had a endoscopic subscore of 0 or 1 and were excluded from the mITT population, leaving 39 patients in the etrolizumab 100 mg group, 39 in the etrolizumab 300 mg plus LD group, and 41 in the placebo group for the primary analyses. No patients in the placebo group had clinical remission at week 10, compared with eight (21% [95% CI 7–36]) patients in the etrolizumab 100 mg group (p=0·0040) and four (10% [0·2–24]) patients in the 300 mg plus LD group (p=0·048). Adverse events occurred in 25 (61%) of 41 patients in the etrolizumab 100 mg group (five [12%] of which were regarded as serious), 19 (48%) of 40 patients in the etrolizumab 300 mg plus LD group (two [5%] serious), and 31 (72%) of 43 patients in the placebo group (five [12%] serious).

Interpretation Etrolizumab was more likely to lead to clinical remission at week 10 than was placebo. Therefore, blockade of both α4β7 and αEβ7 might provide a unique therapeutic approach for the treatment of ulcerative colitis, and phase 3 studies have been planned.

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Introduction

Ulcerative colitis is a chronic inflammatory disease characterised by an aberrant immunological response to microbial antigens in genetically predisposed individuals.[1] Immunomodulators (azathioprine, mercaptopurine, and tumour necrosis factor [TNF] antagonists [infliximab, adalimumab, golimumab]) are used in patients who do not respond to therapy with aminosalicylates and corticosteroids; however, these agents do not work in many patients, and non-selective immune suppression is associated with an increased risk of serious infection and cancer.[2,3]

Inhibition of the interaction of the α4β7 integrin with its ligand, mucosal addressin cell adhesion molecule-1 (MAdCAM-1), interferes with immune-cell trafficking into the intestine and is an effective therapy for both ulcerative colitis and Crohn's disease.[4–6] Furthermore, this selective treatment approach avoids broad-spectrum immunosuppression. Etrolizumab, a humanised monoclonal antibody that selectively binds the β7 subunit of both the α4β7[7,8] and αEβ7[9] integrin heterodimers, antagonises α4β7-MAdCAM-1-mediated egress of lymphocytes from the mucosal vasculature and αEβ7-E-cadherin interactions that are believed to be involved in retention of αEβ7 cells in the intraepithelial compartment.[9–11]

We assessed the efficacy and safety of etrolizumab in patients with moderately or severely active ulcerative colitis.

Methods

Study design and participants

This parallel-group, double-blind, placebo-controlled, randomised, phase 2 study assessed patients with moderately-to-severely active ulcerative colitis who had

not responded to conventional therapy. Patients in the USA were required by the US Food and Drug Administration (FDA) to have not responded to both immunomodulators and TNF antagonists. Patients were recruited from 40 referral centres in 11 countries (Australia, Belgium, Canada, Czech Republic, Germany, Hungary, Israel, New Zealand, Spain, UK, and USA).

Eligible patients were aged 18–75 years, with a diagnosis of ulcerative colitis and a Mayo Clinic Score[12] (MCS) of 5 points or higher (≥6 points in the USA as required by the FDA), a centrally read MCS endoscopic subscore of 2 points or higher, a rectal bleeding subscore of 1 point or higher, and disease extending 25 cm or more from the anal verge. Patients had disease duration of 12 weeks or more, and doses had to be stable if they were receiving oral mesalazine (2·4–4·8 g per day), corticosteroids (≤20 mg per day of prednisone), azathioprine, mercaptopurine, or methotrexate. Tapering of concomitant immunomodulator therapy (USA only) and oral corticosteroids was mandated according to the defined protocol (appendix). Patients with an extensive colonic resection or colectomy, presence of an ileostomy or colostomy, risk factors for infection, major organ dysfunction, or disorders other than ulcerative colitis that might have needed treatment with more than 20 mg per day of prednisone were not eligible (appendix).

See Online for appendix

Institutional review boards at each study site approved the protocol and all patients provided written informed consent. The study was undertaken and reported in accordance with the study protocol.

Randomisation and masking

Patients were randomly assigned in a 1:1:1 ratio via an interactive voice and web response system to one of two dose levels of subcutaneous etrolizumab or matching placebo. Randomisation was balanced through stratification according to the following hierarchy: concomitant treatment with corticosteroids, immunomodulators, previous TNF antagonist exposure, and study site. All patients, assessing physicians, the funder and its agents, and study personnel were masked to treatment assignment, except for the site pharmacists who prepared the study drug but who did not interact with the patient. Both etrolizumab and placebo appeared as a transparent fluid within the syringes to maintain masking.

Procedures

Patients were assigned either to subcutaneous etrolizumab (Genentech, South San Francisco, CA, USA) at 100 mg at weeks 0, 4, and 8, with placebo at week 2 (etrolizumab 100 mg group), to etrolizumab 420 mg at week 0 followed by 300 mg at weeks 2, 4, and 8 (etrolizumab 300 mg plus loading dose [LD] group), or to matching placebo. Patients who had a disease flare, defined as a 2-point increase from the time of remission in the partial MCS with 3 days of continuous rectal bleeding confirmed by flexible sigmoidoscopy with an endoscopy subscore of 2 points or higher, were permitted to receive rescue therapy consisting of an increase in corticosteroids, mesalazine, or immunomodulators. Use of TNF antagonists, ciclosporin, or tacrolimus was not permitted.

Assessments done before randomisation and at regular intervals throughout the study period included physical examination, safety assessments, MCS, electrocardiogram, haematology and serum chemistries, serum for pharmacokinetic analysis, antidrug antibody tests, stool sample analysis for faecal calprotectin, colonic biopsies for biomarker analysis by quantitative PCR, and immunohistochemistry (see schedule of assessments and protocol in the appendix). Flow cytometry was undertaken on the peripheral blood of all patients and on the colonic biopsy samples of a subgroup of patients. Flow cytometry assays used competing and non-competing antibodies to allow for detection of β7-expressing cells in the tissue or peripheral circulation (appendix).

Outcomes

The primary endpoint was clinical remission at week 10, defined as the proportion of patients with MCS of 2 points or less with no individual subscore of greater than 1 point. Secondary endpoints were clinical remission at week 6, clinical response (3-point decrease and 30% reduction in MCS and 1-point decrease or more in rectal bleeding subscore or absolute rectal bleeding subscore of 0 or 1), and the achievement of both an endoscopic subscore of 0 and a rectal bleeding subscore of 0 at weeks 6 and 10. Exploratory outcomes included changes from baseline in mucosal healing (endoscopic subscore of 0 or 1), histological active disease severity score,[13] and pharmacodynamic biomarkers in the peripheral blood (β7 occupancy and expression on T and B lymphocyte subsets) and colonic tissue (β7 occupancy and expression on T-lymphocyte subsets, quantification of αE+ cells, and cytokine and adhesion molecule gene expression). We did an exploratory diagnostic analysis of gene expression and immunohistochemistry in baseline colonic biopsy samples.

Statistical analysis

We estimated that randomisation of 120 patients would provide 80% power to detect a 25% difference in the proportion of patients in clinical remission between either etrolizumab dose group and placebo, under the assumption of a two-sided type I error rate of 0·2 and a placebo remission rate of 20%. We used a conservative estimate of 20% instead of the 15% remission rate reported in the placebo group of the ACT1 study.[2]

We used descriptive statistics to summarise differences in demographic and baseline characteristics. We assessed efficacy in the modified intention-to-treat (mITT) population, which included all randomly assigned patients who received at least one dose of study drug, had at least one post-baseline disease-activity assessment,

and had a centrally read screening endoscopic subscore of 2 points or higher. We compared primary and secondary endpoints with the Cochran-Mantel-Haenszel χ^2 test, with adjustment for stratification variables. Patients who discontinued the study before week 10 and those who received rescue therapy before week 10 were classified as non-responders. Patients with sample collection that was incomplete or of insufficient quality were excluded from the pharmacodynamic analysis.

Subgroup analyses of the primary endpoint were done in the subsets of patients defined by the stratification variables using Fisher's exact test. Sites within countries were grouped according to geographical region: eastern European (Hungary and Czech Republic) versus non-eastern European countries (USA, Canada, UK, Belgium, Germany, Spain, Israel, Australia, and New Zealand). We did post-hoc subgroup analyses of the effect of αE (*ITGAE*) levels on clinical remission using median cutoff values in baseline colonic biopsy samples to define high and low αE levels. We compared changes from baseline in the pharmacodynamic covariates between each of the two etrolizumab groups and the placebo group, and between the patients who had achieved clinical remission and those who had not in the etrolizumab group, with the use of the Wilcoxon signed rank test. p values were not adjusted for multiple comparisons and should be interpreted with caution. We assessed safety in all randomly assigned patients using descriptive statistics.

This study is registered with ClinicalTrials.gov, number NCT01336465.

Role of the funding source

The funder of the study was involved in the study design and the data collection and analysis. All authors had full access to all the data in the study, made the decision to submit these data for publication, were involved in writing the manuscript, and agreed upon the final content of the paper. The study funder provided funding for editorial assistance with manuscript preparation. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between Aug 23, 2011, and July 11, 2012, 187 patients were assessed for eligibility (figure 1). Of the 124 randomly assigned patients, 41 were assigned to receive etrolizumab 100 mg, 40 to etrolizumab 300 mg plus LD, and 43 to placebo. Five patients had a centrally read screening endoscopic subscore of 0 or 1 and were excluded from the mITT population, leaving 39 patients in the etrolizumab 100 mg group, 39 in the etrolizumab 300 mg

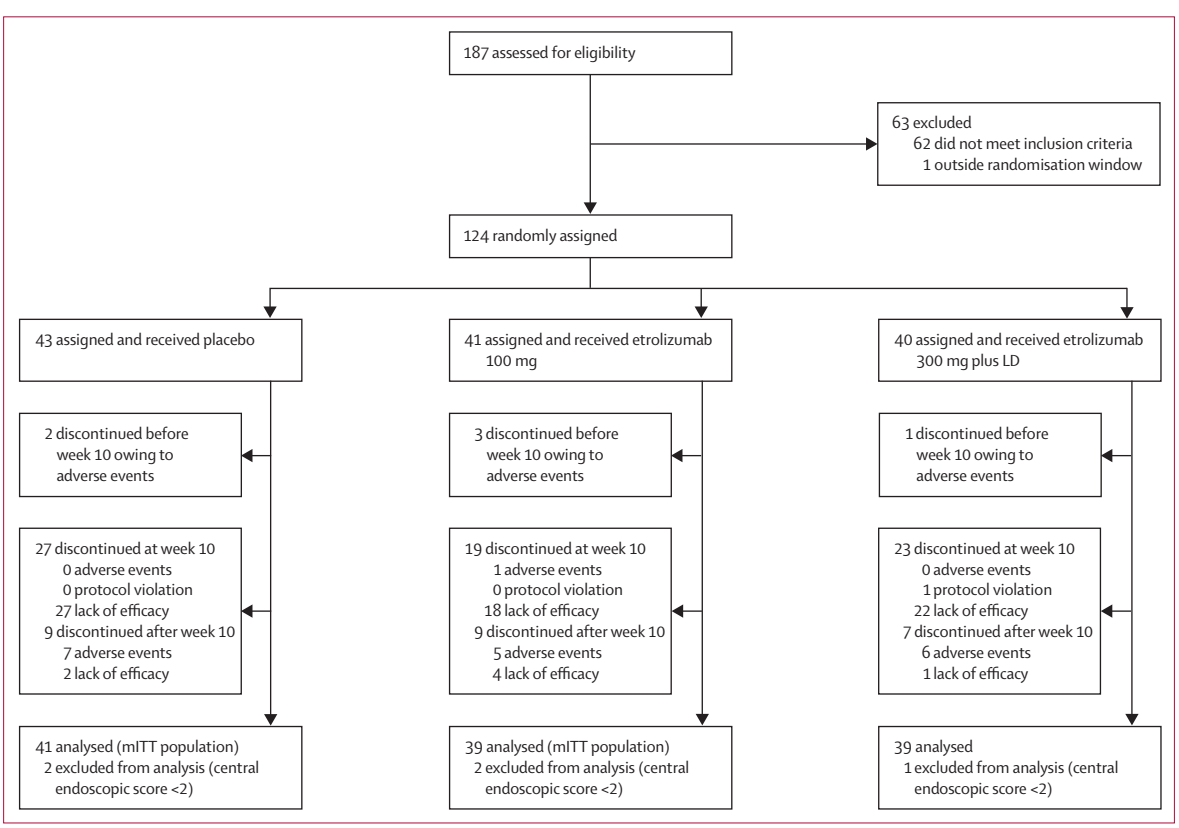

Figure 1: **Trial profile**
LD=loading dose. mITT=modified intention-to-treat.

plus LD group, and 41 in the placebo group for the primary analyses. Within each country the enrolment was balanced between the treatment groups (appendix). Baseline characteristics were generally similar between the treatment groups, with the exception of sex, age, bodyweight, and concomitant treatment with mesalazine (table 1; appendix). The pooled etrolizumab treatment groups contained a higher proportion of men than did the placebo group (64% [52 of 81] *vs* 44% [19 of 43]). Mean age was higher in the etrolizumab 100 mg group than in the placebo group. Mean bodyweight was higher in the etrolizumab 100 mg group than in the etrolizumab 300 mg plus LD group and the placebo group. A greater proportion of patients in the placebo group received concomitant treatment with mesalazine than did patients in the etrolizumab groups (table 1).

In the mITT population at week 10, none of 41 patients in the placebo group were in clinical remission compared with eight (21% [95% CI 7–36]) of 39 patients in the etrolizumab 100 mg group (p=0·0040) and four (10% [0·2–24]) of 39 patients in the etrolizumab 300 mg plus LD group (p=0·048; figure 2A).

For the secondary endpoints, no significant treatment group differences were noted for clinical remission at week 6, with two (5%) of 41 patients in the placebo group in clinical remission compared with four (10%) of 39 patients in the etrolizumab 100 mg group (p=0·66) and three (8%) of 39 in the etrolizumab 300 mg plus LD group (p=0·97; figure 2A). 14 (34%) of 41 patients in the placebo group had a clinical response at week 6 compared with 19 (49%) of 39 patients in the etrolizumab 100 mg group (p=0·27) and 15 (38%) of 39 in the etrolizumab 300 mg plus LD group (p=0·68). At week 10, 12 (29%) of 41 patients in the placebo group had a clinical response compared with 13 (33%) of 39 in the etrolizumab 100 mg group (p=0·83) and 12 (31%) of 39 patients in the etrolizumab 300 mg plus LD group (p=0·90; figure 2B). One (2%) patient in the placebo group had simultaneous endoscopic and rectal bleeding subscores of 0 at week 6 compared with three (8%) of 39 patients in the etrolizumab 100 mg group (p=0·96) and one (3%) of 39 in the 300 mg plus LD group (p=0·59; figure 2C). At week 10, no patients in the placebo group had simultaneous endoscopic and rectal bleeding subscores of 0 compared with four (10%) of 39 patients in the etrolizumab 100 mg group (p=0·16) and three (8%) of 39 in the 300 mg plus LD group (p=0·19; figure 2C). The proportions of patients with MCS subscores of 1 point or less, and those with subscores of 0 points, were, numerically, generally higher in patients in the etrolizumab groups than in those in the placebo group (appendix).

The proportions of patients in each treatment group who achieved clinical remission at week 10 when analysed by stratification variables (concomitant steroid use, concomitant immunomodulator use, previous TNF antagonist exposure, and study site) showed a similar trend to that reported in the overall study population, but with a greater difference between the etrolizumab 100 mg group and placebo group for patients taking steroids, those not taking immunomodulators, and those naive to TNF antagonists (figure 3; appendix). A greater difference between the etrolizumab 100 mg group and placebo group was also noted in those who live in eastern Europe; however, this difference was not significant owing to the small sample size (p=0·055). In the subgroup of patients who were naive to TNF antagonists, seven (44%) of 16 patients in the etrolizumab 100 mg group (p=0·0068 when compared with none of 15 in the placebo group) and three (25%) of 12 patients in the etrolizumab 300 mg plus LD group (p=0·0752 *vs* placebo group) were in clinical remission at week 10. In the subgroup of patients who had previously not responded to treatment with TNF antagonists, one (5%) of 22 patients in the etrolizumab 100 mg group (p=0·47) and one (4%) of 25 in the etrolizumab 300 mg plus LD group (p=1·00) were in clinical remission at week 10 (figure 3).

In the exploratory analyses, six (15%) of 41 patients in the placebo group had mucosal healing at week 10, compared with ten (26%) of 39 in the etrolizumab 100 mg group (p=0·32) and eight (21%) of 39 in the etrolizumab 300 mg plus LD group (p=0·82; appendix). Histopathology active disease score decreased from baseline to week 10 in patients in the etrolizumab 100 mg group, but the decrease was not significant (p=0·099;

	Etrolizumab 100 mg (n=41)	Etrolizumab 300 mg + LD (n=40)	Placebo (n=43)
Age, years	44·4 (13·9)	40·3 (13·4)	37·5 (12·8)
Male	28 (68%)	24 (60%)	19 (44%)
White	38 (93%)	38 (95%)	41 (95%)
Bodyweight, kg	88·8 (29·9)	74·8 (17·1)	74·2 (19·7)
Duration of ulcerative colitis, years	9·2 (8·3)	8·0 (7·1)	9·8 (8·4)
Concomitant medication use			
Corticosteroids	17 (41%)	18 (45%)	20 (47%)
Dose, mg/day	13·1 (6·0)	14·5 (5·7)	13·7 (6·6)
Immunosuppressants	17 (41%)	14 (35%)	16 (37%)
Mesalazine	28 (68%)	25 (63%)	38 (88%)
Previous anti-TNF therapy	25 (61%)	28 (70%)	27 (63%)
No response to previous anti-TNF therapy	24 (59%)	26 (65%)	26 (60%)
Unacceptable adverse event	1 (2%)	2 (5%)	1 (2%)
Disease extent			
Rectosigmoid	10 (24%)	8 (20%)	13 (30%)
Left sided	14 (34%)	14 (35%)	17 (40%)
Pancolitis or extensive	15 (37%)	18 (45%)	13 (30%)
Non-specified	2 (5%)	0	0
Mayo Clinic Score	9·3 (1·5)	9·2 (1·6)	9·1 (1·9)
CRP, mg/dL	1·4 (2·4)	1·8 (2·6)	1·4 (1·9)
Faecal calprotectin, µg/g	1547·0 (1808·5)	1301·3 (1482·6)	1087·8 (1118·1)

Data are mean (SD) or number (%). LD=loading dose. TNF=tumour necrosis factor. CRP=C-reactive protein.

Table 1: **Patient demographics and baseline characteristics in all randomly assigned patients**

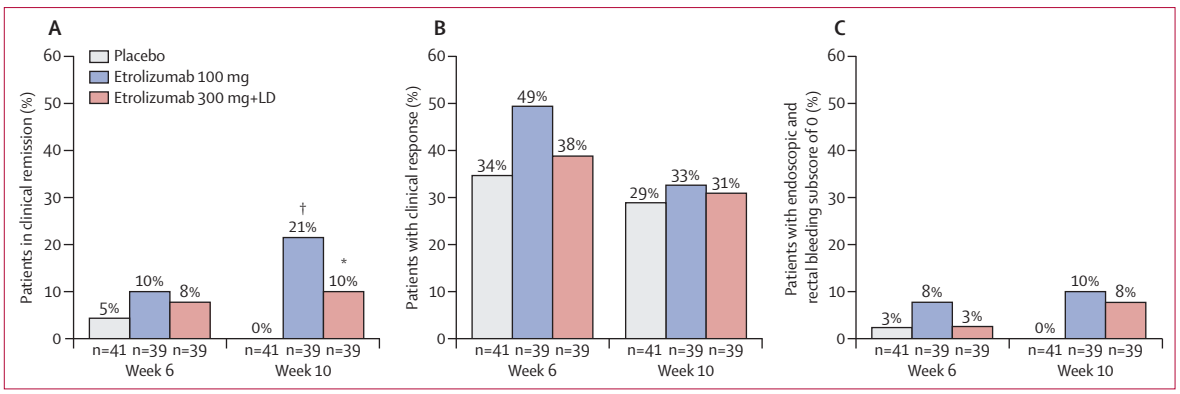

Figure 2: **Proportion of patients with clinical remission, clinical response, and endoscopic remission/rectal bleeding score of 0 in the mITT population**
(A) Clinical remission at week 6 and week 10. (B) Clinical response (3-point decrease and 30% reduction in Mayo Clinic Score and 1-point decrease or more in rectal bleeding subscore or absolute rectal bleeding subscore of 0 or 1) at week 6 and week 10. (C) Endoscopic and rectal bleeding subscores of 0 at week 6 and week 10. LD=loading dose. mITT=modified intention-to-treat. *p<0·05 (*vs* placebo). †p<0·01 (*vs* placebo).

appendix). In the mITT population, CRP concentration decreased in both etrolizumab groups compared with the placebo group from baseline to week 10 (data not shown). In the subgroup of patients with raised CRP (>0·4 mg/dL), CRP concentration in only the etrolizumab 300 mg plus LD group decreased compared with placebo; however, this difference was not significant (appendix).

Etrolizumab displayed linear pharmacokinetic profiles. Exposure for the etrolizumab 300 mg plus LD group was about 4·4 times higher than that for the etrolizumab 100 mg group (appendix). At week 10, the mean etrolizumab serum concentration was 8·52 mg/mL (SD 4·76) for the etrolizumab 100 mg group (n=34) and 37·8 mg/mL (16·9) for the etrolizumab 300 mg plus LD group (n=38). A drug concentration quartile versus response (clinical remission at week 10) analysis did not show an exposure–response correlation (appendix).

Of 81 patients assigned to either etrolizumab group with available blood samples, four (5%) patients had detectable antidrug antibodies after treatment (all were in the etrolizumab 100 mg group). One additional patient in the etrolizumab 100 mg group had detectable antibodies before receiving treatment and remained positive with consistent titres throughout the study. The number of adverse events did not seem to be associated with the presence of antidrug antibodies (data not shown). Additionally, a positive antidrug-antibody result did not have noticeable effect on etrolizumab serum concentrations in patients in either etrolizumab group (data not shown).

Etrolizumab maximally occupied β7 receptors on circulating CD4+ and CD8+β7+ T lymphocytes at both doses (p=0·0006 [etrolizumab 100 mg *vs* placebo] and p<0·0001 [etrolizumab 300 mg plus LD *vs* placebo]; appendix), with a corresponding specific increase in intestinal homing CD4+β7+ T lymphocytes in the peripheral blood (p=0·071 [etrolizumab 100 mg *vs* placebo] and p=0·0008 [etrolizumab 300 mg plus LD *vs* placebo]; appendix). We noted similar results with CD19+β7+ B lymphocytes (p<0·0001 for both etrolizumab 100 mg and 300 mg plus LD etrolizumab groups *vs* placebo; appendix). In the colonic mucosa, we also noted maximal occupancy of β7 receptors with etrolizumab 100 mg at week 6 (p=0·0043 *vs* placebo) and week 10 (p=0·0081), and

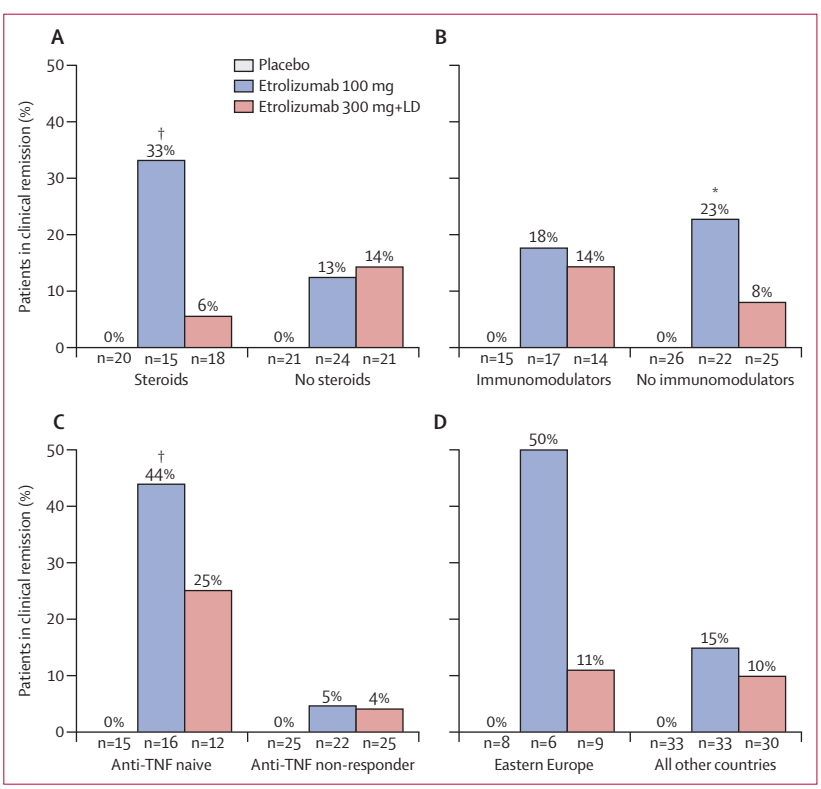

Figure 3: **Subgroup analyses of clinical remission at week 10 in the mITT population**
(A) Proportion of patients by concomitant treatment with steroids. (B) Proportion of patients by immunomodulators. (C) Proportion of patients by previous TNF antagonist exposure; one patient in the placebo group, one patient in the etrolizumab 100 mg group, and two patients in the etrolizumab 300 mg plus LD group group who received anti-TNF but had an unacceptable adverse event to it were excluded from the analysis. (D) Proportion of patients by geographical region; specific country data can be found in the appendix. LD=loading dose. mITT=modified intention-to-treat. TNF=tumour necrosis factor. *p<0·05 (*vs* placebo). †p<0·01 (*vs* placebo).

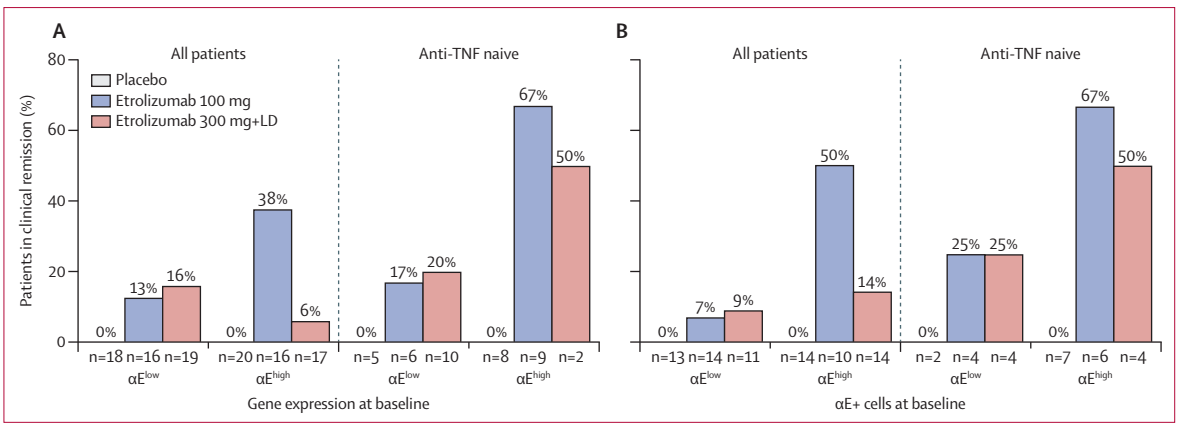

Figure 4: **Clinical remission according to baseline colonic biopsy αE levels**
(A) Clinical remission according to gene expression of integrin αE, as measured by quantitative PCR, in the colonic biopsy sample taken at baseline. (B) Clinical remission according to levels of αE+ cells in the colonic biopsy sample taken at baseline. LD=loading dose. TNF=tumour necrosis factor.

	Etrolizumab 100 mg (n=41)	Etrolizumab 300 mg+LD (n=40)	Placebo (n=43)
Any adverse event	25 (61%)	19 (48%)	31 (72%)
Serious adverse events	5 (12%)	2 (5%)	5 (12%)
Serious infections	0	0	1 (2%)
Adverse events occurring in ≥5% of any treatment group			
Ulcerative colitis	7 (17%)	9 (23%)	8 (19%)
Nausea	2 (5%)	2 (5%)	2 (5%)
Nasopharyngitis	4 (10%)	6 (15%)	8 (19%)
Fatigue	2 (5%)	2 (5%)	4 (9%)
Asthenia	0	0	4 (9%)
Influenza-like illness	3 (7%)	0	1 (2%)
Nervous system disorders	6 (15%)	4 (10%)	6 (14%)
Headache	5 (12%)	4 (10%)	5 (12%)
Dizziness	1 (2%)	0	3 (7%)
Arthralgia	6 (15%)	2 (5%)	4 (9%)
Cough	2 (5%)	2 (5%)	2 (5%)
Rash	3 (7%)	1 (3%)	1 (2%)
Iron-deficiency anaemia	0	2 (5%)	2 (5%)

Data are number of patients with one or more event (% of patients). *All randomly assigned patients received at least one dose of study treatment.

Table 2: **Adverse events in the safety population (all randomly assigned patients)***

with etrolizumab 300 mg plus LD (p=0·0021 at week 6 *vs* placebo and p=0·0087 at week 10; appendix). However, there was no difference in the overall relative frequencies of mucosal β7-expressing CD3+CD4– T cells reported in patients in the etrolizumab groups compared with those in the placebo group (appendix). Similarly, no apparent change in β7, β1, or αE gene expression was identified by quantitative PCR, whereas α4 gene expression in colonic tissue seemed to be reduced at week 10 in patients in the etrolizumab groups who achieved remission compared with those who did not (p=0·0284; appendix). On assessment of the intestinal lymphocyte compartments in colonic biopsy samples by immunohistochemistry, we noted a decreasing trend in the proportion of αE+ cells in the intestinal crypt epithelium in patients in the etrolizumab groups compared with those in the placebo group, and this was most pronounced in patients who achieved clinical remission at week 10 (appendix), with no apparent decrease in αE+ cells in the lamina propria (appendix). Additionally, expression of MAdCAM-1 was reduced in patients in the etrolizumab group who achieved clinical remission compared with those who did not (p=0·0019), as were inflammatory cytokines (interleukin 17A, p=0·0084; interleukin 17F, p=0·0215; interleukin 23, p=0·0088; interleukin 1β, p=0·0041; TNFα, p=0·0126; interleukin 6, p=0·0008; and interleukin 12p40, p=0·15) and lymphocyte gene expression (CD19, p=0·0039; CD4, p=0·051; CD8, p=0·14; CD3 p=0·14; appendix). By contrast, expression of E-cadherin in biopsy samples increased in patients in the etrolizumab groups who achieved clinical remission compared with those who did not (p=0·0022; appendix).

In a post-hoc analysis, more patients in the etrolizumab 100 mg group who had high αE (*ITGAE*) gene expression in their baseline colonic biopsy sample achieved clinical remission at 10 weeks than did those with low αE gene expression (using a median cutoff value to define high and low expression; figure 4A; appendix). Additionally, baseline colonic biopsy samples showed a range of αE+ cells per total cells, with improved clinical remission in patients with high numbers of αE+ cells, defined by a median cutoff (figures 4B; appendix). Baseline characteristics were balanced across treatment groups in the subgroups of patients defined by baseline colonic biopsy sample αE (*ITGAE*) gene expression (appendix).

Patients in the etrolizumab 100 mg group had higher rates of rash, influenza-like illness, and arthralgias than did those in the placebo or etrolizumab 300 mg plus LD groups; all of these events were regarded as mild to

moderate in severity (table 2). Serious adverse events were reported in 12 patients (table 2); five of these were related to ulcerative colitis (two in the etrolizumab 100 mg group; one in the etrolizumab 300 mg plus LD group; and two in the placebo group; appendix). No serious opportunistic infections were reported. Mild injection site reactions occurred in four patients in the etrolizumab 300 mg plus LD group and in two patients in the placebo group.

Discussion

Etrolizumab at both doses studied significantly improved clinical remission at 10 weeks compared with placebo in patients with moderately or severely active ulcerative colitis. Most patients in this study (61%) had previously not responded to anti-TNF therapy and thus are representative of a refractory patient group. In support of this fact, no patient assigned to placebo achieved clinical remission. Clinical remission was mainly reported in patients who were naive to TNF antagonists. Although the comparison is indirect, the placebo-corrected proportion of patients in the etrolizumab 100 mg group who achieved clinical remission in our study (21%) seemed to be higher than the placebo-corrected proportion of patients in the vedolizumab group who achieved clinical remission in a phase 2 study (18·5%) in a less refractory patient population who were naive to anti-TNF therapy and not taking concomitant corticosteroids or immunosuppressants.[4]

Additionally, our study is, to the best of our knowledge, the first prospective, randomised, placebo-controlled trial in which a centrally read MCS endoscopy subscore of at least 2 was an eligibility requirement, to better ensure that the patients included had moderately or severely active disease. As opposed to clinical remission, for which the total MCS needs to be 2 or lower (ie, most of the four subscores need to be 0 with only two subscores of 1 point or one subscore of 2 points), clinical response requires a 3-point decrease and 30% reduction in MCS and a 1-point decrease or more in rectal bleeding subscore or absolute rectal bleeding subscore of 0 or 1. Therefore, if the patients selected for the study had a total baseline MCS of 9–12 points (the mean in this study for all groups combined was 9·2 [SD 1·7]), they could fulfil the criteria for clinical response while continuing to have an MCS suggestive of clinically significant ongoing disease. In our study, a relatively high proportion of patients in the placebo group achieved a clinical response—probably because, as noted in the previous sentence, this endpoint is less rigorous—and this proportion did not significantly differ from those in the etrolizumab groups. By contrast, endoscopic remission (ie, endoscopic score of 0) is an extremely rigorous endpoint, especially for the treatment-refractory patients included in this study, and thus was achieved in a small proportion of actively treated patients compared with no patients in the placebo group. The definition of mucosal healing (endoscopic score 0 or 1) is less restrictive than that of endoscopic remission, with more patients meeting this endpoint at week 10 across all treatment groups. The patients who had previously not responded to anti-TNF therapy in this study were a particularly refractory patient population (21% did not respond to more than one anti-TNF). Although we noted no benefit for this subgroup of patients at week 10 in this induction study, this finding was also noted in a larger phase 3 study[6] of vedolizumab, in which patients who had not responded to anti-TNF therapy did not significantly benefit at induction at week 6, although they did improve after 52 weeks of therapy.

Adverse events occurred at a similar frequency in the three treatment groups. No patients developed progressive multifocal leukoencephalopathy, an adverse event that has been associated with the non-selective anti-α4 integrin antibody natalizumab. The risk of progressive multifocal leukoencephalopathy with etrolizumab is expected to be negligible in view of the selectivity of the β7 receptor for the mucosal epithelium. However, the safety profile for etrolizumab thus far is based on short-term induction studies with low patient numbers and will be further assessed in larger trials with longer-term dosing.

Panel: Research in context

Systematic review

We searched PubMed for clinical trials of existing and emerging biological therapies for moderately-to-severely active ulcerative colitis using the search terms "ulcerative colitis treatment" and "moderate to severe" published between Jan 1, 2000, and Feb 28, 2014. The search was limited to positive, phase 1–3 clinical trials and trials were included if they were of therapies, not procedures, and included adult patients with moderate to severe ulcerative colitis who were outpatients (studies that included patients with severe ulcerative colitis admitted to hospital were excluded). We found that etrolizumab was one of nine therapies (including infliximab, adalimumab, golimumab, vedolizumab, AMG 181, PF-00547659, BMS-936557, and tofacitinib) that have entered or completed phase 2 and phase 3 clinical trials for the treatment of ulcerative colitis.

Interpretation

Our study is, to the best of our knowledge, the first double-blind, randomised, placebo-controlled trial of etrolizumab in patients with moderately-to-severely active ulcerative colitis. Patients who received etrolizumab were more likely to have clinical remission at week 10 than were patients who received placebo, and etrolizumab was well tolerated. During treatment with etrolizumab, β7 receptors were fully occupied in the peripheral blood and in the colonic tissue. Patients with higher levels of αE expression in the colonic tissue were more likely to achieve clinical remission than patients with lower levels. These results support further long-term study to investigate the potential of etrolizumab to bring clinically meaningful benefit to patients with moderately-to-severely active ulcerative colitis.

Importantly, the lowest serum concentration of etrolizumab associated with full colonic tissue occupancy reported in this study was 1·7 μg/mL, a concentration similar to the EC90 value (1·26 μg/mL) for receptor occupancy in the peripheral blood.[14] Thus, in this trial of patients with moderately or severely active ulcerative colitis, the serum concentration of etrolizumab required to occupy β7 receptors in the colonic mucosa was similar to that required for occupancy in the peripheral blood. Furthermore, the low subcutaneous dose of etrolizumab 100 mg was sufficient to maximally occupy β7 receptors in both the blood and the colonic mucosa, and hence might have contributed to the significant clinical benefit reported. Although we noted maximum β7 occupancy in both etrolizumab dose cohorts, and did not detect any apparent exposure–response relation in the quartile-concentration response analysis, patients in the etrolizumab 300 mg plus LD group did seem to have reduced clinical remission when compared with those who received the 100 mg monthly dose. Etrolizumab treatment might alter cellular migration of different cell types (eg, regulatory T cells) in a dose-dependent manner. Identification of human regulatory T cells by gene expression is not straightforward, because genes expressed by regulatory T cells, such as *FOXP3*, are also expressed by activated T cells.[15] We noted no significant change in gene expression of *FOXP3* between the two etrolizumab dose groups or between the etrolizumab groups and placebo (data not shown). More specific regulatory-T-cell markers, such as epigenetic modifications at the *FOXP3* locus, would have to be assessed prospectively in a subsequent study. Although we made every effort to ensure that the treatment groups were well balanced with respect to demographics, baseline characteristics, and concomitant medications for ulcerative colitis, some unknown imbalance in patients could have possibly led to the dose response reported. Similarly, although the numbers of patients per treatment group (about 40) are adequate for a phase 2 proof-of-concept study, we cannot rule out that the attenuated effect in the higher dose group was a by-chance observation. In support of this interpretation, an analysis of the MCS by subscore of 1 point or less or 0 points across the dose groups showed an inconsistent effect of dose (appendix).

Consistent with the role of β7 receptors in mediation of lymphocyte trafficking to the intestine, there was a corresponding increased frequency of β7-expressing lymphocytes in the peripheral blood. The proportion of α4β7 versus αEβ7 T cells in the peripheral blood was not specifically assessed in this study; however, exploratory analysis in healthy volunteers and patients with inflammatory bowel disease has shown that the concentrations of αEβ7 T cells in peripheral blood are too low to track by flow cytometry and most to all β7+ cells in the periphery are α4β7+ (unpublished data). By contrast, in our colonic substudy, α4 expression was assessed and all β7+ cells were found to coexpress αE and α4. Although maximal β7 occupancy was noted in both the peripheral circulation and, in a representative patient subgroup, in the colonic mucosa for a minimum of 10 weeks in our study, a clinical benefit was not found in all patients, suggesting that the inflammatory process continues in some patients despite blockade of the β7 receptor. This finding could be explained by the proinflammatory activity of immune cells already present in the gut before treatment with etrolizumab, or a potential β7-independent mechanism of leucocyte trafficking to the intestinal mucosa. Further understanding of alternative mechanisms of inflammation will require exploration in patients undergoing long-term therapy with etrolizumab.

Although mucosal proinflammatory cytokine expression decreased in patients in the etrolizumab groups who achieved clinical remission, expression of E-cadherin increased. E-cadherin has been shown to be expressed at lower concentrations in patients with inflammatory bowel disease than in healthy controls,[16] suggesting that the observed increase in E-cadherin is related to mucosal healing in these patients. This finding is supported by the improvement in the histological active disease severity score in patients who received etrolizumab in our study.

The results from the post-hoc exploratory diagnostic analysis done in this phase 2 study provide an indication of possible heterogeneity in treatment benefit for patients with varying αE concentration. Additional prospective studies involving larger groups of patients are necessary to confirm these findings. If validated, these results suggest two possible hypotheses: αE+ cells themselves contribute to the pathogenesis of ulcerative colitis; or αE expression is correlated with the activity of a pathogenic pathway that is inhibited by etrolizumab treatment. With respect to the former hypothesis, αE and αE-expressing cells have been reported to have several roles in the regulation of immune responses.[17] In-vitro studies of both mouse and human cells have shown that αEβ7+ dendritic cells can imprint T cells with a gut-homing phenotype and induce regulatory T-cell differentiation.[18–20,21] Additionally, αE has been suggested to be a marker of distinct regulatory T-cell subpopulations,[22,23] although the function of αE in regulating the activity of this cell type is unclear.[24] By contrast, results of several studies in both human beings and animal models have shown that αE-expressing lymphocytes can produce proinflammatory cytokines, and disrupting αE function in mice can ameliorate intestinal inflammation.[25–29] Our findings—that baseline colonic αE expression could improve response to etrolizumab and that treatment with etrolizumab reduced αE+ cell association with the intestinal epithelium—suggest that αEβ7+ lymphocytes contribute to the pathobiology of ulcerative colitis. Hence, blockade of both α4β7 and αEβ7 function might provide a unique therapeutic approach for the treatment of this disease. Further prospective studies will be important to better elucidate the effect of etrolizumab on the trafficking and function of various α4β7-expressing and αEβ7-expressing immune cells.

Contributors

SO'B, MK, MW, DL, PR, JCM, JP, AS, DCB, SS, WJS, and GDH participated in the design of the study. SV, JCM, CAL, BGF, JP, AS, DCB, SS, ID, WJS, GDH, CP, JAK, GvA, and PR participated in patient accrual and data collection. All authors analysed and interpreted the data. DL was the study biostatistician responsible for the statistical analyses. All authors were members of the writing group and participated in development of the report, agreed on the content, reviewed drafts, and approved the final version.

Declaration of interests

SV has received research/grant support from UCB, has received speaker fees from Abbott Laboratories/AbbVie, Ferring Pharmaceuticals, MSD, Merck/Schering-Plough, and UCB, has served on advisory committees or review panels for Ferring Pharmaceuticals, Pfizer, MSD, and Shire, and has done consulting for AstraZeneca Pharmaceuticals and Ferring Pharmaceuticals (employment, spouse). MW is an employee of Gilead Sciences and a former employee of Genentech. JCM has served on advisory committees or review panels for Abbott Laboratories/AbbVie and Genentech, and has received speaker fees from Ferring Pharmaceuticals, grants from Wellcome Trust and Genentech, non-financial support from Genentech, Roche Tissue diagnostics, Techlab, and Immundiagnostik, personal fees from Genentech, Takeda, Sanofi, and Tillots; and other from Tillotts and Abbott. 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