Vedolizumab to prevent postoperative recurrence of Crohn's disease (REPREVIO): a multicentre, double-blind, randomised, placebo-controlled trial

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Summary

Background Approximately half of patients with Crohn's disease require ileocolonic resection. Of these, 50% will subsequently have endoscopic disease recurrence within 1 year. We aimed to evaluate the efficacy and safety of vedolizumab to prevent postoperative recurrence of Crohn's disease.

Methods REPREVIO was a double-blind, randomised, placebo-controlled trial conducted at 13 academic or teaching hospitals in France, Italy, the Netherlands, and Spain. Eligible participants were adult patients aged 18 years or older with Crohn's disease who underwent ileocolonic resection and had one or more risk factors for recurrence. Patients were randomly assigned within 4 weeks of surgery (1:1 ratio) to receive intravenous vedolizumab (300 mg) or placebo at weeks 0, 8, 16, and 24. Randomisation was performed centrally with a computer-generated validated variable block model and patients were stratified according to disease behaviour (fibrostenotic *vs* inflammatory or perforating). Ileocolonoscopy was performed at week 26 and videorecorded. Endoscopic recurrence was centrally assessed with the modified Rutgeerts score, a categorial score ranging from i0 to i4. The primary endpoint was the distribution of modified Rutgeerts scores between treatment groups at week 26, analysed by non-parametric methods. The first-ranked secondary endpoint was the proportion of patients with severe endoscopic recurrence of Crohn's disease at week 26 (modified Rutgeerts score ≥i2b). Primary and safety analyses included all patients who underwent randomisation and received at least one dose of study drug. The trial is registered with the EU Clinical Trial Register (EudraCT; 2015-000555-24).

Findings Between May 16, 2017, and April 8, 2022, 84 patients were randomly assigned to treatment, of whom four did not receive study treatment, leaving 43 patients in the vedolizumab group and 37 in the placebo group. At week 26, the probability of a lower modified Rutgeerts score with vedolizumab versus placebo was 77·8% (95% CI 66·4 to 86·3; p<0·0001). Severe endoscopic recurrence was observed in ten (23·3%) of 43 patients in the vedolizumab group versus 23 (62·2%) of 37 patients in the placebo group (difference –38·9% [95% CI –56·0 to –17·3]; p=0·0004). Serious adverse events occurred in three (7·0%) of 43 patients who received vedolizumab (bilateral tubo-ovarian abscesses, thrombosed haemorrhoids, and pancreatic adenocarcinoma) and in two (5·4%) of 37 patients who received placebo (intestinal perforation related to Crohn's disease and severe abdominal pain).

Interpretation Vedolizumab treatment within 4 weeks of ileocolonic resection was more likely to prevent endoscopic Crohn's disease recurrence than placebo, making this an attractive option for postoperative management in patients with risk factors for recurrence. Larger studies with longer follow-up would be desirable.

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Introduction

Surgical resection for disease-related complications or medically refractory disease is often required in patients with Crohn's disease.[1,2] However, disease recurrence is common and can be observed histopathologically within 8 days of faecal stream restoration.[3] Endoscopic disease recurrence is observed in approximately 50% of patients within 1 year, despite treatment.[4–7] Typical clinical symptoms of Crohn's disease, including diarrhoea and abdominal pain, occur later, such that approximately half of patients have symptomatic recurrence within 5 years of initial surgery, with an additional resection required in approximately 21% of patients by that time.[8–11] Importantly, the risk of clinical Crohn's disease recurrence has been estimated in a meta-analysis to be 27·3 (95% CI 10·2–73·4) times greater in patients with endoscopic recurrence than in those without endoscopic recurrence.[7]

The acceptance of endoscopic recurrence as a prognostic marker in the management of Crohn's disease is reflected in American Gastroenterological Association

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Research in context

Evidence before this study

Prophylactic treatment of Crohn's disease post-surgery is recommended in patients with reported risk factors such as smoking, previous intestinal resection for Crohn's disease, perforating disease, perianal location, and microscopic granulomas or myenteric plexitis (or both) in the resection specimen. However, no treatment has been approved for this indication. Guidelines suggest postoperative prophylaxis with TNF antagonists and thiopurines. We searched PubMed and Embase using the following terms: "post-surgery", "Crohn's disease", "recurrence" and "prophylaxis" from database inception to June 25, 2024, with no restrictions for article type. Of the 66 results, 32 were randomised controlled trials performed with prophylactic treatment of mesalazine, budesonide, metronidazole, immunomodulators, or TNF antagonists. To the best of our knowledge, no randomised controlled trials have investigated other biologics for Crohn's disease, except for TNF antagonists. Four retrospective studies have reported the use of vedolizumab for prophylaxis in small patient cohorts.

Added value of this study

This study is, to the best of our knowledge, the first to show that vedolizumab prevents postoperative recurrence of Crohn's disease in patients with at least one risk factor for recurrence. The likelihood of developing postoperative recurrence with prophylactic administration of vedolizumab was 77·8% lower than in patients who received placebo. Moreover, severe endoscopic recurrence was significantly less frequent with vedolizumab than with placebo. The frequency of adverse events was low in both groups.

Implications of all the available evidence

Our results show that vedolizumab prevents postoperative recurrence of Crohn's disease and should be considered as a prophylactic treatment in patients with at least one risk factor for recurrence, making this an attractive option for postoperative management in patients with risk factors for recurrence. Larger studies with longer follow-up would be desirable.

guidelines that recommend ileocolonoscopy 6–12 months after surgical resection, with initiation of medical therapy for severe endoscopic recurrence, defined as a modified Rutgeerts score of i2b or greater.[12–14] This instrument evaluates the severity of endoscopic recurrence at the anastomosis and neoterminal ileum according to a five point scale (i0–i4), with higher scores indicating more severe recurrence.[8] Although national guidelines recommend various preventive treatments for post-surgical Crohn's disease, no medical therapy has been approved for this indication.[15–19]

Vedolizumab, an α4β7 integrin antibody that inhibits migration of T lymphocytes into the gut, is approved for the treatment of moderately to severely active ulcerative colitis and Crohn's disease in adults.[20,21] Given that the influx of inflammatory cells into the intestinal mucosa precedes the development of endoscopic lesions,[3] inhibition of this process might prevent postoperative endoscopic recurrence of Crohn's disease. Here, we report the results of REPREVIO, a study that aimed to evaluate the efficacy and safety of vedolizumab for the prevention of postoperative recurrence of Crohn's disease.

Methods

Study design and participants

REPREVIO was an investigator-initiated, double-blind, randomised, placebo-controlled trial conducted at 13 academic or teaching hospitals in France, Italy, the Netherlands, and Spain. REPREVIO evaluated the efficacy and safety of vedolizumab over a 26-week period in patients who underwent ileocolonic resection with anastomosis. The trial protocol was approved by institutional review boards or ethics committees at each site and all participants provided written informed consent before enrolment.

The trial was conducted in accordance with the International Council for Harmonization Tripartite Guidelines for Good Clinical Practice, applicable regulatory requirements, and the Declaration of Helsinki.

Eligible patients were aged at least 18 years with established Crohn's disease who had undergone ileocolonic resection, with removal of all macroscopically affected tissue, and ileocolonic anastomosis. Patients also had at least one risk factor for postoperative recurrence that included active smoking (more than ten cigarettes per day), perforating complications (abscess or fistula), previous exposure to TNF antagonists, or more than one previous resection.[12,19,22,23] Effective means of birth control were mandatory for inclusion of female patients of childbearing age. Patients were asked for their sex (at birth).

The following patients were excluded: those who required continued postoperative medical treatment other than the study drug; those who previously received vedolizumab treatment; those with clinically significant Crohn's disease in other locations not surgically removed; those with short bowel syndrome; those with a current or historical malignancy (other than resected cutaneous basal or squamous cell carcinoma or in-situ cervical cancer) with less than two documented disease-free years; those with a history of colonic dysplasia or colonic cancer; those with a contraindication for endoscopy; and those with clinically important laboratory abnormalities (white blood count $<3\times10^9$/L; lymphocyte count $<0\cdot5\times10^9$/L; haemoglobin <8 g/dL; platelet count $<125\times10^9$/L or $>800\times10^9$/L; ALT or AST >3·0 times the upper limit of normal [ULN]; alkaline phosphatase

For the **trial protocol** see https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000555-24/NL

>2·0 times the ULN; serum creatinine more than two times the ULN; and prothrombin time [international normalised ratio] >1·5 times normal). Treatment with TNF antagonists was discontinued at least 6 weeks before screening. Likewise, all other preoperative medications were discontinued, except for loperamide, cholestyramine, and corticosteroids. Corticosteroids were tapered according to a defined schedule (appendix p 4) over 4 weeks after surgery. Full eligibility criteria are listed in the appendix (p 3). Patients gave written informed consent before the initiation of any study procedures.

Randomisation and masking

Randomisation (1:1) was performed centrally by the project manager with the use of a computer-generated validated variable block model and stratified according to disease behaviour (fibrostenotic *vs* inflammatory or perforating disease). The randomisation outcome was communicated to local trial pharmacies via email. Patients were enrolled by the study team at each institution. Patients and all trial personnel, except for the study pharmacist, were unaware of treatment assignment. Masking was achieved as follows: the solution bag was covered with a blinding sleeve, a fake needle prick was applied at the injection site or port of the infusion bag to imitate injected fluid (in the placebo group), and a blinded sticker was applied on the solution bag and the blinding sleeve.

Procedures

Intravenous vedolizumab at a dose of 300 mg or placebo was administered within 4 weeks of surgery (week 0) and at weeks 8, 16, and 24. Patient demographics and medical and surgical history were recorded, and a physical examination was performed at the screening visit. Vital signs, haematocrit, and serum chemistry were evaluated, concomitant medications were recorded, and adverse events were assessed at screening, and at weeks 0, 8, 16, and 24 before study drug infusion. Serum vedolizumab and anti-vedolizumab antibody concentrations were determined before each infusion. Serum C-reactive protein and faecal calprotectin concentrations were measured, and the Crohn's Disease Activity Index (CDAI), Inflammatory Bowel Disease Questionnaire (IBDQ), and Short Form-36 (SF-36) health survey scores (Physical Component Scale and Mental Component Scale) were calculated on the basis of patient diaries and questionnaires. The CDAI ranges from 0 to 600, with higher CDAI scores indicating more severe disease activity. The IBDQ scores range from 32 to 224 and SF-36 scores range from 0 to 100, with higher scores indicating better quality of life.

Ileocolonoscopy with neoterminal ileal biopsy (when approved by the patient and taken from the edge of ulcers) was performed and video-recorded at week 26. Endoscopy could be performed earlier than week 26 for symptomatic exacerbation (defined as an increase of >70 points in the CDAI from baseline) and elevated serum C-reactive protein (>5 mg/L) or faecal calprotectin concentrations (>50 µg/g), or both. Anonymised video-recordings were assessed by two independent endoscopists (KBG and MD) with the modified Rutgeerts score for postoperative recurrence of Crohn's disease.[8] This categorical score ranges from i0 (absence of endoscopic lesions in the neoterminal ileum) to i4 (severe diffuse inflammation of the neoterminal ileum with large ulceration or stenosis, or both; appendix p 12). Modified Rutgeerts scores of i2b or greater are generally considered to convey a risk of symptomatic recurrence.[12,13] Scoring disagreements were adjudicated by a third masked endoscopist (GD'H). Histological inflammation in week 26 biopsies was assessed by a pathologist (AM) with the Robarts Histopathology Index (RHI) and the Geboes scores. The RHI scores range from 0 to 33 and Geboes scores range from 0 to 5·4, with higher scores indicating more severe inflammation. All readers assessing endoscopic and histological inflammation were unaware of any clinical information and randomisation. Protocol-defined criteria for a patient to be removed from the study were as follows: a significant protocol deviation, loss to follow-up, voluntary withdrawal, study termination, pregnancy, lack of efficacy, exacerbation of disease, a significant adverse or serious adverse event, or if prednisone tapering after surgery was unsuccessful.

See Online for appendix

Outcomes

The primary endpoint was the distribution of modified Rutgeerts scores between treatment groups at week 26 (centrally assessed as described above). The first ranked secondary endpoint compared the proportion of patients with severe endoscopic recurrence of Crohn's disease (defined as a modified Rutgeerts score ≥i2b) at week 26. Subsequent secondary endpoints were the proportion of patients with any endoscopic recurrence of Crohn's disease (defined as a modified Rutgeerts score >i0) at week 26, clinical recurrence (defined as a CDAI increase of >70 points compared to baseline), normal serum C-reactive protein (<5 mg/L) at all visits, normal faecal calprotectin (<50 µg/g) at all visits, adverse events and serious adverse events, quality of life measured by IBDQ and SF-36, serum concentrations of vedolizumab and anti-drug antibodies before every infusion, and the incidence and severity of histological recurrence (defined as RHI score >3; Geboes score >2B.0). Safety assessments comprised emergent clinical adverse events, laboratory measurements, vital signs, and physical examination. Treatment discontinuation was recorded together with the reason for discontinuation. A full description of study outcomes and definitions is provided in the appendix (p 4).

Statistical analysis

The sample size calculation assumed a 40% rate of severe endoscopic recurrence (modified Rutgeerts score ≥i2b) in the placebo group compared to a 10% rate in the vedolizumab group at week 26. The 40% endoscopic recurrence rate in the placebo group was based on an earlier recurrence prevention study with mesalazine, 6-mercaptopurine, and placebo, in which patients had 42% endoscopic recurrence after 24 months.[24] The total sample size was estimated at 80 patients based on 80% power, a one-sided alpha error of 0·05, and correcting for a 5% dropout rate.

Primary and safety analyses included patients who underwent randomisation and received at least one dose of study drug. The primary endpoint was analysed with a non-parametric (win probability) approach to estimate the probability that a patient treated with vedolizumab would have a lower modified Rutgeerts score relative to a patient treated with placebo.[25] The original primary endpoint was the dichotomous proportion of patients with severe endoscopic recurrence, which was amended in October, 2022, based on new statistical insights and methods showing that win probabilities and associated confidence intervals provide a more sensitive readout.[26] Win probability estimates with 95% CIs and two-sided p values were calculated as described elsewhere.[26] The first ranked secondary endpoint of severe endoscopic recurrence (≥i2b) and secondary endpoints of any endoscopic recurrence (>i0) and clinical recurrence were analysed with a χ^2 test, supplemented with a point estimate and 95% CI for the difference in proportions. Patients with missing modified Rutgeerts scores were counted as having the worst possible score (i4) for all analyses except for correlations. If two or more timepoints were missing for CDAI (clinical recurrence), the patient was excluded from this analysis.

For the other secondary endpoints, continuous variables were expressed as medians (IQRs) or means (SDs), depending on the distribution. Differences between treatment groups at each timepoint were analysed with a two-sample *t* test or Mann-Whitney *U* test for continuous variables, depending on the distribution. For categorical variables, χ^2 tests or Fisher's exact tests (based on cell count) were conducted. If two or more timepoints were missing, the patient was excluded from the analysis for vedolizumab serum concentrations. Patients with any missing data for normal C-reactive protein and normal calprotectin concentrations at all visits were excluded from the analysis. A mixed-effects model was performed to analyse quality of life (IBDQ and SF-36) and CDAI over time. Analyses included the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction. We reported the estimate of the difference between treatment groups in the mean SF-36, IBDQ, and CDAI over the treatment period. The correlation between histopathology and endoscopy scores was assessed with the Spearman's rank correlation coefficient. Statistical analyses were performed in SPSS Statistics (version 28.0). Statistical tests were two-sided, with a p value of 0·05 as the criterion for statistical significance. There was no data monitoring committee. The trial is registered with the EU Clinical Trial Register (EudraCT; 2015-000555-24).

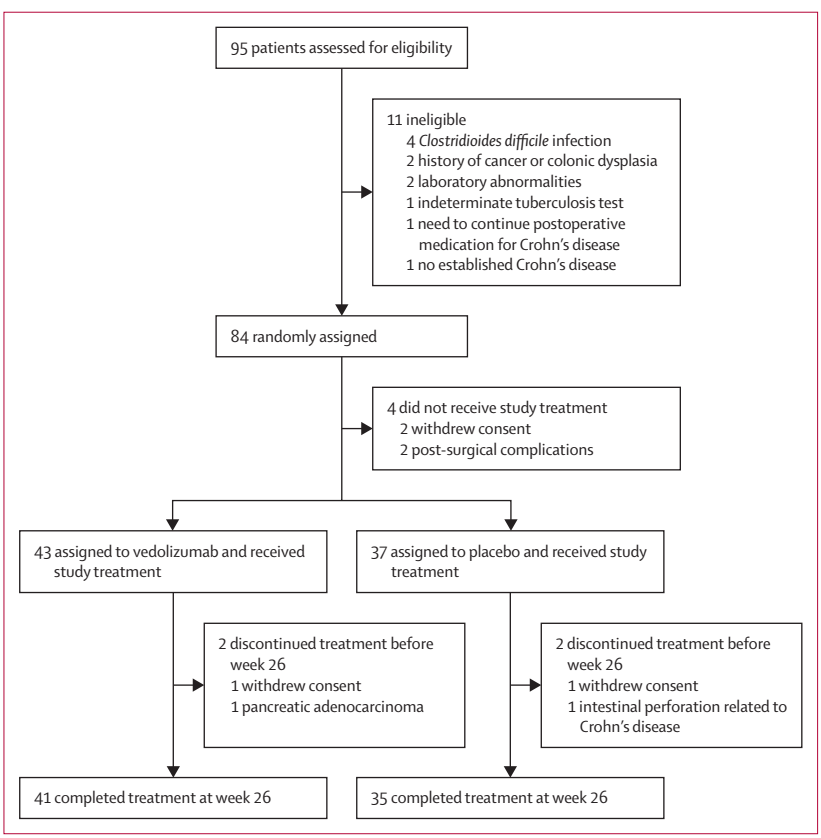

Figure 1: **Trial profile**

Role of the funding source

The study was supported in part by Takeda Nederland, which provided vedolizumab and placebo. Takeda Nederland had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the paper for publication.

Results

Between May 16, 2017, and April 8, 2022, 95 patients underwent screening, of whom 84 patients were randomly assigned. Four patients were subsequently excluded because of withdrawal of consent (two in the placebo group) and post-surgical complications (one in each group) before the baseline infusion, leaving 80 patients enrolled to receive at least one dose of study drug (43 in the vedolizumab group and 37 in the placebo group). Overall, 41 patients in the vedolizumab group and 35 patients in the placebo group completed treatment (figure 1). The reasons for discontinuation were pancreatic adenocarcinoma (one patient in the vedolizumab group), intestinal perforation related to

Crohn's disease (one patient in the placebo group), and withdrawal of consent (one patient in each group). Four patients underwent colonoscopy early because of symptoms suggestive of recurrence (one in the vedolizumab group and three in the placebo group). We used the Rutgeerts score of this early colonoscopy as the end of study visit for the endoscopic outcome analyses. The median time between baseline and colonoscopy was 26 weeks (IQR 26–28). Two patients in each group had missing modified Rutgeerts scores and were counted as having the worst possible score (i4). The baseline characteristics of patients were similar across the two groups, except for active smoking (more than ten cigarettes per day) as a risk factor for postoperative recurrence, which was numerically lower in the vedolizumab group than in the placebo group (five [11·6%] of 43 patients *vs* eight [21·6%] of 37 patients; table 1).

At week 26, patients in the vedolizumab group had a 77·8% (95% CI 66·4–86·3, p<0·0001) probability of having a lower modified Rutgeerts score than patients in the placebo group. The distribution of the modified Rutgeerts scores in the two treatment groups is shown in figure 2A.

At week 26, the proportion of patients with severe endoscopic recurrence (modified Rutgeerts score ≥i2b) was lower in the vedolizumab group (ten [23·3%] of 43 patients) than in the placebo group (23 [62·2%] of 37 patients; difference –38·9% [95% CI –56·0 to –17·3], p=0·0004; figure 2B). A lower rate of any (>i0) endoscopic recurrence was also seen in the vedolizumab group than in patients assigned to placebo (25 [58·1%] of 43 patients *vs* 36 [97·3%] of 37 patients; difference –39·2% [95% CI –54·8 to –23·5], p<0·0001; figure 2B). Clinical recurrence was similar for patients who received vedolizumab relative to those assigned to placebo (nine [20·9%] of 43 patients *vs* eight [21·6%] of 37 patients, difference –0·7% [95% CI –18·7 to 17·3], p=0·94; figure 2B).

A normal serum C-reactive protein concentration at week 8, 16, and 24 was more frequently seen in the vedolizumab group than in the placebo group (34 [85·0%] of 40 evaluable patients *vs* 17 [56·7%] of 30 evaluable patients, difference 28·3% [95% CI 7·0 to 47·5], p=0·008; appendix p 5). Normal faecal calprotectin concentration at week 8, 16, and 24 was similar in patients who received vedolizumab relative to those assigned to placebo (eight [33·3%] of 24 evaluable patients *vs* four [17·4%] of 23 evaluable patients, difference 15·9% [95% CI –9·1 to 38·4], p=0·21; appendix p 5).

The incidence and severity of histological recurrence was lower in patients treated with vedolizumab than in those assigned to placebo at week 26 (0 [IQR 0–7] *vs* 7 [3–14], p=0·0026, for RHI scores; 0 [IQR 0–31] *vs* 3·1 [IQR 2·1–5·2], p=0·00076, for Geboes scores). There

	Vedolizumab (n=43)	Placebo (n=37)
Age, years	36 (19–79)	36 (18–74)
Sex		
Female	19 (44·2%)	18 (48·6%)
Male	24 (55·8%)	19 (51·4%)
Disease duration, years	9 (0–30)	8 (0–45)
Current smoking	11 (25·6%)	12 (32·4%)
Corticosteroids at baseline	3 (7·0%)	3 (8·1%)
CRP at baseline, mg/L	2 (0–208)	2 (0–493)
CDAI at baseline	108 (11–312)	111 (21–349)
Faecal calprotectin at screening, µg/g	148 (9–2400)	167 (4–1800)
Active smoking (more than ten cigarettes per day)	5 (11·6%)	8 (21·6%)
Second, third, or later resection	16 (37·2%)	12 (32·4%)
Surgery for perforating complication	17 (39·5%)	12 (32·4%)
Previous exposure to TNF antagonist	27 (62·8%)	23 (62·2%)

Data are n (%) or median (range). The full analysis set includes all patients who underwent randomisation and received at least one dose of vedolizumab or placebo. CRP=C-reactive protein. CDAI=Crohn's disease activity index. TNF=tumour necrosis factor.

Table 1: **Demographic and clinical characteristics at baseline in the full analysis set**

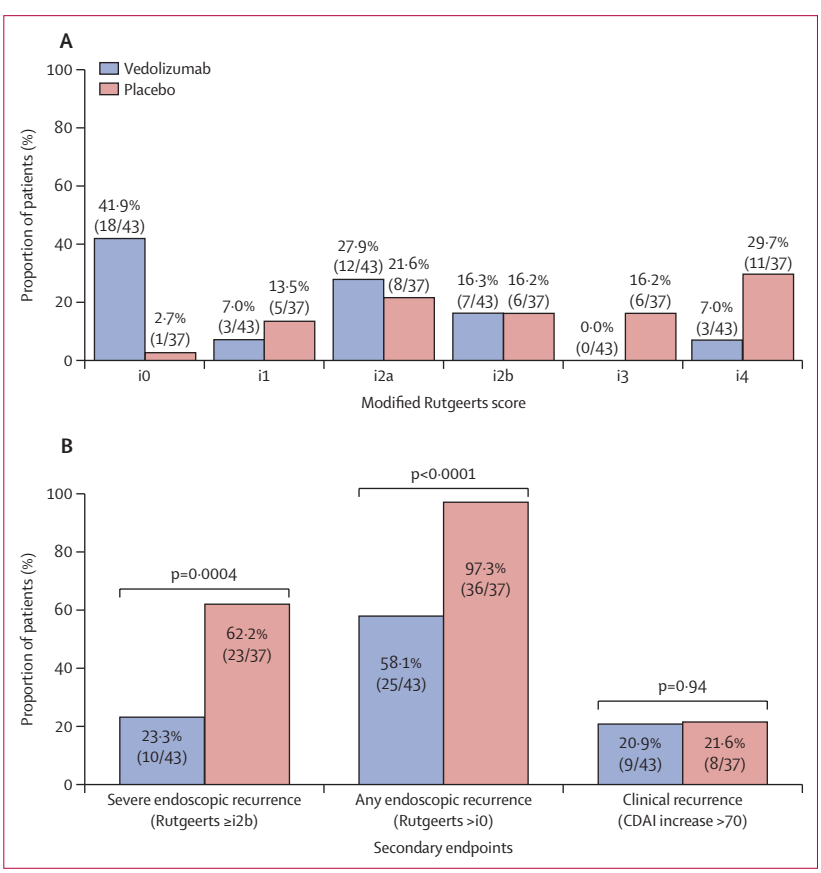

Figure 2: **Endoscopic and clinical outcomes (full analysis set)**
(A) Distribution of the modified Rutgeerts scores. Proportions of patients (as well as the numbers) are shown. The full analysis set includes all patients who underwent randomisation and received at least one dose of vedolizumab or placebo. (B) First-ranked secondary endpoint of severe endoscopic recurrence and secondary endpoints of any endoscopic recurrence and clinical recurrence. CDAI=Crohn's Disease Activity Index.

	Vedolizumab (n=43)	Placebo (n=37)
Adverse events reported in >5% of patients		
Abdominal pain	5 (11·6%)	4 (10·8%)
Arthralgia	5 (11·6%)	6 (16·2%)
Liver test abnormalities	4 (9·3%)	0
Flare or worsening	0	6 (16·2%)
Headache	3 (7·0%)	2 (5·4%)
Upper respiratory infection	4 (9·3%)	4 (10·8%)
Infectious gastroenteritis	4 (9·3%)	2 (5·4%)
Serious adverse events		
Any serious adverse event	3 (7·0%)	2 (5·4%)
Bilateral tubo-ovarian abscesses	1 (2·3%)	0
Thrombosed haemorrhoids	1 (2·3%)	0
Pancreatic adenocarcinoma	1 (2·3%)	0
Intestinal perforation related to Crohn's disease	0	1 (2·7%)
Severe abdominal pain	0	1 (2·7%)

Data are n (%). *The safety analysis set was identical to the full analysis set.

Table 2: **Adverse events in the safety analysis set***

was a significant correlation between histopathology and endoscopy for both scoring systems (Spearman's rank correlation coefficient 0·37 [95% CI 0·10–0·59], p=0·0085, for RHI scores; 0·36 [95% CI 0·09–0·58], p=0·012, for Geboes scores; appendix p 11).

There were no substantial differences between the groups in the IBDQ and total SF-36 scores (appendix p 17). Pharmacokinetic data were consistent with those observed in a general population of patients with Crohn's disease (appendix p 17).[27] We found no evidence suggesting a correlation between the serum concentration of vedolizumab at week 8, 16, or 24 and the severity of endoscopic recurrence (appendix p 18). None of the patients developed anti-vedolizumab antibodies.

Serious adverse events occurred in three (7·0%) of 43 patients who received vedolizumab (bilateral tubo-ovarian abscesses, thrombosed haemorrhoids, and pancreatic adenocarcinoma) and in two (5·4%) of 37 patients who received placebo (intestinal perforation related to Crohn's disease and severe abdominal pain). Adverse events reported in more than 5% of the patients are listed in table 2. We found no evidence suggesting a correlation between the serum concentration of vedolizumab at week 8, 16, or 24 and adverse events (appendix p 19).

Discussion

In the REPREVIO trial, we showed that postoperative treatment with vedolizumab resulted in a 77·8% likelihood of less severe endoscopic recurrence of Crohn's disease at 26 weeks relative to placebo following ileocolonic resection. Furthermore, severe endoscopic recurrence (defined as a modified Rutgeerts score ≥i2b) was significantly less frequent with vedolizumab than with placebo. There was a significant correlation between histopathology and endoscopy, which underlines the consistency of the findings. No clinically important safety signals were observed.

Multiple studies have shown a strong association between development of a modified Rutgeerts score of i2b or greater and the risk of symptomatic recurrence and additional bowel resections.[7,8] Although we observed no reduction in the risk of clinical recurrence, this circumstance was anticipated given the relatively brief duration of follow-up. Moreover, symptomatic recurrence is not specific for endoscopic recurrence in these patients, who often have non-specific abdominal pain and increased stool frequency following surgical resection and removal of the ileocecal valve.[28] This circumstance raises an important issue for drug development. Although current regulatory policy has focused on clinical or patient-reported outcome benefits in the postoperative setting as well, the International Organization for the Study of Inflammatory Bowel Diseases recently issued guidance underscoring that endoscopy should be the primary endpoint for interventional studies in this indication.[29]

Several risk factors have been associated with early recurrence in epidemiological studies. Therefore, we only included patients who had at least one of these risk factors, to maximise the possibility of detecting a benefit of vedolizumab, should one exist. However, more recent studies have questioned the validity of these currently listed risk factors, with the exception of smoking and microscopic inflammation in the resection margins.[14,30]

Previously, the PREVENT trial compared infliximab with placebo, and did not meet the primary objective of preventing symptomatic recurrence at 18 months. By contrast, a substantial benefit was observed for prevention of endoscopic recurrence.[14] It should be recognised that trials that use a symptom-based definition of recurrence require approximately 5 years to complete, with a sample size requirement of approximately 350 patients. These requirements have hindered drug development in this area and a more pragmatic approach is needed.

Collectively, the two placebo-controlled trials to prevent postoperative recurrence of Crohn's disease with biologics used infliximab (with endoscopy assessment as a secondary endpoint) and vedolizumab (with endoscopy assessment as a primary endpoint). However, given the comparative safety profiles of TNF antagonists and vedolizumab, the latter appears more attractive for the treatment of these usually asymptomatic patients.[31]

Potential limitations of this trial are the small sample size, relatively short duration of follow-up, and absence of stratification based on histopathology. The safety profile of vedolizumab is well established and our findings are consistent with previous literature.

In conclusion, vedolizumab treatment prevented postoperative recurrence of Crohn's disease following

ileocolonic resection and should be considered as a prophylactic treatment in individuals with risk factors for recurrence.

Contributors

The first draft of the manuscript was developed by MSH, GD'H, and BGF. All authors reviewed subsequent drafts and approved and agreed to submit the final manuscript. All authors had access to the data and vouch for its accuracy and completeness, and for the fidelity of the trial to the protocol. GZ and LO have directly accessed and verified the underlying data reported in the manuscript.

Declaration of interests

GD'H served as a consultant for AbbVie, Alimentiv, AstraZeneca, Bristol Myers Squibb, Celltrion, Eli Lilly, Exeliom Biosciences, Johnson & Johnson, Pfizer, and Takeda; and has received speakers bureau fees from AbbVie, Eli Lilly, Pfizer, Bristol Myers Squibb, and Takeda. CT declares counselling, advisory boards, transports, or fees from AbbVie, MSD, Pfizer, Takeda, Janssen, Galapagos, Lilly, Chiesi, Ferring, Kern Pharma, Fresenius Kabi, Sandoz, and Tillotts. PN has served as speaker, consultant, and advisory board member for, or has received research funding from, MSD, AbbVie, Janssen, Takeda, Sandoz, Biogen, Ferring, Adacyte, Faes, Kern, Pfizer, Vifor, Chiesi, and Tillotts. 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Data sharing

Deidentified data will be made available to others upon request via email to the corresponding author (g.dhaens@amsterdamumc.nl) and within GDPR legislation. The data will be made available with publication to researchers whose proposed use of the data has been approved for a specific purpose. The data will be made available with a signed data access agreement after approval of a proposal. Additional related documents (eg, study protocol, statistical analysis plan, and informed consent form) will be made available at the same time.

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