Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial

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Summary

Background Conventional management of Crohn's disease features incremental use of therapies. However, early combined immunosuppression (ECI), with a TNF antagonist and antimetabolite might be a more effective strategy. We compared the efficacy of ECI with that of conventional management for treatment of Crohn's disease.

Methods In this open-label cluster randomised controlled trial (Randomised Evaluation of an Algorithm for Crohn's Treatment, REACT), we included community gastroenterology practices from Belgium and Canada that were willing to be assigned to either of the study groups, participate in all aspects of the study, and provide data on up to 60 patients with Crohn's disease. These practices were randomly assigned (1:1) to either ECI or conventional management. The computer-generated randomisation was minimised by country and practice size. Up to 60 consecutive adult patients were assessed within practices. Patients who were aged 18 years or older; documented to have Crohn's disease; able to speak or understand English, French, or Dutch; able to access a telephone; and able to provide written informed consent were followed up for 2 years. The primary outcome was the proportion of patients in corticosteroid-free remission (Harvey-Bradshaw Index score ≤4) at 12 months at the practice level. This trial is registered with ClinicalTrials.gov, number NCT01030809.

Findings This study took place between March 15, 2010, and Oct 1, 2013. Of the 60 practices screened, 41 were randomly assigned to either ECI (n=22) or conventional management (n=19). Two practices (one in each group) discontinued because of insufficient resources. 921 (85%) of the 1084 patients at ECI practices and 806 (90%) of 898 patients at conventional management practices completed 12 months follow-up and were included in an intention-to-treat analysis. The 12 month practice-level remission rates were similar at ECI and conventional management practices (66·0% [SD 14·0] and 61·9% [16·9]; adjusted difference 2·5%, 95% CI −5·2% to 10·2%, p=0·5169). The 24 month patient-level composite rate of major adverse outcomes defined as occurrence of surgery, hospital admission, or serious disease-related complications was lower at ECI practices than at conventional management practices (27·7% and 35·1%, absolute difference [AD] 7·3%, hazard ratio [HR]: 0·73, 95% CI 0·62 to 0·86, p=0·0003). There were no differences in serious drug-related adverse events.

Interpretation Although ECI was not more effective than conventional management for controlling Crohn's disease symptoms, the risk of major adverse outcomes was lower. The latter finding should be considered hypothesis-generating for future trials. ECI was not associated with an increased risk of serious drug-related adverse events or mortality.

Funding AbbVie Pharmaceuticals.

Lancet 2015; 386: 1825–34

Published Online September 3, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00068-9

See Comment page 1800

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Introduction

Conventional management of Crohn's disease consists of a step-care algorithm that features sequential use of corticosteroids, antimetabolites, and TNF antagonists. Treatment decisions are based on severity of symptoms and response to therapy.[1] Although step-care avoids overtreatment of low-risk patients,[2] important limitations exist. First, step-care is incremental and delays administration of highly effective therapy[3,4] in patients at the greatest risk of complications. Second, it prolongs corticosteroid exposure, drugs that increase the risk of infection and mortality.[5] Finally, symptoms correlate poorly with endoscopically-defined disease[6–10] and might not be a reliable criterion for treatment intensification.

The concept of early combined immunosuppression (ECI) emerged in response to these concerns. The TOP-DOWN[3] and SONIC[4] trials showed superiority of ECI to conventional management in treatment-naive patients. Despite these findings, step-care remains the standard management strategy in Crohn's disease since barriers exist to implementation of ECI, including concerns regarding infection, the complexity of multi-drug regimens, cost, and generalisability to community practice.[11–13] To address these considerations we did a trial of ECI in community gastroenterology practices.

Methods

Study design and participants

The study protocol is available on the Robarts Clinical Trials website. In this cluster randomised trial, we selected gastroenterology practices in Belgium and Canada and assigned them to either ECI or conventional management.

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For the **protocol** see https://www.robartsclinicaltrials.com

Practices were eligible if they were willing to be randomly assigned to either ECI or conventional management, participate in all aspects of the study, and provide data on up to 60 patients with Crohn's disease. The practices enrolled 60 consecutive patients with Crohn's disease who had been seen within the previous 12 months or who attended the clinic during the study period.

Practices accrued a cohort of consecutive patients who were aged 18 years or older; documented to have Crohn's disease based on endoscopic, radiological, or histological criteria; able to speak or understand English, French, or Dutch; able to access a telephone, internet, or email; and able to provide written informed consent. Patients were included regardless of disease activity or existing Crohn's disease treatments. Those with conditions which, in the investigator's opinion, would interfere with study procedures or who were participants in another study were ineligible.

This study was approved by the Canadian Shield Research Ethics Board. Institutional consent was obtained in Belgium. Participants provided written informed consent.

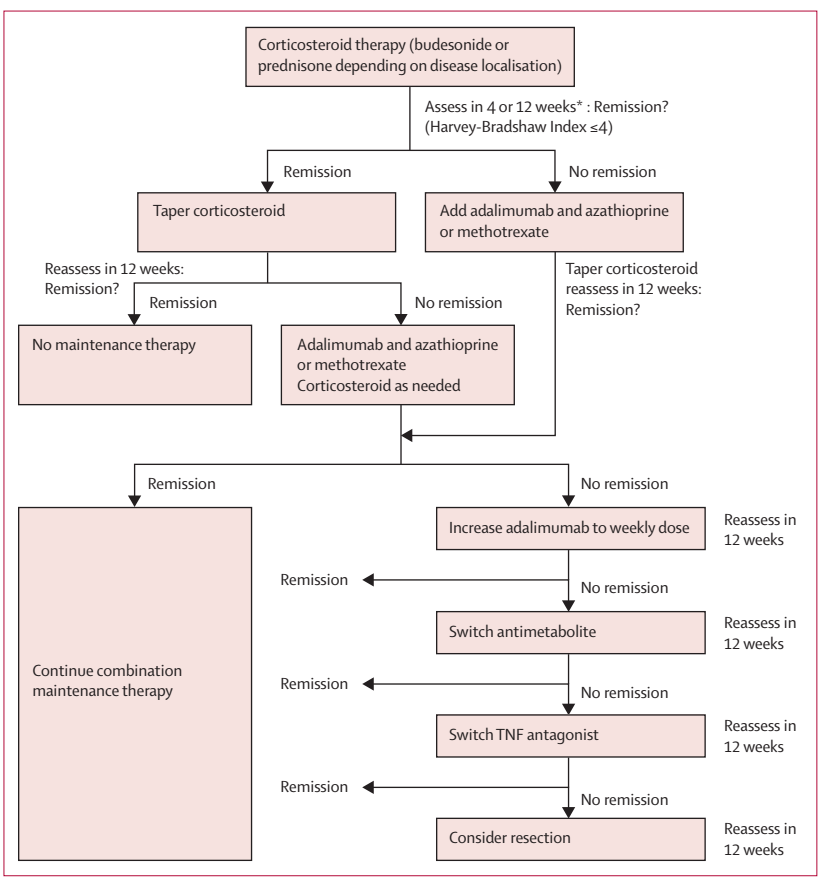

Figure 1: **The early combined immunosuppression algorithm**
Patients could enter the algorithm receiving any baseline treatment. In patients with a simple fistula, treatment with antibiotics was required before initiation of immunosuppressive therapies. In patients with complex fistula, evaluation with imaging or examination under anaesthesia to rule out an abscess was required. Treatment of the abscess, if present, and antibiotics were required before initiation of immunosuppressive therapies. *4 weeks at Canadian practices, 12 weeks at Belgian practices.

Randomisation and masking

Practices were randomly assigned (1:1) to either ECI or conventional management. A computer-generated minimisation procedure[14] balanced treatment effects of country and practice size (≤100 Crohn's disease patients treated annually) between intervention groups.

Because of the complex multidrug algorithm that was evaluated, masking of participants, providers, or assessors to group assignment was not possible. A cluster design was chosen to minimise the potential effects of this limitation. Investigators assigned to usual care were unaware of the details of the algorithm.

Procedures

After randomisation, training regarding the algorithm was provided at ECI practices (figure 1). At these practices those patients with continuing disease activity (defined as an HBI score >4) after initiation of corticosteroids received combined therapy with a TNF antagonist and antimetabolite. Belgian regulatory requirements mandated a 12-week trial of corticosteroid therapy before ECI, compared with a 4-week trial in Canada. Adalimumab was offered as initial therapy for TNF antagonist-naive patients but infliximab could be prescribed at the investigators' discretion. Likewise, choice of antimetabolite (azathioprine, 6-mercaptopurine, methotrexate) was decided by the physician and patient. The presence of active disease (Harvey-Bradshaw Index [HBI][15] score of ≥7), resulted in dose intensification of the TNF antagonist. The HBI assesses abdominal pain, stool frequency, general wellbeing, extra-intestinal manifestations, and presence of abdominal masses. Scores range from 0 (no disease activity) to 12 (severe disease). Scores of 4 or less indicate remission. Disease activity was reassessed at 12-week intervals and sequential treatment modifications (switching the antimetabolite, or the TNF antagonist, and, ultimately, consideration of surgery) were applied until remission was attained.

Practitioners assigned to conventional management were unaware of the ECI-algorithm details and managed patients according to usual practice. Patients at conventional management sites were treated according to the usual practice of their physicians. Telephone interviews and clinic visits were conducted in the same way as for the ECI group.

Patients were followed up for a maximum of 24 months. During scheduled clinic visits (months 0, 6, 12, 18, and 24) disease activity was assessed with the HBI,[15] and medication use and major adverse outcomes (serious disease-related complications, surgery, and hospital admissions) for Crohn's disease were recorded.

Quality of life was assessed with the Short Form-36 Version 2.0 (SF-36)[16,17] and European Quality of Life Index Version 3L (EQ-5D).[18–21] Patient and provider satisfaction

with treatment were assessed at month 24. Patients were seen as needed on an interim basis. Coordinating centre personnel contacted patients by telephone, email, or mail at months 2, 4, 8, 10, 14, 16, 20, and 22 to obtain HBI scores. The abdominal mass score from the preceding clinic visit was used for these assessments. Patients were questioned regarding medication use; and the occurrence of hospital admissions, surgery, and disease or therapy-related complications. Serious worsening of Crohn's disease was defined as increased bowel frequency, abdominal pain, or rectal bleeding reported by the site investigator that required a treatment intervention. Blinded gastroenterologists graded severity of complications and assigned causality for serious events. At ECI practices, patients with an HBI score of 7 or higher were told to contact their physician for re-assessment and possible treatment escalation according to the algorithm. ECI practices received weekly notifications from the coordinating centre of patients who met this criterion. The coordinating centre undertook source verification of these outcomes and a committee of three masked investigators (JCM, MKV, and RK) determined their validity and attribution to drug therapies or Crohn's disease by consensus.

Outcomes

The primary outcome was the mean proportion of patients in corticosteroid-free remission (HBI score ≤4) at month 12. The pre-specified secondary outcomes were the mean proportion of patients in remission and differences in mean HBI scores at months 6, 18, and 24; time to occurrence of the first major adverse outcome, defined as the composite of surgery or hospital admission for Crohn's disease, or development of a serious disease-related complication (the individual components of this outcome were also assessed independently); time to introduction of and the proportion of patients treated with specific Crohn's disease medications; serious drug and disease-related events; mortality; SF-36 and EQ-5D scores; and patient and provider satisfaction, which was assessed by questionnaires.

Statistical analyses

We analysed data from all practices with at least one patient who was followed up after randomisation, according to a pre-specified plan. Descriptive statistics assessed demographic characteristics. We used SAS version 9.3 (SAS Institute Inc, Cary, NC, USA) to conduct the analyses.

Since the intervention was implemented at the level of the practice, statistical inferences for the primary outcome were based on the proportion of patients in remission at the practice-level. Therefore, we did the primary analysis using analysis of covariance weighted by cluster size and adjusting for the design elements (country, practice size) and baseline remission rate.[22] We used a similar approach to compare remission rates at 24 months.

We analysed secondary outcome measures at both practice and patient-level. Since these approaches yielded highly concordant results only patient-level results are reported here. We estimated the time to disease-related surgery, hospital admission, and development of serious

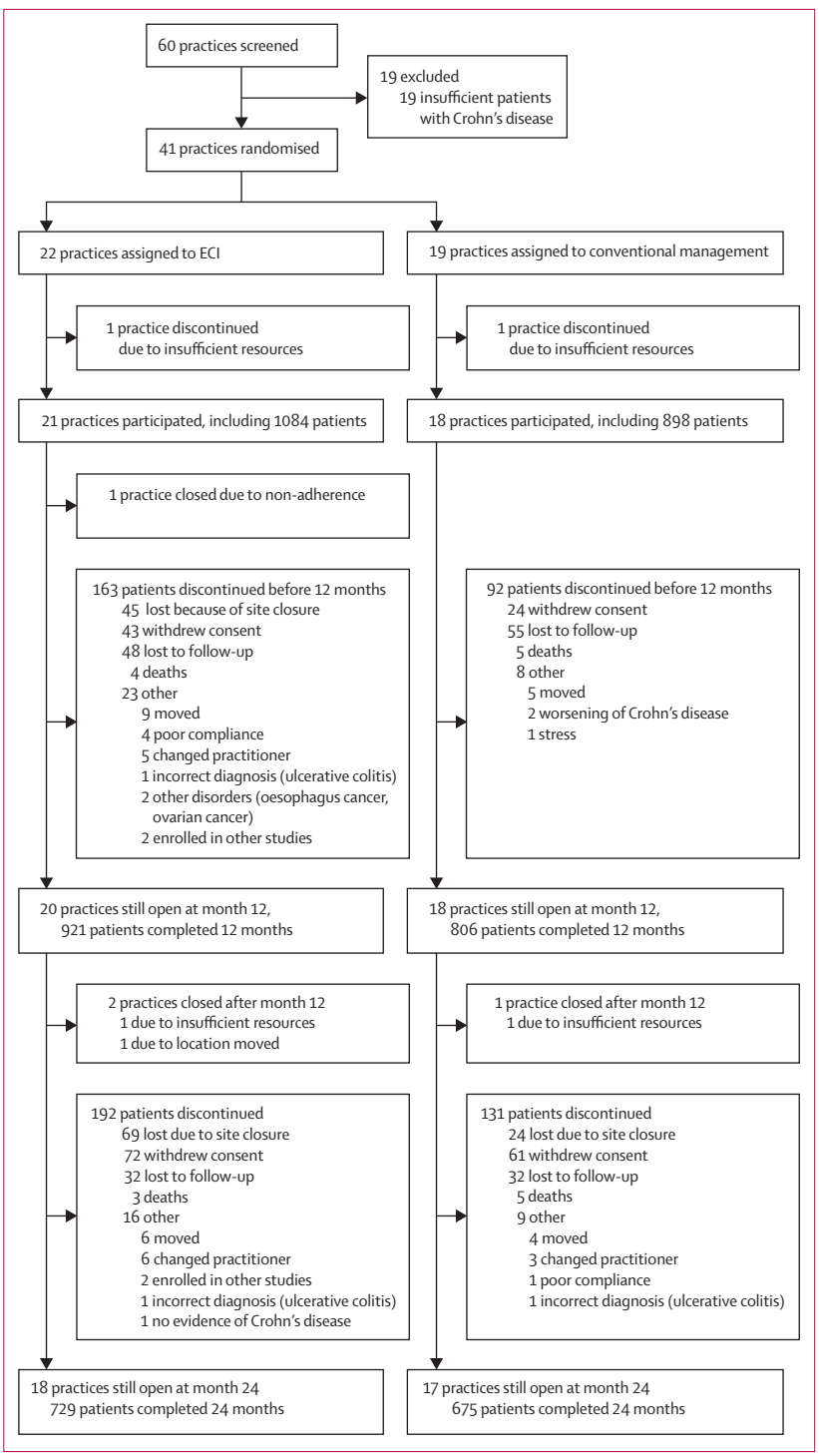

Figure 2: **Trial profile**

complications (presence of a new abscess, fistula, or stricture; serious worsening of disease activity; extra-intestinal manifestations); drug-related adverse events; treatment with specific drugs (corticosteroids, antimetabolites, TNF antagonists, and combination therapy); and death using Kaplan-Meier methods and we made comparisons using Cox regression controlling for the design elements (country, practice size) and adjusting for clustering effects.[23]

For SF-36 scores, EQ-5D scores, and patient and physician satisfaction, we used analysis of covariance to make adjusted practice-level comparisons, whereas we used linear mixed-models, incorporating practice as a random factor, for patient-level comparisons.

Two multivariable models examined potential predictors of remission and occurrence of major adverse outcomes. We assessed associations between month-24 remission and relevant clinical variables using generalised estimating equations.[24] We assessed associations between these clinical variables and the time to occurrence of major adverse outcomes using Cox regression adjusting for clustering effects.[23] Statistical tests were two-sided and done at the 0·05 level of significance.

A feasibility study, done at two practices in Canada, reviewed patients with a diagnosis of Crohn's disease assessed in the preceding year. At 12-months, the mean proportion of patients in symptomatic remission at the practice-level was 70% (SD 16) of patients. A sample size of 18 evaluable practices per group was required to detect a difference of 15% in remission rates with a two-sided 0·05 significance level and 80% power. A sample of 40 practices was targeted to accommodate a 10% non-evaluable rate.

	Early combined immunosuppression (N=21 practices, n=1084 participants)	Conventional management (N=18 practices, n=898 participants)
Practice characteristics		
Number of patients per site	51·6 (11·8)	49·9 (12·9)
Based in Canada	18 (86%)	16 (89%)
Patient characteristics*		
Age, years	44·1 (3·8)	44·1 (2·7)
Male	42·2% (8·2)	43·1% (6·9)
Disease duration, months	149·0 (40·0)	158·1% (29·2)
Current smoker	25·0% (8·2)	18·0% (6·2)
Medications		
Corticosteroids	19·2% (8·6)	17·5% (13·6)
Antimetabolites†	32·8% (16·0)	28·3% (14·7)
TNF-antagonists‡	19·7% (14·8)	21·0% (15·6)
Combined therapy with antimetabolites and TNF antagonists	12·1% (7·6)	13·1% (13·8)
Previous surgery for Crohn's disease location	45·4% (13·3)	49·3% (12·9)
Colon	24·0% (9·2)	20·1% (5·2)
Small bowel	32·3% (10·7)	36·7% (15·6)
Both	43·7% (13·4)	43·2% (14·3)
Fistula, active	6·6% (4·0)	8·2% (4·4)
HBI score	4·0 (1·0)	4·1 (1·1)
Steroid-free with HBI score ≤4	57·3% (12·4)	53·5% (15·3)
Short Form-36 Mental Component Summary score	44·6 (3·3)	45·9 (1·8)
Short Form-36 Physical Component Summary score	46·0 (2·1)	45·5 (2·2)
EQ-5D score	0·81 (0·04)	0·81 (0·03)

Data are mean (SD). HBI=Harvey-Bradshaw Index. EQ-5D=European Quality of Life Index. *Composite practice-level data are presented; for detailed practice-level data see appendix. †Antimetabolites not in combination with TNF antagonists. ‡TNF-antagonists not in combination with antimetabolites.

Table: **Baseline characteristics**

See Online for appendix

Role of the funding source

AbbVie Pharmaceuticals had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. Two authors (BGF and LWS) had full access to the data. RK had responsibility for manuscript submission.

Results

This trial took place in Belgium and Canada between March 15, 2010, and Oct 1, 2013. Of 60 practices screened, 41 were randomly assigned to either ECI (n=22) or conventional management (n=19; figure 2). Of these, two practices were excluded before randomisation because of insufficient resources. Subsequent to randomisation, one conventional management practice discontinued before patients were enrolled and an ECI practice withdrew before 12 months, because of insufficient resources, after randomly assigning 13 patients who had no follow-up visits before practice closure. Consequently, the intention-to-treat analyses included data from 39 practices and 1982 patients. Three additional practices (two ECI practices, with 69 patients; one conventional management practice, with 24 patients) withdrew after month 12 because of insufficient resources. All available data from these practices were included for analyses.

1084 patients were recruited at the 21 ECI practices and 898 patients at the 18 conventional management-practices. 921 (85%) of 1084 patients at ECI practices and 806 (90%) of 898 patients at conventional management practices completed the 12 months follow-up. 729 (67%) patients at ECI practices and 675 (75%) patients at conventional management practices completed 24 months of follow-up. The difference between groups in the proportion of patients completing follow-up was not significant.

The table shows practice-level demographics. Individual practice-level data are shown in the appendix. Patient baseline characteristics were well balanced between groups (table). Mean HBI baseline scores were 4·1 in both groups, indicating low disease activity.

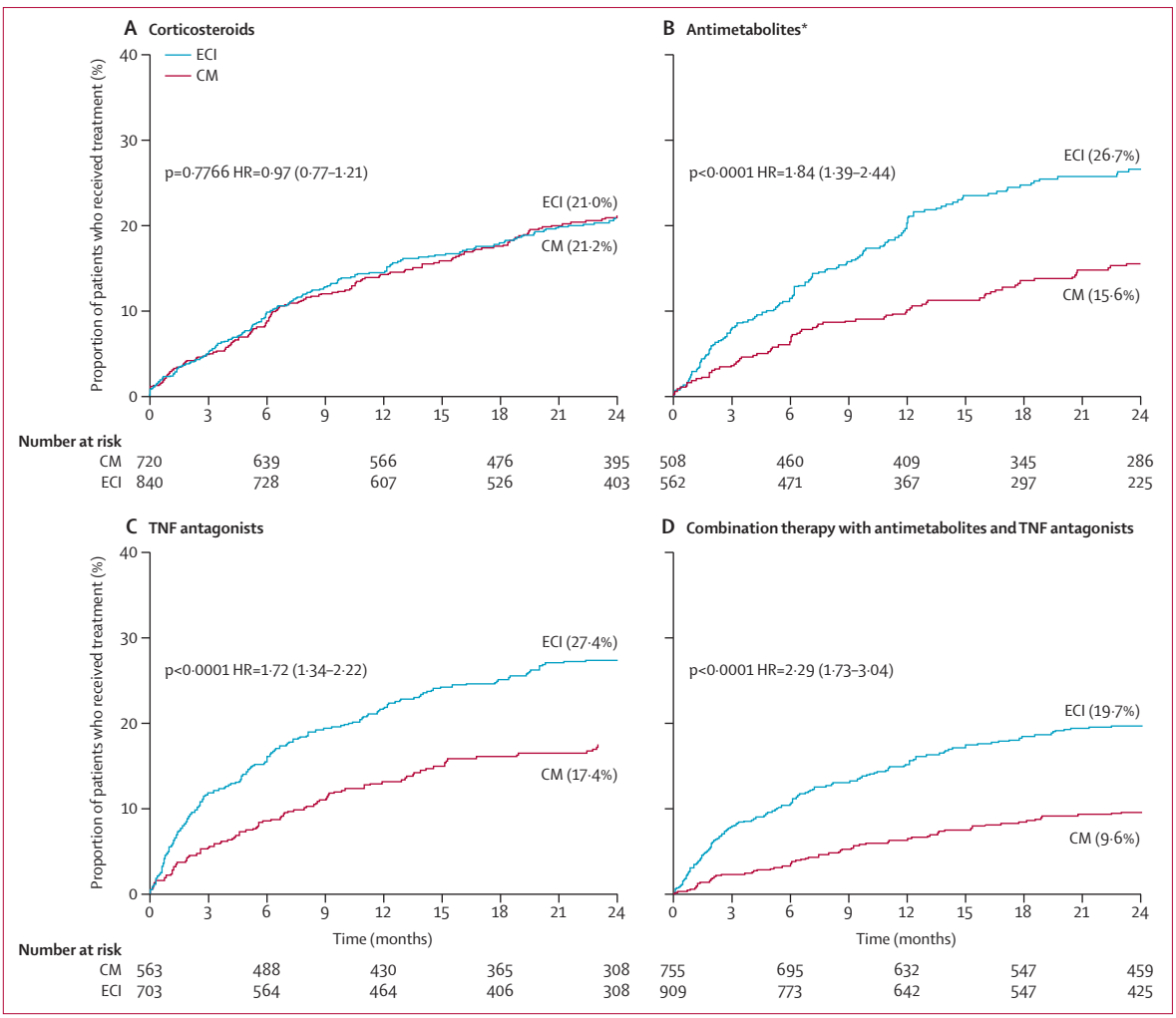

Figure 3: **Time to initiation of treatment**
Proportion of patients who received corticosteroids, antimetabolites, TNF antagonists, and combination therapy over time. Data were analysed at the patient level with a Cox regression model that adjusted for the design elements. CM=conventional management. ECI=early combined immunosuppression. HR=hazard ratio. *Azathioprine, 6-mercaptopurine, and methotrexate. †Adalimumab, infliximab, and certolizumab pegol.

For patients who met the criteria to escalate therapy according to the algorithm, the adherence rates were 85% (363 of 425 patients at 12 months and 87% (187 of 215 patients at 24 months) in the ECI group. In the conventional management group, the use of algorithm-specified therapy was low, 8% (28 of 357 patients) at 12 months and 8% (18 of 234 patients) at 24 months (appendix).

Patients at ECI practices were treated with antimetabolites, TNF antagonists, and combination therapy earlier than patients at conventional management practices (figure 3). No such difference was noted for corticosteroids. The proportion of patients who received combination therapy was greater at ECI practices by both 12 months (21·7% [195 of 900 patients] *vs* 16·5% [129 of 782], p=0·0082) and 24 months (21·8% [159 of 729] *vs* 17·0% [115 of 675], p=0·0147; appendix).

The primary outcome (remission rate at month 12) was 66·0% (SD 14·0) at ECI practices and 61·9% (16·9) at conventional management practices (adjusted difference 2·5%, 95% CI –5·2% to 10·2%, p=0·5169). At month 24, remission rates were 73·1 (SD 7·1) at ECI practices and 65·1 (17·4) at conventional management practices (6·4%, –0·9% to 13·6%, p=0·0829). Although the proportion of patients in remission was consistently higher in the ECI group, these differences were not significant (figure 4).

Similarly the differences between groups in mean HBI scores over time were not significant (appendix).

Significant differences were noted in favour of ECI for the composite outcome of time to occurrence of major adverse outcomes (HR=0·73, 95% CI 0·62 to 0·86, p=0·0003, absolute risk reduction [ARR] at 24 months 7·3%, number needed to treat [NNT] 14), surgeries (0·69, 0·50 to 0·97, p=0·0314, ARR 2·9%, NNT 35), and

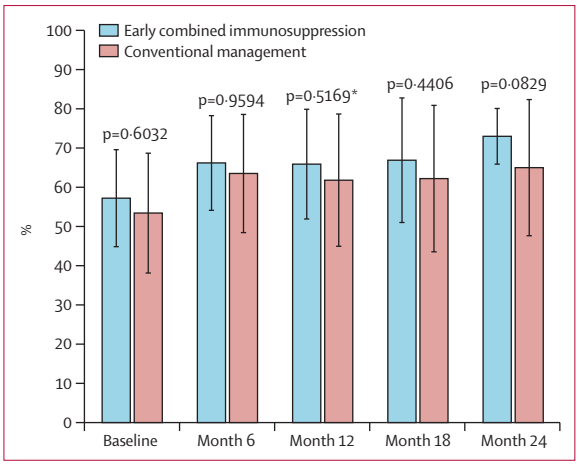

Figure 4: **Proportion of patients in symptomatic remission over 24 months**
*The primary outcome was assessed at month 12. We obtained p values using ANACOVA weighted by cluster size and adjusted for design elements, and baseline remission rates. Remission was defined as a Harvey-Bradshaw Index score of 4 or lower and no corticosteroids. Error bars are standard deviations.

serious disease-related complications (0·73, 0·61 to 0·87, p=0·0005, ARR 6·5%, NNT 16; figure 5). The difference in hospital admission rates was not significant (0·84, 0·65 to 1·08, p=0·1625, ARR 2·6%, NNT 39).

For serious disease and drug-related complications, the most common event was worsening Crohn's disease, which occurred in 98 (9%) of 1084 patients at ECI practices and 96 (11%) of 898 patients at conventional management-practices (appendix). The proportion of patients with serious drug-related adverse events did not differ between groups (1% [10 of 1084] at ECI practices *vs* 1% [10 of 898] at conventional management practices). Two serious opportunistic infections were noted in patients at ECI practices treated with adalimumab. A man aged 31 years who developed pulmonary tuberculosis was successfully treated without complications. A man aged 47 years developed a *Mycobacterium marinum* skin infection, which responded to antibiotics. A man aged 71 years, in the ECI group, who developed ataxia and confusion 2 weeks after starting adalimumab was diagnosed with possible acute demyelination secondary to adalimumab. He made a complete recovery.

Mortality was low and did not differ between the treatment groups (seven patients [1%] in the ECI group and ten [1%] patients in the conventional management group; HR 0·62, 95% CI 0·24–1·63, p=0·3336; appendix). One patient in each group died of sepsis. Most deaths occurred in elderly patients with important comorbidities. Descriptions of these events are provided in the appendix.

The results of the multivariable models are shown in the appendix. Male sex, no previous surgery, low disease activity, remission at baseline, and shorter disease duration were independently associated with remission. Although assignment to ECI was not independently associated with remission, a significant interaction was noted between treatment assignment and baseline corticosteroid therapy (p=0·0049). The 24 month remission rate for patients receiving corticosteroids at baseline in patients at ECI practices was 61·5% (83 of 135 patients) compared with 36·4% (43 of 118) in the conventional management group (risk ratio 1·72, 95% CI 1·18–2·50). Assignment to conventional management, low caseload, high disease activity, perianal or fistulising disease, corticosteroid therapy, younger age, and treatment in Belgium were independently associated with an increased risk of major adverse outcomes (appendix).

EQ-5D scores, SF-36 scores, or patient satisfaction did not differ between groups (appendix). Provider satisfaction was greater with conventional management than with ECI (appendix).

Discussion

In REACT, the benefits of ECI for clinical remission were modest and non-significant compared with those of conventional management. However, patients treated at ECI practices received combination therapy earlier than did patients at conventional management practices, and we noted a reduction in major adverse outcomes, such as surgery, hospital admission, or serious disease-related complications. These results suggest that early initiation of highly effective therapy might alter the natural history of Crohn's disease.

Although TNF antagonists have greatly improved management of Crohn's disease, no consensus exists regarding timing of their initiation, or the role of combination therapy.[25] In REACT, patients treated at ECI practices received combination therapy earlier than did those at conventional management practices. However, the benefits of ECI for clinical remission were modest and non-significant. By contrast, differences were noted for major adverse outcomes, such as surgery, hospital admission, or serious disease-related complications, which favoured ECI. These outcomes are responsible for substantial morbidity and societal costs. In the past, about half of all treatment costs for Crohn's disease were related to hospital admission,[26,27] but more recently, drug therapies such as TNF antagonists have become a dominant factor.[28,29] It is unknown whether the increased drug costs resulting from use of ECI can be offset by a potential reduction in hospital admission and serious adverse events such as was observed in REACT. The differences in these outcomes should be interpreted cautiously since they were secondary endpoints.

How can these benefits be reconciled with the absence of a difference in clinical remission rates? One explanation is the poor correlation that exists between symptoms and objective measures of disease activity such as endoscopy. Symptom-based outcomes are

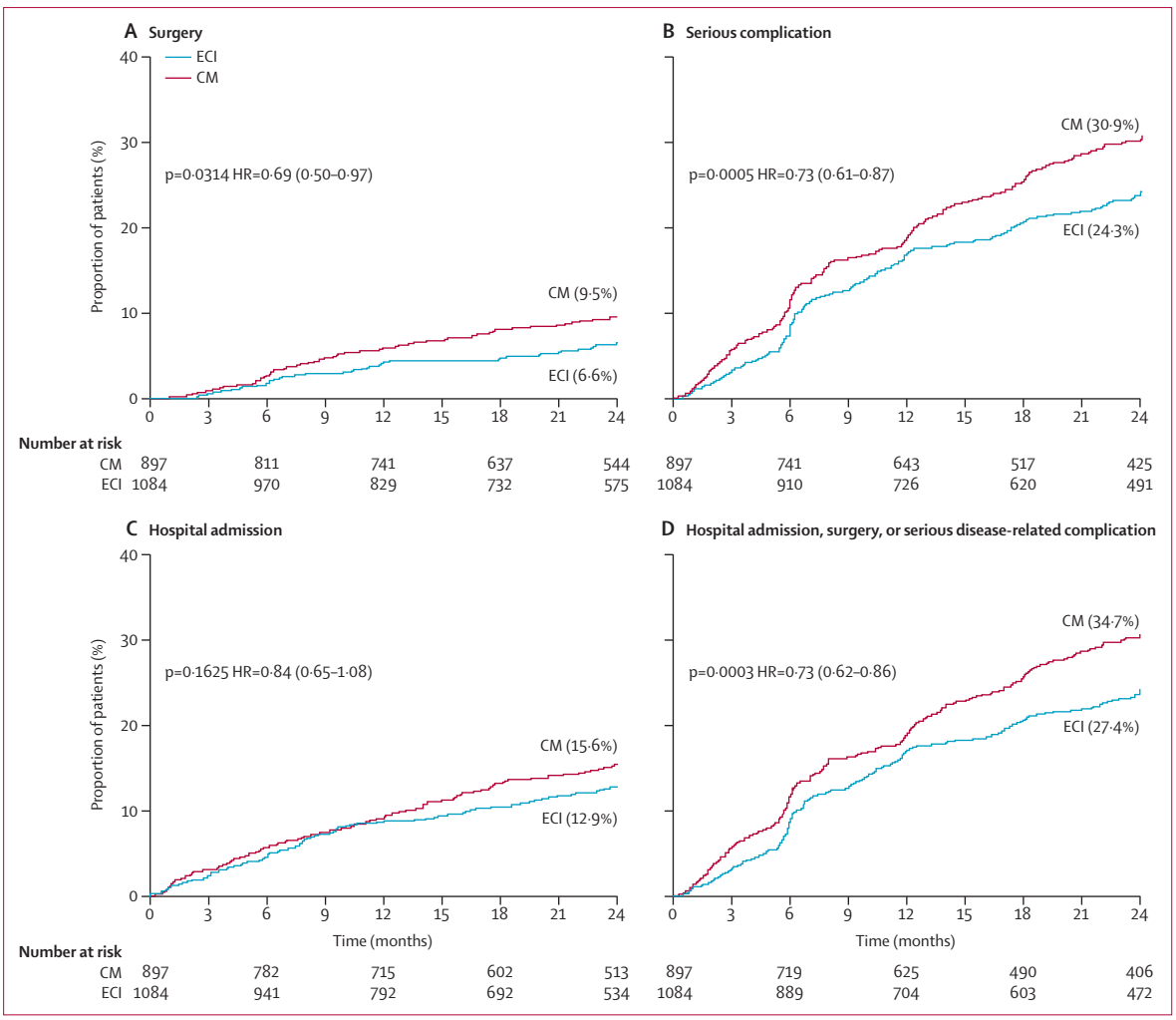

Figure 5: **Proportion of patients with major adverse outcomes at 24 months**
Time to occurrence of surgery, serious complications, or hospital admission, and the composite of these measures. Serious complications were the occurrence of substantially worsening disease activity defined by new abscess, fistula, stricture, extra-intestinal manifestations, or a serious drug complication. Data were analysed with Cox regression models adjusted for practice size and country. CM=conventional management. ECI=early combined immunosuppression. HR=hazard ratio.

neither sensitive nor specific for inflammation.[4,6–10,30–32] Thus, the lower rate of major adverse outcomes associated with ECI might have been due to better control of inflammation. These observations call into question the validity of symptom-based treatment targets. A second possible explanation concerns the patient population assessed. At baseline, 55·5% of patients enrolled were in clinical remission. Although differences in remission rates favoured ECI at both 12 and 24 months, these were substantially less than the 15% specified in the sample size calculation. Inclusion of higher-risk patients, such as those receiving corticosteroids, might have increased the chance of detecting differences in remission and major adverse outcomes. Finally, the use of TNF antagonists and antimetabolites by the conventional management practices approached that of ECI by month 24. Despite these findings, differences in surgery and disease-related complications seemed to be in favour of ECI. This finding is consistent with the notion that time of introduction of combination therapy is highly important.[3]

Male sex, no previous surgery, low disease activity or remission at baseline, and a shorter disease duration were independently associated with the presence of remission. Although no such association was noted with assignment to ECI, a strong interaction was noted between remission and ECI-corticosteroid use at baseline. This finding is consistent with the concept that the benefits of ECI might be greater in high-risk patients. Assignment to conventional management, younger age, perianal or fistulising disease, high clinical disease activity, and corticosteroid therapy were associated with an increased risk of major adverse outcomes. Although treatment in Belgium was also a risk factor for the development of these events, three of

Panel: **Research in context**

Systematic review

We searched the Cochrane Library and Medline for randomised controlled trials of treatment algorithms of immunosuppression using the terms Crohn*, combined immunosuppression, treatment algorithm, and randomised controlled trial. The eligibility criteria were randomised trials in patients with Crohn's disease that used an accelerated step-up algorithm. The search yielded six articles. One report was removed as a duplicate and four did not meet eligibility criteria after review of the abstracts. The remaining article (TOP-DOWN)[3] was assessed using GRADE criteria, and was determined to be high quality.

TOP-DOWN[3] described a trial conducted at specialty IBD centres in which 133 treatment-naive patients, with moderate to severely active Crohn's disease and an average disease duration of 6 months, were randomly assigned to early combined immunosuppression (ECI), defined as early introduction of a TNF antagonist and an antimetabolite, or conventional step-up therapy. At week 26, 60·0% of patients in the ECI group and 35·9% in the control group were in corticosteroid-free remission, p=0·0062. Corresponding values at week 52 were 61·5% in the ECI group and 42·2% in the control group, p=0·0278. No differences in serious adverse events were noted between groups (30·8% in the ECI group and 25·3% in the control group, p=1·0). The sample size was inadequate to assess the effect of ECI on Crohn's disease-related complications. Although these data support the safety and efficacy of ECI early in the course of Crohn's disease in specialty centres, the role of this approach in community-based practices remains unknown.

Interpretation

REACT was performed to address concerns regarding the safety of ECI in community practices and the efficacy of this approach in patients with long-established disease. In this cluster randomisation study, 1084 patients with Crohn's disease were recruited at 21 practices randomised to ECI and 898 patients with Crohn's disease were recruited at 18 conventional management practices. All of the participating practices were community based. Although symptom-based remission rates, defined as a Harvey-Bradshaw Index Score of 4 or lower and no corticosteroid use at 12 months, were not significantly different between groups, the 24 month composite outcome of surgery, hospital admission, and serious disease-related complications was lower at ECI practices than at conventional management practices. No differences between groups in serious drug-related adverse events were observed. This trial provides evidence for the safety of early combined immunosuppression in community practice and supports the notion that complications of Crohn's disease are preventable even in patients with long-standing disease if highly effective therapy is administered promptly. However, further research is required to more accurately define which patients will derive the greatest benefit of early combined immunosuppression.

five Belgian practices had a low caseload, a predictor of poor outcome. Additionally, regulatory requirements in Belgium mandated a 12 week trial of corticosteroid therapy before initiation of combination therapy, compared with 4 weeks in Canada.

Rates of serious infection and neoplasia were similar in the treatment groups. Two cases of opportunistic infection and a case of possible demyelination were associated with the use of adalimumab in combination with azathioprine. The risk of mortality was low in both groups. These results are reassuring since we did not restrict trial participation by application of the multiple exclusion criteria routinely used in phase 3 clinical trials and provide strong evidence that ECI can be used safely by community gastroenterologists.

Although patient satisfaction was similar between ECI and conventional management, provider satisfaction was lower at ECI practices than at conventional management practices, which probably reflects the complexity and more intensive management paradigm specified in the algorithm.

To our knowledge, REACT is the largest randomised controlled evaluation of a therapy for Crohn's disease and the only cluster randomised trial that has been done in this specialty (panel). It provides 2-year follow-up data that documents the safety of ECI in community practices. However, our study had some limitations. First, we did not perform ileocolonoscopies to assess disease activity and thus the possibility that ECI resulted in better control of inflammation was not verified by objective criteria. A symptom-based outcome was chosen for simplicity, to minimise cost, and to reflect current real-world practice. The REACT2 trial (ClinicalTrials.gov, NCT01698307) is currently assessing the use of endoscopy to guide treatment intensification. A second limitation is that it was not possible to blind the study because of the complex nature of the ECI algorithm. This could have increased the risk of bias, however, we used cluster randomisation to minimise this possibility, and the major adverse outcomes were relatively objective measures. Finally, about 5% of patients were lost to follow-up during the first 12 months of the study and an additional 4% during the remaining study duration, however, there were no large differences in follow-up between the experimental groups.

Although ECI was not more effective than conventional management for treating Crohn's disease symptoms, lower rates of major adverse outcomes were noted in practices that followed this approach. ECI is a safe intervention in community gastroenterology practice.

Contributors

RK participated in the analysis and interpretation of data, the drafting of the manuscript, and the critical revision of the report. BB, GRG, RP, AB, PP, SV, GDH, and DM participated in the study concept and design and the critical revision of the report. BGL participated in the analysis and interpretation of data and the critical revision of the report. GZ, WJS participated in the study concept and design, the analysis and interpretation of data, the statistical analyses, and the critical revision of the report. LWS participated in the analysis and interpretation of data and in the statistical analyses. AD participated in the analysis and interpretation of data, the statistical analyses, and the critical revision of the manuscript, MKV and JCM participated in administrative and study supervision. BGF participated in the study concept and design, the analysis and interpretation of data, the drafting of the manuscript, and the critical revision of the report.

Declaration of interests

RK has received personal and consulting fees for participation in AbbVie, Janssen, and Takeda Canada Inc Advisory Boards outside the submitted work. BB and PP have received personal fees from AbbVie and Janssen Inc outside the submitted work. BGL has received personal fees from AbbVie, Prometheus Labs Inc, Nestlé Health Sciences, Santarus, Takeda, Warner Chilcott, and UCB Pharma, outside the submitted work. LWS, AD, and MKV have received grants from AbbVie, during the conduct of the study. GRG has received personal fees from AbbVie, grants and personal fees from Janssen, grants from Millennium, and personal fees from Prometheus Lab Inc outside the submitted work. RP has received

grants, personal fees, and non-financial support from AbbVie, outside the submitted work. SV has recieved grants and personal fees from AbbVie, MSD, Centocor, UCB Pharma, and personal fees from Takeda, Pfizer, Ferring, and Shire during the conduct of the study; also grants and personal fees from MSD, Abbvie, Centocor, Pfizer, Takeda, Ferring, UCB, and personal fees from Shire outside the submitted work. GDH has received grants and personal fees from AbbVie, during the conduct of the study; personal fees from AbbVie, Ablynx, ActoGeniX, AM Pharma, Boehringer Ingelheim GmbH, Centocor, ChemoCentryx, Cosmo Technologies, Elan Pharmaceuticals, Engene, Dr Falk Pharma, Ferring, Galapagos, Giuliani SpA, Given Imaging, GlaxoSmithKline, Jansen Biologics, Merck Sharp and Dohme Corp, Millennium Pharmceuticals Inc (now Takeda), Mitsubishi Tanabe Pharma, Neovacs, Novonordisk, Otsuka, PDL Biopharma, Pfizer, Receptos, Salix, Sandoz, Setpoint, Shire Pharmaceuticals, Schering-Plough, Sigma, Takeda, Tillotts Pharma, UCB Pharma, Versant, Vifor Pharma, Norgine, Tramedico; and grants from Abbott Laboratories/Abbvie, Janssen Biologics, Given Imaging, MSD, Dr Falk Pharma, Photopill, and Takeda, outside the submitted work. WJS has received personal fees from Robarts Clinical Trials; consulting fees from Abbott, ActoGeniX NV, AGI Therapeutics Inc, Alba Therapeutics Corp, Albireo, Alfa Wasserman, Amgen, AM-Pharma BV, Anaphore, Astellas, Athersys Inc, Atlantic Healthcare Ltd, Aptalis, BioBalance Corp, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Celek Pharmaceuticals, Cellerix SL, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals, EnGene Inc, Eli Lilly, Enteromedics, Exagen Diagnostics Inc, Ferring Pharmaceuticals, Flexio Therapeutics Inc, Funxional Therapeutics Ltd, Genzyme Corp, Gilead Sciences, Given Imaging, GSK, Human Genome Sciences, Ironwood Pharmaceuticals, KaloBios Pharmaceuticals, Lexicon Pharmaceuticals, Lycera Corp, Meda Pharmaceuticals, Merck Research Laboratories, Merck Serono, Millennium Pharmaceuticals, Nisshin Kyorin Pharmaceuticals, Novo Nordisk, NPS Pharmaceuticals, Optimer Pharmaceuticals, Orexigen Therapeutics Inc, PDL Biopharma, Pfizer, Procter and Gamble, Prometheus Laboratories, ProtAb Ltd, Purgenesis Technologies Inc, Relypsa Inc, Roche, Salient Pharmaceuticals, Salix Pharmaceuticals, Santarus, Schering-Plough, Shire Pharmaceuticals, Sigmoid Pharma Ltd, Sirtris Pharmaceuticals, SLA Pharma UK Ltd, Targacept, Teva Pharmaceuticals, Therakos, Tillotts Pharma, TxCell SA, UCB Pharma, Viamet Pharmaceuticals, Vascular Biogenics Ltd, Warner Chilcott UK Ltd and Wyeth; research grants from Abbott, Bristol Myers Squibb, Genentech, GSK, Janssen, Millennium Pharmaceuticals, Novartis, Pfizer, Procter and Gamble, Shire Pharmaceuticals and UCB Pharma; payments for lectures/speakers bureaux from Abbott, Bristol-Myers Squibb and Janssen; and holds stock or stock options in Enteromedics. JCM reports grants and non-financial support from AbbVie Corporation during the conduct of the study; and grants and non-financial support from AbbVie Corporation and grants from Janssen Inc outside the submitted work. BGF reports grants from AbbVie during the conduct of the study; grants and personal fees from AbbVie/Abbott, Amgen, Astra Zeneca, Bristol-Myers Squibb, Genentech/Roche, Janssen, Pfizer, Tillotts Pharma, and UCB, outside the submitted work personal fees from Actogenix and Albireo; personal fees from Avaxia Biologics, Axcan, Baxter Healthcare Corp, Boehringer-Ingelheim, Calypso Biotech, Celgene, Elan/Biogen, EnGene, Ferring, GiCare, Gilead, Given Imaging, GlaxoSmithKline, Ironwood, Kyowa Kakko Kirin Co Ltd, Lexicon, Lilly, Merck, Millennium, Nektar, Novo Nordisk, Prometheus Therapeutics, Receptos, Salix, Santarus, Shire, Sigmoid, Synergy, Takeda, Teva, Vertex, Warner-Chilcott, Wyeth, Zealand, and Zyngenia, outside the submitted work; and grants from Sanofi. The other authors declare no competing interests.

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Acknowledgments

Partial funding for the trial was provided by AbbVie Pharmaceuticals. We thank Beverley Jasevicius, Robarts Clinical Trials, for assistance in preparation of the report.

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