Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial

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Summary

Background Most patients who have active Crohn's disease are treated initially with corticosteroids. Although this approach usually controls symptoms, many patients become resistant to or dependent on corticosteroids, and long exposure is associated with an increased risk of mortality. We aimed to compare the effectiveness of early use of combined immunosuppression with conventional management in patients with active Crohn's disease who had not previously received glucocorticoids, antimetabolites, or infliximab.

Methods We did a 2-year open-label randomised trial at 18 centres in Belgium, Holland, and Germany between May, 2001, and January, 2004. We randomly assigned 133 patients to either early combined immunosuppression or conventional treatment. The 67 patients assigned to combined immunosuppression received three infusions of infliximab (5 mg/kg of bodyweight) at weeks 0, 2, and 6, with azathioprine. We gave additional treatment with infliximab and, if necessary, corticosteroids, to control disease activity. 66 patients assigned to conventional management received corticosteroids, followed, in sequence, by azathioprine and infliximab. The primary outcome measures were remission without corticosteroids and without bowel resection at weeks 26 and 52. Analysis was by modified intention to treat. This trial was registered with ClinicalTrials.gov, number NCT00554710.

Findings Four patients (two in each group) did not receive treatment as per protocol. At week 26, 39 (60·0%) of 65 patients in the combined immunosuppression group were in remission without corticosteroids and without surgical resection, compared with 23 (35·9%) of 64 controls, for an absolute difference of 24·1% (95% CI 7·3–40·8, p=0·0062). Corresponding rates at week 52 were 40/65 (61·5%) and 27/64 (42·2%) (absolute difference 19·3%, 95% CI 2·4–36·3, p=0·0278). 20 of the 65 patients (30·8%) in the early combined immunosuppression group had serious adverse events, compared with 19 of 64 (25·3%) controls (p=1·0).

Interpretation Combined immunosuppression was more effective than conventional management for induction of remission and reduction of corticosteroid use in patients who had been recently diagnosed with Crohn's disease. Initiation of more intensive treatment early in the course of the disease could result in better outcomes.

Introduction

Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract. Current practice guidelines recommend that most patients with active disease should be treated initially with corticosteroids.[1,2] Although this approach is usually effective for control of symptoms, many patients become resistant to, or dependent on, these drugs.[3] Long exposure to corticosteroids is also associated with the complications of Cushing's syndrome, and therefore with an increased risk of mortality.[1,2,4–6] For this reason, most clinicians initiate treatment with corticosteroid-sparing drugs such as azathioprine, mercaptopurine, or methotrexate once corticosteroid-resistance or dependence develops, but initiation of these immunosuppressive drugs earlier in the course of the disease is not recommended.[7–10] However, since these antimetabolites are only moderately effective,[1,7,10–12] repeated or long courses of corticosteroids are frequently given.

Treatment directed towards tumour-necrosis factor (TNF) has improved the management of refractory Crohn's disease.[13–15] TNF antagonists, such as infliximab, are conventionally reserved for patients who have failed, in sequence, both corticosteroids and antimetabolites. In rheumatoid arthritis, however, which has many pathophysiological similarities to Crohn's disease, the early introduction of TNF antagonists in combination with methotrexate has been shown to treat early disease better than does monotherapy with either agent.[16–18]

Moreover, one randomised controlled trial has suggested that the combination of azathioprine and infliximab in corticosteroid-dependent Crohn's disease was more effective than azathioprine alone.[19] On the basis of these observations, we did a randomised trial of early combined immunosuppression in patients with recently diagnosed Crohn's disease. We aimed to investigate the effectiveness of short-term infliximab combined with azathioprine or 6-mercaptopurine in

patients with active Crohn's disease who were receiving induction therapy with corticosteroids.

Methods

Study design and participants

We did an investigator-initiated trial at 18 centres in Belgium, Holland, and Germany between May, 2001, and January, 2004. The investigational review board at each of these centres approved the protocol. All patients gave written informed consent before random assignment.

We defined eligible patients as those who were aged 16–75 years; who had been diagnosed with Crohn's disease within the past 4 years; and who had not previously received corticosteroids, antimetabolites, or biological agents. We defined active disease as a Crohn's disease activity index (CDAI)[20] score of greater than 200 points for a minimum of 2 weeks before randomisation. We excluded any patients who had an immediate need for surgery; symptomatic stenosis or ileal or colonic strictures with prestenotic dilatation; signs, symptoms, or laboratory tests that indicated severe comorbidity; documented chronic infection; a positive stool culture for pathogens; a positive tuberculin test or a chest radiograph consistent with tuberculosis; or a malignancy. We also excluded any patient who was allergic to murine proteins, was pregnant, or was a substance abuser.

2 weeks before randomisation, eligible patients were given a physical examination; blood tests, including for C-reactive protein; and a skin test for tuberculin. We obtained a chest radiograph and a stool sample from each patient. Patients were instructed about the use of the inflammatory bowel disease questionnaire (IBDQ)[21] and of a diary card to score the CDAI. The disease activity index generates a score between 0 and 600, where scores of 150 or less define clinical remission. The IBDQ is a disease-specific instrument that measures quality of life. Scores range from 32 to 224, and higher scores indicate better quality of life.[21]

Procedures

We randomly assigned patients in blocks of four according to a computer-generated schedule. The investigator who generated the randomisation schedule was independent from the rest of the trial. We used a minimisation procedure to balance differences between treatment groups in prognostic factors (baseline CDAI score, cigarette smoking, and disease location). Allocation was not concealed from investigators or patients.

Patients assigned to early combined immunosuppression received three infusions of infliximab (Remicade, Centocor, Malvern, PA, USA) in doses of 5 mg/kg bodyweight at weeks 0, 2, and 6, in combination with azathioprine (Imuran, GlaxoSmithKline, Middlesex, UK) in doses of 2–2·5 mg/kg per day from day 0 onwards. If a patient responded to and tolerated both drugs, azathioprine was continued for the duration of the trial. Patients who were intolerant to azathioprine were given subcutaneous methotrexate (Ledertrexate, Wyeth Lederle, Seattle, WA, USA) at an initial dose of 25 mg each week for 12 weeks with the dose reduced to 15 mg per week thereafter. We defined response according to the CDAI score: for patients with an initial score between 200 and 250 points, a 50-point decrement was regarded as a response; corresponding criteria for patients with scores between 250 and 350 points and scores greater than 350 points were 75 and 100 points, respectively. After initial treatment, patients whose symptoms worsened (a CDAI increase of greater than 50 points, to give a score greater than 200) were given additional infusions of infliximab. If symptoms persisted, we initiated methylprednisolone (Medrol, Upjohn, Kalamazoo, MI, USA) and continued azathioprine or methotrexate.

Patients in the conventional management group were treated according to usual clinical practice and current guidelines. Patients received induction treatment with either methylprednisolone (Medrol, Upjohn, Kalamazoo, MI, USA) or budesonide (Budenofalk, FalkPharma, Freiburg, Germany and Entocort AstraZeneca, Lund, Sweden). For those who responded to these treatments, the dose of corticosteroid was tapered. For methylprednisolone, an initial daily dose

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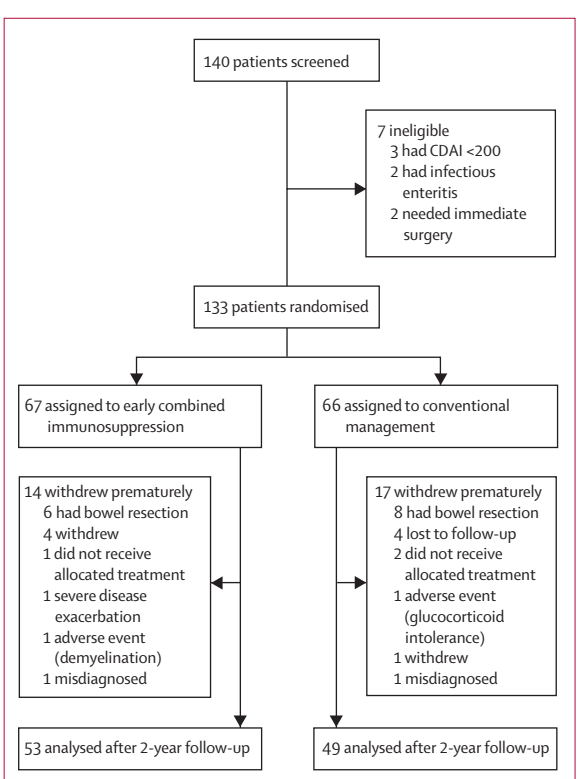

Figure 1: **Trial profile**

	Early combined immunosuppression (n=65)	Conventional management (n=64)	p value
Sex (female)	43 (66·2%)	37 (57·8%)	0·33*
Race (white)	64 (98·5%)	61 (95·3%)	0·37†
Age (years)	30·0 (11·8)	28·7 (10·9)	0·50‡
Weeks from diagnosis to treatment	2·0 (1·0–5·0)	2·5(1·0–11·0)	0·65†
Height (m)	1·71 (0·09)	1·71 (0·10)	0·93‡
Weight (kg)	63·1 (13·4)	62·5 (12·1)	0·82‡
Smoking			0·18*
Current	28 (43·1%)	23 (35·9%)	
Former	8 (12·3%)	16 (25·0%)	
Never	29 (44·6%)	25 (39·1%)	
Mesalazine use	3 (4·6%)	2 (3·1%)	1·00†
Disease location			0·90*
Small bowel	14 (21·5%)	15 (23·4%)	
Ileocolitis	31 (47·7%)	28 (43·8%)	
Colitis	20 (30·8%)	21 (32·8%)	
CDAI score§	330 (92)	306 (80)	0·12†
IBDQ¶	122 (33)	136 (28)	0·11†
C-reactive protein concentration (mg/L)	19 (5–75)	25 (8–59)	0·22†

Data are number (%), mean (SD), or median (IQR) unless otherwise specified. *χ^2 test for dichotomous variables. †Student's *t* test for continuous variables. ‡Fisher's exact test. §Crohn's Disease Activity Index scores range from 0 to 600; higher scores indicate greater disease activity. ¶Inflammatory Bowel Disease Questionnaire scores range from 32 to 224; higher scores indicate better health-related quality of life.

Table 1: **Baseline characteristics**

of 32 mg was prescribed for 3 weeks, followed by tapering by 4 mg per week to discontinuation. Patients who received budesonide were prescribed 9 mg per day for 8 weeks with tapering to discontinuation by 3 mg per week thereafter. Hence treatment with either drug lasted 10 weeks. If a patient's symptoms worsened during the course of corticosteroid tapering, we increased the dose to the initial dose and repeated the induction treatment. If their symptoms continued to worsen despite this manoeuvre, we introduced azathioprine (2–2·5 mg/kg per day).

Patients who relapsed after withdrawal of corticosteroids were given a second course of corticosteroids in combination with azathioprine. For patients who failed 4 weeks of corticosteroid treatment, we increased the methylprednisolone dose to 64 mg per day and added azathioprine. We gave 64 mg methylprednisolone per day for 2 weeks and then tapered this dose by 8 mg per week to a daily dose of 32 mg. Thereafter, methylprednisolone was tapered by 4 mg each week. Any patients who remained symptomatic after 16 weeks of azathioprine treatment received an induction course of infliximab (5 mg/kg bodyweight at weeks 0, 2, and 6) and continued antimetabolite treatment. Patients who relapsed despite the use of methotrexate or those who were intolerant to both azathioprine and methotrexate also received infliximab, without antimetabolite treatment. We repeated the infusion on relapse of symptoms in these patients.

We assessed patients at a clinic at weeks 2, 6, 10, 14, and 26, and at every 12 weeks thereafter for 104 weeks. At each visit, we calculated a CDAI score, obtained blood for chemical analyses, did a physical examination, and recorded drug treatments and doses. Patients completed the IBDQ at each visit. At eight of 18 centres, patients underwent ileocolonoscopy at week 104. Lesions on endoscopy were scored with a validated index[22] consisting of a four-point scale (in which 0=no ulcers, 1=aphthoid ulcers, 2=large ulcers, and 3=ulcerated stenosis) that assessed five defined regions of the bowel, for a composite score between 0 and 15.

Since long exposure to corticosteroids has detrimental effects, complete corticosteroid withdrawal is generally seen as an essential element of the clinical definition of remission.[23] Therefore, we defined our primary outcome as a CDAI score of less than 150 points, absence of corticosteroid treatment, and no intestinal resection. Secondary measures included the time to relapse after successful induction treatment; mean CDAI and IBDQ scores; median concentrations of serum C-reactive protein; and mean endoscopic severity scores. Other secondary outcomes were the proportion of patients who were in remission (CDAI <150 and no corticosteroid therapy) at week 14; the proportion given infliximab, methylprednisolone, and antimetabolites at any time during the study; the proportion without ulcers after 24 months of treatment; and the daily dose of methylprednisolone.

Statistical analysis

For the primary analysis, we used Pearson's χ^2 test to test the hypothesis that the rate of remission was not different between the two treatment groups. To adjust for comparisons (of weeks 26 and 52), we prespecified the alpha errors to declare statistical significance at these times as 0·01 and 0·048, respectively.[24] We calculated nominal p values for comparisons at other time points. The time to relapse was compared by the log-rank test. We compared differences in the CDAI and IBDQ scores by use of repeated-measures analyses of variance. The use of methylprednisolone was described by calculating the 95th percentile of the daily dose. We assessed total exposure to corticosteroids by examining the distribution of the average daily dose of methylprednisolone, calculated by estimating the cumulative dose for each group and dividing this number by the total number of patient days of follow-up. We compared the change in the median serum concentration of C-reactive protein by the Wilcoxon Mann-Whitney test; changes in endoscopy scores by the Wilcoxon test; and the proportion of patients without ulceration on endoscopy by the χ^2 test. Fisher's exact test was used to compare the rate of adverse

events. We used two-sided tests for significance. We analysed patients who were treated as per protocol in a modified intention-to-treat analysis.

We anticipated that 40% of patients assigned to the conventional treatment algorithm would enter clinical remission, and therefore that that we would need a sample size of 130 patients to give 80% power to detect an absolute difference of 25% between the groups. This trial was registered with ClinicalTrials.gov, number NCT00554710.

Role of the funding source

Financial support for data monitoring (DRC, Wetteren, Belgium) was provided by Centocor BV and Schering Plough, who also provided infliximab. Robarts Clinical Trials analysed the data (Robarts Research Institute, University of Western Ontario, London, Ontario, Canada). All authors had access to the data and jointly decided to submit the manuscript.

Results

Figure 1 shows the trial profile. Of the 133 patients who were randomly assigned, four did not receive treatment as per protocol. One patient in the early combined intervention group had a gastric carcinoma, and one in the conventional management group had ulcerative colitis. One patient in each group was not willing to accept the treatment to which they had been assigned. 65 patients had combined immunosuppression and 64 had conventional management. Baseline characteristics of the two groups were similar (table 1), although patients assigned to conventional treatment had better quality of life scores.

Four patients, all in the conventional management group, were lost to follow-up. Three patients did not comply with the treatment protocol and three withdrew consent after randomisation. Nine patients withdrew from the group assigned to combined immunosuppression, compared with eight controls. Most patients withdrew because they had bowel resection for Crohn's disease. One patient in the treatment group withdrew because of severe disease exacerbation and another because of demyelination; one control withdrew because of glucocorticoid intolerance. The baseline characteristics of the patients who underwent ileocolonoscopy were not different from those of the overall study population.

By week 14, a greater proportion of patients in the combined immunosuppression group were in remission than were patients given conventional treatment (p=0·0001; figure 2). After 26 weeks, 39/65 (60·0%) of patients given combined immunosuppression were in remission, compared with 23/64 (35·9%) controls (p=0·0062), an absolute difference of 24·1% (95% CI 7·3–40·8). At 52 weeks, 40/65 (61·5%) in the early combined immunosuppression group were in remission compared with 27/64 (42·2%) of those assigned to conventional management, an absolute difference of 19·4% (95% CI 2·4–36·3, p=0·0278). After week 52, the proportion of patients in remission did not differ between the two groups (figure 2).

The median time to relapse after successful induction therapy at week 14 was longer for patients assigned to early immunosuppression (329·0 days, IQR 91·0–not reached) than for controls (174·5 days, IQR 78·5–274·0, p=0·031) (figure 3).

Patients assigned to early immunosuppression were exposed to substantially less methylprednisolone than were those in the conventional management group (figure 4). Budesonide use was minimal in both groups. At week 52, 2% of patients assigned to early combined immunosuppression were receiving budesonide, com-

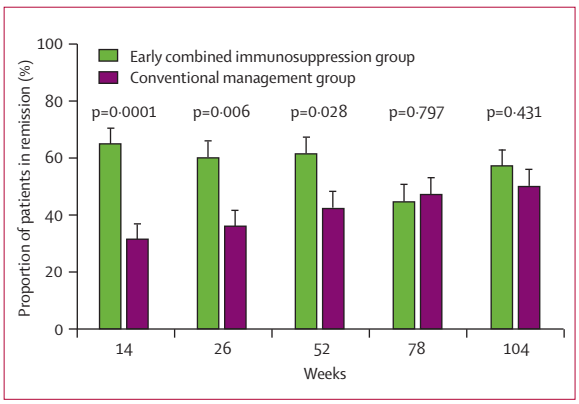

Figure 2: **Proportions of patients in remission**
Remission was defined as a score of less than 150 on the Crohn's Disease Activity Index, absence of a bowel resection, and complete withdrawal of corticosteroid treatment with budesonide or methylprednisolone. Primary endpoints were the proportion of patients in remission at weeks 26 and 52. p values were derived by Pearson's χ^2 test. p values of less than 0·01 and less than 0·048 were considered statistically significant for the week 26 and week 52 comparisons, respectively.

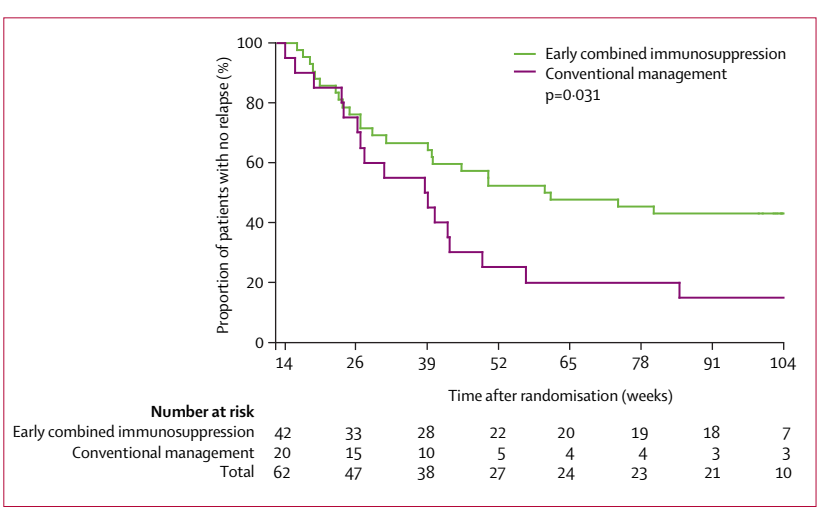

Figure 3: **Proportion of patients who did not relapse**
Kaplan-Meier estimates of the time to relapse after successful induction treatment at week 14. Relapse was defined by a score of greater than 200 on the Crohn's Disease Activity Index, need for a bowel resection, or the need to add additional treatment according to assigned regimen. The p value was calculated by the log-rank test.

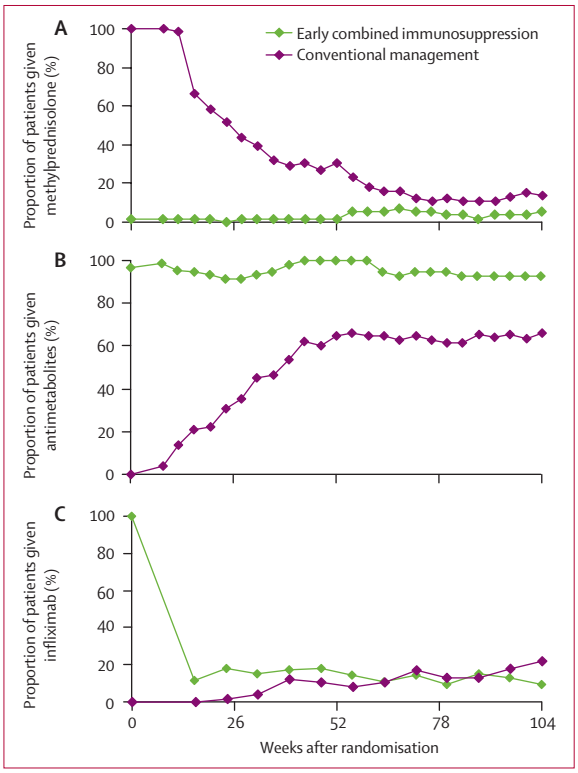

Figure 4: **Proportion of patients who received methylprednisolone (A), antimetabolites (B), and infliximab (C)**
Proportions were estimated using 4-week windows for use of corticosteroids (either methylprednisolone or budesonide) and antimetabolites and an 8-week window for infliximab use.

pared with 7% of those in the conventional management group. The 95th percentile of the daily methylprednisolone dose was 35 mg for patients assigned to conventional management and 0 mg for those assigned to early combined immunosuppression.

Conversely, figure 4 shows that patients assigned to combined immunosuppression received consistent treatment with antimetabolites (azathioprine and methotrexate). Nevertheless, by the end of the trial 76·0% of patients in the conventional treatment group were receiving an antimetabolite.

At week 52, the overall proportion of patients receiving azathioprine and methotrexate was 77% and 25% respectively in the early combined immunosuppression group. Corresponding proportions for the conventional management group were 60% and 13%, respectively.

After patients in the early immunosuppression group had completed their induction course of infliximab, the proportion of patients on infliximab was similar in the two groups (figure 4). 24 (36·9%) patients in the early combined immunosuppression group needed at least one additional dose of infliximab, compared with 9 (14·0%) patients in the conventional management group.

At week 10, patients assigned to combined immunosuppression showed a more rapid drop in CDAI scores; the mean reduction was 231 (SD 123) points, compared with 178 (116) points in controls (difference 53·3, 95% CI 9·2–97·4, p=0·0184). After week 10, mean scores in both groups were similar and consistently below 150 points. Results from the IBDQs were similar. For patients assigned to early combined immunosuppression, the mean IBDQ score at week 10 increased by 59·2 (SD 36·6) points from baseline, compared with 37·4 (32·8) points in controls (difference 21·8 points, 95% CI 8·7–34·9, p=0·0014).

Patients who were assigned to the combined immunosuppression strategy had a more rapid reduction in the median serum concentration of C-reactive protein at week 10 than did controls (–15·0 mg/L, IQR –52·0 to –2·1 *vs* –4·2 mg/L, –25·0 to 1·0, p=0·0244).

At week 104, no ulcers were seen for 19/26 (73·1%) patients assigned to the combined immunosuppression group, compared with 7/23 (30·4%) of controls (p=0·0028). The corresponding endoscopy scores were 0·7 (SD 1·5) and 3·1 (2·9) (p=<0·001). Endoscopic healing was not associated with CDAI-defined remission.

Table 2 shows adverse events. In the combined immunosuppression group, six patients had a bowel resection and one had a fistulotomy. One 25-year old female patient in the combined immunosuppression group developed loss of sensation in her left leg, and MRI showed demyelination in the conus medullaris. Infliximab was discontinued, after the patient had received four infusions. The symptoms resolved and she had no recurrence. Two cases of asymptomatic neutropenia occurred in the combined immunosuppression group. Eight controls needed surgery for intestinal complications of Crohn's disease and seven were operated on for a perianal abscess or fistula. All eight cases of glucocorticoid-related adverse events (four of moon facies, two of acne, one of hyperphagia, and one of mood swings) were in the conventional management group. Nine women were pregnant; four of their 10 pregnancies led to miscarriage (two in each group).

	Early combined immunosuppression (n=65)	Conventional management (n=64)	p value†
Serious adverse events			
Appendicitis	1 (1·5%)	0 (0·0%)	1·00
Pancreatitis‡	3 (4·6%)	2 (3·1%)	1·00
Bowel resection	6 (9·2%)	8 (12·5%)	0·58
Hepatitis C	0	1 (1·6%)	0·50
Pneumonia	1 (1·5%)	0	1·00
Bowel obstruction	5 (7·7%)	1 (1·6%)	0·21
Demyelinating disease	1 (1·5%)	0	1·00
Perianal abscess or fistula	3 (4·6%)	7 (10·9%)	0·21
Total	20 (30·8%)	19 (25·3%)	1·00

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Discussion

Treatment algorithms in early Crohn's disease and their effect on long-term outcomes have not been studied in randomised trials. We have shown that in patients with Crohn's disease who had not previously received corticosteroids, antimetabolites, or biologicals, use of early combined immunosuppression resulted in remission more quickly than did treatment according to existing consensus guidelines.[25–28] Although conventional guidelines support the use of corticosteroids as first-line treatment, they also recommend that the duration of this treatment should be limited to a short period, usually 3 to 4 months. By 6 months, however (or 26 weeks as in our study) patients should have discontinued corticosteroids to avoid toxic effects. Patients assigned to early combined immunosuppression also had more rapid normalisation of serum C-reactive protein and consistently higher rates of remission than did controls within the first year of treatment.

Corticosteroid treatment is a major source of morbidity that is independently associated with an increased risk of mortality.[5] We showed that remission rates in patients given combined immunosuppression were higher than those reported in other trials in which infliximab was added to pre-existing treatments for Crohn's disease.[13–15] This observation is consistent with the enhanced efficacy of combination treatment, and might also reflect the early initiation of treatment relative to the course of the disease.[8] On average, Crohn's disease was diagnosed in study participants less than 4 months before randomisation. In rheumatoid arthritis, early intervention with combined immunosuppression has been shown to control disease activity more rapidly than conventional treatment, and to prevent progressive joint destruction and improve long term functional outcomes.[16–18] Accordingly, patients who received early combined immunosuppression were less likely to have mucosal ulceration after 2 years of treatment. We speculate that significant mucosal ulceration in Crohn's disease is analogous to radiographically defined joint lesions in rheumatoid arthritis and that healing of these lesions could change the natural history of the disease. In support of this concept, the healing of ulcers has been previously associated with a reduction in admissions to hospital and in surgery for complications of Crohn's disease.[15,29] Indeed, regulatory agencies now recommend that clinical trials should use remission with endoscopic healing as an endpoint.[30] We noted differences in mucosal healing in the two groups, even though patients assigned to conventional management received more corticosteroids and in most cases were also receiving treatment with antimetabolites (77·0% at week 104). These observations are consistent with the results of previous studies in which corticosteroid treatment was shown to be ineffective for healing of intestinal ulcers,[31] and sequential use of corticosteroids with delayed introduction of antimetabolite treatment did not decrease the need for surgery.[32]

One controversial aspect of our study was that patients in the combined immunosuppression group received intermittent treatment with infliximab. Although controlled trials in refractory patients have shown better clinical and endoscopic results for scheduled treatment every 8 weeks, our results suggest that intermittent infliximab use, in combination with antimetabolite treatment, might be an effective strategy for treatment of newly diagnosed patients, since responsiveness was not diminished on repeat infusions, and no patients developed clinical manifestations of hypersensitivity to the drug. A strategy of maintenance treatment with

	Early combined immunosuppression (n=65)	Conventional management (n=64)	p value†
(Continued from previous page)			
Adverse events*			
Gastrointestinal disorders			
Epigastric Pain	18 (27·7%)	16 (25·0%)	0·84
Worsening of Crohn's disease	10 (15·4%)	14 (21·9%)	0·37
Vomiting	7 (10·8%)	7 (10·9%)	1·00
Heartburn	4 (6·2%)	4 (6·3%)	1·00
Anal fissure	3 (4·6%)	5 (7·8%)	0·49
Constipation	4 (6·2%)	3 (4·7%)	1·00
Elevated liver function tests	4 (6·2%)	3 (4·7%)	1·00
Infections			
Common cold	26 (40·0%)	31 (48·4%)	0·38
Upper respiratory tract infection	22 (33·8%)	20 (31·3%)	0·85
Gastrointestinal infections	12 (18·5%)	13 (20·3%)	0·83
Vaginal infections	7 (10·8%)	7 (10·9%)	1·00
Urinary tract infections	6 (9·2%)	6 (9·4%)	1·00
Eye infections	4 (6·2%)	3 (4·7%)	1·00
Dermatological disorders			
Acne	3 (4·6%)	9 (14·1%)	0·08
Eczema	8 (12·3%)	2 (3·1%)	0·10
Hair loss	5 (7·7%)	5 (7·8%)	1·00
Rash	7 (10·8%)	3 (4·7%)	0·32
Pruritus	1 (1·5%)	6 (9·4%)	0·06
Orthopaedic disorders			
Arthralgia	16 (24·6%)	10 (15·6%)	0·27
Muscle cramps or myalgia	6 (9·2%)	4 (6·3%)	0·74
Low back pain	4 (6·2%)	5 (7·8%)	0·74
Psychiatric disorders			
Headache	6 (9·2%)	10 (15·6%)	0·30
Depression	5 (7·7%)	4 (6·3%)	1·00
Insomnia	2 (3·1%)	5 (7·8%)	0·27
Miscellaneous			
Fatigue	10 (15·4%)	15 (23·4%)	0·27
Pregnancy	4 (6·2%)	6 (9·4%)	0·53

Data are number (%), unless otherwise specified. *Adverse events that occurred in at least 5% of patients. †p values were calculated with Fisher's exact test. ‡All five cases of pancreatitis were associated with the use of azathioprine.

Table 2: **Incidence of adverse events***

infliximab every 8 weeks could potentially have greater effects, but was not yet standard practice when we initiated our trial.

We identified no important differences in the occurrence of adverse events between the two groups. Serious infection was not more frequent in either group. However, the number of patients was inadequate to address safety differences between the strategies.

Our study had two main limitations. First, investigators and patients were aware of the treatment assignment, which could have biased their assessment of its efficacy. However, combined immunosuppression was also more effective for both mucosal healing and serum C-reactive protein concentration, which are objective measures of inflammation. Second, although remission was more rapid for patients assigned to the early combined immunosuppression strategy than for those given conventional treatment, simultaneous initiation of antimetabolites and corticosteroids could potentially have produced similar results. However, both azathioprine and methotrexate have a slower onset of action than infliximab.[7,11,23] Furthermore, the conventional management regimen reflected current clinical practice in that combined antimetabolites and corticosteroids are not commonly used as initial treatments, and are not recommended by experts.[25–28,33,34]

Contributors

GD'H had the original idea for this trial, designed the protocol with SVD, served as lead investigator for Belgium, and drafted the manuscript with BGF. SVD designed the protocol with GD'H, served as a lead investigator for the Netherlands, and participated in the writing process. LS and AD analysed the data. SV analysed the results of the endoscopic substudy. PR assisted in the design of the trial and the writing process. BGF was a member of the study safety committee, coordinated the analysis of the results at Robarts Clinical Trials, and drafted the manuscript. DH was a lead investigator for the Netherlands, and participated in the writing of the manuscript. FB, JVDW, GVA, PC, PV, HT, MDV, FVDM, JCC, TO, AAVB, PVH, GL, and FM were investigators. All authors participated in the data analysis and reporting stage of this manuscript, and have seen and approved the final version.

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Conflict of interest statement

PC, PV, HT, LS, AD, FVDM, JCC, PVH, GL, and FM reported no conflicts of interest. GD'H, FB, and GVA have served as consultants and speakers for Centocor and Schering Plough. SVD has acted as a consultant for Centocor. SV has received grant and research support from UCB, consultancy fees from AstraZeneca and Ferring, and speakers fees from Shering Plough, Ferring, and UCB, and has been on the Advisory Committee for Shire, Ferring, and UCB. TO has received honoraria, consultancies, and educational grants from Centocor, Schering Plough, Essex-Germany, UCB, and Abbott, and payments for consultancies from Shire and Boston Scientific. PR has received consulting fees, lecture fees, and grant support from Centocor and Schering Plough, and has served as an expert witness for those companies. DH has received consulting fees from Abbott, Centocor, UCB, and Schering Plough; lecture fees from Centocor, AGA and Schering Plough; and grants from Schering Plough, Abbott and UCB; and is a member of the Initiative on Crohn's and Colitis, Independent Dutch Academic Non-profit Organisation for IBD Research. MDV has received consulting fees from Schering Plough; Altana lecture fees from Schering Plough and UCB; and grant support from AstraZeneca, Roche, Schering Plough, Novartis Fund for Scientific Research Flanders, and Special Research Fund University Ghent. SV has received consulting fees from Shire; lecture fees from Ferring, UCB, Abbott, Schering Plough, and Tillotts; and grant support from UCB. JVDW has received consulting fees from UCB Schering Plough, Elan, and Abbott; lecture fees from Schering Plough and Tramedico; and grant support from Initiative on Crohn's and Colitis. AAVB is a member of the Initiative on Crohn's and Colitis, to which Schering Plough BV and other companies that provide anti-TNF monoclonals (Abbott BV and UCB Pharma) provide a yearly unrestricted grant. SVD has received consulting fees from Centocor, Elan, Schering Plough, and ISIS and lecture fees from Elan. BGF has received research funding from Synta, Millennium, Schering Canada, Celltech, Centocor, Elan/Biogen, Berlex, Ortho-Biotech, Protein Design Labs, ISIS, Santarus, Schering Plough, Celgene, UCB Pharma, Napo Pharma, BMS, Abbott, and Otsuka; and consulting and lecture fees from UCB Pharma, Schering Canada, Proctor and Gamble, Elan/Biogen, Millennium, Protein Design Labs, Berlex, AstraZeneca, Celgene, Abbott, Santarus, GeneLogic, Cerimon Pharmaceuticals, Tioga Pharmaceuticals, BMS, ISIS, Serono, Teva, Genentech, and CombinatoRx.

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