# Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial

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## Summary

**Background** Treatment of patients with ileocaecal Crohn's disease who have not responded to conventional therapy is commonly scaled up to biological agents, but surgery can also offer excellent short-term and long-term results. We compared laparoscopic ileocaecal resection with infliximab to assess how they affect health-related quality of life.

**Methods** In this randomised controlled, open-label trial, in 29 teaching hospitals and tertiary care centres in the Netherlands and the UK, adults with non-stricturing, ileocaecal Crohn's disease, in whom conventional therapy has failed were randomly allocated (1:1) by an internet randomisation module with biased-coin minimisation for participating centres and perianal fistula to receive laparoscopic ileocaecal resection or infliximab. Eligible patients were aged 18–80 years, had active Crohn's disease of the terminal ileum, and had not responded to at least 3 months of conventional therapy with glucocorticosteroids, thiopurines, or methotrexate. Patients with diseased terminal ileum longer than 40 cm or abdominal abscesses were excluded. The primary outcome was quality of life on the Inflammatory Bowel Disease Questionnaire (IBDQ) at 12 months. Secondary outcomes were general quality of life, measured by the Short Form-36 (SF-36) health survey and its physical and mental component subscales, days unable to participate in social life, days on sick leave, morbidity (additional procedures and hospital admissions), and body image and cosmesis. Analyses of the primary outcome were done in the intention-to-treat population, and safety analyses were done in the per-protocol population. This trial is registered at the Dutch Trial Registry (NTR1150).

**Findings** Between May 2, 2008, and October 14, 2015, 73 patients were allocated to have resection and 70 to receive infliximab. Corrected for baseline differences, the mean IBDQ score at 12 months was 178·1 (95% CI 171·1–185·0) in the resection group versus 172·0 (164·3–179·6) in the infliximab group (mean difference 6·1 points, 95% CI –4·2 to 16·4; p=0·25). At 12 months, the mean SF-36 total score was 112·1 (95% CI 108·0–116·2) in the resection group versus 106·5 (102·1–110·9) in the infliximab group (mean difference 5·6, 95% CI –0·4 to 11·6), the mean physical component score was 47·7 (45·7–49·7) versus 44·6 (42·5–46·8; mean difference 3·1, 4·2 to 6·0), and the mean mental component score was 49·5 (47·0–52·1) versus 46·1 (43·3–48·9; mean difference 3·5, –0·3 to 7·3). Mean numbers of days of sick leave were 3·4 days (SD 7·1) in the resection group versus 1·4 days (4·7) in the infliximab group (p<0·0001), days not able to take part in social life were 1·8 days (6·3) versus 1·1 days (4·5; p=0·20), days of scheduled hospital admission were 6·5 days (3·8) versus 6·8 days (3·2; p=0·84), and the number of patients who had unscheduled hospital admissions were 13 (18%) of 73 versus 15 (21%) of 70 (p=0·68). Body-image scale mean scores in the patients who had resection were 16·0 (95% CI 15·2–16·8) at baseline versus 17·8 (17·1–18·4) at 12 months, and cosmetic scale mean scores were 17·6 (16·6–18·6) versus 18·6 (17·6–19·6). Surgical intervention-related complications classified as IIIa or worse on the Clavien-Dindo scale occurred in four patients in the resection group. Treatment-related serious adverse events occurred in two patients in the infliximab group. During a median follow-up of 4 years (IQR 2–6), 26 (37%) of 70 patients in the infliximab group had resection, and 19 (26%) of 73 patients in the resection group received anti-TNF.

**Interpretation** Laparoscopic resection in patients with limited (diseased terminal ileum <40 cm), non-stricturing, ileocaecal Crohn's disease in whom conventional therapy has failed could be considered a reasonable alternative to infliximab therapy.

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## Introduction

Crohn's disease is an idiopathic, chronic inflammatory bowel disease that leads to lifelong morbidity and decreased quality of life. It can occur at any site in the gastrointestinal tract. In about a third of patients, the disease is limited to the terminal ileum.[1] The most recent 2016 update of the European Crohn's and Colitis Organisation (ECCO) guideline[2] on medical management

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See Online for appendix

For the **LIR!C study protocol** see http://www.ibd-amc.nl

## Research in context

### Evidence before this study

Treatment of patients with ileocaecal Crohn's disease in whom conventional therapy fails is commonly scaled up to biological agents. However, surgery can offer excellent short-term and long-term results. We searched PubMed and Embase from March 14–17, 2017, with the following terms: "laparoscopic ileocaecal resection", "infliximab", "anti-TNF", Crohn's disease", and "quality of life". Publications in English between Jan 1, 1990, and Jan 1, 2017, were accepted.

### Added value of this study

Effectiveness of laparoscopic ileocaecal resection and infliximab in restoring quality of life has previously been shown, but no randomised controlled trials had compared these strategies directly. We showed that laparoscopic ileocaecal resection did not improve quality-of-life scores to a significantly greater extent than infliximab treatment, but results in similar quality-of-life scores and is not associated with more serious adverse events. Long-term follow-up data indicated that more than a third of the patients who started on infliximab required an ileocaecal resection within a few years, whereas only one in four patients who initially had resection needed anti-TNF therapy later.

### Implications of all the available evidence

Based on this trial, we conclude that laparoscopic ileocaecal resection is a reasonable alternative to infliximab in patients with limited, non-stricturing, ileocaecal Crohn's disease in whom conventional therapy fails.

of Crohn's disease recommends that, for mild to moderately active ileocaecal Crohn's disease, a prednisolone course is indicated together with starting an immunomodulator. For severely active disease, the first choice is a biological agent, but prednisolone with an immunomodulator can also be considered.[2]

Surgical resection is usually reserved for patients who are refractory or intolerant to medical therapy, or have complications such as clinically relevant fibrostenotic or fistulising disease, as recently expressed in the 2016 guidelines from the ECCO.[3] Up to 80% of patients with ileocaecal Crohn's disease undergo surgical resection eventually,[3] although the need for surgical resection in general has recently been reported to have declined by 30% since the start of the use of biological agents.[4]

Following resection, clinically overt Crohn's disease typically recurs in 28–45%[5] of patients in population-based studies, which is similar to the reported cumulative 5-year occurrence of infliximab and adalimumab treatment failure.[4,6] About 30% of patients have endoscopic recurrence 1 year after ileocaecal resection, which is similar to the number of recurrences observed in people who initially respond to infliximab.[7,8] Re-resection for recurrent Crohn's disease has been shown to occur in 10–22% of people after 5·0–8·5 years of follow-up.[9,10] This finding suggests that resection can be a valuable alternative to biological agents for inducing and maintaining clinical remission.

Apart from the symptoms associated with Crohn's disease, medication used for maintenance treatment can have a profound effect on quality of life.[11,12] Both anti-tumour necrosis factor (TNF) α antibodies and surgery have been shown to improve quality of life, but the short-term and long-term effects have not yet been compared.[13,14] We hypothesised that laparoscopic resection for ileocaecal Crohn's disease in patients in whom conventional treatment fails could improve quality of life, potentially providing a benefit over biological agents.

## Methods

### Study design

The LIR!C study is a multicentre, randomised controlled, open-label, parallel group trial done at 29 teaching hospitals and tertiary care centres in the Netherlands and the UK (six centres were tertiary referral centres, five of which were in the Netherlands). The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and is reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The trial received central approval from the medical ethics committee at the Academic Medical Center in Amsterdam and from the corresponding committees in all participating centres. The study was monitored by an independent monitor from the Clinical Research Unit of the Amsterdam Academic Medical Center. The study protocol is available online.[15]

### Patients

Eligible adult patients were aged between 18 and 80 years, had active Crohn's disease of the terminal ileum, and had at least 3 months of conventional therapy with glucocorticosteroids, thiopurines, or methotrexate that failed. Patients were excluded if they had previous ileocaecal resection, obstructive Crohn's disease of the terminal ileum that would probably require surgery as indicated by prestenotic dilatation or absence of inflammation on screening magnetic resonance enterography, a diseased small bowel segment longer than 40 cm, or abdominal abscesses. Patients with an American Society of Anesthesiologist score of III or IV were also excluded. All participants provided written informed consent.

### Randomisation and masking

Randomisation was done by an internet randomisation module with biased-coin minimisation for participating centres and perianal fistula. Patients were allocated (1:1)

to the infliximab or ileocaecal resection groups. Patients and study staff could not be masked to treatment allocation due to the vastly different nature of treatments (medical *vs* surgical).

## Procedures

Patients allocated to infliximab treatment received three infusions of 5 mg/kg at weeks 0, 2, and 6 after group assignment, and further maintenance infusions every 8 weeks. Dose escalation to every 6 weeks or dose increase to 10 mg/kg, or both, was allowed when the treatment response was insufficient. Combination therapy with azathioprine (2·0–2·5 mg/kg per day) or mercaptopurine (1·0–1·5 mg/kg per day) was recommended for all patients allocated to infliximab treatment, but not mandatory.

Patients allocated to laparoscopic ileocaecal resection were allowed a 4-week prednisolone course starting at 40 mg and reduced by 10 mg per week to 0 mg during the waiting time for surgery at the discretion of the treating physician. Surgery was done by multiport or single-port laparoscopy. Extraction of the resection specimen was preferably done via an up and down transumbilical incision or, in the case of a large inflammatory mass, via a Pfannenstiel incision. Postoperative maintenance immunomodulatory therapy was allowed at the discretion of the treating physician.

Patients were seen by a surgeon or gastroenterologist at the outpatient clinic at 2 and 6 weeks and after 3, 6, 9, and 12 months after the start of treatment. Questionnaires were issued to the patients at baseline and at each follow-up visit. At the 1-year follow-up, patients had ileocolonoscopy. At the time of the last patient's 1-year follow-up, charts of all participants were reviewed for steroid courses, Crohn's-related surgery, perianal fistula, use of biological agents, concurrent use of immunomodulators, and follow-up colonoscopies.

At the end of follow-up, inflammation was assessed by ileocolonoscopy using the Crohn's Disease Endoscopic Index of Severity (CDEIS) or the modified Rutgeerts score in the resection group. All endoscopies were reviewed by a single experienced reader (CYP). A CDEIS score of less than 6[16,17] and a modified Rutgeerts score of less than 2b were considered to indicate remission.[18,19]

## Outcomes

The primary outcome was disease-specific quality of life, assessed with the Inflammatory Bowel Disease Questionnaire (IBDQ). The IBDQ was assessed locally and consists of 32 questions; each with a 1–7 scale, and hence the score ranges from 32–224. Secondary outcomes were general quality of life, measured with the Short Form-36 (SF-36) health survey, which contains eight subscales measuring various aspects of physical, mental, social, and emotional functioning that, after transforming each into a 0–100 scale, yield both a physical component summary and a mental component summary; days unable to participate in social life; days on sick leave; morbidity (additional procedures and hospital admissions); and body image and cosmesis. Body-image and cosmesis were assessed in the resection group only using the body image questionnaires.[20] Costs per quality-adjusted life-year and total inpatient and outpatient medical and non-medical costs were specified outcomes that will be addressed elsewhere.

Patients were contacted monthly to assess infusion-related adverse events, postoperative complications according to the Clavien-Dindo classification (grade IIIa or worse with surgical, endoscopic, or radiological intervention was considered clinically relevant), readmissions to hospital, and days of sick leave.[21] Serious adverse events were those resulting in death or those that were life threatening (at the time of the event), requiring or prolonging admission to hospital, or resulting in persistent or substantial disability or incapacity.

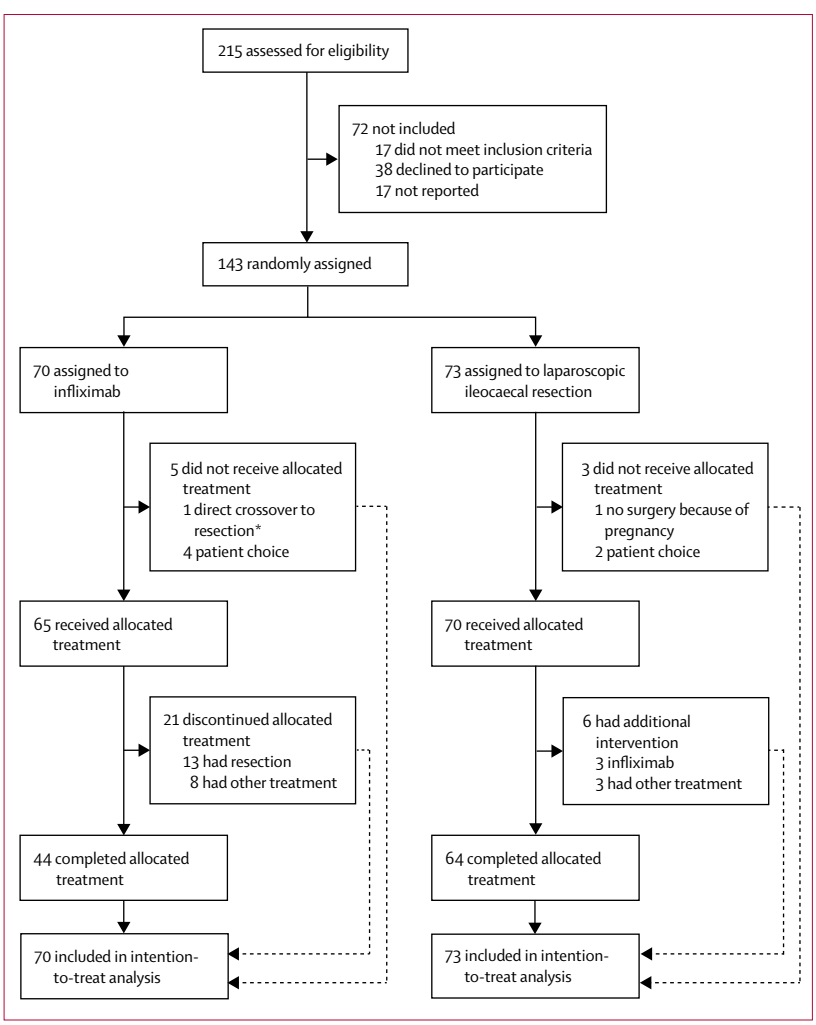


***Figure 1:*** **Patient flow diagram**
*Patient had urgent resection because of sudden deterioration of health.

| | Infliximab (n=70) | Laparoscopic ileocaecal resection (n=73) |
|---|---|---|
| Men | 21 (30%) | 26 (36%) |
| Women | 49 (70%) | 47 (64%) |
| Age at randomisation, years | 26·5 (21·0–37·5) | 28·0 (23·0–41·0) |
| Age at diagnosis, years | 23·0 (19·0–34·0) | 25·0 (20·0–37·8) |
| Disease duration at randomisation, months | 14·0 (6·0–30·0) | 12·5 (4·3–39·5) |
| Length of diseased ileum at imaging at randomisation, cm | 11·5 (8·8–20·0) | 13·0 (8·8–25·0) |
| Body-mass index, kg/m² | 23·3 (0·5) | 24·2 (0·6) |
| Smokers* | 30/67 (45%) | 21/67 (31%) |
| Family history of inflammatory bowel disease* | 9/60 (15%) | 14/61 (23%) |
| Perianal fistulas ever*† | 10/69 (14%) | 2/73 (3%) |
| Abdominal fistulas ever* | 2/68 (3%) | 3/73 (4%) |
| Medical therapy at time of randomisation | | |
| Prednisolone | 28 (40%) | 40 (55%) |
| Budesonide | 24 (34%) | 19 (26%) |
| Mesalazine | 5 (7%) | 3 (4%) |
| Thiopurines | 49 (70%) | 47 (64%) |
| Methotrexate | 6 (9%) | 1 (1%) |

Data are n (%), n/N (%), median (IQR), or mean (SD). *Denominator shows the number of patients for whom the parameter was known. †One patient in the resection group had an active perianal fistula at the time of randomisation (stratification was done for current perianal fistulas).

*Table 1:* **Demographic and clinical baseline characteristics**

### Statistical analysis

To attain a power of at least 80% at an α level of 0·05, inclusion of 65 patients in each group was necessary. To accommodate an estimated loss to follow-up of 10%, the target sample size was 143 people. We used a linear mixed model to analyse differences over time in the primary outcome measure, allowing for a time effect and a differential treatment effect, and adjusting for the baseline value. All analyses were based on the intention-to-treat principle except the safety analyses, which were done in the per-protocol population. We used multiple imputation for items missing in questionnaires, according to the fully conditional specification method with ten imputations, but completely missing questionnaires were not imputed. We also used the predictive mean matching method for scale variables. We tested differences in proportions with $\chi^2$ or Fisher's exact test where appropriate. We analysed the distribution of the primary outcome scores before our analyses, and observed that they were unimodal, without influential skewness. Therefore, we did not distribute the data to better approximate normality.

Data are presented as model-based estimated means and corresponding 95% CIs. SPSS statistics for Windows (version 22) was used. p values of less than 0·05 was considered significant.

We considered a medium 0·5 between-group effect size in total IBDQ score to be clinically relevant, in line with the Grading of Recommendations, Assessment, Development and Evaluations working group.[22] The trial is registered at the Dutch Trial Registry (NTR1150; EudraCT 2007–005042–20; enrolment closed on Oct 14, 2015).

### Role of the funding source

The funder of the study had no role in the study design, data collection, analysis, or interpretation, or writing of the report. EJE, TJG, EJdG, BM, PMMB, AJdG, and CYP had access to the raw data in the study; CYP, EJdG, PMMB, and WAB had final responsibility for the decision to submit for publication.

## Results

Between May 2, 2008, and Oct 14, 2015, 215 patients were assessed for eligibility, of whom 62 were excluded because they did not meet the inclusion criteria, declined to participate, or their data were not reported. 143 patients (47 [33%] male) with a median age of 27 years (IQR 22–40) were enrolled and randomly assigned to either infliximab (n=70) or resection (n=73; figure 1). Baseline characteristics were similar between the two groups, except smoking status, which was higher in the infliximab group than the resection group (table 1). Median time between random allocation and start of therapy was 5·0 weeks (IQR 3·8–6·0) in the resection group and 2·0 weeks (1·0–3·0) in the infliximab group. 45 (62%) of 73 patients had a prednisolone course before surgery.

The mean IBDQ score at baseline was 137·8 (95% CI 130·6–144·9) in the infliximab group and 142·2 (135·3–149·1) in the resection group (appendix p 3; figure 2A). At 2 weeks, the patients in the resection group reported a significantly worse quality of life than those in the infliximab group (mean difference –20·7 [95% CI –30·0 to –11·3]), which became non-significant at 6 weeks. The mean IBDQ at 12 months was 178·1 (95% CI 171·1–185·0) in the resection group and 172·0 (164·3–179·6) in the infliximab group; a mean difference of 6·1 points (95% CI –4·2 to 16·4; p=0·25; figure 2A).

The mean SF-36 total score was significantly higher in the resection group than in the infliximab group at 6 months (112·7 [95% CI 108·7–116·7] *vs* 105·6 [101·5–109·8]) and 9 months (111·4 [107·3–115·4] *vs* 111·4 [107·3–115·4]; figure 2B). At 12 months, the mean SF-36 total score was 112·1 (95% CI 108·0–116·2) in the resection group versus 106·5 (102·1–110·9) in the infliximab group (mean difference 5·6, 95% CI –0·4 to 11·6). The mean physical component summary score was significantly higher in the resection group from 6 months onwards; at 12 months, the mean physical component score was 47·7 (95% CI 45·7–49·7) in the resection group versus 44·6 (42·5–46·8) in the infliximab group (mean difference 3·1, 95% CI 4·2–6·0, p=0·04; figure 2C). The mental component summary scores were also slightly higher in the resection group than in the infliximab group, but not significantly so; at 12 months, the mean mental component

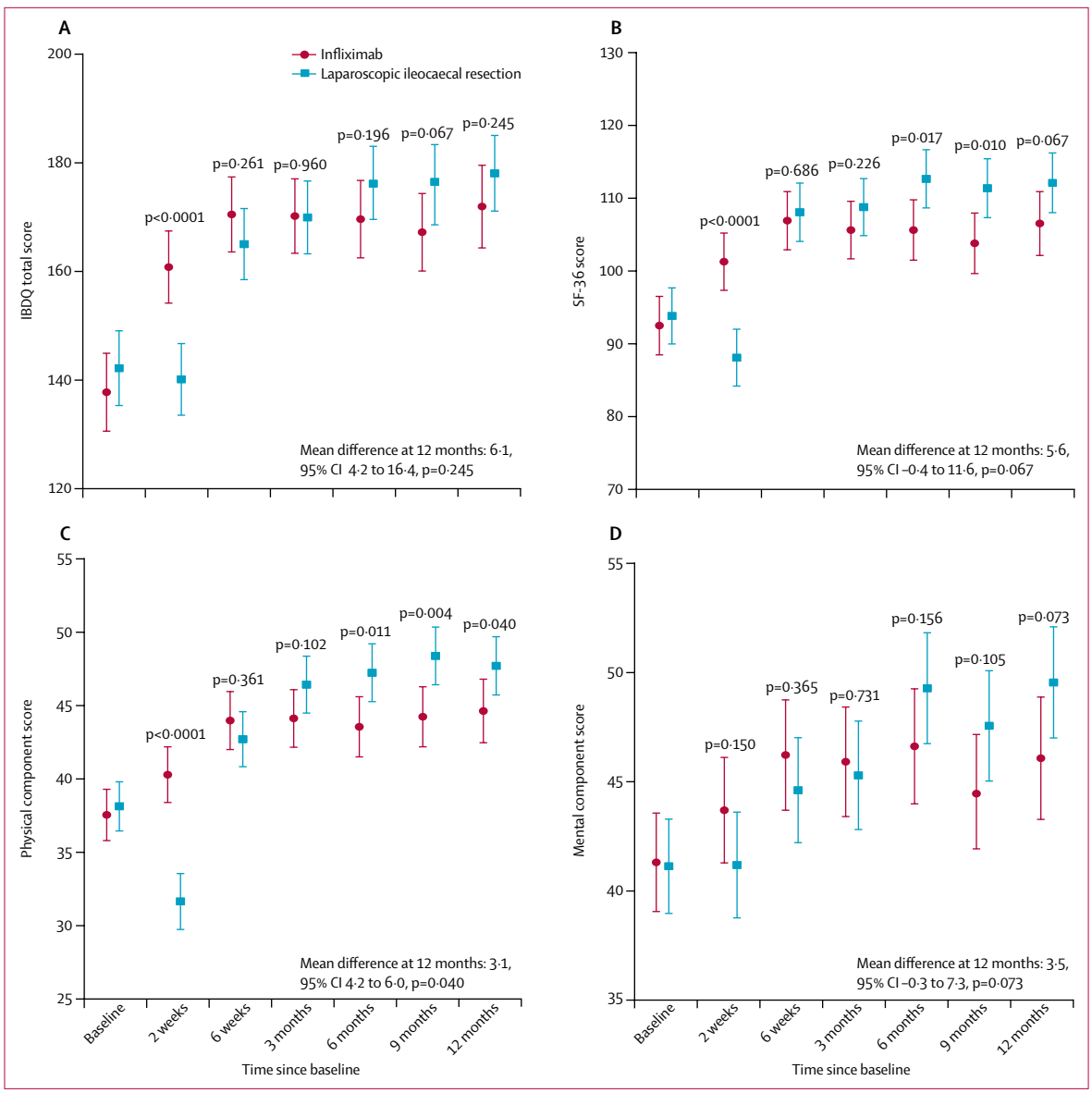


***Figure 2:*** **Quality of life scores**
(A) Mean IBDQ total score. (B) SF-36 total score. (C) SF-36 physical component score. (D) SF-36 mental component score. Mean scores with 95% CI corrected for baseline difference at 2 and 6 weeks and 3, 6, 9, and 12 months. IBDQ=Inflammatory Bowel Disease Questionnaire. SF-36=Short Form-36.

score was 49·5 (95% CI 47·0 to 52·1) in the resection group versus 46·1 (43·3 to 48·9) in the infliximab group (mean difference 3·5, 95% CI −0·3 to 7·3; figure 2D).

Patients in the laparoscopic ileocaecal resection group reported more days on sick leave (3·4 days [SD 7·1, suggesting considerable skewness]) than those in the infliximab group (1·4 days [4·7]; p<0·0001; data not shown). The mean numbers of days that patients were not able to participate in social life were similar between groups (1·1 [SD 4·5] in the infliximab group *vs* 1·8 [6·3] in the resection group; p=0·20; data not shown).

The mean numbers of scheduled admission days (6·8 days [SD 3·2] in the infliximab group *vs* 6·5 days [3·8] in the resection group; p=0·84) and the numbers of patients who had unscheduled hospital admission during follow-up (15 [21%] of 70 in the infliximab group *vs* 13 [18%] of 73 in the resection group; p=0·68) were similar between groups (table 2).

Perceived body image and cosmesis in the resection group improved throughout the year (body-image scale mean was 16·0 [95% CI 15·2–16·8] at baseline *vs* 17·8 [17·1–18·4] at 12 months; cosmetic scale mean was 17·6 [16·6–18·6] *vs* 18·6 [17·6–19·6]; appendix p 2).

Of the patients allocated to infliximab therapy who had no ileocaecal resection, and in whom endoscopy was done, 38 (84%) of 45 were in endoscopic remission

| | Infliximab (n=70) | Laparoscopic ileocaecal resection (n=73) |
|---|---|---|
| **Unscheduled admissions** | | |
| Number of patients readmitted | 15 (21%) | 13 (18%) |
| Time spent in hospital per patient, days | 7·0 (3·0–11·0) | 5·0 (3·5–10·0) |
| Total number of days spent in hospital by all patients | 122 | 149 |
| Patients admitted to intensive care unit | 0 | 2 (3%) |
| Mean time spent in intensive care unit, days* | 0 | 17·0 |
| **Scheduled admission** | | |
| Time spent in hospital per patient, days | 6·8 (3·2) | 6·5 (3·8) |
| Total number of days spent in hospital by all patients | 473 | 471 |

Data are n (%), median (IQR), or mean (SD) unless otherwise stated. All patients had at least one scheduled admission for either infliximab infusions or surgery. *No SD is available for the mean number of days spent in an intensive care unit because only two patients were admitted.

***Table 2:*** **Unscheduled and scheduled admissions**

| | Infliximab (n=65) | Laparoscopic ileocaecal resection (n=70) |
|---|---|---|
| Total | 2 (3%) | 8 (11%) |
| Pneumonia | 1 (2%) | 0 |
| Perianal abscess | 1 (2%) | 0 |
| Ileus | 0 | 3 (4%) |
| Anastomotic leakage | 0 | 3 (4%) |
| Intra-abdominal abscess or haematoma* | 0 | 2 (3%) |

Data are n (%). *One patient with an anastomotic leakage also developed an intra-abdominal abscess. Difference in total proportion of patients with serious adverse events tested with Fisher's exact test (p=0·10).

***Table 3:*** **Primary treatment-related serious adverse events in the per-protocol population**

at follow-ups, which were done 7–18 months after randomisation (appendix p 1). In the resection group, 42 (79%) of 53 patients who did not have infliximab were in endoscopic remission at follow-up (appendix p 1).

In the first year after randomisation, 21 (32%) of the 65 patients who begun infliximab treatment discontinued use because of intolerance or insufficient therapeutic response, of whom 13 had an ileocaecal resection after a median time of 27 weeks (IQR 11–34). Of note, seven (35%) of 20 patients with known smoking status who stopped infliximab in the first year were smokers. 21 (48%) of the 44 patients who continued infliximab use for whom smoking status was known were smokers. Hence, in 25% of smokers and 36% of non-smokers, infliximab treatment failed. Two-thirds of the patients in the infliximab group were treated with combination therapy. Use of immunomodulators and steroids at 1 year is listed in the appendix p 3. Three (4%) of 73 patients in the laparoscopic ileocaecal resection group started treatment with infliximab within 12 months after surgery. Conversion to open surgery was reported in five (7%) of 70 patients in the laparoscopic ileocaecal resection group because of technical difficulties during the operation.

Treatment-related serious adverse events are summarised in table 3 (non-serious adverse events were not systematically recorded). Complications classified as Clavien-Dindo IIIa or worse occurred in four (6%) of the 70 patients in the laparoscopic ileocaecal resection group who had surgery, two of whom were admitted to the intensive care unit after anastomotic leakage, one for pulmonary embolism and one following relaparotomy. An ileostomy was constructed in three patients in the resection group. Of the 13 patients in the infliximab group who had an ileocaecal resection in the first year after enrolment, an ileostomy was constructed in one patient. In another patient in the ileocaecal resection group a relaparotomy was done, which appeared negative for leakage. All stomas were closed within 1 year of construction. Treatment-related serious adverse events occurred in two patients in the infliximab group (table 3).

Long-term follow-up data were available for 68 patients in the infliximab group and 71 patients in the resection group. During a median follow-up of 4·0 years (IQR 2·0–6·0), an additional 13 patients in the infliximab group had ileocaecal resection. One other patient had a sigmoid resection, one had a subtotal colectomy, and another had a stricturoplasty. In the resection group, 16 more patients received anti-TNF therapy (seven infliximab and nine adalimumab) after initial follow-up. The median time to resection in the infliximab group (all 26 patients who had resection) was 70 weeks (IQR 27–172) and median time to the start of anti-TNF treatment in the resection group (all 19 patients who had anti-TNF treatment) was 112 weeks (56–177).

## Discussion

Our study, to our knowledge, is the first randomised controlled trial comparing surgery with infliximab treatment for limited non-stricturing Crohn's disease of the terminal ileum. Although this trial did not show that surgery confers higher IBDQ scores than infliximab treatment at 12 months, and although the trial was not designed to show non-inferiority, the estimated mean difference and corresponding 95% CI suggest that quality of life after surgery is similar to that with infliximab treatment. Of note, baseline IBDQ scores showed moderately to severely active disease, whereas IBDQ scores at 12 months in both groups indicated remission,[23] and improvements were similar to those reported in the literature for both groups.[13,24,25]

Additionally, the mean score on the more generic SF-36 survey, in particular the physical component score, was significantly higher from 6 months onwards in the resection group than the infliximab group. The mean difference at 12 months of 3·1 is clinically relevant, as established by Samsa and colleagues[26] in their study on clinically important differences in health status measures. The fact that the general SF-36 score

was significantly higher in the resection group than the infliximab group could be because the patients in remission with anti-TNF still consider themselves as having a chronic disease because of the maintenance therapy and associated hospital visits, whereas patients in the ileocaecal resection group might not require further treatment. An explanation for the difference in the physical component score could be that the affected bowel segment in the infliximab group might still be dysfunctional because of fibrosis, despite the high proportion of people with endoscopic remission.

From a patient perspective, both therapeutic modalities are associated with drawbacks. Surgery could be perceived as the more profound disruption of daily functioning, but our results show that overall, both scheduled and unscheduled days of hospital admission were similar between groups.

Surgery is generally regarded as too invasive to use before medical therapy has been tried, because hospital admission and general anaesthesia are required. Additionally, the procedure can be associated with potentially severe complications (eg, anastomotic leakage). Our study showed that laparoscopic ileocaecal resection in daily practice is a safe procedure with only a temporary impairment of disease-specific quality of life; after 6 weeks, quality-of-life improvements similar to those in the infliximab group were seen.

Mucosal healing is regarded as an important endpoint for clinical trials in Crohn's disease, because it can alter mid-term and long-term outcomes. Surgery has been thought to be associated with a high rate of endoscopic recurrence at 1 year, fuelling the argument against early surgery. Traditionally, endoscopic recurrence has been scored using the Rutgeerts classification. A modified Rutgeerts classification has now been introduced to exclude the lesions at the anastomotic site that are due to anastomotic healing rather than endoscopic recurrences. In our study, we found that endoscopic recurrence scored with the modified Rutgeerts score occurred in 21% of those who had ileocaecal resection, and endoscopic recurrence in the infliximab group, as assessed by the CDEIS, was 16%. The low rate of endoscopic recurrence after ileocaecal resection, despite the fact that only a few patients received prophylactic medical therapy, suggests that early resection in limited terminal ileitis with careful follow-up could be an attractive alternative to long-term infliximab therapy.

Post-hoc analyses showed that the alternative strategy of starting with infliximab did not prevent surgery in the long term in 37% of patients (median follow-up 4 years); after loss of response to infliximab, pre-existing irreversible damage to the bowel wall might necessitate surgery.

The strength of our trial lies in its reflection of clinical practice. Patients were recruited to, and treated in, 29 teaching hospitals and tertiary care centres, balancing the putative confounder of expert centre bias with regard to surgical expertise. Some limitations should also be acknowledged. Because of the nature of the comparison in our study, participants and staff could not be masked, which might have affected the outcome measurements. The proportion of patients in endoscopic remission in both groups was similar at follow-up endoscopy. However, the assessment of endoscopic remission at 1 year could only be done with accepted but not formally validated cutoffs for two different endoscopic scoring systems, meaning that these cutoffs have not been formally validated. Futhermore, not all patients had follow-up endoscopy, which might have resulted in an underestimation of endoscopic activity, although proportions of observed endoscopic remission are similar to those reported in previous studies.[7,8] Data on disease severity were not required for inclusion in the trial, so endoscopic severity could not be assessed in many cases. Information published in 2010 (after our trial began) shows that the combination of infliximab with azathioprine is more effective than monotherapy.[24] Starting or maintaining immunomodulators after primary allocated therapy was deliberately left at the discretion of the treating physicians; at 12 months, the proportion of patients on immunomodulators was higher in the infliximab group. However, this would only have mitigated the effect on the observed favourable results of surgery in the primary outcome.

Recruitment was done over 7·5 years. This might in part reflect a priori patient or physician preference in two radically different treatment strategies. The number of screened patients during the 7·5 years was quite low, which is probably due to under-reporting of screened patients. Although we cannot rule out selection bias, demographic characteristics of our study participants were quite similar to those from a recent population-based Dutch cohort.[1] Our study population was mostly young adults, which could be because Crohn's disease is known to affect young adults, and because we assessed early surgery.

During the study course, the use of therapeutic drug monitoring became more widespread, although for anti-TNF treatment drug monitoring has not been shown to increase therapeutic efficacy.[27–29] Although current practice might differ from country to country with regard to first-line medical therapy, as well as postoperative prophylactic therapy for ileocaecal Crohn's disease, the setting of our trial is still in line with the most recent (2016) ECCO guidelines.[2,3]

At baseline, the proportion of smokers was higher in the infliximab group than in the resection group, which might have had a confounding effect on response to therapy and clinical recurrence, as well as on quality of life. Smoking is known to affect the response to anti-TNF therapy. However, in the infliximab group, the proportion of smokers was considerably higher in the patients in whom infliximab therapy did not fail.

We show in our study that laparoscopic ileocaecal resection, although not superior, seems to be similar to

infliximab treatment in terms of restoring quality of life and is not associated with more serious adverse events. Long-term follow-up data showed that more than a third of patients who started on infliximab needed ileocaecal resection within a few years, while only one in four patients who had resection needed anti-TNF therapy (infliximab or adalimumab) later on. On the basis of these data, we believe that laparoscopic ileocaecal resection should be offered as an alternative to infliximab therapy in patients with limited, non-stricturing, ileocaecal Crohn's disease that does not respond to conventional therapy.

#### Contributors

EJE, PCS, AAvB, and WAB designed the trial. All authors recruited and treated patients in the LIR!C trial. EJdG, EJE, TJG, BM, and AJdG collected the data. EJdG and PMMB analysed the data. CYP, EJdG, PMMB, CJB, PCS, GRD'H, and WAB interpreted the data. CYP, EJdG, PMMB, CJB, GRD'H, and WAB drafted the manuscript. CYP, EJdG, EJE, TJG, AH, JW, CJB, AAvB, MAB, ECJC, BAvW, MCMR, RMPHC, CGN, APJH, RCM, MB, WAM, HBS, PCS, GRD'H, and WAB critically revised the manuscript for important intellectual content.

#### Declaration of interests

CYP declares a grant from Takeda, Dr Falk Pharma, and AbbVie, advisory board fees from Takeda, and GlaxoSmithKline, as well as speaker's fees from Takeda, AbbVie, Ferring, Merck Sharp & Dohme (MSD), and Dr Falk Pharma. AAvB declares educational grants from Takeda and Ferring, consultation fees from MSD, AbbVie, Janssen, Pfizer, and Ferring, and speaker's fees from AbbVie, Janssen, Takeda, and Ferring. GRD'H has served as adviser for AbbVie, Ablynx, Amakem, AM Pharma, Avaxia, Biogen, Bristol-Meiers Squibb, Boehringer Ingelheim, Celgene, Celltrion, Cosmo, Covidien/Medtronics, Ferring, Dr Falk Pharma, Engene, Galapagos, Genentech/Roche, Gilead, GlaxoSmithKline, Hospira, Immunic, Johnson and Johnson, Lycera, Medimetrics, Millenium/Takeda, Mitsubishi Pharma, MSD, Mundipharma, Novonordisk, Otsuka, Pfizer, Prometheus laboratories/Nestle, Protagonist, Receptos, Robarts Clinical Trials, Salix, Sandoz, Setpoint, Shire, Teva, Tigenix, Tillotts, Topivert, Versant, and Vifor and received speaker fees from AbbVie, Biogen, Ferring, Johnson and Johnson, MSD, Mundipharma, Norgine, Pfizer, Shire, Millenium/Takeda, Tillotts, and Vifor. AH declares an advisory board fee from MSD. All other authors declare no competing interests.

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