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The Swedish Crohn Trial: A Prematurely Terminated Randomized Controlled Trial of Thiopurines or Open Surgery for Primary Treatment of Ileocaecal Crohn's Disease

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Abstract

Background and aims: The importance of efficient and safe treatment of Crohn's disease is highlighted by its chronicity. Both medical and surgical treatments have shown good results in the symptomatic control of limited ileocaecal Crohn's disease. The aim of this study was to compare medical treatment with surgical treatment of ileocaecal Crohn's disease.

Methods: Thirty-six patients from seven hospitals with primary ileocaecal Crohn's disease were randomized to either medical or surgical treatment. The medical treatment was induction of remission with budesonide and thereafter maintenance treatment with azathioprine. The surgical treatment was open ileocaecal resection. Crohn's disease activity index over time, expressed as area under the curve at 1, 3 and 5 years, was the primary endpoint. Subjective health measured with the 36-item Short Form Survey Instrument (SF36) and a visual analogue scale (VAS) were secondary endpoints.

Results: There were no differences between the treatment groups in Crohn's disease activity index over time. General health, measured as SF36 score, was higher in patients receiving surgical treatment than in those receiving medical treatment at 1 year, but there was no corresponding difference in VAS. Due to the slow inclusion rate and changes in clinical practice, the study was t=erminated prematurely.

Conclusion: The study ended up being underpowered and should be interpreted with caution, but there was no clinically significant difference between the two treatment arms. Further studies are needed to address this important clinical question.

Key Words: Surgery; clinical trials; quality of life; socio-economical and psychological endpoints

1. Introduction

The incidence of Crohn's disease (CD) is increasing worldwide, although it is still most common in Europe and North America.[1] Globally, there is high variance in the incidence of CD but in Europe it is on average around 5.6/100 000 inhabitants[2] and in Sweden the prevalence is approximately 0.3%.[3] It is a chronic inflammatory disease, which is often diagnosed in adolescence. The disease may affect different parts of the gastrointestinal tract, and varies in both

the location and the extent of the affected intestine. It can cause complications like strictures of the bowel and even intra-abdominal abscesses and fistulas. The importance of efficient and safe control of symptoms is increased by the combination of the high incidence, onset early in life and chronicity of the disease.

To achieve efficient and safe control of symptoms, CD is often jointly managed by gastroenterologists and surgeons.[4] The treatment of choice is sometimes more or less clear-cut, such as medical treatment (MT) in extensive inflammatory disease or surgical treatment (ST) if there are abdominal abscesses or severe stricturing, but in many cases both ST and MT could be justified. Different locations of CD have in previous studies shown different risks of requiring surgery, classical CD with ileocaecal involvement having the highest risk.[5] There are a number of studies looking at the effect of MT[6,7] as well as ST[8, 9] in ileocaecal CD, but there are no randomized studies directly comparing the two treatments.

Corticosteroids are the first-line treatment for induction of remission in CD,[10,11] but they are not effective as a maintenance treatment.[12] Thiopurines, e.g. azathioprine and its metabolite 6-mercaptopurine, are not used to induce remission as their effect is slow.[13] On the other hand, they are effective in preventing relapse of the disease due to their steroid-sparing effect.[14,15] Their use is, however, limited by various adverse effects that cause withdrawal from treatment in 10–26% of patients.[16,17] Earlier reports have shown an increased risk of non-Hodgkins' lymphoma associated with treatment with thiopurines,[18] but later studies have either not confirmed this[19] or have questioned whether this risk is larger than the benefits for the patients.[20]

Biologics such as anti-tumour necrosis factor (TNF) agents have become increasingly common as a treatment option. In some European countries 15–30% of CD patients are treated with biologics.[21] However, this is a fairly recent development and at the time of the design and start of this study biologics were not used as a standard treatment. They were therefore not included in this study, which was designed to compare corticosteroids and thiopurines with open surgery. The increasing use of immunomodulation has not affected the number of resections for CD.[22] Previous retrospective studies have shown that ST can be a good treatment for ileocaecal CD[23,24] and early surgery prolonged the time to clinical recurrence.[25] We therefore hypothesized that there is no difference in efficiency between thiopurines (azathioprine or 6-MP) and ST in the treatment of ileocaecal CD. The aim of this study was to test this hypothesis in a prospective, multicentre randomized controlled trial.

2. Methods

The study was approved by the Regional Ethics Committee, Linköping, Sweden, and conducted according to the Declaration of Helsinki.

2.1. Inclusion

Patients were recruited from seven hospitals in southern Sweden from1999 to 2007 and randomized with stratification for smoking and recruiting hospital before starting treatment. Inclusion criteria were adults (age 18 or above) diagnosed with CD not more than 1 year before inclusion with a CD activity index (CDAI) of at least 200, or obstructive symptoms within 3 weeks before inclusion. Patients should not have received any previous treatment for CD, i.e. they had to be drug-naive.

Obstructions had to require in-hospital care or to present more often than every 3 months. Both CDAI and obstructive symptoms had to be considered as caused by CD by the treating physician. When calculating CDAI, obesity was not given a negative value but was assigned the value of zero, and thus had no impact on the CDAI score. Intestinal inflammation, evaluated by radiology of the small intestine and colonoscopy, had to be limited to the ileocaecal region and not extend beyond 60 cm proximal to the terminal ileum. Colonoscopy had to have been done no more than 3 months prior to inclusion and colonic involvement limited to the caecum, even though single aphthous ulcers in an otherwise healthy mucosa visualized at colonoscopy were accepted. Fertile women had to have had anti-conception during the 5-year follow up of the study.

Previous surgery for CD or bowel resection other than appendectomy, pregnancy and/or breastfeeding (planned or ongoing), psychiatric comorbidity or substance abuse (that might cause lack of compliance) and other diseases or conditions considered to be contraindications for thiopurines or ST were used as exclusion criteria. Treatment failure led to exclusion from the study and individualized treatment.

2.2. Medical treatment (thiopurines)

Medical treatment comprised induction of remission with budesonide and treatment with azathioprine from the start. Budesonide was given at 9 mg/day for 8 weeks and the dose was then reduced to 6 mg/day for 18 weeks before withdrawal. The initial azathioprine dose was 50 mg/day and the dose was increased to 2–2.5 mg/kg/day. Intolerance of azathioprine led to a switch to 6-mercaptopurine at a dose of up to 1.5 mg/kg/day. Relapses or failure to induce remission led to budesonide treatment at 9 mg/day for 8 weeks and then 6 mg/day for 4 weeks. Patients receiving MT were followed clinically and endoscopic evaluation was done only when needed.

2.2.1. Treatment failure in the MT

Treatment failure in the MT arm was defined as need for two remission-inducing budesonide treatments in 1 year or more than three such treatments during the study period. Intolerance to both azathioprine and 6-mercaptopurine was also considered as a treatment failure as well as patients in MT arm needing surgery were a resection would lead to a resection of >60 cm at first surgery or a cumulative resection length of >80 cm.

2.3. Surgical treatment

Surgical treatment consisted of ileal or ileocaecal resection of macroscopically inflamed intestine with free resection margins of at most 2–5 cm. Relapse or failure to induce remission was treated with budesonide as for MT. As surgery requires in-hospital care and affects the daily life of patients during this time, the CDAI and VAS were set to 400 and 0, respectively, on the day of surgery. Colonoscopy was performed in patients receiving ST at 1, 3 and 5 years using the Rutgeerts' score.[26]

2.3.1. Treatment failure in the ST

Treatment failure in the ST arm was defined as need for two remission-inducing budesonide treatments in 1 year or more than three such treatments during the study period. A cumulative resection length of >80 cm if renewed resection was indicated was also considered as a treatment failure.

2.4. Endpoints

CDAI over time, expressed as area under the curve (AUC) at 1, 3 and 5 years, was the primary endpoint. Subjective health, measured using the 36-item Short Form Survey Instrument (SF36) and a visual analogue scale (VAS), was the secondary endpoint.

2.5. Statistics

Statistical computations were done using GraphPad Prism 5. Mann–Whitney and Fisher's exact tests were used as appropriate. Results are presented as median and range as applicable. Power was calculated to show a difference of 50 points in CDAI AUC with a certainty of 80%, giving a minimum group size of 40 patients. The inclusion rate was estimated at 40 patients per year.

3. Results

Thirty-six patients (15 male, 21 female) aged 19–70 years were included and randomized to the two treatments (18 MT, 18 ST). Two patients were excluded as the pathological examination after surgical resection showed diagnoses other than CD (normal mucosa in one patient, non-specific inflammation and carcinoid in the other). One patient received surgery but required a resection of more than 60 cm and thus met criteria for exclusion. Thus, 18 MT and 15 ST patients were available for follow-up (Figure 1).

The MT patients had a higher body mass index (BMI) than the ST group (p = 0.03) but otherwise no significant differences were found between the groups at inclusion. The groups were also similar in the subjective VAS and SF36 measurements at time of inclusion (Table 1).

During the study an additional 11 and 4 patients in the MT and ST groups respectively were excluded because of the need for individualized treatment for the following reasons: in the MT group, intolerance of study drugs (n = 3), side effects of medicine (n = 2), need for surgery, patient emigrated, pregnancy, patients' choice, compliance or unsuitability for surgery (n = 1 for each) (Figure 1); in the ST group, pathological examination of the surgical specimen showed a carcinoid tumour, patient developed stenosis at the anastomosis site, developed colitis, or treatment failure (n = 1 for each).

One patient in the MT group required surgery because of treatment failure according to the study protocol. No patient required more than one operation because of CD. There were, however, some complications of surgery. The MT patient who later needed surgery had thromboembolism as a postoperative complication. In the ST group there were three postoperative complications: one each of minor wound infection, wound dehiscence and late anastomotic leak. The anastomotic leak was diagnosed 1 month after surgery and required antibiotic treatment as well as re-operation with a stoma, which could be reversed after another 6 months. Three of these four patients with surgical complications were smokers. In patients undergoing surgical resection, endoscopical recurrences were evaluated using Rutgeerts' score after 1, 3 and 5 years (Table 2).

Data were analysed based on intention to treat. According to the study design, excluded patients were included as if they had been included with their last CDAI until the next time of comparison (1, 3 or 5 years). There were no differences in CDAI between the groups at 1 year (CDAI AUC of 2291 [768–10269] in MT and 1951 [395–20798] in ST). At 3 and 5 years CDAI AUC was 3711 (1698–10289) and 5941 (4403–9723) respectively in MT vs 3494 (1252–10217) and 5461 (1782–20798) in ST. A statistically significant difference in the social function (SF) score of the SF36 was present after 1 year, favouring ST (9 [5–10] vs 10 [8–10] in the MT group [p = 0.01]). A trend was seen towards a higher general health (GH) score of the SF36, also in favour of ST (15 [10–22] vs 10 [10–13] in the MT group [p = 0.06]).

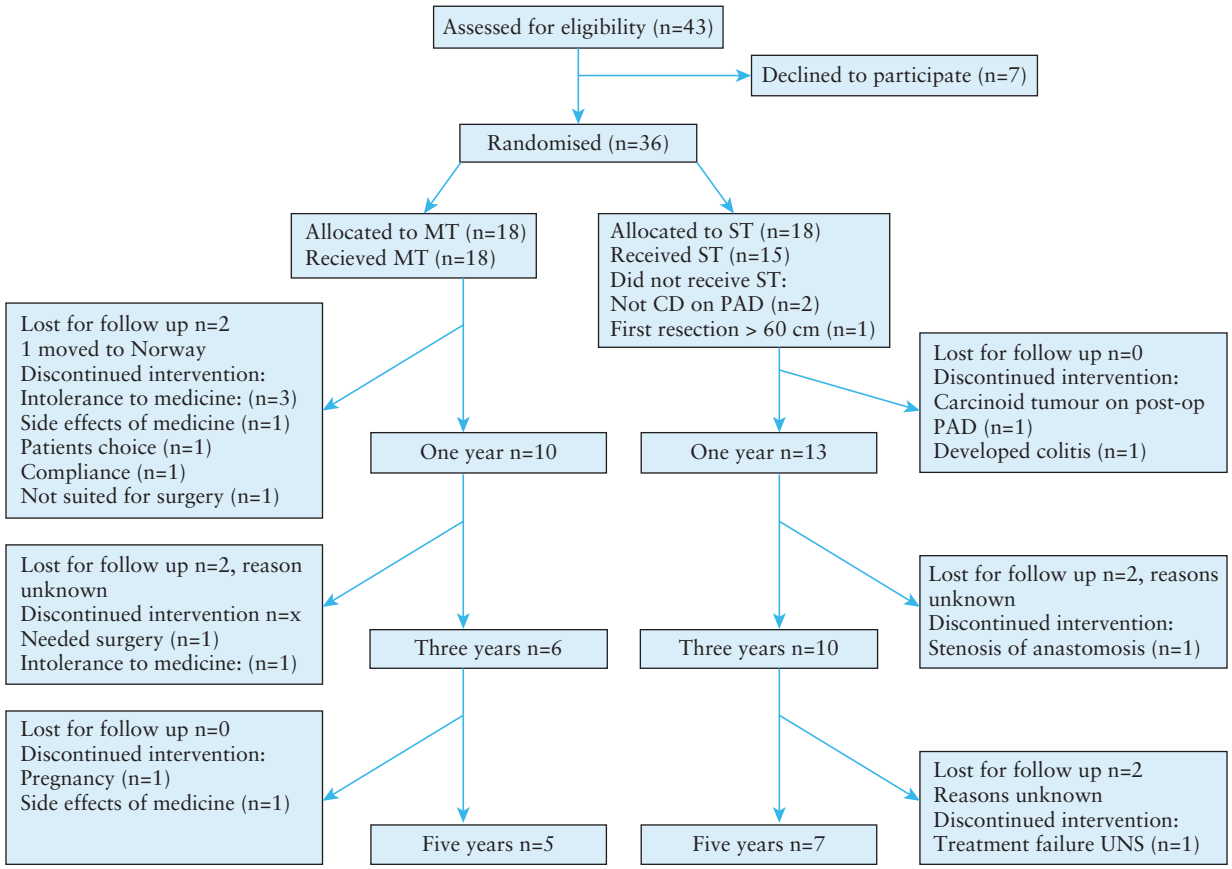

Figure 1. CONSORT diagram of the study. Total number of patients evaluated to enrollment in the trial and reasons and timing of exclusions during the 5-year follow up period.

On the other hand, there was a trend towards a lower vitality (VT score) of the SF36 in the ST group (16 [9–18] vs 16 [10–18] in the MT group [$p = 0.06$]). There were no differences between the groups later in the study, either in SF36 or in VAS estimates of general health.

Data were also analysed per protocol, showing no differences in CDAI at any time (Figure 2). There was a similar difference in the SF36 category GH at 1 year (10 [10–13] for MT and 15 [10–22] for ST respectively [$p = 0.02$]), but, as in the intention-to-treat analysis there were no corresponding differences in estimates of general health according to VAS at the same time.

No factors predicting exclusion or treatment failure reached significance using Fisher's exact test, although among the smokers 7 were excluded and only 3 remained in the study ($p = 0.26$).

Table 1. Patient characteristics. Subjects allocated to medical treatment had a higher body mass index at the time of inclusion. There were no other significant differences between the groups.

Medical therapy	Surgical therapy, $n = 18$ (IQR or %)	Medical therapy, $n = 18$ (IQR or %)	Significance
Age, y (median)	48.0 (26.3–57.8)	32.5 (25.3–49.3)	NS
Sex, female:male	11:7	9:9	NS
Smokers	5	5	NS
BMI (median)*	25.8 (22.8–28.9)	22.5 (20.3–24.3)	$p = 0.03$
CDAI (median)*	256 (237–306)	263 (225–284)	NS
CRP (median)*	18 (10–41)	16 (13–35)	NS
Extraintestinal symptoms*	7 (39%)	4 (22%)	NS
Fistulating disease*	0 (0%)	0 (0%)	NS
Fever*	6 (33%)	7 (39%)	NS

*At time of inclusion.

BMI, body mass index; CDAI, Crohn's disease activity index; CD, Crohn's disease; CRP, C-reactive protein; NS, not significant.

Table 2. Postoperative endoscopical recurrences in patients randomized to primary surgical therapy 1, 2 and 5 years after ileocaecal resection.

Rutgeerts score	1 year ($n = 11$)	3 years ($n = 11$)	5 years ($n = 6$)
0	9 (82%)	6 (55%)	1 (17%)
1	1 (9%)	3 (27%)	2 (33%)
2	0 (0%)	1 (9%)	1 (17%)
3	1 (9%)	1 (9%)	2 (33%)
4	0 (0%)	0 (0%)	0 (0%)

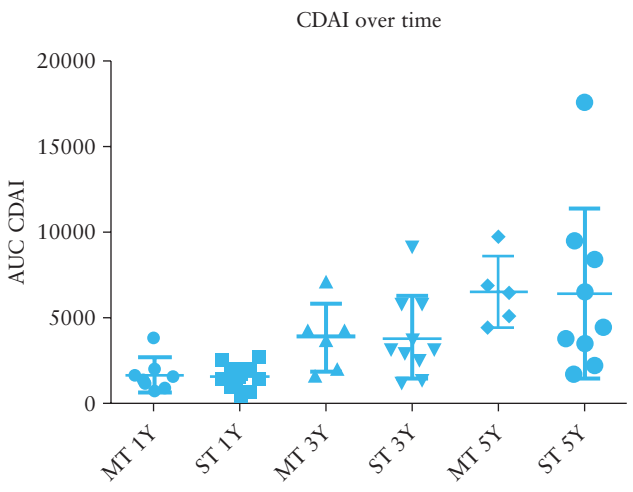

Figure 2. There were no significant differences in CDAI over time at any of the time points. AUC CDAI was calculated as area under the curve for CDAI integrated over time (in months) during follow up. CDAI, Crohn's disease activity index; AUC, area under the curve; MT, medical treatment; ST, surgical treatment.

4. Discussion

The main findings were that there were no clinically important differences favouring either MT or ST in objective parameters during the 5 years of follow-up. The statistically significant difference in self-estimated health (SF36) at 1 year was no longer significant at 3 years and in year 5 the trend was gone. Moreover, there were no differences in general well-being measured with the VAS between the groups at any point in time during the follow-up. This suggests that the differences in SF36 at 1 year were not of clinical significance.

The number of included patients was considerably lower than expected, maybe because the inclusion criteria were strict and required inclusion before the start of steroid treatment. An additional possible explanation for the low rate of inclusion is that the TNF-α inhibitors became a quite frequent choice of treatment close after the initiation of the study. Further, it was difficult for some of the patients to accept randomization between MT and ST and quite often the patients had been introduced with MT as the standard treatment by other medical staff prior to the informed consent discussion.

Due to the chronicity of the disease there is often a demand for different types of treatment over the years. Medical treatment offers good symptomatic control while ST eradicates strictures and sometimes all macroscopic inflammation, which could be an explanation of the difference in failure rates between MT and ST.[15] However, in the long run both regimens have quite high rates of recurrence,[6] possibly supporting postoperative maintenance therapy with e.g. azathioprine[4–5]after an initial excision of the damaged bowel segment.

Another factor that affected the power of the study was the exclusion rate being higher than expected due to a high CDAI that was not related to the CD but rather to concomitant disorders, the implementation of steroids or repeat surgery according to the study protocol. The CDAI is still often used as an outcome for randomized controlled studies but has previously been shown not to be disease-specific as the index is heavily based on general well-being, diarrhoea and abdominal pain,[27] which in our trial caused severe problems when the change of treatment regimen was based on the CDAI. The use of the CDAI is further even less used postoperatively in surgical trials, and might be even less useful as many of the patients will have, for example, more loose stools after an ileocaecal resection. Thus, 50% of the patients did not complete the intended 5-year follow-up of the study as the scored high on CDAI despite no signs of active disease.

This is, as far as we know, the first randomized trial comparing the long-term outcome of MT with the outcome of ST for ileocaecal CD. Previous studies on the long-term outcome of surgery for ileocaecal CD have shown clinical remission rates of 48%, with only 35% of patients needing a second resection after 10 years,[28] well in line with more recent meta-analyses on immunomodulators and anti-TNF therapies, which showed remission rates of 36[29]–55[30]% after 1 year. Since the initiation of this study, there have also been changes in surgical treatment. Nowadays laparoscopic surgery has emerged as a common alternative, with fewer incisional hernias and a reduction in perioperative complications.[31]

We believe that this study, although underpowered, supports the view, presented by, among others, the ECCO committee,[32] that

surgery is a treatment option for ileocaecal CD and not just a last resort when medical treatment fails, and the management of CD requires a joint effort by medical gastroenterologists and surgeons.

More studies of treatment alternatives including surgery are needed and important results may come from the ongoing multicentre LIR!C trial[33] comparing laparoscopic ileocaecal resection with biologics in newly diagnosed CD.

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None.

Conflict of Interest

None.

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