

Is Early Ileo-cecal Resection for Crohn's Disease an Appropriate Primary Treatment?



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TBD

This summary reviews Agrawal M, Ebert AC, Poulsen G, et al. Early ileocecal resection for Crohn's disease is associated with improved long-term outcomes compared with anti-tumor necrosis factor therapy: A population-based cohort study. *Gastroenterology* 2023; 165:976-985.

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STRUCTURED ABSTRACT

Question: What are the long-term outcomes of ileo-cecal resection (ICR) and anti-tumor necrosis factor (TNF)- α therapy as the initial primary treatment for ileal and ileo-cecal Crohn's disease (CD) within 1 year of diagnosis?

Study Design: Retrospective cohort study in a population-based cohort's cross-linked national registers.

Setting: All people living in Denmark between January 1, 2003 and December 31, 2018.

Patients: Study inclusion criteria included: (a) patients with Crohn's disease in ileal or ileocecal region were identified based on *International Classification of Disease -10th Edition (ICD-10)* diagnoses and cross-linked with the Danish Pathology

Register to ensure pathologic confirmation of disease; and (b) primary treatment was ileocecal resection (ICR) or anti-TNF therapy within 30 days before and 1 year after CD diagnosis based on medication and hospital procedure codes identified using Anatomical Therapeutic Chemical (ATC) codes and Nordic Classification of Surgical Procedures. Patients were excluded if CD was diagnosed before the start of the study period, did not receive ICR or anti-TNF therapy within 30 days before or 1 year after CD diagnosis, were treated with other biologic medications or CD-related operations before ICR or anti-TNF primary treatment, had perianal Crohn's disease before primary treatment, and individuals who did not live in Denmark for at least 1 year prior to primary treatment.

Intervention/Exposure: The primary exposure was primary treatment of Crohn's disease with anti-TNF therapy versus ileo-cecal resection within 30 days before or 1 year after CD diagnosis. Cohort assignment was done by the first of the 2 treatments received, regardless of whether the other treatment was received at a later time.

Outcomes: The primary outcome was a composite of ≥ 1 of the following >30 days after primary treatment: (a) CD-related hospitalization; (b) systemic corticosteroid exposure; (c) major CD-related surgery; or (d) perianal CD.

Data Analysis: Kaplan-Meier survival analyses were conducted to compare proportion of individuals who experienced the primary outcome in both arms (anti-TNF therapy vs ICR). Cox proportional hazards regression analyses were used to estimate adjusted hazard ratios for the composite outcome. Their models were adjusted for age at CD diagnosis, sex, and year of treatment, as well as variables that were different between the 2 intervention arms: all-cause hospital contacts, unique prescription medications, systemic corticosteroid and immunomodulator exposure. They tested for interaction for a number of variables and conducted a number of sensitivity analyses. Finally, to adjust as much as possible for confounding by indication, they conducted propensity-weighted analysis with a propensity score including age at CD diagnosis, sex, number of unique prescription medications, number of hospital contacts and systemic corticosteroid and immunomodulator exposures in the year prior to primary treatment.

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Results: From 2003 to 2018, 1,279 Danish CD patients met inclusion criteria with 45% (n=581) receiving ICR and 55% (n=698) receiving anti-TNF as primary therapy within 12 months of CD diagnosis. Other demographic data included 58% female (both groups); median age was 30 (interquartile range [IQR] 22-51) and 22 (IQR 17-31), respectively. Patients in the ICR group were more likely to have complicated CD, defined as stricture, ileus, internal fistula, or abscess (21% vs 2%), but less likely to have received corticosteroids (34% vs 68%) or immunomodulators (18% vs 56%) in the preceding 12 months. Total follow-up was 2,474 person-years with median follow-up of 1.7 years per patient.

Patients getting ICR as primary treatment were less likely to suffer from the composite primary outcome compared to patients getting anti-TNF agents: incidence rate: 110/1000 person-years vs 202/1000 person-years; adjusted hazard ratio (aHR) = 0.67 (95% confidence interval [CI]: 0.54-0.83) (**Figure 1**). After adjusting for age, sex, and calendar year, ICR as primary therapy was also associated with lower risk of corticosteroid exposure (aHR = 0.61; 95% CI: 0.49-0.77) and CD-related surgery (aHR = 0.49; 95% CI: 0.36-0.67), but only trended toward lower rates of CD-related hospitalization (aHR = 0.84; 95% CI: 0.68-1.04) or perianal CD diagnosis (aHR = 0.62; 95% CI: 0.37-1.04). Also, among ICR-treated patients with 5 years of follow-up, 49.7% were on no therapy with 46% only on immunomodulator and 17% on anti-TNF agents.

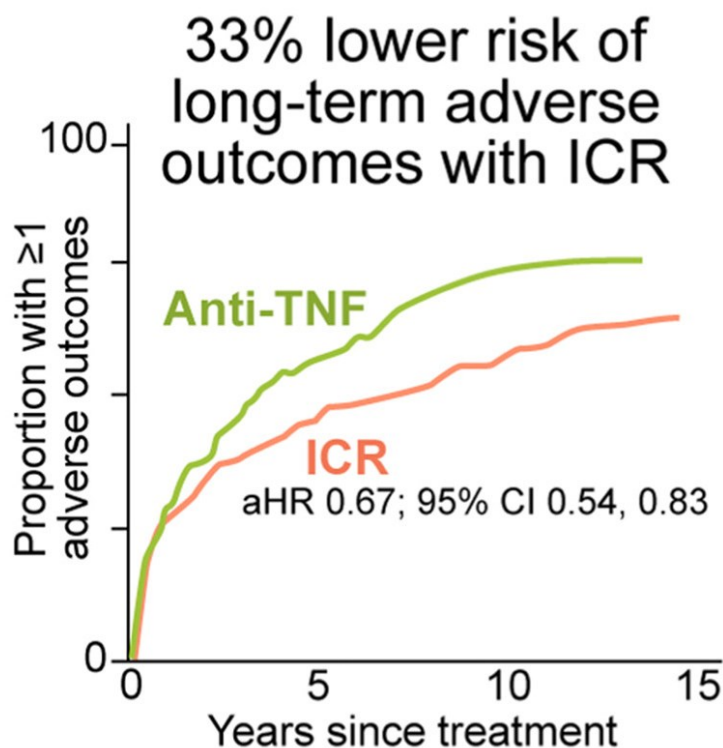


Figure 1. The risk of long-term adverse outcome, including hospitalization, repeat Crohn's disease-related surgery, systemic corticosteroid exposure, and perianal Crohn's disease was 33% lower with ileocaecal resection compared with anti-tumor necrosis factor agents as primary therapy.

ICR, ileocaecal resection; TNF, tumor necrosis factor.

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COMMENTARY

Why Is This Important?

This is a very well done, robust retrospective cohort study which demonstrates that early ileo-cecal resection is a reasonable first line option for select patients with isolated terminal ileal or limited ileo-cecal inflammation. In the era of expanding inflammatory bowel disease (IBD) treatments and declining rates of surgery, this trial highlights that Crohn's disease remains a disease process that merits true medical-surgical interdisciplinary collaboration.

The findings from this analysis are not entirely surprising. In 2017, the LIR!C trial, a prospective open-label randomized controlled trial (RCT), assigned 143 patients with limited (<40 cm) inflammatory ileo-cecal CD that was not responsive to conventional therapy to laparoscopic ileocecal resection or infliximab¹. The primary outcome was quality of life at 12 months with morbidity as a secondary outcome. While this small RCT did not detect a difference in the primary outcome, the anti-TNF arm had a higher number of unscheduled hospital admissions. Four patients in the resection arm had serious surgical-complications and 2 patients in the TNF arm had treatment-related serious adverse events. During long-term follow-up (median 64 months) of 94% of study patients², 48% in the ICR arm were treated prophylactically with an immunomodulator, 26% were eventually started on an anti-TNF, and none of

the patients required a second resection, while 48% of patients in the anti-TNF treatment arm eventually required a resection for Crohn's disease.

This study includes a much larger cohort (1,279 versus 143 patients), assessed objective outcomes, and found that early surgical resection has a lower risk than anti-TNF therapy for the composite of 4 objective outcomes. This is certainly a more definitive finding than the LIR!C study, and CD patients are identified with high validity in the Danish registers given the robust national data collection and cross-linking of databases. However, the limitations of a retrospective studies must be kept in mind when applying these results to the patient in your clinical practice. Disease behavior, radiologic or endoscopic extent, severity of disease and such details that inform treatment decision making are not available with high validity in such databases. Therefore, despite robust methodological techniques, there is residual confounding by indication. It was likely a highly selective group of patients with limited and mild disease who were offered first-line surgical management and an even more selective group of patients who elected for this option. It is also likely that patients with either more robust inflammation or systemic disease were only offered medical therapy. Given the inherent and unmeasurable differences between the 2 study arms in a retrospective analysis, it is difficult to say with great confidence that ileocecal resection is a superior first line treatment option

for these patients.

Key Study Findings

Ileo-cecal resection was associated with a 33% reduction in long-term adverse outcomes (CD-related hospitalization, systemic corticosteroid exposure, major CD-related surgery, or perianal CD) versus patients receiving anti-TNF agents as primary treatment within 12 months of CD diagnosis. At 5-year follow-up, almost 50% of ICR-treated patients were on no CD therapy.

Caution

As noted above, findings from this retrospective analysis may be biased because there may be residual confounding by indication. In other words, many factors like disease behavior, radiologic and endoscopic findings, and severity of disease may have led physicians to offer ICR only to a highly selective group of CD patients, which could account for more adverse outcomes in the anti-TNF group.

My Practice

In my practice, I discuss limited ileal resection as a treatment option for patients with short segment, non-stricturing, non-penetrating ileal Crohn's disease. While many patients shy away from first line surgical treatment, some express interest in learning more about this. For these patients, I will request a visit with one of our expert IBD

surgeons—even if it's mainly for educational value. I also emphasize to my patients that just because they meet a surgeon doesn't mean they have to have surgery.

However, in the era of selective anti-interleukin agents (ustekinumab, risankizumab) which are effective and seem to have a similar, if not lower concern, for serious adverse events compared with anti-TNF agents, first line anti-interleukin therapy is a much more reasonable treatment option. The loss of an ileo-cecal valve can have significant ramifications with regards to bacterial overgrowth syndromes and bile acid homeostasis. Therefore, despite both the LIR!C RCT and this larger, retrospective Danish study, I have a much higher threshold for recommending surgery. Nevertheless, these studies highlight that surgery for CD can be safe, effective, and transformative for quality of life.

For Future Research

Identifying the right patient for the right treatment, including surgical treatment, remains the holy grail for IBD management. Additionally, understanding patient concerns about early resections for IBD is an important and understudied topic. Further qualitative research may facilitate better communication around medical versus surgical decision making, especially early in the course of disease.

Conflicts of Interest

Dr. Kochar has served on advisory boards for Pfizer and Bristol Myers Squibb.

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