Phenotypic Features of Crohn's Disease Associated With Failure of Medical Treatment

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BACKGROUND & AIMS: **There is conflicting evidence on the effects of thiopurines (azathioprine or mercaptopurine) and anti–tumor necrosis factor (TNF) therapies on rates of surgery among patients with Crohn's disease (CD). We aimed to identify factors that identify patients who are unlikely to respond to medical therapy and will therefore require surgery.**

METHODS: **We performed a retrospective study using the Alberta Inflammatory Bowel Disease Consortium registry to identify 425 patients diagnosed with CD who received a prescription of a thiopurine and/or an anti-TNF agent from a referral center, from July 1, 1975, through September 13, 2012. We collected data on CD-related abdominal surgery after therapy and disease features when therapy was instituted. Cox proportional regression models were used to associate disease features with outcomes after adjusting for potential confounders. Risk estimates were presented as hazard rate ratios (HRRs) with 95% confidence intervals (CIs).**

RESULTS: **Among patients given thiopurines, stricturing disease (adjusted HR, 4.63; 95% CI, 2.00–10.71), ileal location (adjusted HR, 6.20; 95% CI, 1.64–23.42), and ileocolonic location (adjusted HR, 3.71; 95% CI, 1.08–12.74) at the time of prescription were associated significantly with the need for surgery. Prescription of an anti-TNF agent after prescription of a thiopurine reduced the risk for surgery, compared with patients prescribed only a thiopurine (adjusted HR, 0.41; 95% CI, 0.22–0.75). Among patients given anti-TNF agents, stricturing (adjusted HR, 6.17; 95% CI, 2.81–13.54) and penetrating disease (adjusted HR, 3.39; 95% CI, 1.45–7.92) at the time of prescription were associated significantly with surgery. Older age at diagnosis (17–40 y) reduced the risk for abdominal surgery (adjusted HR, 0.41; 95% CI, 0.21–0.80) compared with a younger age group (≤16 y). Surgery before drug prescription reduced the risk for further surgeries among patients who received thiopurines (adjusted HR, 0.33; 95% CI, 0.13–0.68) or anti-TNF agents (adjusted HR, 0.49; 95% CI, 0.25–0.96). Terminal ileal disease location was not associated with a stricturing phenotype.**

CONCLUSIONS: **Based on a retrospective database analysis, patients prescribed thiopurine or anti-TNF therapy when they have a complicated stage of CD are more likely to require surgery. Better patient outcomes are achieved by treating CD at early inflammation stages; delayed treatment increases rates of treatment failure.**

Keywords: IBD; Disease Phenotype; Prognostic Factor; Immune Suppression.

As the incidence of Crohn's disease (CD) increases globally,[1] morbidity and cost associated with therapeutics and surgery will continue to stress health care systems. Referral center[2,3] and population-based studies[4–8] have indicated that the 10-year risk of intestinal surgery ranged from 40% to 71%. A meta-analysis of population-based studies reported that the 10-year

Abbreviations used in this paper: Anti-TNF, anti–tumor necrosis factor; CD, Crohn's disease; CI, confidence interval; HRR, hazard rate ratio.

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incidence of surgery in CD over the past 2 decades was 38%,[9] and that the incidence of surgery may be decreasing over time.[9,10] However, the effect of medical treatment on reducing surgical rates remains controversial.[3,11] A primary driver of surgery in CD is the development of stricturing or penetrating complications.[12] Disease behavior evolves over time,[12,13] with approximately 15% of CD patients experiencing a complication at diagnosis and more than half developing a complication after 10 years of disease.[11] However, the occurrence of CD intestinal complications may have been influenced by the introduction and earlier use of immunosuppressants and anti–tumor necrosis factor (anti-TNF) therapy. Randomized controlled trials suggest that anti-TNF therapy decreases surgical rates over 1 year.[14,15] A retrospective referral center[16] and a population-based study[6] have suggested that thiopurines and anti-TNF agents may reduce surgical rates in CD. In contrast, Cosnes et al[3] found that the increased use of immunosuppressants between 1978 and 2002 was not correlated with a reduction in surgical rates. The heterogeneity between studies may be owing to past studies not accounting for timing of the introduction of immunosuppressants and/or anti-TNF therapies relative to the timing of onset of CD complications. Immunosuppressants and anti-TNF therapies may be less effective when introduced late into the course of CD and particularly after a complication already has occurred.[16]

The main aim of this study was to investigate the effects of disease phenotype at the onset of thiopurine or anti-TNF therapy on surgical outcomes in CD subjects.

Methods

Study Population

CD patients (N = 425) followed up in the Alberta Inflammatory Bowel Disease Consortium patient database registry were identified. A retrospective chart review was conducted between July 1, 2011, and October 9, 2012. Inclusion criteria included a confirmed diagnosis of CD, a current or previous prescription of a thiopurine agent (azathioprine or mercaptopurine), and/or a current or previous prescription of anti-TNF therapy (infliximab or adalimumab). Between July 1, 1975, and September 13, 2012, CD patients were prescribed a thiopurine and/or anti-TNF therapy as per the clinical scenarios described in Supplementary Table 1. Patients with a diagnosis of ulcerative colitis or inflammatory bowel disease unspecified at time of chart review were excluded.

Exposure and Outcomes

All CD patients included were prescribed either a thiopurine agent or an anti-TNF agent, or both in combination. Combination therapy was defined as concomitant onset, if both a thiopurine and an anti-TNF agent were prescribed within 3 months of each other. We stratified our CD population into 2 cohorts: (1) patients prescribed a thiopurine agent for at least 3 months; and (2) patients prescribed anti-TNF therapy for any duration of time. The primary exposure of interest was disease behavior at the onset of the first prescription of a thiopurine agent (cohort A) or an anti-TNF agent (cohort B). The 2 cohorts of CD patients were not mutually exclusive. Disease behavior was defined as per the Montreal Classification,[17] as follows: inflammatory (B1), stricturing (B2), or penetrating disease (B3). The primary outcome of interest was CD-related intestinal resection after the first prescription of thiopurine (cohort A) or anti-TNF agent (cohort B). Perianal surgery in isolation was not included as a primary outcome.

Variables

Data were extracted after a comprehensive chart and electronic health record review including demographic data, laboratory studies, microbiology, diagnostic imaging, surgical and pathology reports, dictation notes, discharge summaries, and medication profiles. The data extraction was conducted independently by 2 trained clinicians (G.W.M. and M.-F.D.) using a standardized data collection form. Data extracted included age at diagnosis; sex; confirmation of tissue diagnosis; disease behavior (B1, B2, and B3, as well as date of change); disease location at follow-up evaluation including terminal ileal (L1), colonic (L2), ileal colonic (L3), and upper gastrointestinal tract (L4); perianal fistulizing disease; prescription of corticosteroid therapy at diagnosis; date of first prescription of thiopurine and/or anti-TNF agent; smoking history; date of all CD-related intestinal resections (stratified as before or after onset of thiopurine and/or anti-TNF agent); and time from diagnosis to first prescription of thiopurine and/or anti-TNF agent and first intestinal resection.

Statistical Analyses

All CD patients were followed up from onset of prescription of thiopurine and/or anti-TNF agent to either event (ie, surgery), migration out of clinical practice, death, or censure. Censure was defined as 5 years of follow-up evaluation after first prescription of a thiopurine (cohort A) and/or anti-TNF agent (cohort B) without surgery. The effect of thiopurine and/or anti-TNF therapy was assessed by constructing life tables, creation of Kaplan–Meier survival curves, and comparison using the log-rank test.

Cox proportional regression models evaluated the effect of disease behavior at the onset of therapy (thiopurine, first analysis, and anti-TNF second analysis) on CD-related intestinal resection (primary outcome) after adjusting for the following potential confounders: age at diagnosis stratified as younger than 16 years (referent),