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Infliximab Reduces Endoscopic, but Not Clinical, Recurrence of Crohn's Disease After Ileocolonic Resection

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BACKGROUND & AIMS: Most patients with Crohn's disease (CD) eventually require an intestinal resection. However, CD frequently recurs after resection. We performed a randomized trial to compare the ability of infliximab vs placebo to prevent CD recurrence. **METHODS:** We evaluated the efficacy of infliximab in preventing postoperative recurrence of CD in 297 patients at 104 sites worldwide from November 2010 through May 2012. All study patients had undergone ileocolonic resection within 45 days before randomization. Patients were randomly assigned (1:1) to groups given infliximab (5 mg/kg) or placebo every 8 weeks for 200 weeks. The primary end point was clinical recurrence, defined as a composite outcome consisting of a CD Activity Index score >200 and a ≥70-point increase from baseline, and endoscopic recurrence (Rutgeerts score ≥i2, determined by a central reader) or development of a new or re-draining fistula or abscess, before or at week 76. Endoscopic recurrence was a major secondary end point. **RESULTS:** A smaller proportion of patients in the infliximab group had a clinical recurrence before or at week 76 compared with the placebo group, but this difference was not statistically significant (12.9% vs 20.0%; absolute risk reduction [ARR] with infliximab, 7.1%; 95% confidence interval: −1.3% to 15.5%; $P = .097$). A significantly smaller proportion of patients in the infliximab group had endoscopic recurrence compared with the placebo group (30.6% vs 60.0%; ARR with infliximab, 29.4%; 95% confidence interval: 18.6% to 40.2%; $P < .001$). Additionally, a significantly smaller proportion of patients in the infliximab group had endoscopic recurrence based only on Rutgeerts scores ≥i2 (22.4% vs 51.3%; ARR with infliximab, 28.9%; 95% confidence interval: 18.4% to 39.4%; $P < .001$). Patients previously treated with anti-tumor necrosis factor agents or those with more than 1 resection were at greater risk for clinical recurrence. The safety profile of infliximab was similar to that from previous reports. **CONCLUSIONS:** Infliximab is not superior to placebo in preventing clinical recurrence after CD-related resection. However, infliximab does reduce endoscopic recurrence. ClinicalTrials.gov ID NCT01190839.

Keywords: PREVENT; Anti-TNF; Inflammatory Bowel Disease; CDAI.

Crohn's disease (CD) often requires intestinal resection, despite treatment with immunosuppressive and biologic therapies.[1,2] Historically, up to 70% of patients who undergo CD-related resection develop postoperative endoscopic recurrence at or proximal to the surgical anastomosis within 1 year.[3,4] Recent systematic reviews and meta-analyses have shown that approximately one-third of patients with CD who have a first resection require a second within 10 years, and the majority of these second intestinal resections occur within 5 years of the first. However, during the past few decades, the risk of a second resection has decreased.[5] Additionally, a decreasing trend has been found during the past 6 decades in the cumulative risk of resection 1, 5, and 10 years after CD diagnosis.[6]

Studies of probiotics, aminosalicylates, and budesonide[7–13] for prevention of postoperative recurrence have overall yielded negative results. Studies of nitroimidazole antibiotics have been positive for prevention of clinical recurrence. Studies of thiopurines have had mixed results for the prevention of clinical recurrence. Neither nitroimidazole antibiotics nor thiopurines have consistently

Abbreviations used in this paper: **ARR, absolute risk reduction; ATI, antibodies to infliximab; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; TNF, tumor necrosis factor.**

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prevented endoscopic recurrence.[14–16] Initial studies,[17,18] a small placebo-controlled trial,[19] and subsequent observational studies[20–25] suggested that tumor necrosis factor (TNF) antagonists might be effective for prevention of postoperative recurrence. In recent studies of CD treatment strategies after intestinal resection, therapy adjusted according to 6-month colonoscopy findings led to effective disease control.[26–28] Overall, optimal postoperative management is unclear.

Given these considerations, we evaluated the efficacy and safety of infliximab for prevention of postoperative CD recurrence.

Methods

Patients

The PREVENT (Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing REMICADE® [infliximab] and Placebo in the Prevention of Recurrence in Crohn's Disease Patients Undergoing Surgical Resection Who Are at an Increased Risk of Recurrence; ClinicalTrials.gov ID NCT01190839) study was a phase 3, multicenter, placebo-controlled, double-blind, randomized study conducted at 104 sites globally between November 2010 and May 2012. The Institutional Review Board or ethics committee at each site approved the protocol, and patients provided written informed consent. All authors had access to the study data and had reviewed and approved the final manuscript.

Enrolled patients were at least 18 years old with a confirmed diagnosis of CD who had undergone ileocolonic resection with ileocolonic anastomosis. An end or loop ileostomy within 1 year was permitted if stoma closure and ileocolonic anastomosis occurred within 45 days of randomization. Patients had no evidence of macroscopic CD, no known active CD elsewhere in the gastrointestinal tract, and were eligible for randomization within 45 days of resection. Patients were ineligible if the qualifying surgery occurred more than 10 years after CD diagnosis and was performed for stricturing disease involving <10 cm of bowel. Patients were also required to have a baseline CD Activity Index (CDAI)[29] score <200 and at least one of the following risk factors for disease recurrence: qualifying surgery that was their second intra-abdominal resection within 10 years; third or more intra-abdominal resection; resection for a penetrating CD complication (eg, abscess or fistula); a history of perianal fistulizing CD, provided the event had not occurred within 3 months; or smoking 10 or more cigarettes per day for the past year. The prespecified risk factors of smoking, perforating disease, and previous resection had been identified from previous studies and were utilized in a recent postoperative study.[28,30–35]

Patients receiving oral mesalamine or immunosuppressives (azathioprine, 6-mercaptopurine, or methotrexate) pre-surgery could continue treatment with maintenance of stable doses after resection. Patients not receiving these agents pre-surgery could not receive them post-surgery. Rectal mesalamine was discontinued at least 2 weeks before randomization. Initiation of corticosteroids or antibiotics for CD treatment was prohibited.

Study Design

Patients were randomized equally to receive infliximab (Remicade; Janssen Biotech, Inc., Horsham Township, PA) 5 mg/kg or placebo every 8 weeks. Placebo and infliximab infusions were administered in a blinded manner. Randomization was stratified by the number of risk factors for recurrence (1 or >1) and current use of an immunosuppressive (yes/no). Unlike dosing regimens used previously and those described in the prescribing information for patients with CD,[36] every-8-weeks dosing without the 3-dose induction regimen was utilized in this study. This dosing regimen was chosen because patients in this study were in surgically-induced remission and did not have active CD at the time they entered the study; thus, every-8-weeks dosing for maintenance of remission was employed. Also, some patients might not have been naïve to infliximab, and data from an infliximab trial in patients with psoriasis showed a higher rate of serious infusion reactions at the week-2 infliximab infusion after a hiatus.[37]

CDAI scores were determined at each visit, and as required at interim assessments; baseline CDAI refers to the CDAI collected during the screening period (ie, no fewer than 10 days and no more than 45 days before randomization) that qualified the patient for the study. Patients who met CDAI criteria (ie, ≥200 and an increase of ≥70 points from the baseline CDAI score) for clinical recurrence or reached week 76 underwent a video ileocolonoscopy. Patients who discontinued study agent before week 76 had a video ileocolonoscopy at the time of discontinuation. If clinical recurrence was observed, patients could receive blinded infliximab doses at an increase of 5 mg/kg for each subsequent scheduled infusion visit, such that patients receiving placebo increased to 5 mg/kg and patients receiving 5 mg/kg to 10 mg/kg.

Serum samples were collected at baseline and week 72 for measurement of infliximab and antibodies to infliximab (ATI).[38] Adverse events, concomitant medications, and CD-related hospitalizations and surgeries were recorded throughout.

End Points

The primary end point was clinical recurrence before or at week 76, defined by a ≥70-point increase from baseline with a total CDAI score ≥200 and evidence of endoscopic recurrence defined by a Rutgeerts score[3] of ≥i2 (i0, no lesions; i1, ≤5 aphthous lesions; i2, >5 aphthous lesions or anastomotic ulcer <1 cm; i3, diffuse aphthous ileitis with diffusely inflamed mucosa; i4, diffuse inflammation with large ulcers, nodules, and/or narrowing) at the anastomotic site or its equivalent elsewhere in the gastrointestinal tract or fistula/abscess development (ie, new draining external fistula, internal fistula, reopening and draining of a previously existing external fistula, perianal abscess, or intra-abdominal abscess >3 months after the index surgery). Patients were considered to have clinical recurrence if they had a treatment failure (ie, initiated a prohibited CD medication, had a prohibited use of a CD medication, or had CD-related surgery).

The major secondary end point was endoscopic recurrence of CD before or at week 76, defined as a Rutgeerts score of ≥i2 either at the anastomosis or elsewhere in the gastrointestinal tract, whether this occurred at the week 76 video ileocolonoscopy, or at a prior video ileocolonoscopy. Patients who