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Methotrexate in Combination With Infliximab Is No More Effective Than Infliximab Alone in Patients With Crohn's Disease

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See related article, Colombel J-F et al, on page 414 in *CGH*; see editorial on page 608.

BACKGROUND & AIMS: Methotrexate and infliximab are effective therapies for Crohn's disease (CD). In the combination of maintenance methotrexate-infliximab trial, we evaluated the potential superiority of combination therapy over infliximab alone. **METHODS:** In a 50-week, double-blind, placebo-controlled trial, we compared methotrexate and infliximab with infliximab alone in 126 patients with CD who had initiated prednisone induction therapy (15–40 mg/day) within the preceding 6 weeks. Patients were assigned randomly to groups given methotrexate at an initial weekly dose of 10 mg, escalating to 25 mg/week (n = 63), or placebo (n = 63). Both groups received infliximab (5 mg/kg of body weight) at weeks 1, 3, 7, and 14, and every 8 weeks thereafter. Prednisone was tapered, beginning at week 1, and discontinued no later than week 14. The primary outcome was time to treatment failure, defined as a lack of prednisone-free remission (CD Activity Index, <150) at week 14 or failure to maintain remission through week 50. **RESULTS:** Patients' baseline characteristics were similar between groups. By week 50, the actuarial rate of treatment failure was 30.6% in the combination therapy group compared with 29.8% in the infliximab monotherapy group ($P = .63$; hazard ratio, 1.16; 95% confidence interval, 0.62–2.17). Prespecified subgroup analyses failed to show a benefit in patients with short disease duration or an increased level of C-reactive protein. No clinically meaningful differences were observed in secondary outcomes. Combination therapy was well tolerated. **CONCLUSIONS:** The combination of infliximab and methotrexate, although safe, was no more effective than infliximab alone in patients with CD receiving treatment with prednisone. ClincialTrials.gov number, NCT00132899.

Keywords: COMMIT; Inflammatory Bowel Disease; IBD; Randomized Controlled Trial.

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract. Corticosteroids remain the cornerstone of first-line therapy in clinical practice.[1,2] Although effective in controlling symptoms, limitations of these agents include failure to induce remission in up to 40% of patients,[1,2] high relapse rates after successful induction therapy,[3–5] and undesired adverse effects especially when used long term.[6,7] Although the purine antimetabolites (azathioprine and 6-mercaptopurine), methotrexate, and tumor necrosis factor antagonists are effective in treating corticosteroid-refractory and corticosteroid-dependent disease, these agents induce and maintain long-term remission in less than half of patients.[8–13] Better approaches to management are needed.

Recently, interest has emerged in combining immunosuppressives to treat immune-mediated diseases. This strategy is well established in rheumatoid arthritis, in which methotrexate in combination with a tumor necrosis factor antagonist is superior to the use of single-drug therapy[14–16]; this also seems promising in CD. A randomized trial that evaluated the combination of azathioprine and infliximab[17] in patients with corticosteroid-dependent disease showed that additive efficacy exists with these agents. Based on these

Abbreviations used in this paper: **CBC, complete blood count; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; SF-36, Short-Form 36.**

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observations we conducted a randomized trial of methotrexate in combination with infliximab in patients with active CD who also recently were treated with corticosteroids.

Materials and Methods

This trial was performed at 15 centers in Canada between December 2005 and February 2008. The investigational review board at each center approved the protocol and all patients provided written informed consent.

Patients

Patients with a diagnosis of CD who had initiated prednisone (15–40 mg/day) for active symptoms within 6 weeks of the screening visit were eligible. Patients who had received methotrexate within the past year, those who had failed to respond to previous methotrexate therapy, and those who had been treated previously with infliximab were not eligible. Patients with risk factors for methotrexate toxicity, as described previously, were ineligible.[10] Similarly, patients with risk factors for infliximab toxicity were excluded (evidence for latent tuberculosis, demyelinating disorders, congestive heart failure, current malignancy, or malignancy within 5 years of screening). Patients who had received azathioprine and/or 6-mercaptopurine within 8 weeks before randomization and those with an immediate need for surgery; symptomatic stenosis or ileal/colonic strictures with prestenotic dilatation; a bowel resection within 6 months of screening; short-bowel syndrome; a stoma; signs, symptoms, or laboratory tests indicating clinically significant medical disease; chronic or serious infection within 6 months of screening; allergy to murine proteins, infliximab, methotrexate, and/or prednisone; pregnant patients; or known substance abusers were not eligible.

Study Design

One week before randomization a physical examination and blood tests, including a C-reactive protein (CRP) determination, were performed. A tuberculin test and chest radiograph were obtained. Patients were instructed on the use of a diary card to score the Crohn's Disease Activity Index (CDAI).[18] CDAI scores range from 0 to approximately 600. Higher scores indicate increased disease activity whereas scores of 150 or less define clinical remission. Patients' quality of life was assessed using the Short-Form 36 (SF-36) Physical and Mental Component Summary measures.[19] Scores range from 0 to 100, with higher scores indicating a better quality of life.

Patients were assigned randomly by computer, in a 1:1 ratio, to receive weekly subcutaneous injections of methotrexate (Mayne Pharma, Saint-Laurent, Quebec, Canada; Novopharm, Toronto, Ontario, Canada; and Bedford Laboratories, Bedford, OH) or identically appearing placebo. A minimization procedure[20] was used to balance the treatment groups with respect to important prognostic factors, as follows: (1) treatment with or without a purine antimetabolite in the past 12 months; (2) prednisone dose less than 20 mg or 20 mg or greater at randomization; and (3) CDAI score less than 150 or 150 or greater at randomization. To avoid potential adverse events related to methotrexate, we used a dose-escalation strategy. The initial subcutaneous methotrexate dose was 10 mg/wk, which was increased to 20 mg at week 3, and further increased to the final dose, 25 mg, at week 5, with continuation through week 50.

All patients received infliximab (Remicade; Centocor, Malvern, PA), 5 mg/kg of body weight given intravenously at weeks 1, 3, 7, 14, 22, 30, 38, and 46. Thirty minutes before each infusion, a 200-mg dose of hydrocortisone was administered intravenously to minimize the risk of infusion reactions and sensitization to infliximab.[21]

Other Treatments and Prednisone Tapering Schedule

To prevent methotrexate toxicity, patients in both groups received oral folic acid (1 mg/day). If patients developed nausea, ondansetron (4-mg oral tablet) was recommended before administration of the study drug. Tapering of prednisone began at week 1 (7 days after randomization). Patients receiving more than 20 mg/day of prednisone decreased the daily dose by 5 mg/wk until 20 mg/day was reached. Patients receiving 20 mg/day or less of prednisone decreased the daily dose by 2.5 mg/wk. The longest duration of prednisone therapy during the study was 19 weeks and the shortest duration was 4 weeks. All patients were required to discontinue prednisone by week 14. Aminosalicylates, budesonide, probiotics, systemic antibiotics for the treatment of luminal CD, immunosuppressives, investigational agents, parenteral nutrition, or topical aminosalicylates or corticosteroids were not permitted. Antibiotics were allowed for non-CD indications and active perianal disease for a maximum of 14 consecutive days.

Efficacy and Safety Evaluations

Patients were seen at weeks 1, 3, 7, 14, 22, 30, 38, 46, and 50 for assessment of CD activity by the CDAI, physical examination, infliximab infusion, monitoring of study drug administration, complete blood count (CBC), measurement of serum aminotransferase levels, and measurement of serum infliximab and antibodies to infliximab immediately before an infusion using a commercially available homogenous mobility shift assay (Prometheus Laboratories, Inc, San Diego, CA).[22] The lower limit for detection of antibodies to infliximab in this assay was 3.13 U/mL.[23] Patients completed the SF-36 at randomization and at weeks 14, 30, and 50. A post-study follow-up visit was conducted at week 66.

An independent unblinded clinician (with no study patient contact) monitored aminotransferase levels and CBC results. If mild leukopenia developed (white cell count, $3.0–3.5 \times 10^9$/L), the dose of the study drug was decreased by 50%. For more severe leukopenia the study drug was held for 1 week, and then resumed at 50% of the original dose once the white count had normalized. A similar approach was taken if the serum aminotransferase concentrations increased to more than twice the upper limit of normal. Dose adjustments were made in the placebo group to preserve blinding. CBC and aminotransferase results were not made available to the attending physicians and nurses. An external data monitoring committee reviewed safety data at regular intervals.

Outcome Measures

The primary outcome measure was the time to treatment failure, defined as failure to enter prednisone-free remission (CDAI, <150) at week 14 or failure to maintain this remission through week 50. Patients who failed to enter prednisone-free remission at week 14 were discontinued from the trial. The occurrence of a relapse was defined by a CDAI score of 150 or greater and an increase in the CDAI score of 70 or more points