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A Note on Methotrexate in Combination with Infliximab is No More Effective than Infliximab Alone in Patients with Crohn's Disease

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Description

The SONIC study (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease) changed the therapeutic paradigm for Crohn's disease (CD) after years of uncertainty due to the lack of prospective data by conclusively showing that combination therapy with infliximab and azathioprine is superior to monotherapy with infliximab or azathioprine in patients with moderate-to-severe CD who are naive to immunosuppressive The COMMIT (Combination of Maintenance Methotrexate-Infliximab Trial) study, the first prospective trial examining the potential superiority of infliximab in combination with methotrexate (MTX) over infliximab alone in patients with CD, reports its findings in this issue of Gastroenterology. Regardless of their CD Activity Index (CDAI), CD patients who had started steroid induction therapy within the previous six weeks and had never received immunosuppressive or biologic therapy were randomly assigned to receive subcutaneous MTX or a placebo for 50 weeks, along with infliximab at weeks one, three, seven, and fourteen, and every eight weeks after that. If tolerated, MTX dosage was increased from the initial 10 mg per week to 25 mg per week by week 5. 200 mg of hydrocortisone and 5 mg/kg of infliximab were given before each infusion. Beginning in week 1, all patients follow a decreasing prednisone treatment, and drugs are stopped no later than week 14. The primary endpoint of treatment failure-lack of steroid-free remission at week 14 or failure to sustain remission through week 50-was not different between the two groups. Several secondary outcomes, such as the percentage of patients who reached steroid-free remission at week 14 and maintained this remission through week 16, did not show any clinically significant changes. 50, the median change in C-reactive protein levels, and the mean change in CDAI.

There was no difference in the proportion of patients experiencing adverse events between the 2 groups when using combination therapy. The findings of this study are unsatisfactory and perhaps unexpected at first glance. The demonstrated efficacy of MTX in chronically active CD the well-documented benefit of this association in rheumatoid arthritis and the reassuring short- and long-term safety profile of MTX in this era of rising concerns regarding risks of lymphomas and skin cancers associated with thiopurines are just a few of the reasons that support the combination therapy with infliximab and MTX. There are two key reasons why this study was unsuccessful. The first is unanticipated design flaws that would have obscured the efficacy data, and the second is a fundamental lack of the drug combination's greater efficacy. Regarding the design, there might have been some confounding factors in the patient selection. First off, there was no minimum CDAI score requirement for study inclusion, and over 30% of patients in each arm had a CDAI score of less than 150.

Therefore, regardless of the treatment they were given, it is likely that a portion of these patients who began the trial in remission would not have ever met the primary end point (treatment failure with a CDAI of 150). Second, as the authors hinted, it's probable that some patients were included even though they had no active disease because there weren't any endoscopic inclusion criteria. In the SONIC study, there were no treatment differences seen in participants without endoscopic lesions. Third, the authors put out the intriguing theory that the use of prednisone induction treatment in combination with infliximab (perhaps supported by the routine administration of a 200-mg dose of hydrocortisone before each infusion of infliximab) may have disguised any benefit of MTX. Indeed, the best success rates in this patient population were observed at weeks 14 and 50, when >75% and >55% of patients, respectively, were in steroid-free remission. These findings strongly imply an additive impact between prednisone and infliximab that calls for additional study. They are reminiscent of the 72 percent success rate at week 12 that was seen in the GETAID study where patients were simultaneously treated with prednisone, azathioprine, and infliximab. The lack of a synergistic impact between infliximab and MTX as opposed to infliximab and azathioprine is yet another explanation for these poor data.

Contrary to the rheumatologic literature, there is virtually little information on anti-tumor necrosis factor (TNF) medications combined with MTX in CD. In a retrospective study from the St-Antoine Hospital in Paris, patients treated with immunomodulators in addition to infliximab had fewer IBD relapses and less need to switch to adalimumab than those treated with infliximab alone; however, this benefit was only seen with azathioprine and not with MTX. Azathioprine and MTX have not been compared head-to-head in a CD trial, although it is important to note that in a recent uncontrolled, open-label study, mucosal healing rates were higher with azathioprine than with MTX. Interestingly, despite its expected strong impact on the formation of antibodies to infliximab (4 percent in the combination therapy arm *vs.* 20 percent in the monotherapy arm) and trough levels (6.35 *vs.* 3.75 mg/mL), the lack of additive effect of MTX on the efficacy of infliximab was not observed despite this [1-5].

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Conflict of Interest

The Author declares there is no conflict of interest associated with this manuscript.

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