CLINICAL AT

Methotrexate Is Not Superior to Placebo in Maintaining Steroid-Free Response or Remission in Ulcerative Colitis

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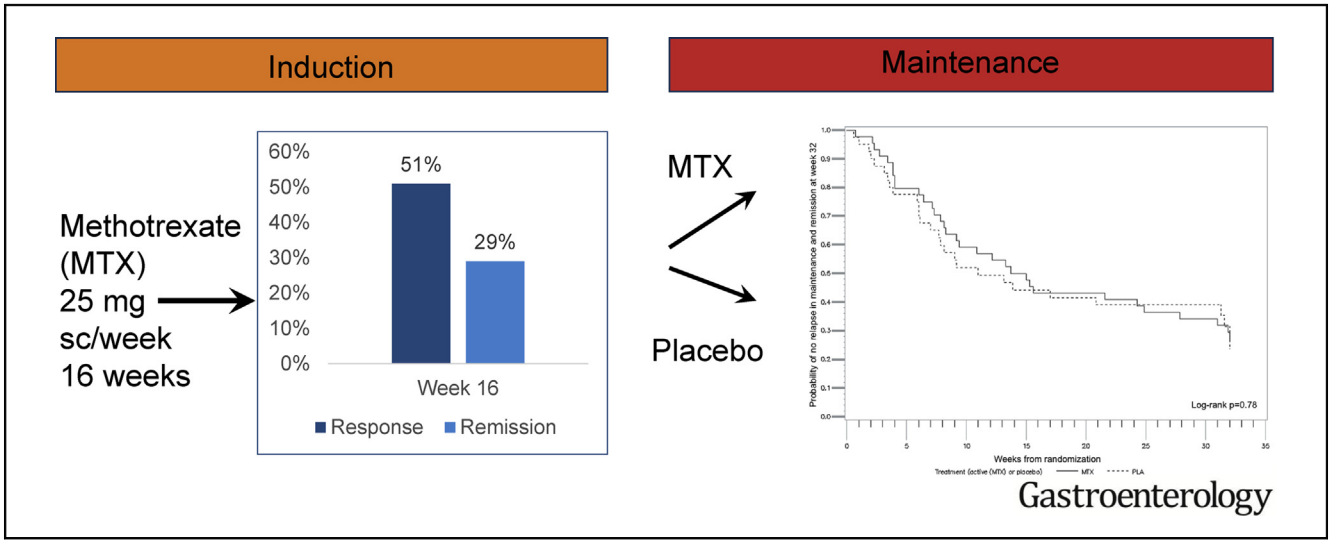

See editorial on page 967.

BACKGROUND & AIMS: Parenteral methotrexate induces clinical remission but not endoscopic improvement of mucosal inflammation in patients with ulcerative colitis (UC). We performed a randomized, placebo-controlled trial to assess the efficacy of parenteral methotrexate in maintaining steroid-free response or remission in patients with UC after induction therapy with methotrexate and steroids. **METHODS:** We

performed a 48-week trial, from February 2012 through May 2016, of 179 patients with active UC (Mayo score of 6–12 with endoscopy subscore $\geq$ 2) despite previous conventional or biological therapy. The study comprised a 16-week open label methotrexate induction period followed by a 32-week double-blind, placebo-controlled maintenance period. Patients were given subcutaneous methotrexate (25 mg/wk) and a 12-week steroid taper. At week 16, steroid-free responders were randomly assigned to groups that either continued methotrexate (25 mg/wk, n = 44) or were given placebo (n = 40) until week 48. We compared the efficacy of treatment by analyzing the proportion of patients who remained relapse free and were in remission at week 48 without use of steroids or other medications to control disease activity. **RESULTS:** Ninety-one patients (51%) achieved response at week 16, and 84 patients were included in the maintenance period study. During this period, 60% of patients in the placebo group (24/40) and 66% in the methotrexate group (29/44) had a relapse of UC (P = .75). At week 48, 30% of patients in the placebo group (12/40) and 27% of patients in the methotrexate group (12/44) were in steroid-free clinical remission without need for additional therapies (P = .86). No new safety signals for methotrexate were detected. **CONCLUSIONS:** Parenteral methotrexate (25 mg/wk) was not superior to placebo in preventing relapses of UC in patients who achieved steroid-free response during induction therapy. ClinicalTrials.gov, Number: NCT01393405.

Keywords: Active Ulcerative Colitis; IBD Therapy; Immunosuppressive Agent; Inflammatory Bowel Diseases.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

The available data for methotrexate (MTX) in the therapy of ulcerative colitis have been inconclusive. The recent METEOR trial showed clinical efficacy of MTX in inducing remission in patients with ulcerative colitis but with no improved endoscopic outcome.

NEW FINDINGS

Parenteral MTX 25 mg/week was not superior to placebo in preventing relapse of disease in patients with UC who achieved steroid-free response after an MTX induction therapy.

LIMITATIONS

The trial was powered to detect a 25% difference between placebo and MTX. However, given the similarity of the relapse rates in the MTX and placebo group and the multiple negative subgroup analyses, a larger study would likely have similar outcomes.

IMPACT

The results of MERIT-UC unquestionably demonstrate that methotrexate monotherapy is not a therapeutic viable option to treat patients with ulcerative colitis

Ulcerative colitis (UC) is a recurrent, chronic inflammatory bowel disease affecting the colon and leading to clinical symptoms, including fecal urgency, bloody diarrhea, abdominal pain, weight loss, and fatigue. For patients with mild to moderate UC despite therapy with aminosalicylates, the therapeutic options include biologics or thiopurines. Although thiopurines are markedly less expensive than the biologic drugs, they are associated with potentially serious adverse effects including pancreatitis, leukopenia, and lymphoma.[1–3] Biological therapies, including anti–tumor necrosis factor (TNF) agents (infliximab, adalimumab, golimumab) or anti-adhesion molecules (vedolizumab) are effective, but are expensive and also not without risks.[4]

Methotrexate (MTX) is an orally, subcutaneously, intramuscularly, or intravenously administered folate antagonist that was developed in 1948 for the treatment of leukemia. MTX targets thymidylate biosynthesis and the enzyme thymidylate synthase.[5,6] MTX is converted intracellularly to MTX-polyglutamates and reduces cell proliferation, increases the rate of apoptosis of T cells, raises anti-inflammatory endogenous adenosine concentrations, and alters cytokine production. The rationale behind the use of high-dose MTX in cancer chemotherapy is the promotion of starvation of cancer cells by eliminating purine and pyrimidine precursors, thus leading to decreased cell proliferation due to insufficient DNA and RNA synthesis. Oral or parenteral low-dose MTX has significantly decreased toxicity compared with high-dose therapy and is used in several autoimmune diseases, including polyangiitis, psoriasis, and rheumatoid arthritis. However, the mechanisms of the therapeutic effects of low-dose therapy, in contrast to high-dose therapy, remain incompletely understood.[7]

In inflammatory bowel diseases (IBDs), MTX's clinical efficacy in inducing and maintaining clinical remission has been established for steroid-dependent Crohn's disease (CD) in adults and also in children refractory or intolerant to thiopurine therapy.[8–14] In contrast to CD, the role of MTX in UC is controversial. In the first prospective, placebo-controlled study, oral low-dose (12.5 mg) MTX weekly was not more efficacious than placebo.[15] Since then, however, observational studies have shown effectiveness of MTX if given parenterally, similar to the dosing used in CD (15–25 mg/wk).[16,17] To more definitively elucidate the clinical value of MTX therapy in patients with mild to moderately active UC, 2 explanatory investigator-initiated clinical trials were conceptualized in the mid-2000s. The French controlled, randomized, double-blind, multicenter study comparing methotrexate vs placebo in steroid-dependent ulcerative colitis, Methotrexate vs Placebo in Steroid Dependant Ulcerative Colitis (METEOR), assessed the efficacy of MTX in inducing steroid-free remission over a 16-week time period.[18] In METEOR, MTX induced clinical remission without steroids in a significantly larger

Abbreviations used in this paper: **AE, adverse event; CD, Crohn's disease; FCP, fecal calprotectin; IBD, inflammatory bowel disease; MERIT-UC, Methotrexate Response in Treatment of Ulcerative Colitis; METEOR, Methotrexate vs Placebo in Steroid Dependant Ulcerative Colitis; MTX, methotrexate; TNF, tumor necrosis factor; UC, ulcerative colitis.**

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