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Methotrexate Is Not Superior to Placebo for Inducing Steroid-Free Remission, but Induces Steroid-Free Clinical Remission in a Larger Proportion of Patients With Ulcerative Colitis

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ABSTRACT

BACKGROUND & AIMS: Parenteral methotrexate is an effective treatment for patients with Crohn's disease, but has never been adequately evaluated in patients with ulcerative colitis (UC). We conducted a randomized controlled trial to determine its safety and efficacy in patients with steroid-dependent UC.

METHODS: We performed a double-blind, placebo-controlled trial to evaluate the efficacy of parenteral methotrexate (25 mg/wk) in 111 patients with corticosteroid-dependent UC at 26 medical centers in Europe from 2007 through 2013. Patients were given prednisone (10 to 40 mg/d) when the study began and were randomly assigned to groups (1:1) given placebo or methotrexate (intramuscularly or subcutaneously, 25 mg weekly) for 24 weeks. The primary end point was steroid-free remission (defined as a Mayo score ≤2 with no item >1 and complete withdrawal of steroids) at week 16. Secondary endpoints included clinical remission (defined as a Mayo clinical subscore ≤2 with no item >1) and endoscopic healing without steroids at weeks 16 and/or 24, remission without steroids at week 24, and remission at both weeks 16 and 24.

RESULTS: Steroid-free remission at week 16 was achieved by 19 of 60 patients given methotrexate (31.7%) and 10 of 51 patients given placebo (19.6%)—a difference of 12.1% (95% confidence interval [CI]: -4.0% to 28.1%; P = .15). The proportion of patients in steroid-free clinical remission at week 16 was 41.7% in the methotrexate group and 23.5% in the placebo group, for a difference of 18.1% (95% CI: 1.1% to 35.2%; P = .04). The proportions of patients with steroid-free endoscopic healing at week 16 were 35% in the methotrexate group and 25.5% in the placebo group—a difference of 9.5% (95% CI: -7.5% to 26.5%; P = .28). No differences were observed in other secondary end points. More patients receiving placebo discontinued the study because of adverse events (47.1%), mostly caused by UC, than patients receiving methotrexate (26.7%; P = .03). A higher

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proportion of patients in the methotrexate group had nausea and vomiting (21.7%) than in the placebo group (3.9%; *P* = .006).

CONCLUSIONS: In a randomized controlled trial, parenteral methotrexate was not superior to placebo for induction of steroid-free remission in patients with UC. However, methotrexate induced clinical remission without steroids in a significantly larger percentage of patients, resulting in fewer withdrawals from therapy due to active UC. ClinicalTrials.gov ID NCT00498589.

Keywords: IBD; Methotrexate; Clinical Trial; Drug.

Abbreviations used in this paper: CD, Crohn's disease; CI, confidence interval; GETAID, Groupe d'Étude Thérapeutique des Affections Inflammatoires Digestives; TNF, tumor necrosis factor; UC, ulcerative colitis.

Ulcerative colitis (UC) is an inflammatory bowel disease characterized by chronic mucosal inflammation, bloody diarrhea, and abdominal pain. UC has a global prevalence of about 8 million, and the incidence and prevalence are increasing worldwide. Current medical therapies have limitations. Aminosalicylates are only effective in mild-to-moderate disease. Glucocorticoids cause unacceptable adverse events and do not provide a benefit as maintenance therapy. Azathioprine is effective for maintenance of remission,[1] but is associated with an increased risk of infection[2] and lymphoma.[3] Although tumor necrosis factor (TNF) antagonists (anti-TNFs) are efficacious,[4,5] they are not effective in all patients; their use is limited by low long-term remission rates and by a risk of severe infections, including opportunistic infections.[6] Anti-adhesion molecules, which reduce inflammation by preventing lymphocytes trafficking to the gut mucosa, constitute a novel drug class in this indication[7], however, their precise role in treatment algorithms is not yet fully defined. The introduction of new biologic therapies has a strong impact on health care expenditures. In the current era of escalating health care costs and growing constraints on health care budgets,[8] need exists for alternative, safe, and inexpensive drugs in UC.

Methotrexate is a dihydrofolate reductase that has been used for decades for treatment of psoriasis and rheumatoid arthritis. In Crohn's disease (CD), methotrexate has proven efficacy as induction and maintenance therapy, at a dosage of 25 mg weekly intramuscularly.[9,10] A Cochrane review concludes that there is insufficient evidence to support the use of methotrexate for induction or maintenance of remission in UC, although the only included controlled trial used an oral dosage of 12.5 mg/wk.[11,12] We therefore conducted a multicenter, controlled, randomized, double-blind study of parenteral methotrexate in patients with steroid-dependent UC.

Methods

Study Design

This METEOR (Controlled, Randomized, Double-Blind, Multicentre Study Comparing Methotrexate vs Placebo in Steroid Dependant Ulcerative Colitis) trial was conducted at 26 medical centers in 6 countries (Austria, Belgium, Finland, France, Greece, and Italy) from 2007 to 2013. French and Belgian centers were affiliated with the Groupe d'Étude Thérapeutiques des Affections Inflammatoires Digestives (GETAID). The trial was designed by investigators of the GETAID and European Crohn's and Colitis Organisation. Written informed consent was obtained from all participants. The study was approved by the Institutional Review Board of the University Hospital of Besançon (France), by the French Health Authority (Agence Française de Sécurité Sanitaire des Produits de Santé) and was registered under ClinicalTrials.gov ID NCT00498589.

Patients

Eligible patients were adults younger than 75 years of age who had been diagnosed with UC for at least 6 months and were steroid-dependent, as defined by at least one unsuccessful attempt to discontinue steroids during the last 12 weeks before inclusion. Steroid therapy may have completely stopped if it had been restarted within the last 90 days.[13] At inclusion, the daily dose of steroids had to range between 10 and 40 mg prednisone or equivalent. Patients could have active or inactive disease at inclusion, as defined by a Mayo Clinic score (range, 0—12, with higher scores indicating more active disease) of >2 or ≤2. At the beginning of the trial, patients included had to have inactive disease, but in November 2009, due to slow recruitment, an amendment allowed inclusion of patients with active or inactive disease. Patients with a child-bearing potential were required to use an adequate method of contraception throughout the study. Patients were ineligible if they were initially refractory to oral steroids (no improvement after 2 weeks of 40 mg prednisone), had received anti-TNFs within 60 days before enrollment, or had received azathioprine, mercaptopurine, cyclosporine, nonsteroidal anti-inflammatory drugs, cotrimoxazole, or probenecid within 30 days before enrollment. Other exclusion criteria included indication for colectomy, alcohol consumption, chronic obstructive pulmonary disease, renal failure,

liver disease, pregnancy or lactation, patients without efficacious contraception, patients infected with human immunodeficiency virus, hepatitis B virus, hepatitis C virus, a history of a malignant condition, obesity (defined by body mass index >30 kg/m^2), or diabetes mellitus.

Screening and Baseline Procedures

Assessments performed during the screening visit, 4 to 12 days before inclusion, included clinical examination, complete blood count, serum folates, C-reactive protein serum concentration, serum transaminases, creatinine and albumin serum concentration, serum pregnancy test for women of childbearing potential, hepatitis B virus, hepatitis C virus, and human immunodeficiency virus antibodies, chest x-rays, and sigmoidoscopy. Total Mayo score was determined immediately before randomization. At the same time, an inflammatory bowel disease quality of life questionnaire (Inflammatory Bowel Disease Questionnaire; range, 0—224, with higher scores indicating a better quality of life) was administered.

Randomization Procedures

Randomization was centralized and balanced by center. The 1:1 randomization sequence was generated independently of the investigators by the Clinical Investigation Center of Lille University Hospital, using a computer procedure, with a block size of 4. The placebo and the active treatment were numbered according to the randomization code and then distributed by Eurofins (Nantes, France). Patients received placebo or methotrexate (intramuscularly or subcutaneously, 25 mg weekly), for 24 weeks. Patients, caregivers, investigators, and data analysis personnel were unaware of the treatment assignment. An independent blinded observer supervised the study and recorded any adverse effects of treatment.

Study Medications

Methotrexate, supplied by Sanofi-Aventis France, was packaged in 25-mg vials. Placebo, identical in appearance to active drug, was manufactured by EVOTEC (Glasgow, Scotland). Methotrexate and placebo were administered intramuscularly or subcutaneously, which is similar as far as pharmacokinetics.[14,15] The injections were performed at patients' homes by nurses who were blinded to the study medication. A 5-mg tablet of folic acid was prescribed every week, 24 to 48 hours after the methotrexate or placebo injection. Ondansetron was allowed in the protocol, but the use of antiemetics was not recorded. The prednisone/prednisolone dosage at inclusion was kept unchanged during the first weeks after inclusion, according to a pre-established scheme in which the duration of maintenance of starting dosage of steroids was inversely correlated with this dosage (Supplementary Table 1). The steroid dosage was tapered by 5 mg every week, up to the dosage of 10 mg/d and then tapered by 2.5 mg every week until discontinuation. Therefore, all patients were scheduled to stop steroids at week 13, irrespective of their starting dosage. In the case of relapse after full weaning, steroids were restarted at a dosage of 20 mg/d and maintained during 1 week after clinical remission (defined by a partial Mayo score ≤2, with no item >1 for the clinical part of the score). Then, the tapering schedule, as described, was resumed. If the patient failed to respond to a dosage of 20 mg prednisone per day, systemic steroid therapy was increased at the investigator's discretion. Most patients who restarted or increased steroids during the tapering process could not be off steroids at week 13 because of the prespecified tapering regimen. But all patients had to be off steroids at week 16 to meet the primary end point.

Cotrimoxazole, salicylates, steroid-based enemas, or suppositories were prohibited. Initiation of azathioprine/ 6-mercaptopurine, cyclosporine, tacrolimus, infliximab, or adalimumab therapy was considered failure of treatment and led to study discontinuation.

Follow-up

At each center, 2 physicians, who were unaware of the treatment assignment, followed the patients. One carried out the clinical follow-up and performed the endoscopies, while the other one reviewed laboratory results and adjusted study drug dosages based on serum transaminases complete blood counts and serum creatinine. The physician who ensured the clinical follow-up was unaware of laboratory results and dosage adjustments. The physician who reviewed biologic results was not involved in patient evaluations.

Patients were evaluated at weeks 2, 4, and then every 4 weeks until week 24. At each visit, a partial Mayo score (ie, the Mayo score without the endoscopic subscore) was assessed and adverse events were recorded. Steroid dosages were recorded and adapted according to the pre-established tapering scheme. Blood samples for biochemical and hematologic testing were obtained at each visit. Flexible sigmoidoscopies were performed at baseline and at weeks 16 and 24 by a local investigator who was unaware of the treatment allocation and scored according to the Mayo endoscopic subscore. No central endoscopy reading was used. Inflammatory Bowel Disease Questionnaire scores were repeated at weeks 16 and 24.

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Outcomes

The primary end point was steroid-free remission at week 16, defined as remission with a Mayo score ≤2 with no item >1 and complete withdrawal of steroids and no use of another immunosuppressives (IS) or anti-TNF therapy or colectomy. Secondary end points were steroid-free remission at week 24, remission at week 16 and 24, endoscopic healing (Mayo endoscopic subscore = 0 or 1), clinical remission (defined as Mayo clinical subscore ≤2 with no item >1), all without steroids, IS, anti-TNF, or colectomy at week 16 and/or 24 as well as adverse events, either severe or not. Additionally, the proportion of patients with CRP concentration <5 mg/L and Inflammatory Bowel Disease Questionnaire score ≥170 without steroids at week 16 were determined. At the beginning of the trial, the primary end point was sustained remission without steroids at weeks 16 and 24. In June 2014, an amendment allowed changing the primary end point to remission without steroids at week 16. The reason was that none of the many UC trials that had been published since the design of the trial included sustained remission as the primary end point. The amendment was allowed while results were still blinded.

Study Oversight

The study was designed and implemented by GETAID. Data were managed by the Département de Biostatistique et Information Médicale (Hôpital Saint Louis, Assistance Publique-Hôpitaux de Paris) and analyzed by the statistical department of Lille University Hospital. Funding was provided by the French Ministry of Health (clinical research hospital program), a private gift from an anonymous patient, the Association François Aupetit, and the Société Nationale Française de Gastroentérologie.

The first draft of the manuscript was written by the first author. All of the authors had access to the data and vouch for the validity of the data and analyses and the fidelity of the study to the protocol. All the authors made the decision to submit the manuscript for publication.

Statistical Analysis

Baseline characteristics of patients were assessed using descriptive statistics. For the analysis of the primary end point, steroid-free remission rates at week 16 were compared between the methotrexate and placebo groups by χ^2 test. Secondary end points were compared between groups with the same methodology. Exploratory subgroup analyses were performed in order to investigate the treatment effect within subgroups defined from different characteristics at baseline. This was done by using the χ^2 test or Fisher's exact test. In addition, a logistic regression with an interaction between treatment and subgroup was used to test the homogeneity of relative risks across the subgroups. Subgroups defined by continuous variables were dichotomized according to the median value. Adverse events, severe adverse events, and study discontinuations were described by frequency and percentage and were compared between groups by χ^2 tests or Fisher's exact test.

All analyses were performed on a full intent-to-treat basis; patients withdrawn before week 16 were considered as failures.

Data were analyzed with SAS software, version 9.3 (SAS, Chicago, IL). Statistical significance was considered if $P \leq .05$.

Sample Size

We expected a steroid-free remission rate of 45% with methotrexate and 20% with placebo. We hypothesized that the effect of parenteral methotrexate in steroid-dependent UC was in the same order of magnitude as rates of remission observed in open trials with methotrexate in UC[16]; rate of steroid-free remission observed with azathioprine in steroid-dependent UC[17]; and rate of steroid-free remission observed in CD with parenteral methotrexate.[9] Considering a 2-sided test, a type I error rate of 5%, a statistical power of 80% and an allocation ratio of 1:1, 110 patients were required (PASS 12).

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Table 1. Baseline Characteristics of Patients Included in the METEOR (Controlled, Randomized, Double-Blind, Multicenter Study Comparing Methotrexate vs Placebo in Steroid-Dependent Ulcerative Colitis) Trial

Characteristics	All (n = 111)	Placebo (n = 51)	Methotrexate (n = 60)
Age, y	42 (32-54)	42 (31 -59)	42 (33-54)
Sex	59 (53.2)	25 (49.0)	34 (56.7)
Body weight, *k*	68 (61-78)	65 (56-80)	69 (63-75)
Current smoker	7 (6.4)	2 (4.0)	5 (8.0)
Duration of disease, *y*	4 (1-10)	5 (1-10)	4 (1-10)
Mayo total score	4.0 (2.0-6.0)	4.0 (2.0-6.0)	4.0 (2.0-6.0)
Partial Mayo score	2 (1-4)	3.0 (1.0-4.0)	2.0 (1.0-4.0)
Endoscopy subscore	1 (1-2)	1 (1-2)	1 (1-2)
IBDQ score	158 (130-195)	157 (132-181)	159 (128-193)
Site of disease			
Distal	28 (25.2)	11 (21.6)	17 (28.3)
Left colon	29 (26.1)	12 (23.5)	17 (28.3)
Extensive	54 (48.6)	28 (54.9)	26 (43.4)
Prednisone-equivalent dosage, *mg/d*	25 (15-30)	30 (20-30)	25 (11 -30)
UC drugs received before enrollment			
At least one UC drug	109 (98.2)	50 (98.0)	59 (98.3)
Mesalamine	99 (89.2)	45 (88.2)	54 (90.0)
Thiopurines	65 (58.6)	30 (58.8)	35 (58.3)
Anti-TNF	25 (22.5)	11 (21.6)	14 (23.3)
Cyclosporine	7 (6.3)	4 (7.8)	3 (5.0)
Hemoglobin concentration, *g/dL*	13.5 (12.1-14.5)	13.7 (12.0-14.3)	13.5 (12.1-15.1)
Abnormal hemoglobin	21 (18.9)	9 (17.7)	12 (20.0)
CRP serum level, *mg/L*	4.2 (1.6-9.5)	3.7 (2.0-8.7)	4.2 (1.1-11.0)
Abnormal CRP, >5 mg/L	38 (35.5)	17 (34.0)	21 (36.8)

NOTE. Quantitative variables are expressed as median (range, quartile 1 -quartile 3) and qualitative variables are n (%). CRP, C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire.

Results

Baseline Characteristics and Patient Disposition

Between October 2007 and January 2013, one hundred and twenty patients were evaluated for eligibility; 111 were randomized and included in the analysis. Fifty-one patients were randomized in the placebo arm and 60 were randomized in the methotrexate arm. Patient characteristics are displayed on Table 1. Twenty-six of 51 (51.0%) patients and 20 of 60 (33.3%) patients discontinued the study in the placebo and methotrexate arms, respectively including 13 of 51 (25.5%) and 8 of 60 (13.3%) before week 16, respectively. Reasons for study discontinuation are shown in Supplementary Figure 1.

No patient underwent colectomy during the trial.

Primary and Secondary Outcomes

Steroid-free remission at week 16 was present in 19 of 60 patients assigned to methotrexate (31.7%) and 10 of 51 (19.6%) patients who received placebo (absolute risk difference = 12.1%; 95% confidence interval [CI]: -4.0% to 28.1%; relative risk = 1.62; 95% CI: 0.83 to 3.15; P = .15). Clinical remission without steroids at week 16 was obtained in 25 of 60 patients assigned to methotrexate (41.7%) and 12 of 51 (23.5%) patients who received placebo (absolute risk difference = 18.1% [95% CI: 1.1%-35.2%]; 1.77 [95% CI: 0.99—3.16]; P = .04). Endoscopic healing without steroids at week 16 was obtained in 21 of 60 (35.0%) patients randomized tothe methotrexate arm and 13 of 51 (25.5%) patients randomized to the placebo arm (difference 9.5% [95% CI: -7.5% to 26.5%]; 1.37 [95% CI: 0.77 to 2.46]; P = .28). The other secondary end points were not significant (Figure 1 and Table 2).

Post-Hoc Analyses

Sixty-five percent of the patients who had reached endoscopic healing without steroids at week 16 were in remission without steroids at week 24. By comparison, 21% of the patients who had not reached endoscopic healing without steroids at week 16 were in remission without steroids at week 24 (relative risk = 3.11; 95% CI: 1.89-5.14; P < .0001).

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We compared the individual items of the Mayo clinical subscore between the 2 arms of the study (Table 3). Patients assigned to methotrexate were more likely to have complete absence of rectal bleeding or diarrhea and no steroids at week 16 than those assigned to placebo.

In subgroup analyses, the largest treatment effect was observed in patients with a dosage of corticosteroids <20 mg/d at baseline (success rate 37.9% for the methotrexate arm compared with 13.6% in those assigned to control; Supplementary Table 3). Nevertheless, the interaction test was not significant (P =.18).

We sought an additional indicator of efficacy by measuring the proportions of patients in each group who continued to experience UC activity as an adverse event. There were significantly more patients with continuing UC activity within the placebo arm than in the methotrexate arm (24 of 51 [47.1%] vs 13 of 60 [21.7%], respectively; P = .005). In addition, more patients who received placebo discontinued treatment due to persistent disease activity than patients who received methotrexate (21 of 51 [41.2%] vs 11 of 60 [18.3%], respectively; P < .008).

Safety

Adverse events are displayed in Table 4. Ten patients had severe adverse events, 4 patients (7.8%) were in the placebo arm and 6 (10.0 %) were in the methotrexate arm (P =.75; Supplementary Table 2). Forty patients discontinued the trial because of adverse events, 24 of 51 (47.1%) in the placebo arm and 16 of 60 (26.7%) in the methotrexate arm (P = .03), most of the withdrawals, as noted previously, were due to continuing disease activity. Significantly more patients treated with methotrexate experienced nausea or vomiting than those who received placebo (21.7% vs 3.9% in the placebo arm; P = .006); however, only 2 patients discontinued the trial for this reason.

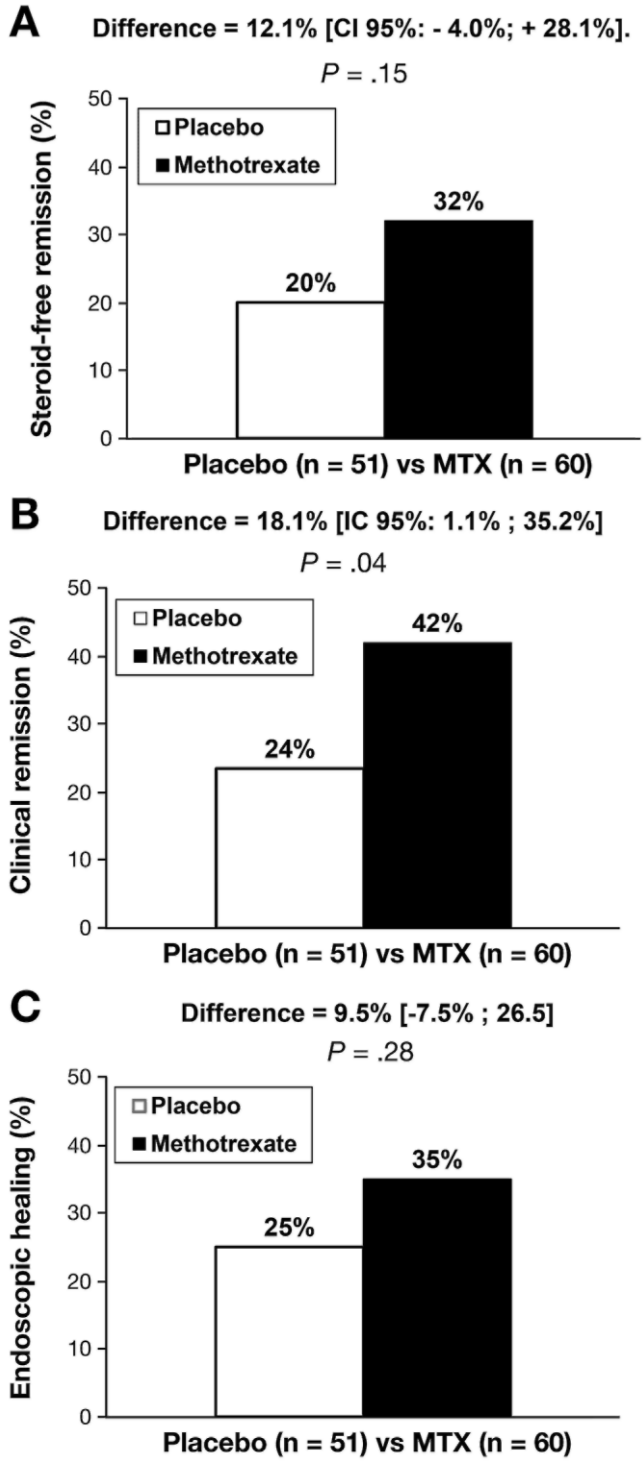
Discussion

This randomized, placebo-controlled, double-blind trial evaluated the efficacy of parenteral methotrexate at a dosage of 25 mg/wk in patients with steroid-dependent UC. Parenteral methotrexate was not superior to placebo based on a composite end point consisting of remission according to all items of the Mayo score and complete steroid withdrawal at week 16. Actually, the observed benefit was below that expected (absolute risk difference of 12% rather than 25%). Methotrexate was, however, superior to placebo for inducing clinical remission without steroids at week 16, a definition based on the 3 clinical items of the Mayo Disease Activity Index. Furthermore, these data suggest that methotrexate may usefully rescue therapy in patients with treatment refractory UC. Indeed, 58% and 22% of the patients, respectively, were refractory or intolerant to thiopurines and anti-TNFs. Prior exposure to these agents did not significantly affect the chances of success or clinical remission. Another relevant indicator of clinical efficacy was also consistent with a benefit of methotrexate. Significantly more patients in the placebo arm experienced continued UC disease activity that required withdrawal from the study.

The strength of the trial is that it is the first study to evaluate an adequate dosage of methotrexate administered parenterally in UC. Several retrospective and prospective open-label studies of methotrexate in UC have been published.[16] Collectively, these studies suggest that 25 mg parenteral methotrexate might be an effective therapy, as in the case for CD.[16] In contrast, low-dose oral methotrexate has been associated with low response rates.[16] The only randomized, placebo-controlled trial of methotrexate performed in UC tested oral methotrexate at a dosage of 12.5 mg weekly[11] No difference in efficacy was demonstrated between methotrexate and placebo. In CD, the bioavailability of oral methotrexate plateaus at approximately 15 mg/wk, and with subcutaneous administration, it increases linearly at higher dosages.[18,19]

Our study had some limitations. First, central reading was not used to score the study endoscopies. This process might have improved the interpretation of this outcome. In recent studies, up to 20%—30% of patients reported to have endoscopically active disease by site readers had inactive disease as judged by central readers.[20] In the present trial, a significantly higher proportion of methotrexate-treated patients reported no rectal bleeding at week 16 compared with patients who received placebo. Given that the absence of rectal bleeding is highly correlated with endoscopic remission,[21] failure to demonstrate a benefit of methotrexate treatment on endoscopic remission may have been due to the poor sensitivity of the site reads. Second, the efficacy of methotrexate as a maintenance therapy in UC was not evaluated. The MERIT-UC (Methotrexate in Induction and Maintenance of Steroid Free Remission in Ulcerative Colitis) study (registered as ClinicalTrials.gov ID NCT01393405) is currently studying the efficacy of parenteral methotrexate as maintenance therapy in UC. Finally, we did not require patients to have endoscopically active disease at entry, and it could be argued that inclusion of endoscopically inactive patients might have reduced the capacity of the trial to detect a difference in the primary outcome measure. However, there was no difference in outcomes (remission or endoscopic remission without steroids at week 16) whether patients had endoscopic activity or not at inclusion (Supplementary Table 4).

Figure 1. Main endpoints of the METEOR trial. (A) Primary end point: steroid-free remission at week 16. (B) Secondary end point: steroid-free clinical remission at week 16. (C) Secondary end point: steroid-free endoscopic healing at week 16.



In this study, severe adverse events were rare and their incidence was similar in both arms. Because low-dose methotrexate has been used for decades in various inflammatory disorders, its safety profile is well characterized.[16] Serious adverse events include liver toxicity, bone marrow suppression, hypersensitivity pneumonitis, serious infection, and teratogenicity. The risk of cancer associated with methotrexate therapy has been assessed in patients with rheumatoid arthritis and most studies have not found an increased risk[22] In comparison, treatment with thio-purines increases the risk of lymphoma and nonmelanoma skin cancer.[3,23-25] Nausea and vomiting were the most common minor adverse events associated with methotrexate therapy.

However, only 2 patients discontinued treatment due to nausea, and most patients' symptoms were controlled or prevented with premedication with antiemetics. The adverse event most frequently reported that led to discontinuation was persistent disease activity, which occurred in a higher proportion of patients in the placebo group.

The results of methotrexate can be compared with those obtained with azathioprine and anti-TNFs. Ardizzone et al[17] randomized 72 patients with steroid-dependent UC between azathioprine and mesalamine. At 6 months, 53% of patients who received azathioprine were in steroid-free remission vs 21% of those who received mesalamine (odds ratio = 4.78; 95% CI: 1.57-14.5). Maté-Jiménez et al[26] randomized 34 patients with UC to 6-mercaptopurine, methotrexate (15 mg weekly), and mesalamine.[26] Steroid-free remission was obtained in 79% of patients who received azathioprine, 58% of patients who received methotrexate, and 25% of patients who received mesalamine ($P < .05$ for azathioprine vs mesalamine; P = NS for methotrexate vs mesalamine and for methotrexate vs azathioprine). Steroid-free remission was a secondary end point of the pivotal trials of anti-TNFs in UC. At week 30, in the ACT-1 and ACT-2 (Active Ulcerative Colitis Trials 1 and 2) trials, 21.5% of the patients on infliximab reached steroid-free remission vs 7.2% with placebo ($P = .007$).[4] In the SUCCESS trial, 24%, 22%, and 40% of the patients who were randomized to azathioprine, infliximab, or both, achieved steroid-free remission at week 16, respectively.[5] In the ULTRA-2 (Ulcerative Colitis Long-Term Remission and Maintenance With Adalimumab 2) trial, approximately 31% of the patients who received adalimumab were off steroids at week 16 vs 16% of patients allocated to placebo.[27] In the PURSUIT (Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment) maintenance trial of golimumab, 34.4% of UC patients treated with golimumab and 20.7% of patients who received placebo reached steroid-free remission at week 54 ($P = .024$).[28] Therefore, anti-TNFs are more efficient than placebo to obtain steroid-free remission. However, it is worth mentioning that steroid-dependent patients were not identified as such in all pivotal trials of anti-TNFs.

In conclusion, our study failed to show that parenteral methotrexate is beneficial for induction of steroid-free remission in UC. However, methotrexate induced clinical remission without steroids at week 16 more frequently than placebo, and was associated with better control of disease-related symptoms. Additional studies are required to define the potential benefit of methotrexate as a maintenance therapy.

Table 2. Other Secondary End Points of the METEOR (Controlled, Randomized, Double-Blind, Multicenter Study Comparing Methotrexate vs Placebo in Steroid-Dependent Ulcerative Colitis) Trial in the Methotrexate and Control Arms

End points	Placebo, n (%)	Methotrexate, n (%)	Absolute risk difference, % (95% CI)	Relative risk (95% CI)	*P* value
Steroid-free remission at wk 24	17 (33.3)	21 (35.0)	1.7 (-16.0 to 19.4)	1.05 (0.62 to 1.76)	.85
Steroid-free remission at wk 16 and 24	8 (15.7)	13 (21.7)	6.0 (-8.5% to 20.4)	1.38 (0,62 to 3,07)	.42
Steroid-free clinical remission at wk 24	18 (35.3)	24 (40.0)	4.7 (-13.3 to 22.8)	1.13 (0.70 to 1.84)	.61
Steroid-free clinical remission at wk 16 and 24	10 (19.6)	16 (26.7)	7.1 (-8.6 to 22.7)	1.36 (0.68 to 2.73)	.38
Steroid-free endoscopic healing at wk 24	17 (33.3)	24 (40.0)	6.7 (-11.3 to 24.6)	1.20 (0.73 to 1.97)	.47
Steroid-free endoscopic healing at wk 16 and 24	9 (17.7)	13 (21.7)	4.0 (-10.8 to 18.8)	1.23 (0.57 to 2.63)	.60
CRP <5 mg/L without steroids at wk 16	11 (21.6)	20 (33.3)	11.8 (-4.7 to 28.2)	1.55 (0.82 to 2.91)	.17
IBDQ ≥ 170 without steroids at wk 16	10 (19.6)	15 (25.0)	5.4 (-10.1 to 20.8)	1.28 (0.63 to 2.59)	.50

CRP, C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire.

Table 3.Success Rates of Individual Items of the Mayo Clinical Subscore in the Methotrexate and Control Arms at Week 16

Items	Placebo, n (%) (n = 51)	Methotrexate, n (%) (n = 60)	Absolute risk difference, % (95% CI)	Relative risk (95% CI)	*P* value
Rectal bleeding score = 0 and no steroids	11 (21.6)	28 (46.7)	25.1 (8.2 to 42.0)	2.16 (1.20 to 3.90)	.006
Stool frequency score = 0 and no steroids	9 (17.7)	22 (36.7)	19.0 (3.0 to 35.1)	2.08 (1.05 to 4.10)	.03
Physician global assessment = 0 and no steroids	9 (17.7)	20 (33.3)	15.7 (-0.2 to 31.6)	1.89 (0.95 to 3.78)	.06

Table 4.Adverse Events Affecting at Least 5% of Patients Receiving Methotrexate

Adverse events	Placebo (n = 51)	Methotrexate (n = 60)
Any AE	37 (72.5)	45 (75)
Serious AEs	4 (7.8)	6 (10)
Discontinued due to AE	24 (47.1)	16 (26.7)
Upper respiratory tract infection	3 (5.9)	8 (13.3)
Nausea or vomiting	2 (3.9)	13 (21.7)
Fatigue	5 (9.8)	9 (15)
Abdominal pain	6 (11.8)	8 (13.3)
Arthralgia	5 (9.8)	7 (11.7)
Diarrhea	1 (2)	4 (6.7)
Headache	3 (5.9)	4 (6.7)
Muscular pain	1 (2)	4 (6.7)
UC activity	24 (47.1)	13 (21.7)
Abnormal liver function tests	1 (2)	4 (6.7)
Injection site reaction	1 (2)	3 (5)
Influenza viral infection	4 (7.8)	4 (6.7)

NOTE. Values are n (%). AE, adverse event.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.10.050.

Algorithm for Methotrexate Dosage Reduction in Case of Serious Toxicity

Leukoneutropenia

In case of leukoneutropenia during the treatment, the following therapeutic attitude will be adopted. If the leukocytes are <3000/mm^3 and/or the neutrophils are <1500/mm^3, the next methotrexate injection will not be performed. A new complete blood count will be performed. If the leukocytes are >3000/mm^3 and/or the neutrophils are >1500/mm^3, the methotrexate will be restarted at a dosage of 20 mg/wk. In case of persistent leukoneutropenia, methotrexate will be stopped.

Abnormal Liver Tests

In case of an unexplained rise of aspartate aminotransferase and/or alanine aminotransferase >2N, the next injection will be suspended. New transaminases analysis will be carried out every week. Once their level reaches the baseline again, methotrexate will be restarted at a dosage of 20 mg/wk. In case of persistent increased transaminase levels, methotrexate will be stopped.

Mucositis, Digestive Intolerance, and Other Abnormalities

In case of mucositis or oral ulcerative lesions, the treatment will have to be stopped. A treatment with folinic acid will be administered (50—100 mg intravenously every 6 hours).

In case of an increased serum creatinine level (>30% compared with day 0 baseline dosage), and confirmed by a second measurement performed with 1-week interval, the treatment will have to be discontinued.

In case of hypersensitivity pneumopathy, the treatment will also have to be discontinued.

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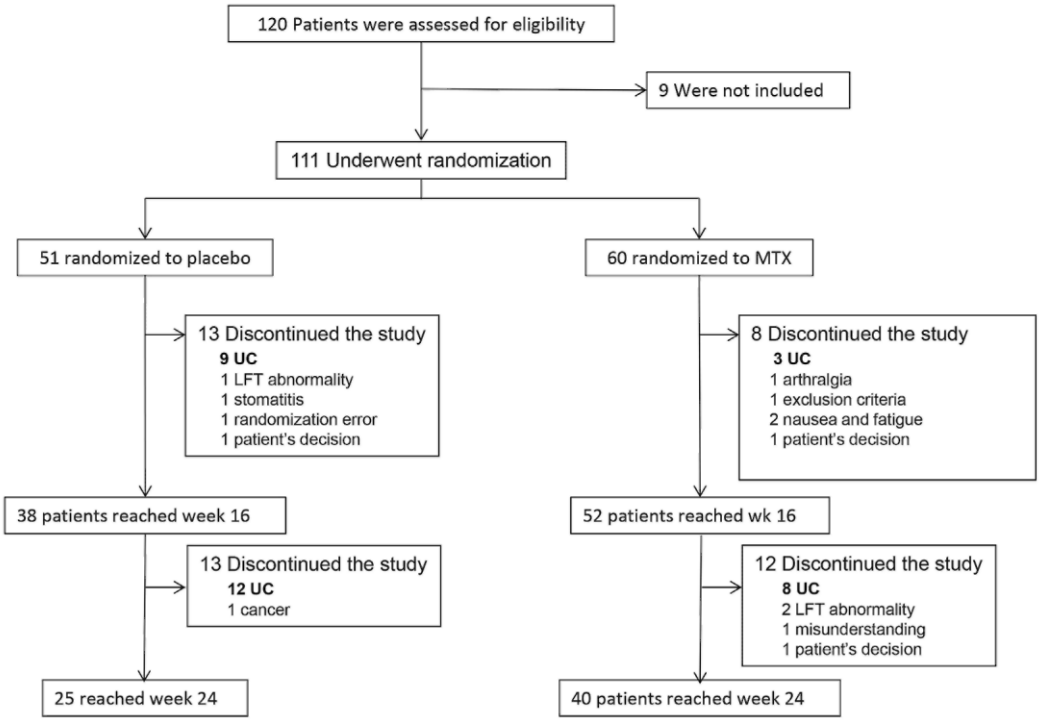
Supplementary Figure 1. Flow diagram of the study.



Supplementary Table 1.Time During Which the Starting Dose of Prednisone or Prednisolone Was Kept Unchanged in the METEOR (Controlled, Randomized, Double-Blind, Multicenter Study Comparing Methotrexate vs Placebo in Steroid Dependent Ulcerative Colitis) Trial

Prednisone dosage at inclusion, *mg/d*	Weeks at the maximum dosage of prednisone
40	4
35	5
30	6
25	7
20	8
15	9
10	10

Supplementary Table 2.Severe Adverse Events in the Placebo and Methotrexate Arm

Adverse events	n
Placebo	
UC activity	2
Atrial fibrillation	1
Cancer relapse	1
Methotrexate	
UC activity	2
Pulmonary embolism	1
Arthralgia	1
Arthralgia, abdominal pain, and tremor	1
Diarrhea	1

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Supplementary Table 3. Subgroup Analyses of the Efficacy of Methotrexate and Placebo in Patients With Steroid-Dependent Ulcerative Colitis

	Placebo, n (%) (n = 51)	Methotrexate, n (%) (n = 60)	Steroid-free remission (methotrexate vs control), RR (95% CI)	*P* value	*P* value interaction
Age					
≤42 y	4/24 (16.7)	8/31 (25.8)	1.55 (0.53-4.54)	.42	.82
>42y	6/27 (22.2)	11/29 (37.9)	1.71 (0.73-3.97)	.2	
Sex					
Male	4/25 (16.0)	11/34 (32.4)	2.02 (0.73-5.61)	.15	.56
Female	6/26 (23.1)	8/26 (30.8)	1.33 (0.54-3.31)	.53	
Duration of disease					
≤4y	6/24 (25.0)	12/33 (36.4)	1.45 (0.64-3.33)	.36	.86
>4y	4/27 (14.8)	7/27 (25.9	1.75 (0.58-5.29)	.31	
Site of disease					
Distal	4/11 (36.4)	5/17 (29.4)	0.81 (0.28-2.37)	1	.33
Left colon	3/12 (25.0)	6/17 (35.3)	1.41 (0.44-4.56)	.69	
Extensive	3/28 (10.7)	8/26 (30.8)	2.87 (0.85-9.68)	.07	
Disease activity					
Inactive disease	4/14 (28.6)	8/18 (44.4)	1.56 (0.59-4.13)	.36	.93
Active disease	6/37 (16.2)	11/42 (26.2)	1.61 (0.66-3.94)	.28	
IS use before enrollment					
No	3/21 (14.3)	9/25 (36.0)	2.52 (0.78-8.12)	.09	.31
Yes	7/30 (23.3)	10/35 (28.6)	1.22 (0.53-2.82)	.63	
Prednisone-equivalent dose, *mg/d*					
≤20	3/22 (13.6)	11/29 (37.9)	2.78 (0.88-8.79)	.054	.18
>20	7/29 (24.1)	8/31 (25.8)	1.07 (0.44-2.57)	.88	
Hemoglobin					
Normal	9/42 (21.4)	15/48 (31.3)	1.46 (0.71-2.98)	.29	.5
Abnormal	1/9 (11.1)	4/12 (33.3)	3 (0.4-22.47)	.34	
C-reactive protein serum level					
Normal	4/33 (12.1)	9/36 (25.0)	2.06 (0.7-6.07)	.17	.47
Abnormal	5/17 (29.4)	7/21 (33.3)	1.13 (0.44-2.94)	.8	

IS, Immunosuppressives; RR, relative risk.

Supplementary Table 4.Subgroup Analysis of the Efficacy of Methotrexate and Placebo in Patients With and Without Endoscopic Activity at Inclusion

	Placebo, n (%) (n = 51)	Methotrexate, n (%) (n = 60)	Steroid-free remission (methotrexate vs control), RR (95% CI)	*P* value	*P* value interaction
Endoscopic Mayo					
Inactive disease	7/27 (25.9)	14/34 (41.2)	1.59 (0.75-3.37)	.21	.85
Active disease	3/24 (12.5)	5/26 (19.2)	1.54 (0.41-5.76)	.70	
			Steroid-free endoscopic healing (methotrexate vs control), RR (95% CI)		
Endoscopic Mayo					
Inactive disease	8/27 (29.6)	16/34 (47.1)	1.59 (0.80-2.14)	.17	.34
Active disease	5/24 (20.8)	5/26 (19.2)	0.92 (0.30-2.80)	1	

RR, relative risk.

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Author names in bold designate shared co-first authorship.

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Conflicts of interest

These authors disclose the following: Franck Carbonnel: advisory board for Genentech, Otsuka, Vifor, and speaker for Hospira. Jean Frédéric Colombel: served as consultant or advisory board member for Abbvie, ABScience, Amgen, Bristol Meyers Squibb, Celltrion, Danone, Ferring, Genentech, Giuliani SPA, Given Imaging, Janssen, Immune Pharmaceuticals, Medimmune, Merck & Co., Millenium Pharmaceuticals Inc., Neovacs, Nutrition Science Partners Ltd., Pfizer Inc., Prometheus Laboratories, Protagonist, Receptos, Sanofi, Schering Plough Corporation, Second Genome, Shire, Takeda, Teva Pharmaceuticals, Tigenix, UCB Pharma, Vertex, Dr. August Wolff GmbH & Co.; and has served as speaker for Abbvie, Falk, Ferring, Janssen, Merck & Co., Nutrition Science Partners Ltd., and Takeda. Jérome Filippi: Abbvie, Astellas Pharma Ferring, Given Imaging, Jansen, MSD, and Takeda. Konstantinos H. Katsanos: served as speaker for MSD and Abbvie. Laurent Peyrin-Biroulet: Consulting fees from Merck, Abbott, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Shire, Therakos, Pharmacosmos, Pilège, BMS, UCB-Pharma, Hospira, Celltrion, Takeda, Biogaran, Boerhinger-lngelheim, Lilly, Pfizer, HAC-Pharma; lecture fees from Merck, Abbott, Takeda, Janssen, Ferring, Norgine, Tillots, Vifor, Therakos, and HAC-pharma. Matthieu Allez received honoraria from Novo Nordisk, MSD, Abbvie, Ferring, Genentech, TxCell, Janssen, Pfizer, GSK, Hospira, and UCB. Maria Nachury: lecture fees from Abbvie, MSD, and Ferring. Gottfried Novacek: Honoraria from AbbVie, MSD, Ferring, Merck, Astro-Pharma, and Takeda. Silvio Danese: served as speaker, consultant, and advisory board member for Abbvie, Astra Zeneca, MSD, Novo Nordisk, Takeda Millennium, Salix Pharmaceuticals, and Pfizer. Fabrizio Bossa: MSD, Abbvie, and Takeda. Jacques Moreau: MSD, Abbvie, Norgine, Ferring, and Vifor. Gilles Bommelaer: Abbvie (lecture fees). Xavier Roblin: Abbvie, MSD, HAC Pharma, Ferring, Takeda, and Theradiag. Mathurin Fumery: lecture fees: Abbvie, MSD, and Ferring. Yoram Bouhnik: Consultancies: BMS, Shire, Sanofi, Norgine Pharma, MSD, Abbvie, Astra Zeneca, Roche, Takeda Millenium; stock ownership in Inception IBD, San Diego, CA; honoraria from BMS, MSD, Abbvie, Teva, Ferring, Vifor Pharma, HAC, Mayoli-Spindler; and paid expert testimony for Abbvie; travel grants: Abbvie, MSD, Ferring, Takeda. Philippe Seksik: consulting fees from Abbvie, Merck-MSD, and Biocodex; grants from Biocodex; sponsored travel from Merck-MSD and Takeda. Walter Reinisch: served as a speaker for Abbott Laboratories, Abbvie, Aesca, Aptalis, Centocor, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka, PDL, Pharmacosmos, Schering-Plough, Shire, Takeda, Therakos, Vifor, and Yakult; as a consultant for Abbott Laboratories, Abbvie, Aesca, Amgen, AM Pharma, Astellas, Astra Zeneca, Avaxia, Bioclinica, Biogen IDEC,

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