Retrospective Cohort Study of Methotrexate Use in the Treatment of Pediatric Crohn's Disease

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Background: Methotrexate (MTX) use as an alternative to thiopurines in the treatment of Crohn's disease (CD) in children is increasing. This study was undertaken to assess safety and efficacy of MTX in children with CD.

Methods: Patients treated with MTX with a minimum of 1-year follow-up were identified in the Pediatric IBD Collaborative Research Group Registry, a prospective inception cohort study started in 2002. The clinical efficacy and safety of MTX were analyzed retrospectively.

Results: Two hundred ninety patients treated with MTX were identified. One hundred seventy-two patients received at least 3 months of MTX without thiopurine or biologicals and had ≥1 year of follow-up. Eighty-one of 172 patients (47%) received MTX as first immunomodulator (IMM), of which 22 (27%) achieved ≥12 months of sustained clinical remission without surgery, thiopurine, biologicals, or corticosteroids. Those receiving MTX as second IMM achieved similar remission rate (35%, P = not significant). Fourteen percent received MTX as first IMM in 2002 and 60% in 2010 ($P = 0.005$). Disease location did not affect outcomes. MTX doses were equivalent in both groups. Fifteen percent of patients developed an alanine aminotransferase >60 international units/liter and 12% developed a white blood cell <4000 cells per microliter while on MTX. Only 4% of these discontinued MTX completely. A small group of 6 centers, which contributed only about one-third of patients with CD in the registry, contributed nearly two-thirds of the patients receiving MTX ($P < 0.001$).

Conclusions: MTX use as first choice IMM is increasing in pediatric CD. MTX provided sustained clinical remission in nearly one-third of patients with minimal toxicity. There is large center-to-center variability in its use.

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Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract with a large spectrum of severity, which accounts for more than 60% of all pediatric inflammatory bowel disease (IBD).[1] The thiopurines (TPs), azathioprine and 6-mercaptopurine, are immunomodulatory (IMM) agents that have been shown to be effective in maintaining remission in pediatric patients with moderate-to-severe CD.[2] TPs have been the first choice agents for maintenance of clinical remission in pediatric CD, with methotrexate (MTX) recommended for patients who fail TP or experience drug intolerance.[3]

In 2006, the Food and Drug Administration (FDA)'s Adverse Event Reporting System identified 8 cases of hepatosplenic T-cell lymphoma in young male patients treated concomitantly with TP and infliximab (IFX).[4–6] Many pediatric gastroenterologists became more uncomfortable with TP usage, particularly in conjunction with IFX. MTX seems to carry a lower risk of hepatosplenic T-cell lymphoma than TP.[7] A number of studies have shown MTX to be an effective IMM in pediatric patients who have failed TP.[8–11] There have been no reported pediatric studies of MTX use as first-line IMM. The goals of this study were to assess: (1) the patterns of use of MTX by different centers over time, (2) the efficacy of MTX in maintaining clinical remission as a first-line IMM, and (3) the toxicity of MTX in the treatment of pediatric CD.

MATERIALS AND METHODS

The Pediatric IBD Collaborative Research Group Registry (PICR) is a prospective multi-center observational study that was initiated in 2002. Patients may be enrolled who are younger than 16 years and within 30 days of diagnosis with IBD. Patients' demographic, disease, and medication information are collected at diagnosis, 30 days after diagnosis, and quarterly thereafter. Medical management of the patients is determined by the treating physicians' customary practice and not by a set protocol.

The registry was queried for patients with CD, who had received MTX at any point during their therapy and who had at least 1 year of follow-up in the PICR. Data were retrospectively reviewed from inception of the PICR through and including the year 2010.

We analyzed the effectiveness of use of MTX as IMM therapy, the duration of clinical remission, and trends in use. Sustained clinical remission was defined as a physician global assessment score of 1 (in this scoring system, disease activity is designated as: 1 = inactive, 2 = mild, 3 = moderate, and 4 = severe) without concomitant use of corticosteroids, TP, biologicals, or surgery for at least 1 year. Duration of remission was determined by the number of quarters (data are submitted to the registry every 3 mo or quarter of a year) of remission until the patient relapsed (physician global assessment > 1), MTX was stopped, adjuvant therapy initiated, or the patient was lost to follow-up. The last observation was carried forward when data were missing. The trends in its use were evaluated by stratifying the patients by MTX as first or second IMM, sex of the patient, and year of initiation of MTX from 2002 to 2010. We also analyzed the frequency of elevated alanine aminotransferase (ALT) (>60 international units/liter [IU/L]) and leucopenia (total white blood cell count <4000 cells/microliter) while on MTX.

Statistical Analysis

A P-value of 0.05 was used as the threshold of significance, with anything less being deemed statistically significant. Kaplan–Meier analysis was used to assess the durability and duration of sustained clinical remission once achieved. Chi-square and exact tests were used for comparison of 2-dimensional categorical variables. The Mantel–Haenszel chi-square test was used for the small sample 3-dimensional categorical variables.

Ethical Considerations

Each institution's participation in the PICR was approved by their own Institutional Review Board. Written and informed consent were obtained from all legal guardians before enrollment of the patient, written assent was obtained from the patients themselves, and patients were re-consented to continue after age 18 years. All patient data were de-identified. All research queries are reviewed and approved by the steering committee of the PICR.

RESULTS

Of the 1333 patients identified who were enrolled in the PICR between 2002 and 2010, 290 patients (22%) from 19 centers had been treated with MTX and had at least 1 year of follow-up; 117 of 290 patients (40%) received it as their first IMM. When use by center was analyzed, 180 of 290 MTX-treated patients (62%) were cared for at a subgroup of 6 centers. These 6 centers only contributed 469 of 1333 patients with CD (35%) in the PICR. Only 110 of the 864 patients with CD (13%) enrolled by the remaining centers were treated with MTX. This difference in MTX use is significant ($P < 0.001$).

Of the 290 patients with CD who had been treated with MTX, 172 had at least 3 months of MTX without concomitant TP or biological therapy. This was the group analyzed for effectiveness of MTX treatment.

Nearly one-third (54/172) of patients achieved at least 12 months of clinical remission without surgery, TP, biologicals, or corticosteroids. More than three-fourths of these patients went on to have an additional year of clinical remission. Figure 1 is a Kaplan–Meier plot of the duration of MTX-induced clinical remission. The timing of MTX usage was assessed. Eighty-one of 172 patients (47%) received MTX as their first IMM. Twenty-two of the 81 patients (27%) achieved at least 12 months (range, 12–63 mo) of clinical remission. A similar fraction of those receiving MTX as second-line IMM (32/91 [35%], P = not significant) achieved clinical remission (duration, 12–48 mo). Fifty percent of all males and 41% of all females had MTX as first IMM (P = not significant). For the patients who received MTX as second-line IMM, reason for TP failure (e.g., lack of response, suboptimal therapy, or drug intolerance) cannot be determined from the registry.

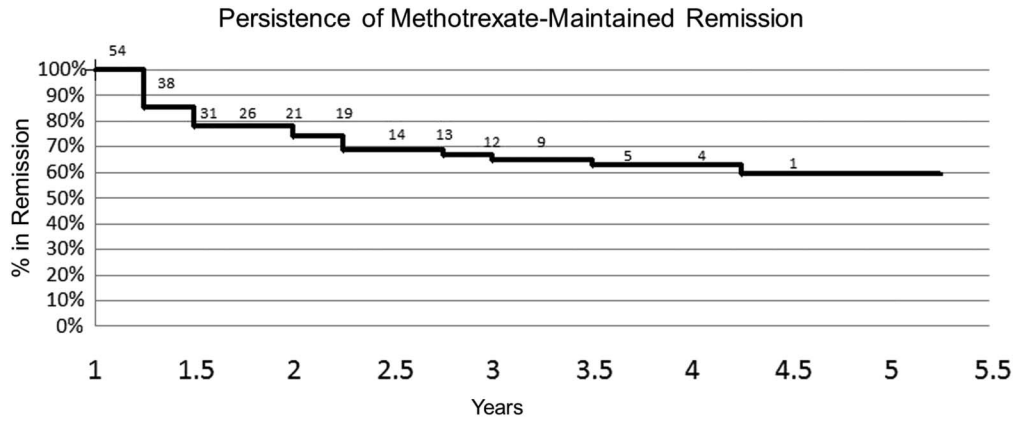

FIGURE 1. Kaplan–Meier graph demonstrating the percent of patients who had additional sustained clinical remission beyond 1 year. The number above the line shows the number of patients being represented at that point in time, population censored for patients lost to follow-up.

There was no difference in disease distribution between those patients who achieved sustained clinical remission and those who did not. The mean MTX dose was 12.7 mg/m^2 in those who achieved sustained remission and 12.4 mg/m^2 in those who did not ($P = 0.68$). Route of MTX administration is not a field in the PICR and could not therefore be analyzed.

Twenty-six of the 172 patients (15%) in the studied subgroup developed an ALT greater than 60 IU/L, and 21 of 172 patients (12%) developed leucopenia (total white blood cell count <4000 cells/microliter) while on MTX therapy. Seven of the 26 patients (27%) who had an ALT greater than 60 IU/L had a dose reduction in the quarter following the elevation and only 4 (15.4%) discontinued MTX therapy completely after the elevation. Five of the 21 patients (24%) who experienced leucopenia had a dose reduction in the quarter following the leucopenia and only 3 (14.3%) patients discontinued MTX therapy completely after experiencing leucopenia. The average dose used by patients who experienced elevated ALT during the time of the laboratory abnormality was 11.4 mg/m^2. The average dose used by patients who experienced leucopenia during the time of the laboratory abnormality was 10.3 mg/m^2. These doses are lower than the average dose used in those who experienced sustained clinical remission. Other reported adverse reactions included rash, abdominal pain, shortness of breath, nausea, vomiting, fatigue, and alopecia. These reactions occurred in 10 of the study patients. Five of those patients continued on the medication despite the ill effects, 2 continued on MTX at a lower dose, and 3 discontinued the medication completely. Of all the study patients, only 8.1% had an adverse reaction that resulted in termination of therapy.

When trends of IMM use by year were examined, the fraction receiving MTX as first choice IMM was found to increase with time. The fraction of MTX as first choice IMM was 14% in 2002 and was 60% by 2010 ($P = 0.005$). There was no gender difference in this trend (Fig. 2).

Further examination of the data revealed that some centers only contributed patients before and others only after the FDA warning in 2006. The 6 centers that enrolled the largest number of patients both before and after the FDA warning were examined to see if they shared that trend. (These 6 centers also happened to be the centers that contributed the largest number of patients treated with MTX.) MTX use as first IMM in these centers before and after the FDA warning in 2006 also followed the trend of a significant increase in frequency of MTX use as a first choice IMM in patients diagnosed after 2006 ($P < 0.001$).

DISCUSSION

This is the first study of MTX use as initial IMM in pediatric CD, and it is the largest pediatric study of the effectiveness of MTX in CD. There have been a number of studies of MTX after TP failure or adverse event.[8–11] The largest of those studies involved less than half as many patients as the current study.[8] The studies differed somewhat in their definitions of clinical remission and inclusion or exclusion of IFX-treated patients. Three of these studies defined clinical remission as steroid-free, IFX-free with a clinical activity score of remission (1 used Harvey Bradshaw index, 1 used physician global assessment, and 1 used PCDAI).[8–10] Their 12-month clinical remission rates

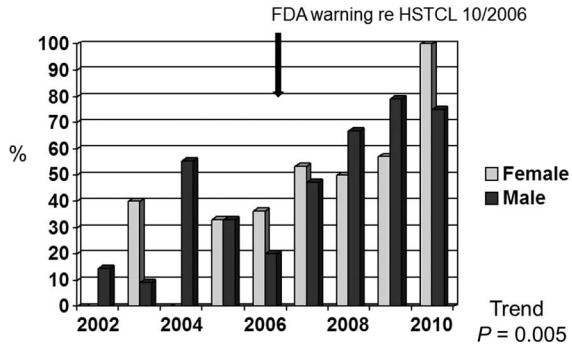

FIGURE 2. Bar graph of the frequency of MTX use as a first-line IMM over time by sex. Arrow on the graph depicts the point in time the FDA warning was released. There is no difference in trends when comparing males to females. There is an increase in percent of patients started on MTX as first IMM when comparing 2002 to 2010 ($P = 0.005$).

ranged from 25% to 42%. One defined remission as Harvey–Bradshaw index of ≤4 with "complete withdrawal of corticosteroids and/or complete fistula closure."[11] The same study did not comment directly on IFX.[11] The 12-month clinical remission rate for that study was 46%. One study included patients who had previously received IFX and there was no difference in MTX response between patients who had or had not previously received IFX.[8] Two studies provided follow-up data to 2 years, and approximately 60% of patients who were in remission at 1 year were still in remission at 2 years.[8,10] The rate of stopping MTX for adverse events ranged from 10% to 18% in the 4 studies. Overall, those findings are similar to the current report.

A Cochrane review of MTX use in CD indicated that parenteral MTX was more effective than lower dose oral MTX but acknowledged that the number of studied patients was small.[12] The large majority of patients reported in the above-mentioned pediatric studies were treated with MTX by injection. The study by Turner et al[10] found that cumulative steroid dosage on MTX was lower in the parenteral group than the enteral group. In a comparison of bioavailability of oral and parenteral MTX in pediatric patients with IBD, Stephens et al[13] found that oral bioavailability tended to be less than parenteral, but it did not reach statistical significance. Unfortunately, route of administration is not a field in the registry used for this study and that could not be analyzed.

The current study indicates that MTX is being used with increasing frequency by pediatric gastroenterologists as their first choice IMM to treat CD. There are no head-to-head comparisons of the efficacy of MTX with the efficacy of TP in treating CD. The pediatric data suggest that TPs are effective for maintaining remission in CD. The steroid-free remission rate in a placebo-controlled prospective study of TP in newly diagnosed pediatric patients with moderate-to-severe CD was approximately 90%.[2] A retrospective study using patients from the current registry with moderate-to-severe CD found a 47% steroid- and IFX-free remission rate at 1 year.[14] There was no difference in remission rates between patients who were started on TP within 3 months of diagnosis and patients started between 3 and 12 months postdiagnosis. A more recent retrospective pediatric study from France reported a steroid, IFX, and surgery-free remission rate of 46% at 1 year.[15] Recent studies in adults (one double-blinded and the other open-label) did not demonstrate efficacy of TP in maintenance of remission at 1 year[16,17] Unlike the Markowitz study, which enrolled patients with moderate-to-severe disease activity, neither of these had disease activity as an entry criterion.[2] The double-blinded study enrolled patients newly diagnosed with CD on corticosteroid therapy, without regard to disease activity at the time of screening.[16] The open-label study enrolled patients with 2 of 3 risk factors for disabling disease: age older than 40 years, active perianal disease, and use of corticosteroids within 3 months of diagnosis.[17] Other recent adult studies have indicated that withdrawal of TP from patients with CD in remission is associated with a high rate of relapse.[18,19]

Although it has been suggested that there is a lower risk of malignancy with MTX in comparison with TP therapy, there are no head-to-head comparisons. Reviews of lymphoma risk in the rheumatoid arthritis population have suggested that MTX is only associated with a minimal (1.7× with 95% confidence interval, 0.9–3.2) increased incidence of lymphoma. Similar reviews in the IBD population have suggested that TPs have a increased incidence of lymphoma (4.2× with 95% confidence interval, 2.07–7.51).[20,21] Although these numbers look to be very different, they were generated using different populations and the 95% confidence intervals do overlap. In addition, these studies were performed in adults in whom the risk of malignancy increases with age. The incidence is likely to be lower in pediatric patients, but it seems likely that the relative risk of lymphoma is increased in pediatric patients by these agents. The data do not allow a conclusion that MTX has a lower risk of lymphoma than TP.

Hepatosplenic T-cell lymphoma has, however, been strongly associated with TP and not with MTX.[7,21] It is attractive to speculate that this difference between the 2 agents is driving the shift in behavior of prescribing physicians after 2006. The large center-to-center variability in use of MTX may also reflect local familiarity with the drug.

There was no significant difference in efficacy of MTX in patients using it as a first IMM when compared with those who are using it as a second IMM after failing TP therapy. That would suggest that responsiveness to MTX and response to TPs are independent patient attributes. If responsiveness to both MTX and TP reflected the same process, then responders to either MTX or TP would be selected out by the first IMM, reducing the number of potential responders in the second group. One might then expect a larger fraction of remission in patients treated with MTX as first IMM than in patients treated as second IMM. However, if patients' response to IMM was an "either/or" phenomenon, either to MTX or to TPs, then TP responders would be selected out when TP are used first, and the second group would be enriched in MTX responders. One might then expect a larger fraction to respond when MTX is used as second IMM. Although the current study does not allow distinction between TP therapeutic failure and drug intolerance, the study by Turner et al[10] found no difference between these groups in response to MTX.[10]

Heptotoxicity and bone marrow suppression have both been seen with MTX along with rash, abdominal pain, shortness of breath, nausea, vomiting, fatigue, and alopecia. The laboratory data reviewed in the current study suggested that the incidence of these events was low, they were uncommon limitations to the use of MTX, and as found by Turner et al,[10] seem to be independent of the dose.

In conclusion, MTX is being used with increasing frequency by pediatric gastroenterologists as their first choice IMM in the treatment of pediatric CD. There is large center-to-center variability in its use. MTX provided clinical remission without surgery, steroids, TPs, or biologicals for at least 1 year in nearly one-third of patients with a low incidence of toxicity.

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