ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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The Current Role of Methotrexate in Patients With Inflammatory Bowel Disease

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G&H What is the mechanism of action of methotrexate?

JR Methotrexate has been used for a long time as a cancer treatment. When high doses are used, methotrexate interferes with folate metabolism and, therefore, with rapidly dividing cells, resulting in decreased cell proliferation. However, when it is used in autoinflammatory diseases and immune-mediated diseases such as inflammatory bowel disease (IBD), methotrexate is given at lower doses that offer different pharmacologic effects. We know that the drug is immunosuppressive and that it has been shown to increase apoptosis (ie, early programmed cell death) in T cells. It is also rapidly incorporated intracellularly and interferes with adenosine concentrations at the cellular level, affecting elaboration of cytokines and proinflammatory mediators. Therefore, low-dose methotrexate likely has a multimodality effect and should be considered as a nontargeted, nonspecific, anti-inflammatory or immune-modulating agent.

G&H What research has been conducted on the use of methotrexate in the induction of remission in Crohn's disease?

JR In the mid-1990s, the pinnacle multicenter study on this issue was conducted by the North American Crohn's Disease Study Group led by Dr Brian G. Feagan. The study showed that 25 mg of intramuscular methotrexate once a week was effective to induce clinical remission in corticosteroid-dependent adult Crohn's disease patients. The number needed to treat was 5, so the drug was not highly efficacious, although it was certainly statistically better than placebo. Around the same time, a multicenter French study had very similar results, and a Cochrane review found that methotrexate is an effective agent for the induction of remission in adult Crohn's disease.

G&H How effective has methotrexate been shown to be in terms of maintenance of remission in Crohn's disease?

JR The North American Crohn's Disease Study Group also performed a double-blind, placebo-controlled maintenance study in which the 25-mg, once-weekly, intramuscular induction dose was lowered to 15 mg intramuscular once weekly. Methotrexate was found to be superior to placebo for the maintenance of clinical remission in adult Crohn's disease. In addition, several small head-to-head trials have shown that methotrexate and thiopurines, the other class of drugs commonly used as immunomodulators for the treatment of IBD, essentially have the same efficacy for maintenance of remission. Overall, both adult and pediatric studies have shown that these immunosuppressive medications are likely to maintain long-term clinical remission in approximately one-third of patients who have Crohn's disease.

G&H Does using methotrexate in combination with anti–tumor necrosis factor agents improve outcomes in Crohn's disease patients?

JR An important early signal for methotrexate being combined with anti–tumor necrosis factor (TNF) therapy came from the COMMIT trial, which was also led by Dr Feagan. This trial is sometimes referred to as the SONIC trial of methotrexate. The SONIC trial famously compared infliximab monotherapy to thiopurines alone or in combination with infliximab, while the COMMIT trial compared infliximab with and without methotrexate. It is important to note the differences in study design between the COMMIT and SONIC trials. Notably, the COMMIT trial actually compared double vs triple therapy because all of the patients had recently been started on corticosteroids in addition to being randomized to infliximab with or without methotrexate. While the COMMIT trial did not show a clinical difference between the 2 study arms, it is notable that there were significantly higher infliximab levels and lower rates of antibodies to infliximab in patients who received methotrexate. Thus, a 1-year trial may not have been long enough to see a clinical difference between the 2 arms, especially because the average corticosteroid dose going into the study was 22 mg, which may have had a tail effect that diminished the clinical impact of adding methotrexate.

In pediatric Crohn's disease, a retrospective study conducted by the Pediatric Inflammatory Bowel Disease Collaborative Research Group, a multicenter North American collaborative, showed that continuing the use of methotrexate had a significant clinical impact. This study, which was led by Dr Victoria Grossi and Dr Jeffrey S. Hyams, showed that pediatric Crohn's disease patients who continued on immunomodulators, including methotrexate, beyond 6 months were more likely to stay on infliximab and to have clinical response. Thus, we have good evidence that methotrexate affects infliximab clearance as well as decreases antibodies to infliximab.

G&H What has research found regarding the use of methotrexate in the induction of remission in ulcerative colitis?

JR The first prospective, randomized study on this issue was the METEOR trial, which was a multicenter French study led by Dr Franck Carbonnel that looked at the induction of remission in corticosteroid-dependent adult ulcerative colitis. The primary endpoint was corticosteroid-free endoscopic remission. The researchers found no difference between methotrexate and placebo at 16 weeks. However, there were numerous secondary endpoints, including symptomatic improvement, and the study did show statistically significant clinical improvement on methotrexate. Thus, we learned from this trial what we have learned from other trials in IBD—that building in a treat-to-target endoscopic endpoint is important. Just looking at symptoms is not enough. Perhaps calprotectin or other surrogate markers can be used as well.

G&H Has there been any research on using this drug to maintain remission in ulcerative colitis patients?

JR The multicenter MERIT-UC trial, led by Dr Hans Herfarth, investigated whether methotrexate was effective at maintaining corticosteroid-free response or remission in moderate to severe adult ulcerative colitis. This impressive investigator-initiated, 48-week, double-blind, placebo-controlled trial demonstrated that methotrexate performed both numerically and statistically inferior to placebo at preventing clinical relapse. Taken together, the METEOR and MERIT-UC studies have demonstrated a lack of efficacy for methotrexate in the treatment of adult ulcerative colitis.

G&H What other research has been conducted on the use of methotrexate in pediatric IBD?

JR There have only been small retrospective case series in pediatric ulcerative colitis, and, not surprisingly, the use of methotrexate for this indication has not been endorsed by evidence-based treatment guidelines. There are more robust data available supporting the use of methotrexate in pediatric Crohn's disease. Dr David Mack led the first study that showed a corticosteroid-sparing effect with methotrexate in pediatric Crohn's disease. Dr Dan Turner led a multicenter retrospective study that showed efficacy out to a year and reported impressive growth data. One of the most important efficacy measures of a drug in pediatric Crohn's disease is whether it facilitates normal childhood statural growth, and methotrexate did in this study. A recent systematic review and meta-analysis from the University of Chicago and Mount Sinai showed that approximately 50% of pediatric patients experienced induction of clinical remission and approximately one-third stayed in clinical remission at 1 year on methotrexate monotherapy.

G&H Has there been any research comparing different routes of administration or different dosages?

JR One of the most important take-home messages is that every study that has compared subcutaneous and intramuscular administration has shown that they are about

the same in terms of efficacy. In addition, patients find that subcutaneous administration hurts less than intramuscular, so if health care providers prescribe parenteral administration, they should recommend a subcutaneous route. The bioavailability of parenteral methotrexate has been shown to be superior to oral, especially when going above doses of 15 mg. Thus, induction doses are best absorbed parenterally. If an even lower dose is being used, such as with adult dosing of 15 mg once a week for maintenance monotherapy or 12.5 mg once a week for combination therapy with an anti-TNF agent, oral administration is likely adequate.

G&H What are the most common side effects associated with methotrexate?

JR Far and away, the most common side effects are gastrointestinal, especially nausea. Even anticipatory nausea can occur. I have had patients who became nauseated as soon as they took out their pill bottle or opened an alcohol prep pad to get ready for their injection. Studies have shown that antiemetics (eg, ondansetron) prevent such nausea, so I always recommend their use a half hour before the methotrexate dose, especially for the first 4 to 8 weeks of therapy. Many providers also give a follow-up antiemetic the day after the methotrexate dose. Split dosing of methotrexate—giving half of the dose in the morning and half in the evening—also can help with nausea. It is critical to remind patients that even with split dosing, methotrexate is still taken only 1 day a week.

Supplemental folic acid should be prescribed when giving methotrexate because the drug can cause folate deficiency, which will enhance the side effects, especially nausea and bone marrow suppression. Although I have yet to see it actually occur, the possibility of pneumonitis should be discussed; patients should tell their health care provider if they develop a cough and/or fever. Providers may be concerned about the liver toxicity of methotrexate. However, with careful monitoring and patient selection, liver toxicity is not nearly as common with the lower doses used for IBD as the higher doses used for cancer chemotherapy. Such careful patient selection means not giving the drug to patients with known liver disease, diabetics, obese patients, and alcohol abusers.

Finally, as with any immunosuppressive, the risk of cancer and lymphoma should be considered. Part of the renewed interest in methotrexate is the recognition that rare cancers such as hepatosplenic T-cell lymphoma (HSTCL) have been associated with thiopurines, especially in younger patients, and the relative risk for such events seems to be much lower with methotrexate. However, the real rate of cancer is still low with thiopurines, and it is important to keep this in mind because thiopurines have been used much more extensively and, therefore, rare side effects would be seen more often. It is not yet clear whether methotrexate is truly safer or whether it has not been used enough to see such rare side effects.

G&H Should methotrexate be avoided in any other patients?

JR Most importantly, methotrexate should not be given to women who are breastfeeding, pregnant, or contemplating conception. In fact, it is usually recommended that women stop methotrexate at least 3 months before trying to become pregnant. These precautions were implemented because methotrexate is associated with higher rates of spontaneous abortion and fetal malformation. For a long time, it was thought that adverse fetal outcomes would also occur if the drug was taken by men who were trying to have a baby with their partner, but that has not been supported by more recent data.

Methotrexate should also be avoided in patients with known kidney disease because the drug is renally excreted.

G&H How should patients be monitored when receiving methotrexate?

JR Because of the potential liver and bone marrow effects, it is recommended that patients on methotrexate have their blood tested at baseline and at weeks 2, 4, and 8; subsequently, doctors should look at complete blood counts, liver chemistries, albumin, and kidney function every 3 months.

An interesting question is whether transient elastography should be part of the monitoring process to noninvasively assess a patient's liver, especially when he or she stays on methotrexate for many years. There are studies currently underway looking at this issue. Liver biopsy is not recommended because the risk-benefit ratio is not favorable due to the rarity of seeing liver fibrosis without a change in liver chemistries with this drug.

G&H Where does this drug currently fit in the IBD treatment armamentarium?

JR There are several clinical scenarios for the use of methotrexate in IBD. In an era of cost containment, it is worthwhile to remember that methotrexate is exceedingly less expensive than other treatment options such as biologic therapy. The onset of action of methotrexate can be a little slower, so if the drug is going to be used for induction in more symptomatic patients, it may be wise to include a course of corticosteroids as a bridge to methotrexate maintenance therapy. This is an approach

that I have used effectively, especially in patients with mild to moderate, noncomplicated, purely inflammatory cases of Crohn's disease. As in all IBD patients, ongoing disease monitoring includes clinical assessment as well as reaching treat-to-target measures of bowel healing. If these goals are not achieved, an anti-TNF agent can then be added in combination with methotrexate, or therapy can be changed to a biologic with a different mechanism of action. With regard to anti-TNF combination therapy, it remains to be seen whether that strategy is better than just anti-TNF monotherapy optimized with therapeutic drug monitoring. This will be an ongoing debate until more data are available.

G&H How common is the use of methotrexate at the current time?

JR It is being used, but I do not think nearly as much as thiopurines for adult IBD. Pediatric gastroenterologists in the United States have moved away from thiopurine therapy significantly due to concerns over HSTCL. Perhaps methotrexate's most common use currently is as a concomitant immunomodulator with anti-TNF therapy.

G&H Do you foresee methotrexate continuing to have a role in IBD management in the future?

JR I think so, although there are a number of new agents in the pipeline, including small molecules and other biologics. The role of concomitant immunomodulators is well established in anti-TNF therapy. The role of combination therapy is less clear for biologics that have different mechanisms of action.

G&H What are the next steps in research in this area?

JR In this era of therapeutic drug monitoring, it may seem surprising that serum levels of methotrexate are not being measured. However, such levels are not clinically informative. There is conflicting literature on the utility of measuring levels of methotrexate polyglutamates, products that are formed when methotrexate is brought intracellularly. It remains to be seen whether monitoring methotrexate polyglutamate levels is clinically helpful in managing IBD, as it would be useful to have a drug monitoring test for methotrexate.

In addition, we need to better answer the question of subcutaneous vs oral administration in both induction and maintenance as well as the question of whether methotrexate in combination with anti-TNF therapy is superior to optimized anti-TNF monotherapy. Finally, we have solid data on methotrexate therapy and clinical improvement in both adult and pediatric Crohn's disease, but we need more robust evidence that methotrexate monotherapy provides bowel healing and changes the natural history of the disease.

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Suggested Reading

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