Methotrexate in IBD: The Return of the Prodigal Son

Twenty years ago, Brian Feagan and colleagues proved the efficacy of parenteral methotrexate [MTX; 25 mg per week] as an induction therapy in steroid-dependent Crohn’s disease [CD]. Since then, the efficacy of MTX has been somewhat eclipsed by the compelling advent of biologics. However, safety and cost of CD therapies remain key issues. Biologics are cost-prohibitive and have a strong impact on healthcare expenditures. In this context, there is a need for alternative, safe and inexpensive drugs in CD as well as in ulcerative colitis [UC]. In these respects, MTX is competitive.

MTX has been used for decades in the treatment of Wegener’s disease, psoriasis, and rheumatoid arthritis. Its safety profile is well known. Side effects of MTX include nausea, vomiting, fatigue, diarrhea, leukopenia, liver fibrosis, hypersensitivity pneumonitis, and teratogenicity. Oral folic acid [5 mg per week] can reduce the severity of side effects, particularly leukopenia and gastrointestinal symptoms. Yet, it is fair to say that many patients have nausea and fatigue, even after the maintenance dose has been reduced and split. Nonetheless, severe side effects are rare. The risk of cancer associated with methotrexate therapy has been assessed in patients with rheumatoid arthritis [RA] and most studies have found that it was not increased. These results compare favorably with those observed with thiopurines (alone or combined with anti-tumor necrosis factor [anti-TNF]), which increase the risk of lymphoma, non-melanoma skin cancer, and acute myeloid leukemias and myelodysplastic syndromes. Methotrexate is inexpensive. Inflammatory bowel disease [IBD] incidence continues to rise, particularly in countries of southern and eastern Europe as well as in the Middle East, North Africa, India, and Brazil. Not all these countries will be able to afford the cost of biologics.

Recent papers, including two published in this issue of JCC, and ongoing studies renew the interest in MTX in IBD. The paper by Haisma et al. is based upon a multicenter retrospective cohort of 130 paediatric patients who had failed thiopurines and were prescribed MTX as a maintenance therapy. Twelve months after initiation of MTX, 52% of the patients were relapse free, decreasing to 29% after 24 months. There was no difference in efficacy between children who were intolerant and those who failed to respond to thiopurines. The paper by Colman et al. is based upon a retrospective chart review of 88 IBD patients who received a combination therapy consisting in anti-TNF and methotrexate at a dose of 15–25 mg/week or less than ≤ 12.5 mg/week. The 46 patients who had reached clinical remission were followed up. The relapse rate was significantly higher in patients who had received the low dose as compared with those who had received the high dose of MTX.

The rate of adverse events leading to discontinuation of MTX was similar in the two groups. Analogous results have been observed in rheumatoid arthritis.

The recently published COMMIT trial compared the efficacy of infliximab + placebo versus infliximab + MTX in patients with CD. There was no difference between the two groups as regard to clinical efficacy [primary endpoint]. It is possible that the high-dose steroids prescribed in all included patients confounded the beneficial effect of combotherapy. Yet, COMMIT did show that patients randomized to the MTX + infliximab arm had a lower rate of immunogenicity and higher trough levels of infliximab.

Prevention of immunization against the drug is crucial in patients who receive anti-TNF.

Most studies concerning MTX in inflammatory bowel disease were performed in CD patients, and very few were conducted in UC. Until recently, no controlled trial had tested parenteral MTX at the dose of 25 mg/week in UC patients. The METEOR trial [NCT00498589], a European prospective, placebo-controlled, randomized trial, did so in steroid-dependent patients. The study has been completed and the results will be submitted soon. The MEthotrexate Response In Treatment of Ulcerative Colitis trial (MERIT-UC [NCT01393405]) is a US prospective, placebo-controlled, randomized trial that tests the efficacy of MTX as a maintenance treatment in UC patients who have responded to MTX. The study is still enrolling patients.

MTX is a safe and inexpensive drug. In CD patients, it is an efficient drug in monotherapy and it prevents immunization when associated with an anti-TNF. It can be prescribed to CD patients who have failed or become intolerant to thiopurines. It is now recommended as a first-line immunosuppressive therapy in Epstein-Barr virus- [EBV-] naive CD patients [ECCO malignancy consensus 2015, in preparation]. Due to its safety profile, it can also be employed as the first-line immunosuppressive, either alone or in combination with biologics, in women and men who do not wish to conceive. Results concerning UC patients will be published soon.

Conflicts of interest

None declared.
References