Methotrexate, a folate antagonist and potent anti-inflammatory agent, is an analog of dihydrofolic acid that inhibits dihydrofolate reductase and folate-dependent enzymes that are pivotal in the synthesis of purines and pyrimidines.\textsuperscript{1-3} It is an effective therapy in rheumatoid arthritis, Crohn’s disease, and psoriasis.\textsuperscript{4-9} The efficacy of methotrexate in the treatment of ulcerative colitis (UC) is not yet established.

The majority of UC patients have moderate disease,\textsuperscript{10} and two-thirds of UC patients requiring steroid induction therapy become either steroid-dependent or steroid-refractory.\textsuperscript{11,12} Furthermore, one-third of UC patients will require colectomy over time.\textsuperscript{13}

Unlike total proctocolectomy and ileostomy, the current surgery—ileal pouch-anal anastomosis—is not curative for UC. Postoperative complications of pouchitis, decreased fecundity, and fistulizing Crohn’s disease are now recognized and raise the question of the role of immunomodulators in UC similar to the established role in Crohn’s disease.\textsuperscript{14-17} Furthermore, 15% of UC patients have indeterminate colitis or unrecognized Crohn’s disease. Serologic markers may identify a subgroup of immunologically vulnerable UC patients more likely to develop postoperative Crohn’s disease and more likely to respond to Crohn’s disease therapeutic strategies including limited use of steroids and aggressive early immunomodulator and biologic therapy.\textsuperscript{18-20} These factors raise the question of limited steroid therapy and more aggressive immunomodulators including methotrexate in moderate-to-severe UC.

The current indications for immunomodulator therapy in UC are steroid-dependent and steroid-refractory UC.\textsuperscript{21-25} Azathioprine and 6-mercaptopurine (6-MP) are purine analogs that modulate immune responses by inhibiting the synthesis of nucleic acid, resulting in anti-proliferative effects on activated lymphocytes.\textsuperscript{26-28}

Both azathioprine and 6-MP are widely used as maintenance in Crohn’s disease but are less well established in steroid-dependent UC.\textsuperscript{21-23} Cyclosporine is effective in steroid-refractory UC.\textsuperscript{24,25,29} Infliximab is indicated for steroid-dependent UC.\textsuperscript{30} While methotrexate is established for both induction and maintenance of remission for Crohn’s disease prior to use of infliximab or in combination with infliximab,\textsuperscript{7-9,30} its role has been less well-studied in either induction or maintenance of remission in UC. Approximately one-third of patients with Crohn’s disease or UC are intolerant or unresponsive to optimized dosing of 6-MP or azathioprine.\textsuperscript{31-33}

**MECHANISM OF ACTION**

Methotrexate is an analog of dihydrofolic acid with a substitution of a hydroxyl group by an amino acid and an insertion of a methyl group allowing methotrexate to enter the cell by active transport or facilitated diffusion. It inhibits dihydrofolate reductase and inhibits the synthesis of purines and pyrimidines. These molecular mechanisms explain its antiproliferative effect although the anti-inflammatory effects remain to be elucidated. It is felt that, in part, the anti-inflammatory effects of methotrexate are related to binding adenosine on target cells, which may lead to inhibition of TNF-\textalpha and other proinflammatory cytokines.\textsuperscript{34-36}