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# Efficacy of Thiopurine Monotherapy in Ulcerative Colitis

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**Medical treatment of ulcerative colitis can be complicated, and it is usually stratified based on disease severity. The goal of therapy is to induce remission, followed by a maintenance regimen to continue clinical and endoscopic remission. The exact role of the thiopurines, azathioprine and 6-mercaptopurine, in UC treatment algorithms has been debated. Specifically, their use in UC remains controversial, since the evidence lies in small clinical trials. We briefly review the evidence for thiopurine efficacy in UC.**

The incidence of ulcerative colitis (UC) has been increasing globally.[1] Moreover, UC leads to significant economic burden; the total direct cost attributed to UC in the United States is an estimated $3.4-8.6 billion annually, and approximately 50% of patient costs arise from hospitalizations.[2] Although some patients with UC ultimately require colectomy, many patients can be managed medically. Medical treatment for UC can be stratified based on disease severity; 5-aminosalicylates such as sulfasalazine, mesalamine and balsalazide form the foundation of therapy for mildly to moderately active disease, followed by immunomodulators and finally anti-tumor necrosis factor alpha (anti-TNF) agents. In recent years, there has been significant debate about the positioning of the thiopurine medications, azathioprine and mercaptopurine, in induction and maintenance treatment algorithms for UC. We sought to review the evidence for the utility of immunomodulator monotherapy in patients with UC.

The use of azathioprine for UC was first reported in 1966.[3] Azathioprine is a pro-drug that is converted to 6-mercaptopurine (6-MP).[3] Xanthine oxidase, thiopurine methyltransferase (TPMT), and hypoxanthine phosphoribosyl transferase then metabolize 6-MP into 6-thiouric acid, 6 methylmercaptopurine (6-MMP), and precursors of the active 6-thioguanine nucleotides (6-TGN), respectively.[3] 6-TGN is integrated into nucleic acid and ultimately inhibits the synthesis of protein, ribonucleic acid (RNA), and deoxyribonucleic acid (DNA); however, the mechanism of action of azathioprine has not been fully discovered.[3] TPMT activity levels are routinely checked prior to initiation of azathioprine, since patients who lack TPMT activity are at high risk of severe myelosuppression. For those with normal TPMT levels, a dose of 2-2.5 mg/kg body weight/day of azathioprine is usually recommended. In addition

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to the risk of myelosuppression, azathioprine and 6-MP carry the risk of idiosyncratic reactions such as fever, pancreatitis, rash, and arthralgias. Hepatotoxicity from azathioprine and 6-MP is specifically associated with 6-MMP levels. Although hepatoxicity can occasionally be seen with low 6-MMP levels, a 3-fold elevation in risk has been observed with high 6-MMP levels (levels >5700 pmol/8 x $10^8$ red blood cells).[4]

In terms of its efficacy as an induction agent, azathioprine has had mixed results in UC. Ardizzone and colleagues studied the efficacy of azathioprine versus mesalamine in achieving corticosteroid-free remission (as defined both clinically and endoscopically) in steroid-dependent UC, and found azathioprine to be more effective.[5] Sood and coworkers studied the efficacy of azathioprine in addition to sulfasalazine and corticosteroids compared to the latter two medications alone in inducing remission in severe UC, and found no significant difference in remission rates between the two groups.[6] In 1990, Steinhart, et al. retrospectively reviewed outcomes of azathioprine initiation in a small clinic population of UC patients who were on corticosteroids.[7] Azathioprine efficacy was defined as the ability to decrease prednisone to less than 50% of the pre-treatment dose without clinical relapse and improvement in clinical symptoms.[7] Most patients (12 out of 16) responded to azathioprine, and the authors concluded that azathioprine was beneficial for UC patients who were resistant to or dependent on corticosteroids.[7]

Studies of the efficacy of azathioprine for maintenance of remission in steroid-dependent UC have also shown variable results. Sood and colleagues conducted a study in 2002 that assessed azathioprine and sulfasalazine or sulfasalazine and placebo in 35 patients with severe UC; all patients initially received corticosteroids.[8] Fewer patients in the azathioprine and sulfasalazine group suffered from UC relapse compared to the group treated with sulfasalazine and placebo, and this difference was statistically significant.[8] On the other hand, Sood and coworkers in another study found no significant difference in remission rates in UC patients who were on maintenance therapy with either azathioprine or sulfasalazine.[9] However, this study was quite small (n = 25). Earlier studies also showed no significant difference between azathioprine and placebo in remission rates; for example, Jewell and Truelove showed no difference in 12-month remission rates (defined by endoscopic finding of inflammation or bright red blood per rectum) when azathioprine was compared to placebo.[10]

Due to the conflicting reports in smaller studies, several groups have tried to address the efficacy of azathioprine in UC using a pooled approach.[11-14] In the systematic review by Leung, et al., 5 studies were analyzed to assess the efficacy of azathioprine on maintenance of UC remission in severe or steroid-dependent cases.[11] Four out of five studies used 2-2.5 mg/kg body weight/day of azathioprine, and there was significant heterogeneity among these studies. Their pooled analysis showed slight efficacy of azathioprine in maintaining clinical remission in UC (risk ratio [RR], 1.42); however, this was not statistically significant (95% confidence intervals [CI], 0.93-2.17; p=0.109). The studies used in the meta-analysis were limited by small sample sizes (ranging between 25-80 participants), significant heterogeneity, and use of specific analyses, such as relative risk in a random effects model versus a fixed effects model and estimation of a pooled relative risk.[11,12]

Another meta-analysis in 2009 aimed to clarify these issues in patients with severe or steroid-dependent UC.[13] Four studies, with a total of 89 patients, were analyzed to assess the efficacy of azathioprine/6-MP compared to 5-ASA or placebo in the induction of UC remission. This comparison did not show a significant difference between the two groups (OR, 1.59; 95% CI, 0.59-4.29.[13] Additionally, six studies with a total of 124 patients were used to compare azathioprine/6-MP with 5-ASA or placebo for maintenance of UC remission; a statistically significant difference was found between the two groups (OR, 2.56; 95% CI, 1.51-4.34).[13] Gisbert and colleagues further subdivided this section of the analysis to compare azathioprine/6-MP versus placebo and then azathioprine/6-MP versus 5-ASA; the former meta-analysis was statistically significant, favoring azathioprine/6-MP in the maintenance of UC remission, while the latter analysis failed to achieve statistically significant difference in efficacy.[13] Therefore, the significance of the pooled estimate of azathioprine/6-MP efficacy in maintenance of UC remission is difficult to interpret.

A systematic analysis and meta-analysis by Khan and colleagues, using more rigorous study inclusion criteria, aimed to study the updated body of literature on the efficacy of azathioprine in the induction of UC remission and prevention of relapses.[14] There were

2 randomized control trials that studied azathioprine efficacy in inducing remission in active UC. They found a trend towards benefit of azathioprine compared to placebo; however, this was not statistically significant (RR, 0.85; 95% CI, 0.71-1.01; p = 0.67). There was no statistically significant heterogeneity between the two studies; however, both studies were small (n=20-25). In the three RCTs that studied use of azathioprine in maintenance of remission, there was a statistically significant benefit of azathioprine compared to placebo in preventing relapse. However, again, the studies included were small. Notably, the studies analyzed in this meta-analysis were the same as those studied in the Leung, et al. meta-analysis. Whereas Leung and colleagues analyzed all the trials together, Khan, et al. divided the studies into two groups, one group studying induction of remission and the other group analyzing maintenance of remission.

In a comparative effectiveness trial, Panaccione and colleagues recently studied 239 moderate-to-severe UC patients to assess corticosteroid-free clinical remission in those treated with infliximab alone, azathioprine alone, or combination therapy with infliximab and azathioprine.[15] The study duration was 16 weeks, and the dose of infliximab was 5 mg/kg at weeks 0, 2, 6, and 14, and that of azathioprine was 2.5 mg/kg of body weight/day.[15] A higher percentage of patients receiving combination therapy achieved corticosteroid-free remission at week 16 compared to either azathioprine monotherapy (p=0.032) or infliximab monotherapy (p=0.017).[15] Additionally, mucosal healing at week 16 based on a Mayo endoscopic subscore of 0 or 1 was more likely to be seen in those treated with combination therapy rather than azathioprine monotherapy (p=0.001).[15] There was a greater improvement in the total Mayo score and Inflammatory Bowel Disease Questionnaire (IBDQ)/Short-Form Health Survey (SF-36) scores in the combination therapy group when compared to the azathioprine or infliximab monotherapy groups.[15] Therefore, this study suggests that combination therapy rather than azathioprine alone is better at inducing clinical and endoscopic remission of moderate-to-severe UC.

Overall, the data on thiopurine efficacy in UC is limited by small studies. While meta-analyses have found trends towards benefit of azathioprine over placebo in the induction and maintenance of remission in UC, these studies are limited by heterogeneity and method of analysis. Moreover, there is no definitive data from these studies that suggest azathioprine monotherapy would be beneficial for induction and maintenance of UC remission. It seems that the most important role of thiopurines in the medical treatment of UC may be as an adjuvant to biologic therapy. Perhaps earlier, more aggressive therapy with biologic therapy is warranted in steroid-dependent or severe UC patients. Thiopurine monotherapy can certainly be considered in steroid-dependent or refractory patients in whom biologic therapy is contraindicated, but this pool of patients seems to be small. Monotherapy with azathioprine or 6-mercaptopurine could also be considered in situations where access to biologic therapy is restricted. ■

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