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Case Report

A Review of Azathioprine-Allopurinol Co-Treatment for Ulcerative Colitis

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Case Report

One of the most significant inflammatory causes of rectal bleeding is Ulcerative colitis (UC). This disease primarily impacts the colon, typically causing continuous mucosal ulcerations in the rectum extending proximally into the large intestine. Although believed to not be as severe as Crohn's disease, Ulcerative colitis has a slightly greater prevalence in North America. Aside from bloody diarrhea, symptoms of UC include left lower quadrant abdominal pain before bowel movements, rectal urgency, fever, and weight loss. Extra-intestinal complications such as ocular disease, arthralgias, and primary sclerosing cholangitis contribute significantly to the morbidity of this disease [1].

The pathophysiology of IBD is not well understood but is believed to be primarily an autoimmune etiology with an environmental or infectious trigger. For UC specifically, a Th2 T-cell response is implicated in the pathogenesis of the disease. There is also a greater risk of development if a first degree relative is diagnosed with UC [1]. There are many therapies that can be used to modulate the autoimmune targeting of the colonic mucosa, but these depend on the severity of the disease [1,2]. Mild UC can be treated symptomatically with an anti-diarrheal such as loperamide while 5-ASA drugs such as sulfasalazine can be used for flare ups [2]. If the disease is refractory to 5-ASA, corticosteroids may be indicated despite having a lower efficacy and greater risk of side effects [2]. Corticosteroid dosage is often tapered after one to two weeks but if the patient requires long term steroid therapy, immunomodulators can provide a more tolerable alternative outside of biologic therapy [2,3].

A popular immunosuppressant used to treat UC is azathioprine (AZA). AZA exerts its effects by being metabolized into 6-mercaptopurine (6MP) where it serves as an antimetabolite by preventing the formation of purines needed for leukocyte DNA synthesis. In one long term study done to determine the efficacy of AZA, researchers used a sample of 255 patients with UC [3]. Each patient was prescribed AZA and assessed after 4 months. Within this period, the treatment showed an 81.2% compliance with 63% of total patients achieving a clinical response. About 34.3% of patients chose to stay on the drug for more than 5 years. At four months, 18% of patients chose to discontinue the drug due to adverse effects. Of the adverse effects, the most common was myelosuppression (7.1%) followed by hepatoxicity (5.5%). AZA serves as a useful immunosuppressant for ulcerative colitis especially when refractory to 5-ASA [3].

There is emerging research on how the efficacy of AZA can be improved if given in conjunction with Allopurinol. The aim of the AZA-allopurinol conjunctive therapy is to increase 6-thioguanine (6TG) levels and decrease 6-methyl-mercaptopurine (6MMP) which lead to higher rates of hepatotoxicity. Classically, allopurinol is used to treat gout by preventing excess production of uric acid. Allopurinol works in the same metabolic pathway as AZA. The metabolic product of AZA, 6MP, can be converted to many byproducts through various enzymes such as TMPT or xanthine oxidase. Allopurinol can inhibit xanthine oxidase along with TMPT allowing for 6MP to be preferably converted to 6TG instead of other byproducts. Allopurinol, therefore, has a strong physiological basis to promote the efficacy of AZA [4,5].

Genetics play a large role in determining the efficacy and safety of AZA therapy. Patients can have a genetically overactive TMPT where 6MP is metabolized into 6MMP where allopurinol adjudication may be indicated. Conversely patients can present with a TMPT deficiency. The prevalence of this deficiency varies by ethnicity with at least 10% of Caucasians presenting with a deficiency in at least one allele. The rates of this deficiency are far lower in Asians with less than 5% having missing one allele of the gene. A mutation in the NUDT15 gene alternatively is far more prevalent in the Asian population. Alterations in either gene are associated with a markedly greater risk of myelosuppression so genetic screening ought to be done when prescribing 6MP or one of its derivatives [5].

Clinical trials have been conducted to test the levels of 6-TG in IBD patients and assess the safety of the AZA-allopurinol drug combination. In a double-blind trial of 73 patients with steroid refractory IBD, 50 mg and 100 mg of allopurinol were prescribed along with a 75% reduction in their original AZA dose.6 All patients were on AZA for a mean time of 108 weeks. Only 37% of the patients in the study had UC. Results were measured via a 6MMP: 6TG ratio which was lowered from 64 to 4 on average. Interestingly, 6-TG levels were lower in the 100mg group. Steroid free remission occurred in 53% of cases and 81% of patients were able to discontinue steroids. Only 3 patients were not able to develop a low ratio. The drug combination was also relatively safe. 4% of patients had transient leukopenia. ALT and fecal calprotectin were also decreased in patients [6]. There are several other studies that present with similar conclusions [4,7-11].

Allopurinol has historically been associated with a significant exacerbation of myelosuppressive effects brought on by AZA [12,13]. Nevertheless, a population-based cohort study compared the side effects of AZA and how its effected by concomitant use of allopurinol in patients with IBD [14]. From a total of 37,360 patients AZA or 6MP, 1077 were also given allopurinol and monitored for side effects. Of the patients also taking allopurinol, a 58% decrease was seen in hepatotoxicity. The prevalence was myelotoxicity was not affected by coadministration while the rates of pancreatitis was increased only in patients with concurrent gout. AZA and allopurinol also increased the average adherence to 6MP based therapy by 2.1 years. Despite established research indicating the dangers of the interactions between allopurinol and AZA, the rates of adverse effects were found to have decreased with appropriate regimens [14].

Careful considerations must be taken when prescribing AZA-allopurinol based therapy for IBD. Despite cautious dosing, one meta-analysis claims that up to 20% of patients may still experience myelosuppression with this regimen [10] This can lead to an increased risk of opportunistic infections as seen in a clinical trial of 27 patients where 2 patients developed shingles, while PCP, EBV and viral meningitis were diagnosed in 3 patients separately [11]. Steven Johnson syndrome is also rare, yet severe adverse effect associated with allopurinol [10] Therefore, it is important to carefully monitor these patients for any decreases in leukocyte counts. The meta-analysis also states that the greatest responders to this treatment tend to have a “skewed” metabolism toward higher levels of 6MMP when AZA is administered alone [10] Thus, metabolic testing of metabolite levels could indicate which patients respond best to adjunct treatment. Appropriate dosing considerations, genomic testing, and continuous monitoring for side effects are practices that would offer the best outcomes to patients prescribed AZA-allopurinol therapy for patients with IBD [15].

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