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Optimising outcome on thiopurines in inflammatory bowel disease by co-prescription of allopurinol

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IIntroduction

The conventional thiopurines, azathioprine (AZA) and mercaptopurine (MP), are the cornerstone of immunosupressive maintenance therapy in inflammatory bowel disease (IBD). Unfortunately, up to half of patients have no benefit from this antimetabolite therapy due to lack of efficacy but mainly because intractable side-effects develop (1). The majority of these thiopurine failing patients is subsequently treated in a step-up regime with methotrexate (in Crohn's disease) or biologicals. The unfavorable outcome of thiopurine administration can in part be explained by the complex metabolism and its generated metabolites (especially the metabolites 6-thioguaninenucleotides (6-TGN) and 6-methylmercaptopurine (6-MMP)). Thiopurine metabolism can be optimized by co-administration of allopurinol (a xanthine oxidase inhibitor, regularly used in the treatment of gout), leading to a striking decrease in 6-MMP levels and mild increase in 6-TGN levels.

Several small scaled studies have demonstrated earlier that low-dose thiopurine (approximately 25-33% of its original weight-based dosage) in combination with allopurinol (100mg/day) can overcome several side effects (especially those associated with high 6-MMP levels, like transaminitis) that developed during regular thiopurine monotherapy. Moreover combination therapy showed good clinical efficacy (2,3). The study by the Sanderson group provides essential data on safety and success in a large real life cohort of 110 IBD patients using this combination therapy with an average follow-up of 16 months.

Key findings

This to date largest published series shows that the majority of IBD patients that cannot tolerate monotherapy with AZA/MP does not develop side effects during combination therapy with allopurinol. This remarkable result is not only observed in patients with (6-MMP related) hepatotoxicity (20/25 patients tolerated combination therapy alongside normalization of earlier liver test abnormalities), but also in those patients who encountered atypical adverse events (like GI disturbances, rash, flu-like symptoms, myalgia and alopecia) on preceding thiopurine monotherapy (24/28 patients). A total of 27 patients were switched to combination therapy due to partial or non-response on monotherapy. The administration of combination therapy for this novel indication showed promising results, as 65% of patients were in clinical remission. Thirteen adverse events were reported during combination therapy, being rash (mild and self-limiting), liver test abnormalities or GI-complaints. Pharmacokinetic evaluation of combination therapy showed a decrease in 6-MMP and increase in 6-TGN levels, confirming the results of earlier studies.

Why is this study imporant?

Although this retrospective study is not a randomized controlled trial, it clearly demonstrates the clinical value of the combination therapy allopurinol & thiopurine in IBD patients, who develop adverse events during thiopurine monotherapy and in patients who do not achieve a proper clinical response on AZA or MP. This promising strategy to optimize thiopurine therapy may lead to an increase in IBD patients who can primarily benefit from this first-line immunosupressive therapy and may avoid or delay the usage of alternative therapies, such as biologicals or surgery.

References

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