# Role of Allopurinol in Optimizing Thiopurine Therapy in Patients with Autoimmune Hepatitis: A Review

Shivani Deswal [*], Anshu Srivastava [†]

[*]Department of Pediatrics, PGIMER and Dr RML Hospital, New Delhi, India and [†]Department of Pediatric Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226014, India

**Autoimmune hepatitis (AIH) is a chronic immune mediated liver disease characterized by elevated transaminases, hyper gammaglobulinemia, presence of autoantibodies and interface hepatitis in the absence of a known etiology of liver disease. Thiopurines (azathioprine [AZA]/6-mercaptopurine [6MP]) and steroids remain the first line of treatment of AIH in both children and adults. However, a small proportion of AIH patients are either non-responders or develop side effects with AZA. The metabolism of AZA is complex and mediated by multiple enzymes. After absorption and getting converted to 6MP, it is converted to 6-thiouric acid, 6-methyl mercaptopurine (6MMP) and 6-thioguanine (6TG) by different enzymes. Elevated 6MMP levels are associated with hepatotoxicity and also poor efficacy due to simultaneous lower levels of 6TG, which is the active drug metabolite related to both efficacy and myelosuppression. Allopurinol, a xanthine oxidase inhibitor shifts the metabolism of AZA away from 6MMP toward 6TG. This combination of allopurinol with reduced dose of AZA is an alternative to more expensive and toxic second line therapy to induce remission in patients with AIH. This article discusses the mechanism of action of allopurinol in inducing response to AZA, reviews the published literature on this combination therapy and gives guidelines on the use of allopurinol in patients with AIH. (J Clin Exp Hepatol 2017;7:55–62)**



Autoimmune hepatitis (AIH) is a chronic immune mediated liver disease characterized by elevated transaminases, hyper gammaglobulinemia (IgG), presence of autoantibodies and typical liver histology (interface hepatitis, portal lymphoplasmacytic infiltrate, rosette formation and emperipolesis) in the absence of a known etiology of liver disease.[1] The disease affects all age groups with a prevalence of 16–18 per 100,000 persons in adults in Europe to 42.9 per 100,000 persons in Alaskan Natives.[1] There is a marked heterogeneity in presentation from asymptomatic elevation of transaminases to acute liver failure to cirrhosis.[2–4] AIH is classified into two types, based on the type of antibodies: Type 1 (antinuclear antibody [ANA] and/or anti-smooth muscle antibody [SMA]) and type 2 (anti-liver kidney microsomal [LKM 1] and/or anti-liver cytosol 1 [anti-LC1] antibody).[1,4] Type I AIH is more common and seen predominantly in adults while type II AIH is more frequently seen in young children. The diagnosis of AIH is based on the revised or simplified diagnostic criteria, with the revised diagnostic criteria being more suited for patients with atypical features.[5,6] In adults, nearly 75–80% patients present with chronic liver disease and a third have cirrhosis.[7] "Overlap syndrome" is used to define AIH patients who have features of both AIH and primary biliary cirrhosis (AIH-PBC) or primary sclerosing cholangitis (AIH-PSC).[3]

Immunosuppression with prednisone alone [60 mg day] or a lower dose of prednisone [30 mg day] along with azathioprine (AZA, 50 mg/day or 1–2 mg/kg body weight/day), is the first line of therapy in AIH with the aim of inducing remission, i.e. normal levels of transaminases, IgG and gamma globulin and absence of inflammation on liver histology.[4] In children, prednisone is given at a dose of 1–2 mg/kg/day (max of 60 mg day) and AZA at 1–2 mg/kg/day or 6-mercaptopurine (6MP) at 1.5 mg/kg/day.[4] Both the induction regimens of prednisone alone vs. prednisone and AZA have been shown to be equally effective in a systematic review of randomized controlled trials.[8] Recently a combination of budesonide and AZA has been shown to be equally effective in inducing remission with less of steroid side effects in non-cirrhotic adults with

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*Address for correspondence*: Anshu Srivastava, Additional Professor, Department of Pediatric Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226014, Uttar Pradesh, India. Tel.: +91 9935219497; fax: +91 522 2668017.
*E-mail:* avaianshu@yahoo.com
*Abbreviations:* ANA: antinuclear antibody; AIH: autoimmune hepatitis; AZA: azathioprine; HGPRT: hypoxanthine guanine phosphoribosyl transferase; IgG: immunoglobulin G; IBD: inflammatory bowel disease; LC: liver cytosol; LKM: liver kidney microsomal; 6MP: 6-mercaptopurine; 6MMP: 6-methyl mercaptopurine; 6-MTIMP: 6-methyl thioinosine monophosphate; PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis; SMA: smooth muscle antibody; 6TG: 6-thioguanine; TIMP: thioinosine monophosphate; TPMT: thiopurine methyltransferase; XO: xanthine oxidase
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AIH.[9] For maintenance therapy, both prednisone and AZA and AZA alone are similar and superior to prednisone monotherapy.[8] In AIH patients presenting as ALF, steroid monotherapy with strict monitoring and early consideration for liver transplantation in non-responders is recommended.[10] For patients with overlap syndrome of AIH-PSC or AIH-PBC a combination therapy of immunosuppression with urso deoxy cholic acid (UDCA) is recommended.[1,11]

AZA and 6MP are well tolerated in majority, with few adverse effects including nausea, vomiting, rash, arthralgia, fever, pancreatitis, hepatotoxicity and/or cytopenia which require dose modification or discontinuation. There is no established second line therapy for AIH patients who fail, i.e. intolerant or non-responsive to AZA therapy due to lack of randomized controlled trials. The choice of second line therapy is largely empiric and options include mycophenolate mofetil (MMF), calcinurine inhibitors (tacrolimus and cyclosporine), rituximab, infliximab, sirolimus and everolimus.[1] However, the experience is limited and in addition these drugs are costly, have serious side effects and need monitoring of drug levels. Thus, there is a need to use strategies to improve the efficacy of AZA in these cases before proceeding to the second line therapy.



## MECHANISM OF ACTION OF THIOPURINES

AZA is a thiopurine analogue prodrug of 6MP and it works by antagonizing endogenous purines and thus interfering with DNA synthesis.[12–14] It has an anti-proliferative effect on T cells. One of the hypotheses explaining its anti-inflammatory effect is that a metabolite of AZA, 6-thioguanine (6TG) accumulates in lymphocytes and blocks expression of cytokines which mediate inflammation.[12,15]

The metabolism of AZA is complex and involves many enzymatic pathways[14] (Figure 1a). After getting absorbed from the gastrointestinal tract, ~85–90% of AZA is non-enzymatically converted to 6MP.[14,15] Thereafter, 6MP is either converted to 6-thiouric acid by xanthine oxidase (XO) or to 6-methyl mercaptopurine (6MMP) after methylation by thiopurine methyltransferase (TPMT) or into thioinosine monophosphate (TIMP) by hypoxanthine guanine phosphoribosyl transferase (HGPRT). TIMP is then converted to 6TG. 6MMP is associated with hepatotoxicity while 6TG is associated with both therapeutic effect as well as the serious side effect of myelosuppression.[14,15]

TPMT is the rate limiting enzyme in the metabolism of AZA. 6MP is targeted competitively by XO, TPMT and HGPRT enzymes. TPMT also metabolizes TIMP to 6-methyl thioinosine monophosphate (6MTIMP), an inactive metabolite. There is wide variation in the activity of TPMT among individuals due to genetic polymorphism to the tune of 50-fold variation.[14,15] Low activity of TPMT enzyme results in a greater conversion of 6MP to 6TG via HGPRT pathway which results in greater efficacy as well as myelotoxicity.[12] In comparison, high TPMT enzyme activity results in increased production of 6MMP and less production of 6TG which results in increased hepatotoxicity with lower efficacy.

Estimation of AZA metabolites (6MMP and 6TG) has been shown to be helpful in management of patients with inflammatory bowel disease (IBD). A 6TG level of >230 pmol/8 $\times$ $10^8$ RBC is supposed to be associated with clinical efficacy of AZA.[15] Thus, if there is no response even with a 6TG level of >400 pmol/8 $\times$ $10^8$ RBC, the patient is labeled as refractory to AZA and will not respond to further escalation of the dose. The optimal levels of 6TG have not been extensively evaluated in patients with AIH, but a 6TG value of >220 pmol/8 $\times$ $10^8$ RBC was associated with clinical response with a sensitivity of 83% and specificity of 62%.[16] If both 6TG and 6MMP are low, it is likely that patient is not ingesting the drug and so compliance needs to be addressed. Higher 6MMP levels (>5700 pmol/8 $\times$ $10^8$ RBC) are associated with hepatotoxicity with raised transaminases and also with therapeutic failure largely due to concomitant lower levels of biologically active 6TG.[17] In adult IBD patients, 4.6–10% cases were shown to develop thiopurine related hepatotoxicity.[18,19] Hepatotoxicity however, is not seen in all patients with high levels of 6MMP. This hepatotoxicity due to high 6MMP is especially problematic in AIH patients as raised transaminases can also be attributed to non-response or relapse of the disease. Similarly, high levels of 6TG are associated with increased myelotoxicity but again it is not seen consistently in all patients. Thus regular monitoring of hemogram and liver function tests is essential in all patients on TP therapy to detect liver and bone marrow toxicity.[15]

## ROLE OF ALLOPURINOL IN OPTIMIZING THIOPURINE THERAPY IN PATIENTS WITH AUTOIMMUNE HEPATITIS

Some patients with failure to therapy have an increased conversion of AZA to 6MMP rather than 6TG, despite genetically determined normal TPMT activity which can be confirmed only by measurement of metabolites (ratio of 6MMP:6TG $\geq$ 15).[20] In adult and pediatric patients with IBD, use of allopurinol, along with lower dose of thiopurines (AZA or 6MP), has been shown to be of benefit in non-responders and patients with hepatotoxicity by achieving higher 6TG and lower 6MMP levels.[21–23] The exact mechanism of action of allopurinol is still not clear. Allopurinol blocks XO, acts as a ''shunter'' which inhibits conversion of 6MP to inactive 6-thiouric acid and most of 6MP is then shunted down the 6TG pathway[22] (Figure 1b). Some evidence suggests that allopurinol gets converted to oxypurinol by aldehyde oxidase which then gets converted to oxypurinol riboside monophosphate which is a competitive inhibitor of TPMT.[24] Recently Blaker et al. suggested that allopurinol mediated increase in thioxanthine levels

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