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Review Article

Role of therapeutic drug monitoring of azathioprine and thiopurine methyltransferase enzyme status in patients with inflammatory bowel disease: Indian scenario

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ABSTRACT

Inflammatory bowel disease is mainly caused by dysragulated immune system. Inflammatory bowel disease incidences are rising in Asian countries with difficulty in their diagnosis and managements. There is rising the incidences and prevalence rate in India. Inflammatory bowel disease has two major subtypes Ulcerative colitis and chron's disease. In ulcerative colitis inflammation occurs in lower part of large intestine that extend from anal verge to proximal colon while in case of chron's disease there is transmural inflammation of gastrointestinal tract. This review is to provide comprehensive review focused on the current status of therapeutic drug monitoring of azathioprine metabolites in patients of inflammatory bowel disease.

Keywords: Inflammatory bowel disease, Ulcerative colitis, Chron's disease, Therapeutic drug monitoring, Azathioprine, 6-Methylmercaptopurine, 6-Thioguanine nucleotides

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of disorders characterized by chronic and relapsing nature of inflammation in gastrointestinal tract. IBD significantly causes gastrointestinal symptoms that include diarrhoea, constipation, abdominal pain and anaemia. It is categorized as ulcerative colitis and CD (CD). Ulcerative colitis is characterized by confluent inflammation of the colon while CD is characterized by transmural inflammation of any part of the gastrointestinal tract. The immunosuppressant drugs azathioprine (AZA), 6-Mercaptopurine (6-MMP) and cyclosporine have a pivotal role in the treatment of IBD in moderate to severe cases. AZA was first developed by George Hitching in 1956 for treatment of leukemia in pediatric population. Later their efficacy has been found in the treatment and remission of IBD.[1] AZA is widely used in Asia in patients of steroid dependent cases.[2] The metabolism of this drug is complex and multiple steps and enzymes are involved in the metabolic pathway of AZA, periodically the therapy with AZA is associated with serious adverse events. Due to this, 8-9% cases therapy has been withdrawn.[3] Therapeutic drug monitoring (TDM) of AZA may provide insight into individual pharmacokinetics. It may be helpful in cases of worsening IBD activity to elucidate noncompliance or inefficient treatment.

IBD started gaining special attention in India only after mid 1980s with wider availability of colonoscope. In the era before 1985, ulcerative colitis (UC) was often difficult to distinguish from more prevalent infectious colitis and CD was only reported in surgical specimens.[4]

The aim of the present review is to clarify the role of TDM of AZA therapy in IBD in Indian population because the predictors of efficacy, optimal dosing and toxicity of AZA have not been much worked in Indian population.

EPIDEMIOLOGY

The incidence and prevalence of IBD varies with geographic location and ethnicity. Diagnosis of IBD may be difficult due to varied clinical manifestations. Differences in health care systems also contribute to inaccurate estimation of cases. The incidence and prevalence rate of IBD is much higher in North America and Northern Europe, England and Australia. In North America, incidence rate ranges from 6.0 to 15.6 cases per 100000 person years and prevalence ranges from 38-246 cases per 100000 persons. In Europe incidence rate ranges from 1.5 to 20.3 cases per 100000 persons years, with prevalence of 21 to 243 cases per 100000 persons. Their appears to be marked ethnic variation in the incidence of IBD. One ethnic group with high incidence of this disease is the jewish populations. Early studies reported that IBD is rare in blacks. Most of these studies were conducted in regions with limited black population. The prevalence of UC in India has been reported to be substantially lower than that among European.[5] The nature of IBD in Indians as a race is well highlighted by early epidemiologic studies in the diasporas and subsequently supported by Indian studies. In the early 90s, studies on South Asians in Leicestershire showed increased incidence of CD in South Asians (2.4/105 in Hindus, 3.4/105 in Sikhs and 5.4/105 in Muslims) and of UC in Sikhs (16.5/105) only but not in Europeans and other South Asians. The subjects had a smaller number of complications and operations. In this context, it is interesting to note that the study from Punjab, a state with a Sikh majority in India, show relatively high incidence and prevalence of UC.[6] The temporal relation is variable in different geographic areas. In North America and northern Europe, UC initially increased from 1935 to 1964, then decreased till 1979 and thereafter has been stable. The incidence of IBD is increasing in southern Europe Japan Singapore South Korea and northern India.[16] CD started increasing from 1960 with plateauing after 1975 but recently have been rising all over the world.[7-9] In India the first case of CD was reported about 23 years later of UC in surgical specimen.[10] Since then two epidemiologic studies have been conducted in north India on UC only.[11,12] A house to house survey of 4796 houses including 21921 persons (>14 years age) in Haryana state revealed 10 cases (5 each in both sexes) which gave a prevalence of 45.5/105 population (42.8/105 for males and 48.6/105 for females).[11] In a later study from the neighbouring state of Punjab where cluster sampling method was employed the crude incidence and prevalence of UC was found to be 6.02/105 and 44.8/105 population which was the highest in Asia but still less than that of North America and Europe.[12] This was similar to the prevalence reported in the study 17 years earlier indicating stability over time. A first population-based study from India reporting on the incidence and prevalence of UC was done by Sood A et Al in which a house to house survey is conducted by questionnaire formulated to inquiry about symptoms that are suggested of UC. The suspected cases were subjected to video sigmoidoscopy, colonoscopy and rectal biopasy. Results shows: A total population of 51 910 were screened from January to March 1999. We identified 147 suspected cases and of these 23 were finally established as ulcerative colitis cases, giving a crude prevalence rate of 44.3 per 100 000 inhabitants (95% CI 29.4–66.6). A second visit to the same areas after one year identified 10 suspected cases in a population of 49 834. Of these, three were confirmed as ‘‘definite’’ ulcerative colitis giving a crude incidence rate of 6.02 cases per 100,000 inhabitants (95% CI 1.2–17.6).[12] There have been no epidemiologic studies from any other part of India though the recent IBD task force data fulfils some of the gaps especially for CD. The IBD Task Force was set up in 2003 to collect data prospectively by questionnaire method from all over India.[13] Participants were all qualified gastroenterologists from all corners of India. Out of 1159 questionnaires analyzed, UC: CD was 750:409 and region wise distribution were north 220 (148:72), east 159 (90:69), central 255 (227:28), south 466 (235:231), west 59 (50:9). Thus, CD was much higher in the south followed by east compared to other regions. Most of this data was however hospital based. In 1990, in an early studies patient attending hospital in India Pakistan Nepal and Bangladesh only 75 cases diagnosed of IBD in 12,272 cases of bloody diarrhea.[14]

IBD occurs at any age, although diagnosis before the age of 5 years and after the age of 75 years is uncommon. 9The peak age of onset of UC and CD is between 15-30 years. A second peak occurs between the age of 60-80 years.[16] Certain life style and socioeconomic factors have been associated with the development of IBD. It is more common in industrialized area and urban populations.[5]

Currently available drugs for the treatment of IBD and their major adverse effects mention in Table 1.

Status of different drugs used in treatment of IBD

5-aminisalicylic acid is used as first line therapy for mild to moderate UC. Glucocorticoids are indicated in moderate to severe IBD. Thiopurine derivatives the cytotoxic thiopurine derivatives mercaptopurine (6-mp, purinethol) and azathioprine (Immuran) are used to treat patients with severe IBD or those who are steroid resistant or steroid dependent. The calcineurin inhibitor cyclosporine is a potent immunomodulator used most frequently after organ transplantation. It is effective in specific clinical settings in IBD, but the high frequency of significant adverse effects limits its use as a first-line medication.

Table 1: Currently available drugs for the treatment of IBD and their major adverse effects.

Drugs	ADRs
5 aminisalicylic acid	Headach, Nausea, fatigue, rash, fever, Stevens-Johnson syndrome, hepatitis, pneumonitis, alopecia, anorexia, agranuloctosis, aplastic anaemia
Thiopurines	Bone marrow suppression, hyper sensitivity reactions, infection, hepatitis, pancreatitis, diarrhea[15].
Antibiotics Metronidazole,	Anorexia, metallic taste and abdominal cramp, disulfiram like reaction, peripheral neuropathy on prolonged use.
Ciprofloxacin	Nausea Dizziness, headache anxiety, Tendinitis. (Harrison)
Corticosteroids	Acne, impaired wound healing, adrenal insufficiency, cushingoid appearance, osteoporosis cataract.
Cyclosporin	Anaphylaxis, diarrhea, hirsutism, hepatotoxicity seizure tremor
Biological agents Infliximab, Adalimumab, Natalizumab	Substantial toxicity, Lowering of resistance to infections.

The role of anti-TNF therapies for steroid-refractory or steroid-dependent ulcerative colitis is less clear. The rationale for their use is based on finding elevated levels of TNF in the mucosa of patients. Large controlled clinical trials have demonstrated that anti-TNF agents significantly reduce the severity of the inflammation. The rates of clinical remission range from 26-34%, with endoscopic healing in about half the treated patients. Unlike CD, ulcerative colitis is cured with surgery thus, the cost and serious adverse events associated with anti-TNF therapy need to be balanced with the effectiveness of the drug at preventing the need for colectomy. Currently, it is not known how effective anti-TNF therapies are for prevention, as opposed to delay, of colectomy. Antibiotics can be used as adjunctive treatment along with other medications for active IBD treatment for a specific complication of CD prophylaxis for recurrence in postoperative CD. The Supportive Therapy in IBD analgesic, anticholinergic, and antidiarrheal agents play supportive roles in reducing symptoms and improving quality of life. These drugs should be individualized based on a patient's symptoms and are supplementary to anti-inflammatory medications.[15]

Pharmacokinetics and mechanism of action of azathioprine

Azathioprine is a prodrug and converted to 6 –MP in liver by the enzyme glutathione-s-transferase. AZA an immunosuppressive antimetabolite is available in tablet form for oral administration. Each scored tablet contains 50 mg AZA. Azathioprine is well absorbed after oral administration. The absorption of AZA is 16-50% in healthy individuals, maximum serum radioactivity occurs at 1-2 hrs after oral dose. Half-life of AZA is 5 hrs and plasma protein binding is 30%. AZA is excreted in urine.

AZA should be introduced in low doses e.g. 50 mg daily (0.5-1.5mg /kg /daily), and increased gradually to doses 2.5 mg/kg daily within two weeks with weekly for adverse effects blood monitoring until maintenance dose reached. AZA is slow acting drug and thus their optimal effect is expected to be reached after 12-17 weeks of treatment. AZA is indicated for the treatment of IBD rheumatoid arthritis, acute lymphoblastic leukaemia and in kidney transplant. If tolerated and effective AZA therapy is continued for 4-5 years.[17] The mode of action of AZA is possible blockade of thiol group by alkylation inhibition of several pathways in nucleic acid biosynthesis and damage to DNA through the incorporation of thiopurine analogue.[18]

ROLE OF PHARMACOGENETICS IN THE METABOLISM OF AZATHIOPRINE

Favourable response to azathioprine and 6-mercaptopurine are seen in two third patients of inflammatory bowel disease. Recent insights into the metabolism of the thiopurine agents and appreciation of genetic polymorphisms in these pathways have provided new insights into variability in response rates and adverse effects.

Azathioprine has three metabolic fates

Conversion by xanthine oxidase to 6-thiouric acid, metabolism by thiopurine methyltransferase (TPMT) to (6-MMP) and conversion by hypoxanthine–guanine phosphoribosyl transferase (HGPRT) to 6-thioguanine nucleotides and other metabolites (Figure 1).[15]

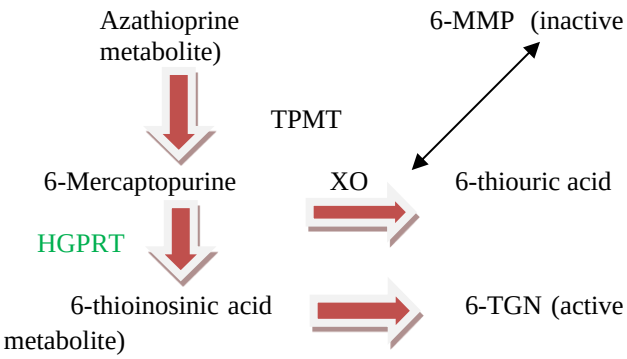

Figure 1: Metabolism of azathioprine and 6-Mercaptopurine.

In the (Figure 1) HGPRT, hypoxanthine–guanine phosphorribosyl transferase; TPMT, thiopurine methyltransferase; XO, xanthine oxidase, 6-TGN 6-

thioguanine nucleotide, 6-MMP, 6-methyl mercaptopurine. The activities of these enzymes vary among humans because genetic polymorphisms are expressed differentially, explaining variation in responses and side effects when azathioprine–mercaptopurine therapy is employed.[15]

Involvement of various genes in pathogenesis of disease can be related with disease occurrence in family members, siblings and twins. The Indian IBD task force data showed positive family history of IBD in 2.9 % cases only (UC 2.3% and CD 4.6%). Studies on causative role of individual genes have only started recently in India especially with the discovery of single nucleotide polymorphisms (SNP).[19] Genetic factors have linked to the development of IBD supported largely by the observation that family history is one of the most important risk factors for occurring the disease. Familial associations generally occur in first degree relatives. In one study, Yang et al described a risk of developing UC and CD among first degree relatives of IBD patients of 1.6% and 5.2%, respectively.[20] A traditional thinking in India has been that of a genetic difference between the North and South Indians which is supported by two studies, one undertaken by the Indian genome variation consortium.[21]

ROLE OF TPMT ENZYME IN IBD

TPMT is a major enzyme involved in the inactivation of AZA and mercaptopurine and catalyze the formation of 6-MMP from 6-MP and indirectly limit the formation of 6-TGN. AZA induced mylosuppression is strongly linked with the low activity of TPMT enzyme and high level of 6-TGN. Hepatotoxicity associated with AZA is linked with inactive methylated metabolites 6-MMP which is mainly dose dependent. Commonly TPMT activity varies in different individual Historically, in a study with 298 patients, TPMT activity had a trimodal distribution approximately 89% had high enzyme activity, 11% intermediate and 0.3% were deficient.[22] TPMT enzyme status can be determined by measuring enzyme activity using radiochemical and HPLC method or by genotying. In phenotype–genotype discordances, particular attention should be paid to patients who received a packed red blood cell transfusion within the last 3 months. As TPMT is assayed on erythrocytes, phenotyping is not reliable during this time.[23-25]

TPMT Phenotyping and genotyping

Most protocol incorporate routine assessment of TPMT status at the start of thiopurine treatment by phenotype and genotype. The phenotype concords with genotype in >98% of healthy adults.[26]

TPMT and 6–MMP associations with Azathioprine induced hepatotoxicity

There are statistically significant positive correlations between the alanine aminotransferase value and 6-MMPR levels, as well as the 6-MMPR/6-TGN ratio, probably reflecting the relationship between hepatotoxicity and high 6-MMPR levels.[27,28] Therefore, the measurement of 6-MMPR level in a patient on AZA or MP might enable us to predict and avoid hepatotoxicity. The proposed threshold cut-off value of 6-MMPR for hepatotoxicity is 5700 pmol/8x108 RBCs.[27] Several recent clinical guidelines have advocated determining 6-MMPR levels in patients on AZA or MP for avoiding hepatotoxicity.[29,30] However, this cut-off value of 6-MMPR cannot practically serve as a complete guide for the dosing of AZA or MP in the treatment of IBD for prediction and avoidance of hepatotoxicity.

Role of TPMT and 6-TGN in Mylotoxicity

Low TPMT activity is associated with increased formation of 6-TGN. The 6-TGN level is linked with therapeutic response and excessive amount of 6-TGN is linked with bone marrow toxicity. Measurement the concentration of 6-TGN guide the dose in individual patient. The therapeutic range and toxicity range of AZA is interlinked. There are several studies that purpose a threshold range of 6-TGN i.e. 230-260 Pmol/8x108 RBC.[27]

Role of TDM of azathioprine metabolites in IBD

Strategies to optimize thiopurine therapy have demonstrated to be valuable in the management of IBD.[31] Currently, therapeutic drug monitoring (TDM) of thiopurine metabolites may be used to increase clinical efficacy and reduce drug associated toxicity.[32,33] In this procedure, 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine (6-MMP) metabolites are measured and related to therapeutic response and adverse events, respectively.[34-36] The definite role of routine measurements of 6-TGN and 6-MMP levels in the management of IBD has not been well established yet. Current data on this issue are derived from mostly small sized and poorly conducted studies as addressed in 2-meta-analyses.[37] Interpretation of therapeutic drug monitoring for metabolites of azathioprine mention in (Table 2).

CURRENT STATUS OF TDM OF AZATHIOPRINE METABOLITES IN INDIA

The prevalence of TPMT genetic variant in India is reported to be up to 4.7%.38 It is reported that the thiopurine metabolism differs in Asian patients who do not tolerate full dose of thiopurine.39

A prospective study was conducted an Indian patient of IBD between 2015-2017 and results were of the 76

patients (32 women, mean age: 35.9 [SD: 14.54] years, 36 Crohn's disease and 40 ulcerative colitis), 1 non-compliant patient had undetectable level of metabolites. Of the 75 patients, 21(28%) had therapeutic level of 6-TGN, 37 (49%) had subtherapeutic level and 17 (23%) had supratherapeutic level. The 6-methylmercaptopurine levels ranged up to 4971 pmol/8×108 red blood cells. Six (8%) patients showed toxicity. Thiopurine dose was optimized in 20 (26.31%) patients. Dose-based metabolite levels were comparable to Asian and Caucasian patients. The toxicity (8%) observed in our patients was less than that reported (12–39%).[40]

Table 2: Interpretation of therapeutic drug monitoring for metabolites of azathioprine.[3]

Drug	Metabolite Range (pmol/ 8x10^8 RBCs)		Interpretation
	5700	**230-260**	
Azathioprine	6-MMP	6-TGN	-
	Absent	Absent	Non-compliance
	Low	Low	Non-compli ance or under-dosing
	High	Low	TPMT enzyme activity is high
	Low	High	Therapeutic dose
	High	High	Overdose

One more study was conducted by Sandeep Kirit Devala et al in 2014 on prevalence of TPMT polymorphism in Indian patients in 126 patients and results were (mean age, 42 [SD 13.6] years; 73 men and 53 women).[41] The disease indications included ulcerative colitis (61), Crohn's disease (43), indeterminate colitis (1), autoimmune hepatitis (16), and others (5). TPMT genotype was wild in 120 patients (95.23%) and heterozygous in 6 patients (4.77%); no patient had homozygous mutation. Seven of 87 patients (6.8%) who received azathioprine developed neutropenia; blood counts normalized on cessation of the drug in all. The incidence of neutropenia in patients with wild type was 6/84 (7.14%) and with heterozygous type 1/3 (33%) (p=0.5764).[42,43]

CONCLUSION

Monitoring metabolite levels of AZA in IBD patients may be useful for individualizing and guiding thiopurine treatment in patients and enhance efficacy and reduce adverse effects. However, a definite place for TDM of thiopurines in the management of IBD is challenging, partially as a consequence of analytical difficulties in this procedure. The metabolism of AZA is complex and multi-steps and multi-enzymatic and varies extensively between individuals, due to difference in TPMT activity. We plan to find the optimal dosing of AZA by measuring its metabolite levels in plasma and enhance the efficacy and reduce the adverse event by using therapeutic drug monitoring in Indian population.

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