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Prevalence of Azathioprine Induced Pancreatitis in IBD Patients

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ABSTRACT

Introduction: Azathioprine (AZA)-induced pancreatitis (AIP) is a known, though relatively uncommon, idiosyncratic drug reaction causing inflammation of the pancreas, often seen in patients with Inflammatory Bowel Disease (IBD) (Crohn's/UC) or autoimmune conditions, manifesting as abdominal pain, nausea, and vomiting, typically resolving quickly after stopping the drug but requiring medical attention for diagnosis and management. It's an unpredictable reaction, not strictly dose-dependent, linked to certain genetic markers (HLA alleles), and emphasizes the need for monitoring when using AZA.

Aim of Study: To determine the prevalence of Pancreatitis in patients of Inflammatory Bowel Disease who reported in Department of Medical Gastroenterology, PGIMS, Rohtak.

Materials & Methods: It was a prospective study conducted at Department of Medical Gastroenterology, Post Graduate Institute of Medical Sciences (PGIMS), Rohtak, over a period of ten years from 1st January, 2016 to 31st December, 2025 during which 5000 patients of IBD. who reported in Medical Gastroenterology OPD were enrolled in the study, after proper written consent. These all IBD patients were confirmed on colonoscopy and histopathological examination of colonic biopsy. They were regularly followed for any episode of pancreatitis which was confirmed by serum amylase, serum lipase levels and Contrast enhanced computed tomography scan and CTSI score was collected. At every visit, all patients were specifically asked about symptoms suggestive of pancreatitis like severe epigastric pain radiating to back, along with non-passage of faeces and flatus.

Results: We enrolled total 5000 patients who reported to Department of Medical Gastroenterology for treatment of Inflammatory bowel disease. Out of these 5000 patients, 4980 (99.60%) were having ulcerative colitis and 20 (0.40%) were having crohn's disease. In total pool of 5000 IBD patients, 2750 (55%) were male and 2250 (45%) were female. There was predominance of rural background i.e. 3150 patients (62%) and 1850 patients (38%) belonged to urban areas. Majority of IBD patients in study pool belonged to poor socio-economic status i.e. 3300 (66%) and 1700 patients (34%) had good socio-economic status. Out of total 5000 patients, only 3 patients (0.06%) developed pancreatitis and 4997 (99.94%) had no episode of pancreatitis. Out of these three patients who developed pancreatitis, two patients had one episode of pancreatitis and one patient had four episodes. In all these three patients, no further episode of pancreatitis occurred, once azathioprine was stopped, none of these three acute pancreatitis patients progressed to chronic pancreatitis.

Conclusion: Azathioprine is used frequently in IBD patients, as the goal of treatment is to keep patient in remission with steroid sparing regimen. It is relatively safe in respect of causing pancreatitis. Moreover, once pancreatitis occurs, it is stopped, hence does not lead to chronic pancreatitis.

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Introduction

Azathioprine is a pro-drug that is converted in the body into active metabolites which disrupt DNA synthesis, primarily in rapidly dividing immune cells like T and B lymphocytes. This process suppresses the overactive immune system, thereby reducing the inflammation. Treatment with azathioprine requires careful monitoring due to potential side effects. Acute pancreatitis occurs in around 2% of inflammatory bowel disease patients exposed to azathioprine or 6-mercaptopurine and is an important limiting toxicity of these thiopurine antimetabolites. Factors determining the risk of pancreatitis are unknown: the risk is not related to dose, though it may occur more commonly in individuals with Crohn's disease than in other disorders [1]. Acute pancreatitis (AP) has become increasingly recognized in children, with an incidence estimated to be 1 in 10,000, approaching the lower range in adults [2-6]. Several risk factors are known for AP, including biliary, anatomic, trauma, drugs, genetic risk factors, immune system-mediated, and metabolic disturbances [7-8]. Among these risk factors, drug-associated pancreatitis (DAP) has higher prevalence in pediatric than adult studies [9-11]. The drugs like azathioprine, cimetidine, interferon-alpha, methyldopa, metronidazole, olsalazine, and oxyphenbutazon all had a definite causal relationship with acute pancreatitis whereas doxycycline, enalapril, famotidine, ibuprofen, maprotiline, mesalazine, and sulindac had a probable causal relationship with acute pancreatitis [12]. Well-recognized dose-dependent adverse events associated with AZA and 6-mercaptopurine (6-MP) include myelosuppression

and hepatotoxicity, which often resolve with dose reduction. These adverse events rarely necessitate termination of therapy [13]. Idiosyncratic adverse drug reactions (i.e. intractable nausea, malaise, fever without leucopenia, arthralgia and acute pancreatitis), while more common in frequency than dose dependent reactions, often demand discontinuation of the offending medication [14]. One review showed with moderate certainty that the use of AZA to induce remission and maintain medical induced remission in Crohn's disease (CD) was probably associated with increased occurrence of pancreatitis [15]. A delayed type II or IV allergic reaction or immune-mediated genetic disposition has been postulated, with the former supported by the fact rechallenge of AZA results in recurrence of symptoms [16].

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Table 1: Showing Aetiological Distribution in IBD Patients on Azathioprine

Total Patients	Ulcerative Colitis	Crohn's Disease
5000	4980 (99.60%)	20 (0.40%)

Table 2: Showing Sex, Geographical and Socio-economic status Distribution in IBD Patients

Total Patients	Male	Female	Rural Background	Urban Background	Poor S.E. status	Good S.E.status
5000	2750 (55%)	2250 (45%)	3150 (62%)	1850 (38%)	3300 (66%)	1700 (34%)

Table 3: Showing Distribution in IBD Patients on Azathioprine on Basis of Pancreatitis

Total Patients	No Pancreatitis	Pancreatitis	Single Episode	Multiple Episode	Acute Pancreatitis	Chronic Pancreatitis
5000	4997 (99.94%)	3 (0.06%)	2 (66.6%)	1 (33.33%)	3 (100%)	0 (0%)

Discussion

Azathioprine (AZA)-induced pancreatitis (AIP) is a known unpredictable side effect in 2-7% of IBD) patients, typically occurring within weeks of starting treatment, causing symptoms like abdominal pain, and usually resolving with drug withdrawal. While often dose-independent, genetic markers (HLA-DQA1/DRB1 polymorphism) and risk factors like smoking, old age or certain Crohn's disease types increase susceptibility, requiring vigilant monitoring for this serious complication. It usually appears 3-6 weeks after starting AZA, but can occur within the first 90 days. It is an idiosyncratic reaction, often independent of the drug dose and symptoms typically resolve within 1-11 days of stopping AZA. In autoimmune hepatitis (AIH), AIP incidence is low (~1.5%) compared to incidence of same drug reaction reported in patients with inflammatory bowel disease (IBD) especially Crohn's disease [17].

Systemic corticosteroids may blunt the T-cell–mediated hypersensitivity cascade underlying AIP. In contrast, budesonide, which is more commonly used in IBD, has high first-pass metabolism and low systemic bioavailability, does not confer the same protection. Nearly all medications used for inflammatory bowel disease (IBD) have been reported as causes of acute pancreatitis (AP), with the thiopurines being among the most frequently described. A total of 4,223 AP episodes were identified for common IBD medications. Azathioprine, 6-mercaptopurine, and 5-aminosalicylic acid all had strong associations with AP, while the biologic/small molecule agents showed weaker or no disproportionality. The association with AP was much higher for thiopurines when used for Crohn's disease, compared to ulcerative colitis or rheumatologic conditions [18]. In a 16-year nationwide Danish study, patients with Crohn's disease and ulcerative colitis were found to have a fourfold and twofold increased risk of acute pancreatitis, respectively, compared to the general population [19]. It is unclear why the rate of drug-induced pancreatitis is significantly higher in the IBD population. In our study group, AZA was found to be very safe in respect to causing pancreatitis, as very minimal percentage developed it, that too after long period

of follow up which varied from 3-10 yrs. This is in contrast to other studies and same can be explained on basis that azathioprine usually causes pancreatitis in crohn's but in our pool was majority were ulcerative colitis (UC). Secondly, azathioprine causes pancreatitis commonly in elderly and but in our pool, maximum was young or in middle age group. Thirdly, smoking increases chances of azathioprine induced pancreatitis but, in our group, female group were non-smokers and in male group only half were smokers and majority of them were convinced to leave smoking. In India, ulcerative colitis is the pre dominant form of IBD in comparison to western world where crohn's is in equal proportion to ulcerative colitis. This is blessing for Indian patients because not only prognosis of UC is better than crohn's and even AZA induced pancreatitis is also less. None of patient who developed acute pancreatitis progressed to chronic pancreatitis because of stoppage of azathioprine in these patients. Only one patient had four episodes of acute pancreatitis because of confusion between steroid and AZA being the culprit for causing pancreatitis. Ultimately, even after stopping of steroids, pancreatitis episode occurred, then AZA was stopped and after that no episode of pancreatitis occurred.

Conclusion

Azathioprine is used frequently in IBD patients, as the goal of treatment is to keep patient in remission with steroid sparing regimen. It is relatively safe in respect of causing pancreatitis. Moreover, once pancreatitis occurs, it is stopped, hence does not lead to chronic pancreatitis.

Conflict of Interest: No conflict of interest and prior permission from patient and relatives was taken before publishing the case report.

Limitation of Study: In our group there was predominance of UC patients, that too in young & middle age group and majority were non -smokers. Hence, a larger group with equal representation from crohn's, elderly and smokers can be more helpful in determining the exact prevalence of azathioprine induced pancreatitis.

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