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Review

Drug-Related Adverse Events in Inflammatory Bowel Disease

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Abstract

The goal in managing inflammatory bowel disease (IBD) is to achieve both clinical and endoscopic remission. Additionally, improving patients' quality of life is a primary objective. With recent innovations in treatment and the expansion of therapeutic options, histological remission has also become a target. In treatment planning, factors such as the patient's current clinical status, age, comorbidities, and previous treatment history are crucial considerations. All available treatments require attention to specific precautions, contraindications, and parameters that need regular monitoring. Although TNF-α inhibitors are highly effective in treating IBD, they increase the risk of complications such as latent tuberculosis (TB) reactivation and opportunistic infections. Therefore, screening for latent TB is conducted before initiating anti-TNF therapy, and TB prophylaxis is administered to patients who require it. Mesalazine, one of the oldest drugs used in IBD treatment, has been associated with acute interstitial nephritis, making it essential to monitor renal function in patients receiving this medication. Azathioprine, commonly used for its immunosuppressive properties, has been linked to side effects such as cytopenia, hepatotoxicity, and acute pancreatitis. Consequently, patients on azathioprine should be closely monitored for these adverse reactions. Treatment strategies for IBD should be individualized, taking into account patients' clinical status, socio-demographic characteristics, and comorbidities. Regular follow-up and monitoring for adverse drug reactions are critical components of care for patients undergoing treatment.

Keywords: Crohn's disease, drug, side effects, ulcerative colitis

INTRODUCTION

In the management of inflammatory bowel disease (IBD), the primary objective is to achieve intestinal healing and alleviate the patient's symptoms, followed by maintaining the remission achieved. When developing a treatment plan, it is essential to consider factors such as disease severity, the location of inflammation, the patient's tolerance to medications, and their previous treatment responses. The goal is to induce and sustain remission while preventing complications.

Drug-related side effects are a significant aspect of the treatment process, as they can affect the patient's quality of life and sometimes lead to unexpected outcomes. Along with their therapeutic benefits, medications may cause unwanted side effects that can vary depending on the dosage and duration of use.

This article will focus on the causes of drug side effects, the most common adverse reactions observed during treatment, and strategies for managing these effects effectively.

TUBERCULOSIS

A meta-analysis examining the risk of developing tuberculosis in patients using tumor necrosis factor-alpha (TNF-α) inhibitors found that the risk was 1.94 times higher in those using TNF-α inhibitors compared to the control group, with a tuberculosis development rate of 0.57% in the TNF-α group (95% CI, 1.1–3.44, P = 0.02).[1] In a separate meta-analysis conducted with rheumatoid arthritis patients, the risk of tuberculosis was shown to increase fourfold in non-randomized controlled studies. However, the same meta-analysis demonstrated that prophylactic treatment reduced the risk of tuberculosis by 65%.[2]

In a meta-analysis that included studies related specifically to IBD, the use of TNF-α inhibitors was found to increase the risk of opportunistic infection by 1.9 times.[3] Another meta-analysis focused on IBD patients showed that the risk of opportunistic infection doubled and the risk of tuberculosis increased 2.5 times with the use of TNF-α inhibitors.[4]

In conclusion, latent tuberculosis can be reactivated by TNF-α inhibitors, and patients receiving this treatment have an elevated risk of developing opportunistic infections.

In patients scheduled to start TNF-α inhibitors, tuberculosis prevention measures (such as BCG vaccination) implemented by the country and the community's tuberculosis prevalence are crucial considerations. Due to BCG vaccination in our country, a positive tuberculin skin test can occur, which may lead to unnecessary prophylaxis with isoniazid (INH) (Table 1). The rate of initiating INH prophylaxis based on a positive tuberculin skin test is 57%, whereas this rate decreases to 29% with the Quantiferon-TB Gold test.[5]

Therefore, in tuberculosis screening, interferon-gamma release assays (IGRA) tests-such as the Quantiferon-TB Gold or T-Spot tests-are preferred over the tuberculin skin test (BCG test) due to their lower false-positive rates. If the IGRA test result is positive, latent tuberculosis treatment should be planned in consultation with an infectious disease specialist or a pulmonologist (Table 1).

MAIN POINTS

- Before starting TNF-α inhibitors, IGRA tests, which have a lower false-positive rate than the tuberculin skin test, should be preferred for latent tuberculosis screening.
- In patients with renal dysfunction, mesalazine should either be avoided or used with caution, with close monitoring of renal function. For patients with normal renal function, it is appropriate to check renal function and perform a complete urinalysis during follow-up visits.
- Acute pancreatitis associated with azathioprine use in IBD typically develops within 6–8 weeks of starting the drug and generally follows a mild clinical course. However, if AZA-induced acute pancreatitis (AZA-AP) occurs, the medication must be discontinued entirely. In suspected cases of acute pancreatitis, gastrointestinal system intolerance should also be considered.

Table 1. Drug related adverse events

DRUGS	SIDE EFFECTS	RECOMMENDATIONS
Azathioprine (AZA) and 6-mercaptopurine (MP)	Approximately 10% of patients, often within the first few months, experience serious side effects that may require discontinuation of treatment in 10-20% of cases. **Common side effects (especially with rapid dose escalation):** anorexia, nausea, vomiting **Dose-dependent side effects:** bone marrow suppression and hepatotoxicity **Dose-independent side effects:** gastrointestinal intolerance, acute pancreatitis, infections, malignancies	**Week 1 and Week 4:** Start AZA or 6-MP at a dose of 50 mg once daily. After starting the medication, laboratory tests should be checked weekly: ✓ Complete blood count (CBC) ✓ Serum aminotransferases ✓ Total bilirubin ✓ Amylase **Dose Adjustment Criteria:** If the patient tolerates the drug well, and if the leukocyte count is >4000/microL and the platelet count is ≥150,000/microL, the AZA dose can be increased. *The maximum daily dose of AZA is 2.5 mg/kg. Perform laboratory tests again two weeks after any dose increase. After 12 weeks of stable dosing, laboratory tests should be checked every three months.
	Cytopenia • If leukopenia (WBC <4000/microL) or thrombocytopenia (platelet count <150,000/microL) develops during treatment, the AZA dose should be reduced by 50% or the drug should be discontinued. • A complete blood count should be checked again in two weeks. • If cytopenia persists, the drug should be discontinued. **Hepatotoxicity** • Mild elevation in transaminases usually resolves with dose reduction. Continue treatment with a 50% dose reduction, checking transaminase levels every two weeks. • If transaminase levels increase to more than twice the normal level, discontinue the drug completely. • Once transaminase levels return to normal, the drug can be restarted at lower doses with close enzyme monitoring. • If cholestasis and jaundice develop, the drug should be completely discontinued. **Acute Pancreatitis** • Discontinue the drug and do not restart. **Dyspeptic Symptoms** • These symptoms can be minimized by taking the drug with meals or starting at a lower dose. If the patient tolerates the drug, discontinuation is not necessary. **Macrocytosis** • Discontinuation of the drug is not necessary. **Lymphomas** • Hepatosplenic T-cell lymphoma and non-melanoma skin cancers are malignancies thought to be associated with AZA.	

Table 1. Drug related adverse events (*continued*)

DRUGS	SIDE EFFECTS	RECOMMENDATIONS
Sulfasalazine and 5-Aminosalicylic Acid (5-ASA)	**Common Side Effects:** • Nausea • Abdominal pain • Headache • Diarrhea **Less Common Side Effects:** • Acute pancreatitis • Fever • Rash **Rare Side Effects:** • Pneumonitis • Pericarditis • Nephritis • Nephrolithiasis • Agranulocytosis **Special Considerations:** • Approximately 3% of patients taking oral 5-ASA may experience paradoxical worsening of colitis symptoms, including diarrhea, bleeding, acute abdominal pain, and in some cases, fever, headache, and rash. These patients should be considered allergic to 5-ASA, and the drug should not be restarted in these individuals.	**Nephrotoxicity** • Nephrotoxicity with 5-ASA is rare. • Most cases of renal failure are due to acute or chronic interstitial nephritis, independent of the 5-ASA formulation and dose. • Serum blood urea nitrogen (BUN) and creatinine levels should be checked at 6 weeks, 6 months, and 12 months after starting 5-ASA therapy, and then annually. • In patients with chronic renal insufficiency, 5-ASA should be used with caution, and renal functions should be monitored more closely.
TNF-α inhibitors	✓ Injection site reactions ✓ Infusion reactions (early and late) ✓ Neutropenia ✓ Hepatotoxicity ✓ Infections ✓ Demyelinating disease ✓ Heart failure ✓ Skin reactions and paradoxical psoriasis ✓ Malignancies ✓ Hepatitis B reactivation ✓ Tuberculosis reactivation	**Neutropenia** • Complete blood count (CBC) should be checked before treatment and repeated at regular intervals. • Generally recommended to monitor CBC every 3-6 months**.** **Tuberculosis Reactivation** • Latent tuberculosis infection screening should be done before starting TNF-alpha inhibitor therapy. • Patients with positive Quantiferon tests should receive INH prophylaxis before treatment. **Demyelinating Disease** • While the causal relationship between TNF-alpha inhibitors and demyelinating disease remains unclear, anti-TNF-alpha agents should generally be avoided in patients with demyelinating diseases like multiple sclerosis (MS). • If symptoms suggestive of demyelinating disease occur (such as ataxia, paresthesia, hemiparesis, optic neuritis), the drug should be discontinued immediately. **Heart Failure** • TNF-alpha inhibitors are associated with the development or worsening of heart failure. • Patients with symptomatic heart failure should not use TNF-alpha inhibitors. **Infections** • Treatment should be paused in the event of a serious infection. **Malignancies** • Except for non-melanoma skin cancer, a history of cancer treatment within the last 5 years contraindicates the use of biological agents. • If the use of biological agents is absolutely necessary in patients with a history of cancer, agents that may be safer based on current literature should be selected.

MESALAZINE AND NEPHROPATHY

Mesalazine is a drug known to cause acute interstitial nephritis. A total of 41 cases have been reported in the literature. It was found that patients had been exposed to mesalazine for an average of 2–3 years before developing acute interstitial nephritis. Despite discontinuing the drug and using corticosteroids, renal failure occurred in approximately 15% of the cases.[6]

Data on the incidence of nephritis associated with 5-aminosalicylic acid (5-ASA) are limited. In a prospective Danish study involving 150 patients, reversible renal dysfunction developed in 2 (1.3%) of the patients who were using 1.5–3 g of mesalazine.[7]

There are differing expert opinions on how frequently renal function should be monitored in patients using 5-ASA (Table 1). The 2010 American Gastroenterological Association (AGA) recommendation suggests monitoring renal function every 3–6 months during the first year of mesalazine use and annually thereafter.[8] The 2012 ECCO guidelines recommend monitoring renal function every 3–6 months in high-risk patients.[9]

In patients with known renal disease or renal dysfunction, it is advisable to either avoid mesalazine use or proceed with caution and close monitoring (Table 1). In patients with normal renal function at the outset, monitoring decisions should be based on the patient's clinical condition. During follow-up, renal function tests and complete urinalysis should be performed regularly.

AZATHIOPRINE-INDUCED ACUTE PANCREATITIS

Patients with IBD have a higher risk of developing pancreatitis, with medication side effects being a primary cause. The pathophysiology of drug-induced pancreatitis is not fully understood; however, azathioprine, sulfasalazine, and 5-aminosalicylic acid have been associated with the development of pancreatitis through a dose-independent hypersensitivity reaction.

Azathioprine (AZA), an immunosuppressant used in the treatment of IBD, is one of the drugs most commonly linked to acute pancreatitis (AP) in these patients. AZA-induced pancreatitis is considered idiosyncratic and unrelated to dosage. However, to diagnose drug-associated pancreatitis, other potential causes must first be ruled out.

CRITERIA THAT MAY HELP IN THE DIAGNOSIS OF AZA-INDUCED ACUTE PANCREATITIS

Azathioprine-induced acute pancreatitis (AZA-AP) often develops within a short period after starting the medication, typically within the first 1–6 weeks of treatment. Acute pancreatitis may resolve after discontinuing azathioprine and reappear if the drug is resumed.[10] The occurrence of AZA-induced pancreatitis is generally considered a contraindication for further use of the drug (Table 1). Therefore, it is crucial to explore alternative therapeutic options for these patients.

The frequency of thiopurine-induced acute pancreatitis in IBD patients is reported to be 3–4%.[11–13] Thiopurine-related pancreatitis usually presents as edematous pancreatitis with a mild clinical course that improves quickly after the drug is discontinued.

Several studies suggest that polymorphisms in the thiopurine S-methyltransferase (TPMT) gene may play a role in the development of AZA-AP.[14] In a study conducted by the European Genome Society with 172 patients, the nucleotide polymorphism Rs2647087 in HLA class II was reported to be potentially associated with AZA-AP. Additionally, the alleles HLA-DQA102:01 and HLA-DRB107:01 were also linked to AZA-AP.[15] This polymorphism may be useful for risk monitoring of AZA-AP in the future.

Studies have demonstrated that 6-mercaptopurine is safe for patients who have developed AZA-AP. In this patient group, 6-mercaptopurine can be used with dose modification. However, it is important to note that acute pancreatitis may still occur due to cross-reaction.

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