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Mini Review

Toxicity of maintenance drugs in Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease is a chronic condition requiring long-term treatment with immunosuppressive medications. There is concern regarding the risks of drug-related toxicity particularly the risk of infections and the risk of malignancy. Pregnancy requires a particular consideration due to the implications from the exposure to the fetus and elderly patients may be at a higher risk of toxicity that merits special precautions.

Keywords: 5-Aminosalicylates; Immunomodulators; Biologics; Toxicity; Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis

Introduction

Inflammatory bowel disease (IBD) is a disease characterized by chronic intestinal inflammation. It is classified under 2 major categories: Crohn's disease and ulcerative colitis. The use of IBD medications over years, while effective, carries a risk of toxicity. This risk applies to patients in general but is also more relevant to special population like pregnant and elderly patients. With the disease onset at a younger age requiring long-term therapy, concerns arise for women going through childbearing age given the intrauterine exposure of the fetus and during the 1st year after delivery. Considering the chronic nature of IBD requiring extended therapy, the aging patient enters the geriatric age group while on immunosuppressive medications that could also be potentiated by immunosenescence [1,2]. A significant number of medications used for maintenance therapy are now available for IBD and can be grouped into 5 major categories: 5-aminosalycilates, immunomodulators, biologics, JAK-2 inhibitors and novel therapy.

5-Aminosalicylates

5-ASA do not have significant immunosuppressive effects and are overall well tolerated. However, 5-ASA can paradoxically worsen colitis in up to 3% of patients [3]. Nephrotoxicity is a rare side effect, reported to develop in 1/4000 patient/year [4] and less than 0.5% [5]. Forms of nephrotoxicity include interstitial nephritis, glomerulonephritis, and minimal-change disease with nephrotic syndrome [6]. The oldest 5-ASA, sulfasalazine, can have sulfa-induced side effects due to its sulfapyridine moiety, like diarrhea and headache, with reported cases of pancreatitis [7]. Sulfasalazine, can also decrease sperm motility. Several studies including a meta-analysis reproduced this toxic effect which is dose independent and reversible after 3 months of discontinuation [8,9,10].

Immunomodulators

Methotrexate

Toxicities from methotrexate include disruption of folate metabolism, hypersensitivity pneumonitis and hepatic fibrosis with a cumulative lifetime dosing of >1.5–2g. There is no clear signal of increased lymphoma with the use of methotrexate. However, it is an abortifacient and can affect sperm function; therefore, it should be stopped 3–6 months prior to planned conception [11].

Thiopurines (6-Mercaptopurine and Azathioprine)

Thiopurines increase the risk of infection even in the absence of bone marrow suppression [12]. The rate of serious infections is estimated to be 1.1% (1 in 91) in patients on thiopurine

monotherapy and 2.2% (1 in 45) in patients on combination therapy with thiopurine and a biologic [13]. The most worrisome malignancies associated with thiopurines are lymphomas. The absolute risk is low 1.7% (336 in 189,000) with a hazard ratio of 2.6 (95% CI 1.96-3.44; p<0.001) [14]. The highest absolute risk of thiopurine-related lymphoma is in men older than 50 years. This risk is proportionate to the duration of therapy but reversible with its discontinuation [15]. Two pathologies linked to thiopurines are particularly lethal: hepatosplenic T cell lymphoma (HTCL) and hemophagocytic lymphohistiocytosis (HLH). HTCL occurs primarily in males younger than 35 years after 2 years of exposure [16]. HLH is a multisystem inflammatory response in which the mononuclear phagocyte system is activated leading to phagocytosis of all bone marrow derived cells [17]. The risk of this disease is particularly high in patients who develop acute EBV infection while taking thiopurines [18].

Cyclosporine

Cyclosporine can cause nephrotoxicity, lower seizure threshold, and increase the risk of infection, particularly in patients previously exposed to corticosteroids and anti-TNF therapies, a scenario commonly encountered in IBD patients before exposure to cyclosporine [19]. Cyclosporine can increase the risk of lymphoma after organ transplant (post-transplant lymphoproliferative disorder), but data in IBD is limited [11].

Biologics

The 3 major types of biologics currently used for IBD are: tumor necrosis factor (TNF) inhibitors, α4β7 receptor blockers and interleukin 12 and 23 inhibitors.

Anti-TNF

TNF inhibitors are monoclonal antibodies that block the inflammatory cytokine TNF. TNF is involved in multiple cell signaling pathways implicated in immune defense and in carcinogenesis.A meta-analysis regarding the safety of anti-TNF that included adalimumab, golimumab and infliximab showed no increased rates of adverse effect except for infliximab with an odds ratio 1.52 (95% CI 1.03–2.24, P 0.04) with most of the adverse effects being mild [20, 21]. Multiple studies showed no concerning safety signals for adalimumab [22, 23, 24]. A more recent systemic review did not find an increased risk of malignancy in IBD patients on anti-TNF [25]. More specifically, the risk of lymphoma with anti-TNF monotherapy was extensively scrutinized in multiple studies due to its association with combination therapy with immunomodulators. However, most current data did not show an increase risk of lymphoma with anti-TNF [26].

Vedolizumab

Vedolizumab blocks the gut-specific integrin on the leukocyte (α4β7) from its receptor (mucosal addressin cellular adhesion molecule or MAdCAM).With up to 5 years exposure of 2800 patients, Vedolizumab has a favorable safety profile without association with serious or opportunistic infections or infusion-related reactions. The reported malignancy rate of 0.1/100 person-year was comparable to the baseline risk in IBD. Risk for progressive multifocal leukoencephalopathy (PML) was not detected [27, 28]. Owing to this gut selectivity, vedolizumab could be considered as the drug of choice for patients at risk of infections, at risk or with history of malignancy and in post-transplant patients on immunosuppression.

Ustekinumab

Ustekinumab is a biologic that binds to interleukin 12 and 23 and prevents their interaction with their cell surface receptor inhibiting cell signaling.Pooled data from 6 phase 2/phase 3 trial in IBD did not show an increased risk of infections overall or of serious infections as compared to placebo [29].

JAK-2 inhibitors:Janus Kinase

Tofacinib is a small molecule that belongs to the Janus Kinase inhibitors drug class. JAK signaling pathway is involved in the transcription of hematopoietic and immune cells. Post-marketing data uncovered an increased risk of death, deep vein thrombosis and pulmonary embolism with a twice daily dose of 10 mg. Based on this discovery, a black-box warning was added to the drug labelling for this higher dosage [30]. In a safety analysis of more than 4 years of exposure, a dose dependent relationship was observed between tofacinib and herpes zoster infection in moderate to severe ulcerative colitis [31].

Newer Therapy

The newest advance in the treatment of IBD is ozanimod. Ozanimod is a sphingosine 1-phosphate (S1P) receptor modulator that binds to S1P receptors 1 and 5. S1P receptor is a signaling lipid that regulates T-cell trafficking in inflammation and vascular permeability among many other functions [32]. Ozanimod blocks the ability of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes circulating in the peripheral blood. Side effects include bradycardia, liver injury, increase in blood pressure, reduction in forced expiratory volume over 1 second and forced vital capacity and macular edema [33].

Special Population

Pregnancy

A large US-based registry, the “Pregnancy Inflammatory bowel disease And Neonatal Outcomes” (PIANO) registry studied the potential toxic impact of IBD medications on pregnancy. Between 2007 and 2019, pregnant women with IBD were enrolled in a prospective, observational, multicenter study across the United States. The primary analysis was a comparison of five outcomes (congenital malformations, spontaneous abortions, preterm birth, low birth weight [LBW] and infant infections) between pregnancies exposed in utero to biologics, thiopurines or a combination and pregnancies not exposed to the mentioned medications. It was found that drug exposure did not increase the rate of congenital malformations, spontaneous abortions, preterm birth, LBW, and

infections in the newborns over the first year of life. There was no differences in rates of pregnancy complications by drug class with no pattern of congenital malformations to suggest an association with a specific drug. Infants of mothers receiving thiopurines or combination therapy had significantly increased birthweight. Otherwise, there were no differences in height or weight outcomes by drug exposure. There were no differences in developmental milestones in the first year of life by exposure status within the cohort or compared to normal [34]. A recent meta-analysis of 48 studies including close to 7000 patients, showed similar adverse outcomes in pregnancies exposed to biologics compared to the general population for spontaneous abortion, preterm labor, stillbirth, LBW and for congenital malformation [35].

Elderly

Geriatric IBD gained a significant interest lately with the aging patients. Important physiologic changes occur with aging that affect metabolism of drugs and their pharmacokinetics secondary to decrease in renal function, lean muscle mass and total body water and increased body fat [36, 37].Elderly patients with IBD on thiopurine are at a 15-fold higher risk of lymphoproliferative disorders compared with the younger patients on thiopurines and at a 6-fold higher risk of non-melanoma skin cancer compared with younger cohorts [38, 39].Elderly patients exposed to thiopurine are at a significantly high risk of pancreatic cancer (SIR 7.29, 95% CI 1.82–29.16) [40]. In a French nationwide study, the absolute risk of infection was increased by 2- to 3-fold in patients 65 years or older on thiopurine monotherapy compared to those who were not exposed [13]. Studies have shown that thiopurine, anti-TNF and anti-TNF/thiopurine combination are associated with reactivation of Herpes Zoster with hazards ratios of 1.85 (1.61-2.13) for thiopurine, 1.81 (1.48-2.21) for anti-TNF and 3.29 (2.33-4.65) for the combination [41]. This effect is further potentiated with the increase in age [42]. Data regarding the safety of vedolizumab in the elderly is conflicting. A retrospective multicenter cohort study showed an increased risk of non-fatal infections (nasopharyngitis, UTI, cellulitis, Clostridium difficile) compared with younger patients (12% vs 2%, p=0.002) [43]. However, Anti-TNF and vedolizumab seem to have comparable safety profile in elderly patients including C. difficile [44, 45]. Based on real world data, ustekinumab appears safe in elderly Crohn's disease with no significant difference in infusion reaction, risk of infections or post-surgical complications when compared to patients younger than 65 years [46]. Tofacinib has a higher rates of Varicella Zoster virus reactivation in elderly IBD population [47]. Considering the increased risk of venous thromboembolism with tofacinib especially at a dose of 10 mg bid, tofacinib is best reserved for use in patients older than 65 years when there is no alternative treatment [48].

Conclusion

Medical therapy of IBD has a variable degree of toxicity. While most data show safety, specific medications carry well-defined yet small risks. These risks can be mitigated by adequate patient selection and a finite duration of therapy. We should keep in mind special patients like pregnant patients with added exposure to the fetus and geriatric patients with accentuated side effects. As we gain more insight into the goals of therapy, the extent of medication exposure can further be refined. Finally, the cumulative exposure to multiple immunosuppressive medication over time remains unknown and requires dedicated investigations.

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Conflict of interest

None.

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