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TREATMENT RELATED ADVERSE EVENTS AND MONITORING OF PATIENTS RECEIVING BIOLOGIC OR SMALL MOLECULE THERAPY FOR INFLAMMATORY BOWEL DISEASE.

Key Takeaways

- Advanced therapies for IBD are generally safe but require treatment specific ongoing monitoring.
- Individual patient characteristics influence treatment choice and should be considered when implementing an ongoing monitoring strategy.
- Regular biochemical monitoring should be individualized to specific treatment requirements.
- Drug interactions must be considered when prescribing small molecule advanced therapy for IBD.

Introduction

The management of Inflammatory Bowel Disease (IBD) has evolved with the emergence of new treatment paradigms and the introduction of novel advanced therapies, including monoclonal antibodies (mAbs) and small molecules. These advanced therapies have improved disease control, but they necessitate careful pre-treatment assessment and ongoing monitoring to manage potential adverse effects and optimize patient outcomes. This review focuses on practical approaches to treatment-specific monitoring of currently available advanced therapies.

Treatment-associated adverse events

Infections

Patients with IBD, and those taking advanced therapies, are at an increased risk for infections. Maintaining vigilance for signs of infection, prompt evaluation and management, and therapy interruption, when necessary, are crucial in avoiding serious complications.

The risk of opportunistic infections is a significant concern with anti-tumor necrosis factor (TNF) therapy, because this treatment method doubles the risk of such infections among IBD patients.[1] In addition, the risk of tuberculosis reactivation can increase up to 25-fold depending on clinical circumstances.[2] The TREAT Registry showed a serious infection rate of 2.15 events per 100 patient-years (PY).[3] However, a meta-analysis of 21 placebo-controlled Crohn's disease (CD) trials did not show an increased risk of serious infections with anti-TNF therapy.[4] Excluding latent infections prior to treatment and ongoing monitoring, especially for opportunistic and atypical infections, is important when administering anti-TNF therapy.

In a phase 3 CD trial, nasopharyngitis was more frequent in the vedolizumab arm, along with apparently higher rates of both infections and serious infections.[5] However, subsequent long-term safety studies and meta-analyses did not show an increased infection risk with vedolizumab.[6-9] The EVOLVE study, a multicenter retrospective real-world study that included 1,095 IBD patients, found a significantly lower rate of serious infections and adverse events with vedolizumab versus anti-TNF.[10]

Ustekinumab therapy has not shown an increased risk for serious or opportunistic infections in long-term studies,[11] with its infection risk being similar to vedolizumab and lower than that of anti-TNF therapies.[12,13] Risankizumab and mirikizumab therapy have also shown no increased risk of serious or opportunistic infections in the registrational clinical trials.[14-16]

The introduction of Janus kinase (JAK) inhibitors has raised specific concerns around Herpes Zoster (HZ) reactivation. Long-term data on tofacitinib suggests that HZ occurs at a rate of 3.[24] events per 100 PY, with other serious infections occurring at a rate of 1.[8] events per 100 PY.[17] An upadacitinib trial reported similar serious infection rates to adalimumab, but a higher risk of HZ.[18] A recent network meta-analysis concluded that tofacitinib and upadacitinib significantly increase the risk of HZ infection,[19] although most cases were reported to be mild or moderate and had resolved without discontinuation of treatment.[20] Routine use of the adjuvanted recombinant zoster vaccine is recommended for adults requiring advanced IBD therapies.

In a phase 3 trial for UC, it was observed that ozanimod exhibited infection rates of 23% (compared to 11.9% with placebo), with low rates of serious infections (0.9% for ozanimod versus 1.8% with placebo) and HZ (2.2% for ozanimod versus 0.4% with placebo).[21] These results were confirmed by a long-term extension study that reported an infection rate of 24.[3] events per 100 PY, a serious infection rate of 1.9 events per 100 PY, and an HZ rate of 1.7 events per 100 PY.[22] Notably, an open-label study involving multiple sclerosis patients highlighted that opportunistic infections were predominantly driven by HZ.[23] Similarly, in a phase 3 trial for UC, it was found that etrasimod demonstrated minimal serious infection rates (1% for etrasimod versus 3% for placebo) and HZ rates (1% for etrasimod versus 0% for placebo), with no reports of opportunistic infections.[24] Consistent with these findings, long-term safety data from an etrasimod open-label extension trial indicated a low risk of infection.[25]

Vaccination Status

Live vaccines are contraindicated in patients receiving biologic and small molecule therapy. It is important to assess measles, mumps, and rubella (MMR) and varicella-zoster virus (VZV) vaccination history and immune status before initiating advanced therapy. If required, administer vaccines before starting therapy; however, do not delay urgent treatment for live vaccine administration.

Recommendations indicate that all IBD patients should receive the following inactivated vaccines, regardless of active treatment: influenza, meningococcal, Haemophilus influenzae type b, diphtheria, tetanus, pertussis, human papillomavirus, and pneumococcal.

Assess viral hepatitis status before initiating advanced therapy for IBD. Unimmunized patients should receive the hepatitis B vaccine. It is important to note that reactivation of hepatitis B is a known complication of anti-TNF therapy. Patients positive for hepatitis B surface antigen (HBsAg) are at the highest risk and should consider prophylactic antiviral therapy before initiating anti-TNF treatment.

All adult IBD patients should consider the recombinant zoster vaccine (non-live), especially those receiving immunomodulator, biologic, or small molecule therapy as it can mitigate HZ risk.

For further details on immunizations for IBD patients, refer to the 2021 Canadian Association of Gastroenterology Clinical Practice Guideline.[26]

Hematologic And Metabolic

Up to 19% of patients receiving anti-TNF therapy for immune-mediated diseases develop at least one episode of neutropenia, with 6% experiencing serious infections related to neutropenia.[27] Thrombocytopenia is infrequently associated with anti-TNF therapies, with data limited to case reports. In cases of significant thrombocytopenia, alternate causes, including autoimmune conditions or viral infections, should be considered.[28]

Weight gain has been observed in patients with IBD who are receiving anti-TNF therapy. However, long-term registry data has not established a direct link between anti-TNF therapy and weight gain, although patients who are underweight at treatment initiation may experience early weight gain.[29] Some patients gain weight due to an improvement in their nutritional status following effective therapy, as suggested by a small cohort study that showed an increase in both body mass index (BMI) and muscle mass parameters after anti-TNF therapy initiation.[30]

Vedolizumab therapy for IBD has not been associated with metabolic adverse effects. While leukocytosis and leukopenia were reported in a small proportion of patients in registration trials, subsequent long-term safety analyses have not confirmed these findings.[9] Therapies that target interleukins do not appear to cause significant adverse hematologic or metabolic effects.[15,16,31,32]

Neutropenia and lymphopenia occurred in upadacitinib-treated patients in the pivotal induction and maintenance trials, with no cases requiring treatment discontinuation. Neutropenia was observed in 6% of patients treated with 30 mg of upadacitinib, 3% of patients treated with 15 mg of upadacitinib, and in 1% of patients who received a placebo. Lymphopenia occurred in 2% of patients who were treated with both 30 mg and 15 mg doses of upadacitinib, and in 1% of placebo-treated patients. Anemia was more common in placebo-treated patients compared to those receiving upadacitinib.[33] With up to 9.2 years of safety data, significant cytopenias have not been reported with tofacitinib.[17] Creatine phosphokinase (CPK) elevations were observed in a small percentage of JAK inhibitor

patients and were mostly asymptomatic and non-serious.

S1P receptor modulators impair the migration of lymphocytes out of lymphoid tissue by blocking S1P receptors, leading to a relative reduction in circulating peripheral lymphocytes. There is generally an expected and measurable relative reduction in lymphocytes by approximately 40%–50%, which resolves after treatment discontinuation in most patients. Profound lymphopenia is rare, occurring in 1% of patients.[21,25,34]

Cardiovascular

Patients with IBD are at an increased risk of cardiovascular disease,[35] likely attributable to chronic inflammation and associated metabolic derangement.[36] While effective management of IBD and its underlying risk factors is key, there are specific treatment-related considerations.

Data from preclinical studies suggested potential benefits of TNFα inhibition for treating congestive heart failure, however, a subsequent clinical trial showed no such benefit, and had reported an increased risk of hospitalization and all-cause mortality.[37] Case reports also link anti-TNF therapy to heart failure exacerbations in patients with IBD.[38] Anti-TNF therapy is contraindicated in New York Heart Association Class III/IV heart failure and should be used with caution in patients at risk for heart failure.

Long-term safety data has not established an increased cardiovascular event risk with vedolizumab therapy.[9] Agents targeting IL-12 and -23 show a favourable safety profile with no significant increase in cardiovascular events compared to other therapies.[39]

Initiation of JAK inhibitor therapy can modestly increase both low density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels by approximately 20%, with the LDL-HDL ratio remaining stable.[33,40-42] It is not clear if increased cholesterol levels results in atherosclerosis. Interestingly, there is some evidence that tofacitinib may positively impact macrophage cholesterol metabolism, which could potentially mitigate the risk of atherosclerosis.[43]

In a long-term extension study of tofacitinib for treating UC, the risk of major adverse cardiovascular events was low, with a rate of 0.27 events per 100 PY.[17] A systematic review and meta-analysis of real-world studies also did not report any major adverse cardiovascular events or thromboembolic complications.[44]

The ORAL Surveillance open-label randomized trial compared tofacitinib at a dose of 5 mg or 10 mg twice daily to anti-TNF therapy in 4,362 patients older than 50 years with active rheumatoid arthritis and at least one additional cardiovascular risk factor. The results of the trial demonstrated a higher incidence of major cardiovascular events with tofacitinib.[45] Post-hoc analyses demonstrated that the increased risk of adverse cardiovascular events was limited to a high-risk patient cohort (age ≥65 years or those with a history of smoking)[46] and was predominantly observed in patients with prior atherosclerotic cardiovascular disease.[47] The SELECT-COMPARE trial compared the effects of upadacitinib and adalimumab for rheumatoid arthritis treatment, and found no difference in the incidence of cardiovascular events.[48]

S1PRMs pose specific cardiac safety concerns due to S1P1 receptors, which are found on cardiac myocytes, and their subsequent effects on cardiac conduction. Transient bradycardia is a common early side effect, within hours of the first dose, which is largely asymptomatic. In the True North induction and maintenance trials, one patient developed a type 1 second-degree heart block, and there were no cases of type II or third-degree heart block.[21,34] A large open-label extension trial of ozanimod for multiple sclerosis reported hypertension at a rate of 2.0 events per 100 PY and no cases of second- or third-degree heart block.[23]

Thromboembolic

IBD has long been recognized as a risk factor for venous thromboembolism (VTE) and arterial events, especially during disease exacerbation.[49-51] Corticosteroid use increases VTE risk, while anti-TNF agents have been associated with a decreased risk of VTE.[51,52]

Despite regulatory warnings prompted by the ORAL Surveillance study, long-term exposure data suggests that the risk of VTE and arterial thrombosis in those treated with JAK inhibitors remains low. Randomized trials and real-world studies have consistently found low rates of these adverse events that do not differ from those observed with anti-TNF therapy.[17,44,48,53,54] A recent consensus process concluded that there is no observable increased risk of VTE in IBD patients treated with tofacitinib.[51]

Hepatic

Anti-TNF therapies have been associated with a variety of liver injury patterns, with events ranging from transient and self-limited, to severe.[55] Anti-integrin and anti-interleukin therapies have a low risk of drug-induced liver injury, although there have been cases of idiosyncratic, clinically apparent liver injury that has resolved with discontinuation.[9,56]

Unlike monoclonal antibodies, small molecule drugs undergo hepatic metabolism through the cytochrome P450 enzyme system, which can result in drug-drug interactions. Elevations of transaminases have been observed with both JAKs and S1PRMs, although they are generally mild and do not require treatment discontinuation.[22,24,33,56]

Neurologic

Anti-TNF agents increase the risk of inflammatory demyelinating and non-demyelinating central nervous system (CNS) events, especially in patients with multiple sclerosis or a history of optic neuritis.[57] Other advanced therapies do not appear to increase the risk of inflammatory CNS events.

One case of progressive multifocal leukoencephalopathy (PML) has been reported in a vedolizumab-treated patient who was HIV-positive and on concomitant immunosuppression, another case of PML was reported in an infliximab-treated patient,[58] and there have been case reports of PML in S1PRM-treated multiple sclerosis patients.[23]

Posterior reversible encephalopathy syndrome (PRES) has been reported in patients treated with anti-TNF agents[59,60] and ustekinumab.[61,62]

Ophthalmologic

Clinical trial data suggest that S1PRMs can trigger macular edema in 1:125 to 1:300 patients. [21,22,34] The cases generally resolve following drug discontinuation, however, patients with pre-existing uveitis or diabetes are at increased risk.

Immunologic

Anti-TNF therapy triggers a spectrum of immune-mediated adverse events, including infusion reactions, injection site reactions, delayed hypersensitivity reactions, paradoxical autoimmune disorders (e.g., lupus-like syndromes and psoriasis), and immunogenicity. Subsequent mAbs and small molecule therapies have largely attenuated these immunologic complications of treatment.

Malignancy

The use of anti-TNF agents has raised concerns around an increased risk of malignancy, specifically non-melanoma skin cancer (NMSC) and lymphoma,[63] although the evidence has been conflicting.[64,65] The S1PRM modulator fingolimod has a slightly increased risk of basal cell carcinoma,[66] which has not been conclusively demonstrated with ozanimod or etrasimod.[21,22,25] Findings on the malignancy risk of JAKs are also varied, with some studies suggesting a risk of malignancy and NMSC.[17,40,67,68]

Treatment Monitoring Strategy

Effective IBD management requires a baseline assessment and ongoing monitoring for treatment-related complications. Regular laboratory investigations, symptom monitoring, infection vigilance, cancer screening, and attention to treatment-specific concerns are crucial. Please see the table below for more information.

Therapeutic Class	Medication	Pre-Treatment Assessment	Ongoing Monitoring
Anti-tumour necrosis factor-α (TNFα)	Infliximab Adalimumab Golimumab Certolizumab	CBC, hepatic function, viral hepatitis (HBV, HCV), TB status, exposure to opportunistic pathogens. Vaccine review (no live vaccination during treatment). Contraindicated if: • Active infection. • Profound cytopenia. • NYHA Class III or IV heart failure. • Pre-existing multiple sclerosis or optic neuritis.	CBC every 3–6 months. Liver panel every 3–6 months. Tb/viral hepatitis if high-risk travel or exposure. Monitor for signs and symptoms of infection with consideration of atypical/opportunistic pathogens. Consider an annual pap-smear and skin exam, especially if concomitant immunosuppressive therapy. Annual influenza vaccine and COVID-19 vaccine as per National Advisory Committee on Immunization (NACI) recommendations.
Anti-integrin	Vedolizumab	Vaccine review (no live vaccination during treatment). Consider TB status assessment.	CBC every 3–6 months. Liver panel every 3–6 months. Annual influenza vaccine and COVID-19 vaccine as per National Advisory Committee on Immunization (NACI) recommendations.
Anti-interleukin	Ustekinumab Risankizumab Mirikizumab	CBC, hepatic function, viral hepatitis (HBV, HCV), TB status, exposure to opportunistic pathogens. Vaccine review (no live vaccination during treatment).	CBC every 3–6 months. Liver panel every 3–6 months. Monitor for signs and symptoms of infection with consideration of atypical/opportunistic pathogens. Annual influenza vaccine and COVID-19 vaccine as per National Advisory Committee on Immunization (NACI) recommendations.

Janus Kinase inhibitor	Tofacitinib	CBC, hepatic function, viral hepatitis (HBV, HCV), TB status, exposure to opportunistic pathogens. Baseline lipid panel and cardiovascular risk factor assessment. If age >65 years or history of cardiovascular disease, use lowest effective dose with careful consideration of risks and benefits. Family planning, if applicable. • Dose adjustment (5 mg BID) if: • eGFR <60. • Strong CYP3A4 inhibitors. • Moderate CYP3A4 inhibitor with a strong CYP2C19 inhibitor. Contraindicated if: • Pre-existing cytopenia (ANC <1.0 × 10^9 cells/L, HGB <90 g/L, ALC <0.5 × 10^9 cells/L). • Severe renal (eGFR <15 ml/min) or hepatic impairment. • Potent CYP3A4 inducers. Vaccine review (recombinant herpes zoster highly recommended, no live vaccines during treatment).	CBC every 3–6 months: • Interrupt treatment if HGB <80 g/L or decrease >20 g/L; or ANC 0.5–1.0 × 10^9 cells/L. • Discontinue if ANC <0.5 x 10^9 cells/L or ALC <0.5 × 10^9 cells/L. • Liver panel at 4–8 weeks, then every 3–6 months. Lipid panel at week 4–8 (tofacitinib)/ week 12 (upadacitinib); then every 6 months. Coordinate hypercholesterolemia management with primary care/ cardiology, per 2021 Canadian Cardiovascular Society Guidelines. Periodic confirmation of medication adherence. Periodic review of family planning, if applicable. Monitor for signs and symptoms of infection with consideration of atypical/opportunistic pathogens. Consider an annual skin exam. Annual influenza vaccine and COVID-19 vaccine as per National Advisory Committee on Immunization (NACI) recommendations.
	Upadicitinib		
Sphingosine-1-phosphate receptor (S1PR) modulators	Ozanimod	CBC, hepatic function, viral hepatitis (HBV, HCV), TB status, exposure to opportunistic pathogens. Cardiac assessment: ECG, heart rate, blood pressure. Ophthalmology evaluation (if diabetes mellitus, uveitis, or retinal disease). Family planning, if applicable. Caution if: • Pre-existing pulmonary disease. • Drugs that slow the heart rate or AV conduction. Contraindicated if: • Concomitant use of MAO inhibitors. • Severe hepatic impairment. • Myocardial infarction, unstable angina, stroke, or transient ischemic attack, decompensated or advanced heart failure, within 6 months. • Cardiac conduction abnormalities (AV node block, SA block) without a pacemaker. • Macular edema. • Severe respiratory disease (pulmonary fibrosis, asthma, or chronic obstructive pulmonary disease); spirometry if indicated. Vaccine review (recombinant Herpes Zoster highly recommended, no live vaccines during treatment).	CBC every 3-6 months: • interrupt treament if ALC < 0.2 x 10^9 cells/L Liver panel every 3–6 months. Assess visual disturbances. Monitor blood pressure regularly. Periodic confirmation of medication adherence. Periodic review of family planning, if applicable. Monitor for signs and symptoms of infection with consideration of atypical/opportunistic pathogens. Consider annual skin exam. Annual influenza vaccine and COVID-19 vaccine as per National Advisory Committee on Immunization (NACI) recommendations
	Etrasimod		

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; AV, atrioventricular; BID, twice a day; CBC, complete blood count; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; ECG, electrocardiogram; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HGB, hemoglobin; NYHA, New York Heart Association; SA, sinoatrial; Tb, tuberculosis; TNFα, tumour necrosis factor-α.

Table 1: Therapeutic class-based guide for advance therapy monitoring in the management of Inflammatory Bowel Disease ; courtesy of Michael Stewart, MD, FRCPC

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