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Adverse events in IBD: to stop or continue immune suppressant and biologic treatment

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Abstract

Crohn's disease and ulcerative colitis affect an increasing number of patients. A variety of medical options exist for the treatment of these diseases including immune suppressants and biologic therapies. Unfortunately, these agents are associated with adverse events ranging from mild nuisance symptoms to potentially life-threatening complications including infections and malignancies. This review discusses adverse events associated with azathioprine, mercaptopurine, and methotrexate as well as anti-TNF-α and anti-integrin antibodies. In addition, adverse events associated with combination therapy are discussed as are clinical scenarios in which it may be reasonable to discontinue or de-escalate drug therapy. It is the responsibility of the treating gastroenterologist to effectively communicate the benefits and risks of therapy with patients; this review offers strategies that may assist providers in communicating risk with patients in addition to offering our perspective on whether modification or cessation of therapy can be considered.

Keywords

adalimumab; azathioprine; certolizumab pegol; Crohn's disease; inflammatory bowel disease; infliximab; mercaptopurine; methotrexate; natalizumab; ulcerative colitis

Inflammatory bowel disease (IBD) consists of two main subtypes, Crohn's disease (CD) and ulcerative colitis (UC). These are chronic, relapsing inflammatory disorders that predominantly affect the gastrointestinal tract. The prevalence and incidence of CD and UC have increased in recent years, particularly in industrialized nations [1]. In the USA, approximately 30,000 new cases are diagnosed annually, most often during the second and third decades of life [2].

Aminosalicylates (5-ASA) are safe and effective in patients with mild-to-moderate UC [3]; however, their benefit in patients with mild-to-moderate CD, particularly those with small bowel disease, is debatable [4]. Approximately one-half of UC patients treated with 5-ASA

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require escalation of therapy [5]. Although corticosteroids are very effective for the induction of remission, their significant side-effect profile precludes their use as a maintenance agent. Patients who respond to corticosteroid therapy are often transitioned to steroid-sparing immune suppressants, such as azathioprine (AZA), 6-mercaptopurine (6MP) or, in some cases, methotrexate (MTX). Immune suppressants are associated with multiple side effects including, but not limited to, myelosuppression and liver toxicity. Monoclonal antibodies directed against TNF-α are also available for treatment of CD and UC. They too are associated with multiple side effects including infusion and injection site reactions, infectious complications and autoimmune phenomena such as psoriasiform eruption. Natalizumab, an antibody directed against the α4 integrin, prevents extravasation of leukocytes into gut mucosal tissue. It has been used for the induction and maintenance of remission in patients with moderate-to-severe CD [6,7]; however, its widespread adoption has been limited due to its association with progressive multifocal leukoencepholopathy (PML).

This review examines adverse events associated with immune suppressant, anti-TNF-α and anti-integrin therapy. We first discuss adverse events associated with the immune suppressants AZA, 6MP and MTX. The latter portion of this review discusses adverse events associated with biologic therapy with or without concurrent immune suppressant administration. We conclude by discussing strategies that may assist providers in communicating risk with patients in addition to offering our perspective on whether modification or cessation of therapy can be considered.

Purine analogs

AZA and 6MP are steroid-sparing agents that have been used to treat CD and UC for over 50 years [8–10]. A Cochrane analysis supports their use for maintenance of remission in patients with moderately active CD [8]. A second Cochrane analysis concluded that AZA and 6MP cannot be recommended as first-line therapy for maintenance of remission in patients with UC due to the efficacy and more favorable side-effect profile of 5-ASA therapy [9].

Downstream metabolites of AZA and 6MP are responsible for their therapeutic effect as well as some of their adverse effects. High levels of 6-methyl mercaptopurine (6MMP) are associated with hepatotoxicity. 6-thioguanine (6TG), the active metabolite of AZA and 6MP, is therapeutic at levels between 230 and 400 pmol/8 × 10^8 red blood cell (RBC). Supratherapeutic levels of 6TG, however, are associated with bone marrow suppression. Because patients metabolize thiopurines differently according to differences in thiopurine S-methyltransferase (TPMT) activity, assessing the activity of this enzyme prior to initiating therapy is recommended by the American Gastroenterological Association [11]. Absent TPMT activity occurs in 1 in 300 patients; therapy with a purine analog should be avoided in this population because of an extremely high risk of myelosuppression. Approximately 1 in 10 patients have low or intermediate TPMT activity and should begin treatment with lower doses of AZA or 6MP to minimize the risk of myelosuppression [12]. Side effects occur in 5–30% of patients taking thiopurines [10], with 10–28% of patients discontinuing therapy as a result [13].

Idiosyncratic reactions

Nausea is common in patients receiving AZA or 6MP. Chaparro *et al*. reported nausea in 8% of patients treated with thiopurines [13]. Of the patients who experienced nausea, greater than 80% discontinued therapy. There was no difference between AZA and 6MP. However, Kennedy *et al*. found that 62% of patients who developed gastrointestinal (GI) toxicity due to AZA were able to tolerate therapy with 6MP [10], suggesting that 6MP may be attempted in these patients. Advising patients to take AZA or 6MP in divided doses, prior to bedtime, or with food are alternate strategies that have been employed successfully to minimize nausea.

Hypersensitivity reactions

Hypersensitivity reactions occur in approximately 5–10% of patients treated with AZA [14–18]. They occur independent of dose, typically within the first 4 weeks of therapy. TPMT activity does not affect the propensity of a patient to develop a hypersensitivity reaction, although there is speculation that genetic polymorphisms could predispose patients to AZA hypersensitivity [19]. The imidazole component of AZA may be responsible for these reactions by binding to endogenous proteins resulting in the formation of haptens that trigger these reactions [20].

A variety of symptoms can accompany hypersensitivity reactions including fever, chills, arthralgias, myalgias, cutaneous eruptions, leukocytosis, liver and/or renal dysfunction and, rarely, shock [15]. The utility of switching to 6MP in patients who develop flu-like symptoms is less well-established than in patients who develop GI toxicity. Lees *et al*. found that 6MP was tolerated in 61% of patients who developed flu-like illness while on AZA [21]. However, a meta-analysis performed by Kennedy *et al*. found that only 36% of patients who developed flu-like illness in response to AZA therapy were subsequently able to tolerate 6MP [10]. Changing therapy to 6MP in AZA-hypersensitive patients can be considered in patients without severe symptoms, although it is our practice to switch to MTX or an anti-TNF-α agent in patients who experience a hypersensitivity reaction to thiopurines [22].

Infections

Thiopurine exposure is associated with an increased rate of infection in solid organ transplant recipients, patients with autoimmune diseases including IBD and patients with other inflammatory disorders, even in the absence of neutropenia [22–24]. In a retrospective cohort study of 285 IBD patients, infectious complications occurred in 3% of patients receiving 6MP, although at least one of these patients was also taking prednisone [25]. A previous retrospective cohort study examined side effects associated with 6MP, finding that 7% of patients treated with 6MP developed infections [26].

In addition to an increased risk for serious infections, patients receiving thiopurines are also at increased risk of developing opportunistic infections (odds ratio [OR]: 3.1; 95% CI: 1.7–5.5) [23]. These findings were also observed in a recent multicenter, prospective study of 570 IBD patients [27]. Patients on thiopurines most commonly contracted viral infections as opposed to fungal, bacterial or mycobacterial infections (Table 1) [23].

Myelosuppression

Bone marrow suppression occurs in 2–5% of patients treated with thiopurines with leukopenia observed in 2–4% treated with AZA or 6MP [9,13,28,29]. Anemia and thrombocytopenia occur in 0.9 and 0.2% of patients, respectively [13]. Bone marrow suppression can be profound and occasionally fatal. Severe myelotoxicity is more likely to occur in patients with absent or decreased TPMT activity [30], although some studies argue that factors unrelated to TPMT activity predispose patients to myelotoxicity [31]. Therefore, clinicians should not be falsely reassured regarding the risk of leukopenia in patients with normal or high TPMT activity. Most patients who develop myelosuppression do so within 1 year of initiation of therapy; however, 25% will not develop signs of myelotoxicity until >1 year of thiopurine exposure [32]. These observations support routine monitoring of patients treated with AZA/6MP (Table 2).

Liver toxicity

Liver injury, from mild transaminasemia to the development of portal hypertension and nodular regenerative hyperplasia (NRH), is linked to thiopurine exposure. Hepatotoxicity is associated with 6MMP levels >5700 pmol/8 × 10^8 RBC [33]. Elevated 6MMP levels occur more frequently in patients with high TPMT activity that preferentially metabolizes thiopurine to 6MMP instead of 6TG. Therefore, patients often have low 6TG and high 6MMP levels. As a result, although dose reduction will improve hepatotoxicity, levels of 6TG will drop further. If, however, patients have an appropriate or supratherapeutic 6TG level, the dose of AZA/6MP may be reduced with subsequent re-evaluation of liver enzymes.

In cases where preferential 6MMP shunting occurs, several options exist for decreasing 6MMP and increasing 6TG levels. Allopurinol, through an unknown mechanism, increases 6TG and decreases 6MMP levels in patients with preferential 6MMP shunting [34]. Allopurinol should be used with caution as severe leukopenia can occur. Studies examining the use of allopurinol to increase 6TG levels have generally decreased the thiopurine dose by 25–50%, with close monitoring of blood counts in the first few months after initiating therapy. Split dosing of thiopurines can also decrease 6MMP levels, from 11,785 pmol/8 × 10^8 RBC to 5324 pmol/8 × 10^8 RBC, without change in clinical disease activity or 6TG levels [35].

Thiopurine exposure is also associated with NRH. NRH is thought to develop in the setting of endothelial injury to the hepatic sinusoids resulting in regions of atrophic hepatic parenchyma interspersed within areas of parenchymal hyperplasia [36]. Data from case–control [37] and prospective cohort [38] studies suggest that approximately 0.5% of patients treated with AZA develop NRH after 5 years of treatment, increasing to 1% of patients after 10 years of treatment. Possible risk factors for NRH in IBD patients receiving thiopurines include male sex and small bowel resection of greater than 50 cm [38]. Unlike transaminasemia, NRH appears to be linked to exposure to 6TG rather than 6MMP [38], which has been highlighted in patients who have received oral thioguanine as a treatment for IBD. Thioguanine can be given orally like AZA, but unlike AZA thioguanine does not generate 6MMP. An early report found that 76% of patients treated with oral thioguanine

with concomitant liver enzyme elevation or thrombocytopenia had biopsy-proven NRH, which was also observed in 33% of thioguanine-exposed patients with normal laboratory parameters [39]. The prevalence of NRH has been evaluated in thiopurine-naïve patients with IBD. In patients undergoing IBD-related abdominal surgery, 6% had NRH by intraoperative liver biopsy; however, this study was not controlled and included patients recently exposed to corticosteroids, which have also been associated with NRH [40]. A recently published review exploring this topic found no cases of NRH in patients treated with <20 mg of thioguanine daily [41], corresponding to a 6TG level of 600 pmol/8 × 10^8 RBC, suggesting that the development of NRH may be dose-dependent.

Pancreatitis

Pancreatitis occurs in approximately 4% of patients treated with thiopurines, usually within weeks of beginning treatment [13]. Females and patients with CD (as opposed to UC) are at increased risk of developing pancreatitis [42,43], although the reasons for this have not been determined. Pancreatic autoantibodies, which develop more commonly in patients with CD than other inflammatory disorders, may contribute to the development of acute pancreatitis in patients receiving thiopurines. However, this link could not be established in a study of 34 CD patients with AZA-induced pancreatitis [44]. Thiopurine-induced pancreatitis is most likely an allergic reaction because of its quick onset and rapid recurrence after re-exposure to the inciting agent. As a result, switching from AZA to 6MP, or vice versa, is not advised in patients who develop thiopurine-induced pancreatitis.

Malignancy

Thiopurines are associated with an increased risk of lymphoma and non-melanoma skin cancer (NMSC) (Tables 3, 4, 5) [45–49]. It is thought that thiopurine exposure causes decreased immune surveillance of Epstein–Barr virus (EBV)-infected B cells as well as mutations in DNA through thiopurine incorporation during DNA replication [50,51]. The risk of lymphoproliferative disorders and skin cancer was evaluated in a prospective cohort study. Approximately 20,000 IBD patients (60% CD, 40% UC) were followed for a median of 35 months, 30% of whom were receiving thiopurines. Twenty-three cases of lymphoproliferative disorders were diagnosed during the follow-up period. The incidence ratio (IR) for patients on thiopurines was 0.9 per 1000 compared with 0.2 per 1000 for patients who had discontinued thiopurines and 0.3 per 1000 for patients never exposed to thiopurines. The adjusted hazard ratio (HR) between patients exposed to thiopurines and those never exposed was 5.3 (95% CI: 2.0–14). This study not only established that IBD patients on thiopurines have a greater risk of lymphoproliferative disorders, but also demonstrated that the risk of these disorders returns to baseline in patients who discontinue therapy (Table 3) [52].

An increased risk of NMSC in IBD patients treated with thiopurines was found in the same cohort of IBD patients [47]. In patients <50 years of age, the incidence of NMSC was 0.7 per 1000 patient-years among those receiving thiopurines and 0.4 per 1000 patient-years among those previously exposed to thiopurines. The incidence of NMSC among patients never exposed to thiopurines was 0 per 1000 patient-years. The risk of NMSC increased with age in patients who continued thiopurine therapy as well as those no longer exposed to

thiopurines (Table 4). Ongoing thiopurine treatment (HR: 5.9; 95% CI: 2.1–16) and past thiopurine exposure (HR: 3.9; 95% CI: 1.3–12) were associated with an increased risk of NMSC [47].

Methotrexate

MTX is a folic acid antagonist with anti-neoplastic as well as anti-inflammatory effects, possibly due to decreased proinflammatory cytokine production and increased immune cell apoptosis [53,54]. MTX is used to treat patients with inflammatory disorders, including IBD, although data supporting its use in UC are less robust than for patients with CD [55–57]. MTX is associated with side effects including liver toxicity, dyspnea, nausea, vomiting, fatigue and neutropenia [58]. Although these reactions are not typically life-threatening, 30% of patients treated with MTX for at least 5 years discontinue therapy because of adverse effects [59]. Other studies have reported a side-effect rate as low as 17% with withdrawal of MTX in only 8% of patients [58]. The rate of adverse events, particularly hepatic and GI effects, is higher (74 vs 38%) in patients who do not receive folic acid supplementation [60]. Some patients experience fewer side effects with oral MTX administration; however, intramuscular or subcutaneous administration is favored in the treatment of patients with CD [56,57].

Idiosyncratic reactions

The most common adverse effects associated with low-dose MTX therapy include nausea, vomiting and diarrhea. These side effects occur in approximately 10% of patients, although a range of 2–19% has been reported [58,60–62]. These reactions are typically mild and occur shortly after drug administration. Fatigue occurs in 2–6% of patients [61,62]. Stomatitis occurs in 6% of patients and alopecia in 1% [63].

Data exist supporting the use of folic acid or leucovorin to prevent or reduce adverse effects associated with MTX therapy [64,65]. It has been our practice to recommend 1 mg of folic acid daily for patients receiving MTX. If fatigue or nausea develop, we increase the folic acid to 2 mg the day of and day after injection and consider the addition of anti-emetics such as ondansetron 8 mg orally before and after injection. If the symptoms do not abate, the folic acid can be increased to 2 mg daily. In addition, leucovorin can be considered in patients who experience persistent side effects related to MTX therapy.

Infection

An increased risk of infection in patients treated with MTX has not been established. A retrospective cohort study by Saibeni *et al*. reviewed approximately 5500 IBD patients at eight referral centers. In total, 112 patients were prescribed MTX. Of these, 32 (34%) discontinued therapy due to adverse effects; however, only 4 did so because of infectious complications [60]. A second retrospective cohort study reviewed the records of approximately 2700 CD patients from three referral centers, 174 of whom were treated with MTX. One of 174 patients developed cytomegalovirus infection and discontinued therapy. No other infections were reported [61]. In addition, a case–control study of 100 IBD patients

from a single center was unable to detect an increased risk of infection associated with MTX use in patients with IBD [23].

Myelosuppression

MTX, like the purine analogs, can cause myelosuppression. Because of concerns regarding these effects, the British Society of Gastroenterology recommends complete blood count (CBC) monitoring before the start of treatment, within 4 weeks of the initiation of treatment, and monthly thereafter [62]. Similarly, the American College of Rheumatology recommends CBC monitoring every 4 weeks while on MTX, although we decrease the frequency of monitoring to every 3 months after the first 4 months of treatment (Table 2) [66]. In a study examining MTX use in patients with UC and CD who had previously received thiopurines, 4 of 132 patients developed neutropenia. One patient underwent dose reduction; the others required more frequent CBC monitoring [58]. Seinen *et al*. did not report any cases of myelotoxicity in their cohort from three hospitals in The Netherlands [61].

Pulmonary toxicity

Lung injury associated with MTX exposure is infrequent, but potentially life-threatening. [67]. MTX-induced lung injury typically occurs after an extended course (weeks to months) of therapy [68,69]. The incidence of acute lung injury attributable to MTX remains unclear because early reports included patients with pulmonary infections and other processes with potential pulmonary manifestations. In addition, studies did not always exclude patients receiving other drugs that could negatively affect lung function. Acute lung injury occurs in 2–5% of RA patients [70]. Patients at greatest risk of developing pulmonary toxicity due to MTX include those who are >60 years of age, have hypoalbuminemia, pre-existing lung disease prior to the initiation of therapy or impaired renal function [67]. It is our practice to obtain a baseline CXR prior to initiating MTX therapy and avoid treatment in patients with pre-existing pulmonary disease.

MTX pulmonary toxicity most commonly presents in a sub-acute fashion. Most patients are diagnosed within 32 weeks of the initiation of therapy [69]. Common complaints include fever, cough, dyspnea and chest pain, which may be accompanied by hypoxia and tachypnea. Some patients may progress rapidly to respiratory failure [67,68]. Peripheral eosinophilia is suggestive of the diagnosis [71]. Imaging findings can vary widely and may include diffuse ground glass attenuation, reticular opacities, traction bronchiectasis and/or centrilobular nodules. Infection can be excluded with sputum culture and/or bronchoscopy. The diagnosis typically requires a combination of imaging findings consistent with pulmonary interstitial or alveolar infiltrates with exclusion of other pulmonary processes including infections. In some cases, surgical biopsy may be required to diagnose MTX-induced lung injury [67,68]. Pulmonary fibrosis occurs in approximately 10% of patients with subacute MTX-induced pulmonary toxicity [67]. Patients usually improve after drug withdrawal; however, patients with significant respiratory compromise may require glucocorticoid therapy and/or support in a monitored setting [68,71].

Liver toxicity

Liver injury, including progression to fibrosis and cirrhosis, is also linked to MTX exposure [72]. Patients may experience mild, transient, asymptomatic elevation of liver enzymes, which usually resolves with dose reduction or temporary discontinuation of therapy [60]. Patients can also develop MTX-induced hepatic fibrosis, which does not typically occur before a cumulative dose of 1500–6000 mg [73]. In patients with psoriasis, liver injury occurs in up to 25% of patients receiving MTX therapy [74]. Because of the high rate of liver toxicity in this population of patients, liver biopsy is recommended when a patient's cumulative dose reaches 1500 mg [75]. Although multiple studies exist in patients with rheumatologic disorders examining liver toxicity and the role of biopsy after high cumulative doses of MTX have been reached, there are relatively little data to guide clinicians treating IBD patients with MTX. In the absence of another indication and/or abnormal transaminases, we do not routinely recommend liver biopsy in patients with high cumulative doses of MTX.

A retrospective review published in 2010 examined 87 IBD patients treated with MTX between 1995 and 2008. Ninety-two percent of patients received 25 mg of parenteral MTX weekly for a mean of 81 weeks; 40% of patients received >1500 mg of MTX. Twenty-five percent of patients with previously normal liver enzymes developed abnormal liver enzymes, 44% of whom had an underlying risk factor for liver disease. However, only 5% of patients discontinued therapy because of liver enzyme abnormalities. Of the patients who ultimately underwent liver biopsy, none had evidence of advanced fibrosis (Table 2) [76].

Teratogenicity

MTX is in pregnancy class X. It is an abortifacient and is associated with the development of congenital malformations [77–79]. Women are advised to avoid pregnancy for at least one ovulatory cycle after the cessation of therapy [80]. Men have been advised to avoid pregnancy for at least 3 months after cessation of MTX [80]; however, recent data suggest that paternal MTX exposure at the time of conception is not linked to congenital malformations [81]. Breastfeeding while on MTX is contraindicated [82]. It is our practice to recommend that patients with childbearing potential use at least two forms of contraception while on MTX and for 6 months after the cessation of therapy. If a patient conceives while on MTX therapy, additional doses of the drug should be held and the patient should be evaluated promptly by a maternal-fetal medicine specialist.

Anti-TNF-α therapy

Monoclonal antibodies directed against TNF-α are used to treat patients with moderate-to-severe IBD or who are refractory to conventional medical therapy. At present, infliximab (IFX) [83,84], adalimumab (ADA) [85,86] and certolizumab pegol (CZP) [87] are approved for the induction and maintenance of remission in CD. IFX [88], ADA [89] and golimumab [90,91] are approved for the induction and maintenance of remission in UC.

Infection

Anti-TNF-α therapy is associated with increased risk of serious and opportunistic infections in patients with IBD [23,92,93], with approximately 36% developing an infection within 51 weeks of the initiation of therapy [84,85,94,95]. Typically, these infections are not serious and are easily treated. However, TNF-α inhibitors have been linked to more serious infections such as pneumonia, sepsis, fungal infections and tuberculosis [23,96]. A retrospective cohort study performed at Mayo Clinic reported 48 infections among 500 CD patients treated with IFX [92]. Fifteen of these patients developed infections classified as serious. In addition, the Crohn's Therapy, Resource, Evaluation, and Assessment Tool registry, which includes >6000 patients with CD, found that IFX exposure was associated with serious infection (HR: 1.4; 95% CI: 1.1–1.8) even after adjusting for other factors such as disease activity, steroid use and narcotic use [96,97]. Rheumatoid arthritis (RA) patients receiving IFX or ADA also have a higher rate of infection when compared with patients receiving placebo (OR: 2.0; 95% CI: 1.3–3.1) (Table 1) [98].

In addition to serious infections, patients exposed to anti-TNF-α therapy are also at risk of developing opportunistic infections. In a case–control study examining 100 consecutive IBD patients with opportunistic infections, the OR for developing an opportunistic infection in patients receiving IFX was 4.4 (95% CI: 1.2–17.1), which increased to 14.5 (95% CI: 4.9–43) when IFX was combined with a thiopurine or corticosteroid [23]. A recent meta-analysis of 22 randomized controlled trials found that opportunistic infections developed in 0.9% of patients receiving anti-TNF-α therapy versus 0.3% of those receiving placebo. The relative risk of developing an opportunistic infection was significantly higher in patients receiving anti-TNF-α therapy (2.1; 95% CI: 1.1–3.9) (Table 1) [99].

The risk of postoperative complications, including infections, in the setting of TNF-α inhibitor use has been debated. Early studies did not detect differences in postoperative infections in patients receiving TNF-α inhibitors [100,101]; however, more recent work found that CD patients exposed to TNF-α inhibitors within 8 weeks of surgery developed more infectious complications than control patients (36 vs 25%). This study also demonstrated that preoperative anti-TNF-α exposure was a predictor of both overall infections (OR: 2.4; 95% CI: 1.2–5.0) and surgical site (OR: 2.0; 95% CI: 1.0–3.8) complications [102]. These findings were confirmed recently in a meta-analysis [103].

Patients exposed to anti-TNF-α agents are also at risk of developing tuberculosis (TB) or re-activating TB in cases of latent infection [93]. In a retrospective cohort study of over 22,000 CD patients, anti-TNF-α therapy was associated with an increased risk of TB (HR: 2.7; 95% CI: 1.0–7.3) [93]. A subsequent study evaluating claims data from patients with CD versus control patients found that exposure to steroids, immune suppressants or anti-TNF-α therapy was associated with increased TB risk (HR: 2.7; 95% CI: 1.0–7.3) [93]. However, a more recent meta-analysis found a relative risk of 2.5 for the development of TB in anti-TNF-α-exposed patients, although the CI crossed unity [99]. Prescribers are advised to evaluate patients for TB risk factors and test for latent infection prior to beginning therapy as well as periodically during therapy (Table 2) [104].

A variety of bacterial, fungal and viral infections have been reported in patients treated with TNF-α inhibitors including oral and esophageal candidiasis, varicella zoster, herpes zoster, EBV, cytomegalovirus, herpes simplex virus, *Listeria monocytogenes*, *Pneumocystis jirovecii* and *Nocardia* [99,105,106]. At present, there are no recommendations to check fungal serologies in patients from endemic areas nor are there recommendations to treat latent viral infections prior to initiating anti-TNF-α therapy. We do not advocate that patients receiving anti-TNF-α therapy or combination therapy receive prophylaxis against *Pneumocystis* pneumonia as the absolute risk of *Pneumocystis* is quite low. Prophylaxis is recommended in patients receiving cyclosporine therapy with concurrent steroids and/or immune suppressants and should be considered in patients on triple immune suppression, patients with lymphopenia or leukopenia, patients with multiple comorbidities particularly chronic obstructive pulmonary disease and patients older than 55 years of age (Table 2). We do not ask patients to avoid raw milk products to prevent *Listeria*.

Patients who are carriers of hepatitis B virus (HBV) are at risk for reactivation when immune suppressed [107]. In a nation-wide Spanish study of patients with IBD and viral hepatitis, treatment with greater than or equal to 2 immune suppressants was associated with an increased risk of HBV reactivation (OR: 8.8; 95% CI: 1.1–65) [107]. A meta-analysis demonstrated that lamivudine prophylaxis is associated with reduced mortality in immune-suppressed patients (OR: 0.34; 95% CI: 0.23–0.6) [108]. Consequently, prophylaxis is recommended in HBV surface antigen-positive patients who are to receive immune suppressant therapy [109,110]. Up to 10% of patients who are HBV core antibody-positive may be occult HBV carriers [111]. An occult HBV carrier reactivating after exposure to TNF-α inhibitor has been reported [112]. At present, prophylaxis is not recommended in HBV core antibody-positive patients, although these patients could have occult disease. It is our practice to refer these patients to a hepatologist prior the initiation of anti-TNF-α therapy (Table 2).

Infusion reactions

Infusion reactions occur with 3–17% of IFX infusions [92,96,113,114]. Acute infusion reactions develop within 24 h and are characterized by fever, chest pain, hypotension, hypertension and/or dyspnea. Delayed infusion reactions occur 24 h to 14 days after the infusion and are characterized by arthralgias, myalgias, urticarial rash, fever and/or malaise. These symptoms typically resolve with acetaminophen, antihistamine and/or steroids. Reactions can be subclassified as mild, moderate or severe.

Infusion reactions were examined in detail by Cheifetz *et al*. [114] They studied a cohort of 165 patients who received 479 infusions at a tertiary medical center over a 3-year period. Infusion reactions occurred in 29 of 479 (6.1%) infusions, affecting 10% of patients. The majority (3.1%) of reactions were mild. One percent of reactions were severe. All infusion reactions resolved with infusion rate adjustments and/or treatment with acetaminophen, antihistamine, steroids and/or epinephrine. Patients who previously developed a mild or moderate infusion reaction were subsequently treated with a prophylaxis protocol prior to their next infusion, permitting these patients to receive additional IFX without ill effect [114]. In 2004, Colombel *et al*. reported acute infusion reactions in 19 of 500 patients

(3.8%). Two infusions were felt to be life-threatening requiring the administration of epinephrine. Infusions were re-attempted in 11 patients. Eight developed a subsequent infusion reaction. The other three patients were able to tolerate re-infusion. Infusions were eventually discontinued in nine patients [92].

We pre-medicate all patients with oral acetaminophen 650 mg, oral diphenhydramine 25 mg and intravenous methylprednisolone 40 mg 30 min prior to anti-TNF-α infusion. Patients who have experienced prior delayed infusion reactions are given a Medrol dose pack after each infusion. Patients who have a 'drug holiday' of 4 months or more are treated with standard pre-medication as well as a Medrol dose pack after the first two re-infusions. We do not reload patients previously treated with IFX because of the increased risk for infusion reactions. Patients who develop an infusion reaction are treated according to the recommendations put forth by Cheifetz *et al*. [114]. We do not re-infuse patients who develop angioedema or significant hypo- or hypertension.

Skin reactions

Injection site reactions occur in 2–5% of patients treated with ADA. Two percent of patients experienced injection site reactions during the induction phase of the Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance trial, which increased to 5% of patients during the maintenance phase of the trial [85]. Injection site reactions are typically characterized by mild erythema, swelling and/or discomfort at the injection site. Baumgart *et al*. analyzed the incidence of skin reactions of the first 50 patients receiving ADA at their center and found that only one patient developed an injection site reaction [115]. It has been hypothesized that worsening injection site reactions over time may reflect the development of an IgE-mediated type I hypersensitivity reaction, potentially requiring cessation of the drug [116]. The frequency of injection site reactions was similar with CZP. However, patients receiving CZP in the Pegylated Antibody Fragment Evaluation in CD: Safety and Efficacy 1 trial had a lower rate of injection site reactions than patients receiving placebo (3 vs 14%) [87].

Psoriasiform and eczematiform lesions may also develop in the setting of anti-TNF-α treatment [117]. A retrospective cohort study conducted in 35 centers found that cutaneous lesions occur most commonly in women and patients with a personal or family history of inflammatory cutaneous lesions. The incidence of eczematiform or psoriasiform lesions is 9–16% [118,119]. An analysis of the US FDA Adverse Event Reporting System found that anti-TNF-α exposure was associated with a psoriasis proportional reporting ratio of 9.2 versus control drugs that that have been implicated in the development of psoriasis [120]. Psoriasiform lesions occur most commonly on the scalp, hands and feet, and are pustular. Cutaneous manifestations of anti-TNF-α therapy have been observed with IFX, ADA and CZP and may occur soon after the initiation of therapy or years after therapy has begun [117,120]. Switching TNF-α inhibitors resulted in improvement of symptoms in only 15% of patients. Conversely, cutaneous lesions resolve in approximately 65% of patients who discontinue therapy [121,122]. Up to 34% of patients who develop dermatologic lesions due to anti-TNF-α exposure ultimately discontinue therapy [117].

Autoimmunity

TNF-α inhibitor therapy is associated with antibody formation and lupus-like syndrome (LLS) [123,124]. Patients who develop LLS report arthralgias, myalgias, fever and/or serositis, with resolution of symptoms after discontinuation of the offending agent. The true incidence of LLS is unknown, although it is estimated that LLS occurs in 0.2–0.4% of patients treated with TNF-α inhibitors [123,125]. A retrospective review conducted at Mayo Clinic found that 14 TNF-α inhibitor exposed patients developed LLS over an 8-year time period [126]. Patients with LLS attributable to TNF-α inhibitor use develop hypocomplementemia, low anti-histone antibodies and high anti-dsDNA antibodies along with a rash typical of systemic lupus erythematosus. This is in contrast to classical drug-induced lupus, which is characterized by the presence of anti-nuclear antibody and anti-histone antibodies [125]. It is thought that a proportion of cases attributed to the effects of anti-TNF-α therapy more likely represents unmasking of latent systemic lupus erythematosus rather than true LLS [125]. Patients who develop severe LLS should have anti-TNF-α therapy withdrawn and be treated with high-dose steroids and immunosuppressive agents. In a small study of 14 patients, 4 of 5 patients who developed LLS were able to tolerate an alternate TNF-α inhibitor [126]. Data suggest that patients receiving TNF-α inhibitors with immune suppressants are at decreased risk of developing LLS compared with those treated with TNF-α inhibitor monotherapy [123].

Demyelinating disease

CNS demyelinating disorders such as multiple sclerosis (MS) have been observed in TNF-α inhibitor-exposed patients, although the incidence of these disorders is unknown [127–129]. In a randomized placebo-controlled trial, etanercept was associated with more frequent MS exacerbations than placebo [130]. Paresthesias, cognitive dysfunction, ocular symptoms and weakness have been reported in post-marketing reports [131–133]. Fortunately, withdrawal of therapy typically leads to resolution of symptoms. In addition to MS-like symptoms, reports of optic neuritis [134] and aseptic meningitis [135] associated with exposure to TNF-α inhibitors also exist. At present, it is not clear if exposure to TNF-α inhibitors unmasks preclinical neurological disease or if exposure induces *de novo* demyelinating processes [133]. If TNF-α inhibitor-induced CNS symptoms develop, the agent should be held, neurologic evaluation should be sought and future exposure to this class of medication should be avoided if demyelinating disease is confirmed.

Heart failure

The prescribing information for IFX, ADA and CZP all warn against the use of these drugs in patients with congestive heart failure (CHF) [104,136,137]. The Anti-TNF Therapy Against Congestive Heart Failure trial was performed because of preliminary data suggesting that TNF-α blockade could favorably affect the clinical course of patients with CHF. After 14 weeks of therapy, no clinical benefit was associated with anti-TNF-α treatment. Furthermore, the combined risk of death or hospitalization was increased in patients who received IFX 10 mg/kg at 0, 2 and 6 weeks [138]. Because of this trial, as well as reports of worsening CHF in association with TNF-α inhibitor use [139], anti-TNF-α therapy should be avoided in patients with moderate-to-severe CHF. Use of anti-TNF-α

therapy in patients with mild CHF can be considered with close monitoring, preferably in conjunction with a cardiologist.

Malignancy

Melanoma occurs more frequently in patients receiving TNF-α inhibitors (Table 5). IBD patients have an increased risk of developing melanoma, particularly those with CD (HR: 1.3; 95% CI: 1.0–1.6). The risk of melanoma increases further with exposure to biologic therapy (OR: 1.8; 95% CI: 1.1–3.3) [46]. These findings were confirmed by a meta-analysis examining the risk of malignancy in RA patients treated with TNF-α inhibitors [140]. Patients using these medications should be counseled to avoid sun exposure if possible and to use sunscreen when sun-exposed. Furthermore, patients should be monitored for the development of skin cancer (Table 2) [46].

There is no convincing evidence that TNF-α inhibitor use is associated with an increased risk of lymphoma. A large longitudinal study evaluated data from 19,562 RA patients with 89,710 person-years of follow-up. An association between lymphoma and exposure to TNF-α inhibitors (OR: 1.0; 95% CI: 0.6–1.8) was not found [141]. A number of meta-analyses have been performed in patients with RA. Although these studies are often confounded by prior or concurrent exposure to immune suppressants, none of these analyses have linked exposure to anti-TNF-α therapy with the development of lymphoma (Table 5) [49,140,142,143].

The risk of cervical dysplasia may be increased in patients exposed to TNF-α inhibitors. A review of claims data from patients with CD found a higher rate of cervical dysplasia in patients receiving immune suppressant, anti-TNF-α or corticosteroid therapy (HR: 1.5; 95% CI: 1.2–2.0) when compared with patients who were not receiving these medications (Table 6) [93].

Anti-integrin therapy

Natalizumab is a humanized IgG4 monoclonal antibody directed against the α4-integrin, preventing leukocyte extravasation from stromal tissues into GI mucosa [6]. In addition to preventing leukocyte trafficking in GI mucosa, natalizumab also decreases immune surveillance within the CNS, increasing the probability of developing PML, a potentially fatal neurological disease caused by the John Cunningham (JC) virus.

Idiosyncratic reactions

Fatigue and headaches are the most common adverse events reported in MS patients receiving natalizumab [144]. However, neither the International Efficacy of Natalizumab as Active Crohn's Therapy (ENACT-1) nor the Evaluation of Natalizumab as Continuous Therapy (ENACT-2) trials reported a difference in fatigue between patients receiving placebo and natalizumab [7]. In addition, in ENACT-2 there was no difference between placebo- and natalizumab-treated patients with respect to rates of headache (~30%), nausea (~25%), abdominal pain (~20%), vomiting (~14%), arthralgia (~20%), influenza-like symptoms (~9%) or diarrhea (~9%) [7]. Adverse effects were reported in 22 of 69 patients

treated at Boston area academic centers including infusion reactions, headache, fever and infections. PML was not reported [145].

Hypersensitivity reactions

Hypersensitivity-like reactions did not differ between placebo- and natalizumab-treated patients in ENACT-1 and -2, occurring in approximately 3% of patients. In ENACT-1, serious hypersensitivity-like reactions occurred in 5 of 650 patients. The rates of anaphylactic or anaphylactoid reactions were not commented upon; however, 'serious' hypersensitivity-like reactions occurred in five patients receiving natalizumab in ENACT-1 versus no patients receiving placebo. In ENACT-2, only one natalizumab-treated patient developed a 'serious' infusion reaction. Hypersensitivity-like reactions occurred more frequently in patients with persistent antibodies to natalizumab [7].

In ENACT-1 and -2, there was no difference in acute infusion reactions between natalizumab- and placebo-treated patients. Approximately 10% of patients in ENACT-1 and 7% of patients in ENACT-2 developed infusion reactions [7]. The incidence of infusion reactions due to natalizumab differs according to the presence or absence of antibodies directed against the drug with infusion reactions occurring in 45% of patients with anti-drug antibodies and 9% of patients without anti-drug antibodies [7]. Sakuraba *et al*. reported four 'mild' infusion reactions in 49 patients with CD receiving natalizumab [146]. Patients were managed with antihistamine and none discontinued therapy as a result.

Infection

In ENACT-1 and -2, patients receiving natalizumab experienced more infections than patients receiving placebo; however, these differences were not statistically significant. In ENACT-1, 43% of patients receiving placebo developed an infection versus 49% of those receiving natalizumab. Approximately 60% of all ENACT-2 patients developed an infection during the follow-up period. Serious infections, such as abdominal infections, intraperitoneal abscesses, sepsis and pneumonia, occurred in approximately 2–3% of patients receiving placebo or natalizumab [7].

One death from PML as part of an open-label extension study was reported by the ENACT-2 study group as a separate brief report. This patient was treated initially with natalizumab in combination with AZA, then placebo in combination with AZA [147]. In 2005, natalizumab was withdrawn from the market after three cases of PML developed. Two cases occurred in MS patients who were receiving IFN-β-1α in addition to natalizumab. The other case occurred in a CD patient who had been exposed previously to immune suppressant therapy [148,149]. Natalizumab was re-introduced to the market in 2006 after a safety review was performed, allowing it to be prescribed for the treatment of MS [150]. Two years later, natalizumab gained approval for the treatment of CD; however, patients and providers were required to participate in a strict monitoring program [149]. The incidence of PML in natalizumab-exposed patients is 1.44 per 1000 patient-years; protracted (≥2 years) exposure to natalizumab, JC virus seropositivity and prior exposure to immune suppressants increase the risk of developing PML (Table 7) [150]. Patients who are JC virus antibody negative have <1:10,000 chance of developing PML [151]. No patients from a cohort of 15

MS patients who developed PML after treatment with natalizumab died, which was attributed to aggressive standardized treatment of PML and immune reconstitution inflammatory syndrome [152]. However, as of early 2013, 22% of patients worldwide with PML attributed to natalizumab have died [152].

Malignancy

No hematologic malignancies occurred during ENACT-1 or -2, although basal cell carcinoma developed in one patient receiving natalizumab and one patient receiving placebo [7]. This observation is supported by results from the natalizumab observation program, a 10-year prospective study of MS patients in Europe, Australia and Canada. Patients received a median of 15 infusions of natalizumab. No malignancies were observed in this cohort [153]. Malignancy was, however, reported by the Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis study group. Six cases were reported, five from the natalizumab group (three breast cancer, one stage 0 cervical cancer, one metastatic melanoma) and one from the placebo group (basal cell carcinoma) [154]. Case reports have described melanoma and peripheral T-cell lymphoma in patients receiving natalizumab, although a causal association has not been established [155,156].

Combination therapy

The Study of Biologic and Immunomodulator Naïve Patients in CD (SONIC) trial found that a greater proportion of immune suppressant and biologic-naïve patients with moderate-to-severe CD who were treated with a combination of immune suppressant and biologic therapy achieved steroid-free remission at 6 months, when compared with patients treated with biologic or immune suppressant alone (57 vs 44 vs 30%) [157]. The Combination Of Maintenance Methotrexate-Infliximab Trial evaluated the efficacy of MTX combined with IFX versus IFX alone, with no difference detected at week 50 [158]. Of note, these patients were induced with both corticosteroids and IFX, which may have obscured the effect of MTX. Despite these conflicting studies, combination therapy with a TNF-α inhibitor and immune suppressant is increasingly being recommended for treatment of patients with CD.

Infection

In a case–control study, combination therapy was associated with an increased risk of opportunistic infections (OR: 14.5; 95% CI: 4.9–43) in comparison with treatment with a thiopurine alone (OR: 3.1; 95% CI: 1.7–5.5) [23]. In SONIC, the rates of serious infection were similar between AZA alone, IFX alone and combination therapy (5.6, 4.9 and 3.9%) [157]. However, an analysis of claims data from patients with CD who were treated with steroids, immune suppressants and/or anti-TNF-α agents found that CD patients receiving at least two of these medications had higher rates of infections including TB (HR: 7.4; 95% CI: 2.1–26), candidiasis (HR: 3.8; 95% CI: 2.0–7.6) and herpes zoster (HR: 3.7; 95% CI: 1.8–7.5) compared with control patients as well as patients who received only one of these medications [93].

Malignancy

The risk of lymphoma is increased in the setting of anti-TNF-α agents combined with immune suppressants in patients with CD (Table 2). Twenty-six studies including 8905 CD patients with 21,178 patients-year of follow-up were examined. The baseline rate of non-Hodgkin lymphoma (NHL) was 1.9 per 10,000 patient-years. Four cases of NHL were reported in patients treated with immune suppressants (4 per 10,000 patient-years). Thirteen cases of NHL were reported in patients treated with anti-TNF-α agents (6 per 10,000 patient-years), the majority of whom had prior exposure to an immune suppressant. Compared with the expected rate of NHL in the Surveillance, Epidemiology and End Results database, patients treated with anti-TNF-α therapy (in reality combination therapy) had a standardized incidence ratio of 3.2 (95% CI: 1.5–6.9) [49].

The risk of hepatosplenic T-cell lymphoma (HSTCL) appears to be increased in young men receiving concomitant immune suppressant and anti-TNF-α therapy [159]. HSTCL is a type of peripheral T-cell lymphoma and has been linked in case reports to combination therapy in men <35 years of age. HSTCL is particularly concerning because diagnosis is associated with a median survival of <1 year. It has been reported in 36 IBD patients receiving immune suppressant therapy, 20 of whom were treated with concomitant anti-TNF-α therapy [159].

Health maintenance strategies for patients treated with immune suppressants & biologics

As described above, uncommon but serious side effects are associated with both immune suppressant and biologic therapy. It is imperative to minimize these adverse effects to the greatest degree possible. One way to minimize adverse events it to reduce infections through utilization of effective vaccines as well as ongoing monitoring via history, physical exam and laboratory studies (Table 2).

Vaccinations

Adult patients with IBD, particularly those who are on immune suppressant or biologic therapies, should be vaccinated against tetanus, diphtheria and poliomyelitis every 10 years. In addition, patients should be vaccinated against influenza annually. Patients should also be vaccinated against pneumococcal disease once with a booster 5 years later. Patients with IBD should be screened for HBV exposure at the time of diagnosis or prior to initiating therapy with an anti-TNF-α agent [160].

Because IBD patients have a high likelihood of requiring immune suppressant therapy, HBV vaccination has been recommended at the time of diagnosis if the patient is not immune [161,162]. Patients who have no history of varicella should be vaccinated; however, practitioners should be cautious and avoid using this vaccine in patients receiving immunosuppressive or biologic therapy as this vaccine is a live attenuated virus [27]. In addition, vaccination against human papillomavirus should be considered in women on immunosuppressive therapy [163,164].

Laboratory monitoring

Patients treated with thiopurines or MTX are at risk for myelosuppression and hepatotoxicity. In patients receiving AZA or 6MP, it is our practice to monitor CBC and liver function tests every 2 weeks for the month after the initiation of therapy, then at week 8 of therapy, then every 3 months thereafter. We monitor CBC and liver function tests monthly for the first 4 months then every 3 months thereafter in patients receiving MTX.

Dermatologic

Thiopurines and anti-TNF-α agents increase the risk of NMSC and melanoma, respectively. Patients who are on either or both of these medications should be counseled to avoid prolonged sun exposure, use sunscreen and/or use sun-protective clothing [165]. In addition, Peyrin-Biroulet *et al*. have advocated for dermatologic screening of all patients receiving or who have previously been treated with thiopurines [47]. We recommend annual or semi-annual dermatologic exams in patients receiving either immune suppressants or anti-TNF-α agents.

Expert commentary

Risk

In order to successfully treat patients with CD or UC, particularly those with moderate-to-severe disease, patients and gastroenterologists must be willing to accept a risk of adverse events, such as serious infection, opportunistic infection and malignancy, as well as less serious side effects including nausea, vomiting and fatigue. Clearly, articulating the risk associated with the use of these medications is challenging for numerous reasons including limited time during office visits, the need to overcome previously attained misinformation and poor provider communication skills [166]. Interestingly, a recent study suggests that patients may be more willing to accept risk than providers, particularly if the increased risk is likely to result in significant improvement or complete resolution of their symptoms [167]. The decision to initiate, continue or discontinue therapy is an individualized one rooted in the severity of an individual's disease, likelihood of disease recurrence/progression and probability of side effects associated with the available therapeutic options.

When discussing potential therapies with patients, it is important to present the risk of medication side effects along with the complications that may develop from untreated or inadequately treated disease. Not surprisingly, patients are willing to accept higher risks if they have advanced disease or if greater therapeutic benefit is expected. Additionally, patients with disease of greater duration are less risk averse than those recently diagnosed. The manner in which risk data are conveyed to patients dramatically affects a patient's perception of that risk. For this reason, clinicians should discuss absolute risks with patients rather than relative risks. A patient who is told that his or her risk of lymphoma is one per 1000 is more likely to agree to thiopurine therapy than one who is told that his or her risk of lymphoma is increased fivefold with use of a thiopurine. In addition, it is also helpful to communicate the absolute benefit of therapy. In this case, using data from SONIC, patients may be told that approximately 300 of 1000 patients receiving AZA monotherapy experience steroid-free remission. It is also helpful to discuss the risk associated with

everyday events such as death due to car accident, estimated to occur in approximately 4 of 1000 persons over the course of a lifetime. The likelihood of complications associated with untreated or inadequately treated disease should also be discussed (e.g., 700 of 1000 CD patients will require surgical resection after 15 years of disease) [168]. Finally, it is important to use a consistent denominator, as done above, which permits patients to more easily compare risks associated with different treatment options [166,167].

Starting, continuing & stopping therapy

In the majority of patients, the decision to initiate therapy is relatively simple and based on symptoms of disease, prior treatment history and the risk tolerance of the patient and provider. The decision to initiate therapy can be more complex in patients with comorbid conditions such as advanced age, liver disease, heart failure, neurologic disease and/or prior or current malignancy. As discussed above, the treatment pursued should be based on a careful assessment of the risks associated with inadequate IBD therapy when compared with the risks associated with medical or surgical therapy. For patients with a history of malignancy, we consider the severity of the patient's IBD, the type of malignancy, the ability to monitor for recurrence of the malignancy and the length of time between treatment of the malignancy and start of immune suppressant or anti-TNF-α treatment. A prospective cohort study of IBD patients found no increase in the risk of new or recurrent cancer in patients exposed to immune suppressants [169,170]. The transplantation literature reports that the risk of cancer recurrence is dependent on the type of cancer treated and time between completion of cancer therapy and initiation of immune suppression [171]. Thus, we try to delay initiation of immune suppressant or biologic therapy if possible in a patient with recent malignancy. If possible, patients with active malignancies should not receive immune suppressant or anti-TNF-α therapy. We recommend oncology consultation prior to initiating immune suppressant and/or anti-TNF-α therapy in patients with a history of recent malignancy. We also try to use mono-therapy as opposed to combination therapy in patients with a history of prior malignancy. If patients develop a malignancy on treatment, we assess the association of the malignancy with treatment. In most situations, there is no association between the malignancy and treatment and we often continue treatment after consultation with oncology. The development of skin cancer while on immune suppressant and/or anti-TNF-α therapy warrants further discussion. It is our practice not to stop the thiopurine for a single NMSC. However, if recurrent NMSC develops thiopurine cessation should be considered strongly. We would recommend discontinuation of anti-TNF-α therapy in a patient who develops melanoma on therapy.

The decision to continue, decrease or stop therapy is individualized and based on the patient's disease history, response to current therapy, the specific complication (if present) and provider/patient preference. Even in patients who develop serious adverse effects such as serious infections, therapy may be continued if the risk/benefit ratio is favorable. Factors to consider when deciding if therapy can be continued include causality (i.e., did the treatment definitively cause the adverse event?), whether the adverse event was life-threatening and whether the adverse event is a recurrence of a prior similar event. For example, an otherwise healthy patient with a history of CD refractory to immune suppressant therapy on treatment with an anti-TNF-α agent develops pneumonia requiring

hospitalization and is treated successfully with antibiotics. Because it is not clear that anti-TNF-α exposure led to pneumonia, it would be reasonable to continue therapy even though a serious infection occurred. However, if a similar patient were to develop disseminated histoplasmosis, we would stop anti-TNF-α therapy because the patient developed a life-threatening infection likely associated with treatment. In cases where therapy is stopped, surgical options could be considered, if appropriate, and/or consideration could be given to re-instituting medical therapy with an alternative agent depending on the patient's clinical course.

Determining when therapy can be safely withdrawn in the absence of adverse events is hotly debated and was recently addressed by a European multidisciplinary expert panel [172]. In addition to safety of long-term monotherapy or combination therapy, cost of prolonged therapy with biologic agents is an increasing concern. Studies have attempted to characterize relapse rates in patients treated with immune suppressants, finding that in patients treated with immune suppressants, depending on their clinical characteristics, 40–60% relapse 5 years after discontinuation of immune suppressant therapy. However, retreatment was successful in 80% of patients who relapsed [173]. The ability to stop thiopurine therapy in CD patients has also been examined via a multicenter, double-blind, non-inferiority withdrawal trial. Patients in clinical remission on AZA for at least 42 months were randomized to continued AZA therapy or to placebo. Relapse occurred in 21% of patients assigned to placebo and 8% of patients who continued AZA [174]. Similar studies have examined the effects of anti-TNF-α withdrawal in patients on combination therapy [175]. Louis *et al*. followed 115 patients with CD prospectively who had been in steroid-free remission for at least 6 months and received IFX for at least 1 year in combination with an immune suppressant. The 1-year relapse rate was approximately 44% after cessation of IFX. Risk factors associated with relapse included male sex, lack of prior surgical resection, leukocytosis, anemia and elevation in C-reactive protein or fecal calprotectin. In this study, re-treatment with IFX was successful in 90% of patients [175]. In addition, a multicenter, prospective, randomized superiority trial was conducted to determine if continuing immune suppressant therapy beyond 6 months in patients receiving combination therapy contributed to the efficacy of biologic therapy. Van Assche *et al*. found that there was no difference in changes to IFX dosing in the group that stopped immune suppressant therapy versus the group that continued immune suppressant therapy. The authors concluded that immune suppressant therapy in combination with IFX offers no clear benefit beyond 6 months [176]. We do not advocate for cessation of therapy at this time for patients in clinical remission. However, the above data can be used in patients who experience adverse events of drug therapy, serious infection, opportunistic infection or malignancy to help counsel patients on the risks of stopping therapy.

Five-year view

The treatment options for patients with UC and CD continue to expand. Several new medications, including vedolizumab, ustekinumab and tofacitinib, may be approved for the treatment of patients with IBD. With approval of these drugs, long-term safety registries will be mandated by regulatory agencies to determine uncommon to rare side effects not

identified in clinical trials. In addition, clinicians will be challenged to position these new agents in existing treatment algorithms for IBD.

It is likely that in the coming years more patients will be treated with biologic therapy, including biologic therapy in combination with immune suppressants. We anticipate that interactive decision aids will continue to be developed to help providers counsel patients on the benefits and risk of therapy. In addition, as we transition to an era of personalized medicine, new diagnostic and prognostic tools will be developed to help better predict which patients will respond to therapy and which patients are at greater risk for adverse effects of therapy. Additional research is needed to determine which patients can safely tolerate withdrawal of drug therapy.

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Key issues

- Crohn's disease and ulcerative colitis are chronic inflammatory conditions in which the immune system inappropriately targets the gastrointestinal tract.
- Immune suppressants and biologic therapy are effective treatments for patients with moderate-to-severe Crohn's disease or ulcerative colitis.
- Thiopurines are associated with an increased risk of infection, myelosuppression, liver toxicity, pancreatitis and malignancy.
- Methotrexate is associated with an increased risk of myelosuppression, pulmonary toxicity, liver toxicity and birth defects.
- Anti-TNF-α agents are associated with an increased risk of infection, autoimmunity, demyelinating disease, congestive heart failure and malignancy.
- Anti-integrin therapy is associated with an increased risk of progressive multifocal leukoencepholopathy.
- Hepatosplenic T-cell lymphoma is associated with thiopurine monotherapy as well as thiopurine therapy in combination with anti-TNF-α therapy.
- Physicians have a responsibility to discuss risks with patients in a manner that is understandable and allows them to appreciate the benefits as well as risks associated with therapy. Physicians should also ensure that patients understand which complications of disease are likely to occur if IBD is inadequately treated.
- Patients may be more risk-tolerant than physicians, particularly in situations where clinical remission may be achieved.
- The decision to initiate, continue or cease therapy should be individualized and based on the severity of disease, likelihood of disease progression in the future and the risk associated with the available therapeutic options.

Table 1

Risk of infection in patients exposed to immune suppressant, methotrexate or biologic therapy.

	AZA/6MP [23]	MTX [23,60,61]	Anti-TNF-α [23,177,178]	Anti-integrin† [7,149]
Viral	+	0	+	+
Bacterial	+	0	+	ID
Fungal	+	0	+	ID
Mycobacterial	+	0	+	ID

† Natalizumab only.

6MP: 6-mercaptopurine; AZA: Azathioprine; ID: Insufficient data; MTX: Methotrexate.

Table 2

Health maintenance recommendations for patients on immune suppressant and/or biologic therapy.

	Thiopurine	MTX	Anti-TNF-α	Anti-integrin	Combination
Vaccinations	TdaP vaccine every 10 years	TdaP vaccine every 10 years	TdaP vaccine every 10 years	TdaP vaccine every 10 years	TdaP vaccine every 10 years
	Influenza vaccine annually	Influenza vaccine annually	Influenza vaccine annually	Influenza vaccine annually	Influenza vaccine annually
	Pneumovax once then 5 years later	Pneumovax once then 5 years later	Pneumovax once then 5 years later	Pneumovax once then 5 years later	Pneumovax once then 5 years later
	Consider HPV vaccine in patients <26 years of age	Consider HPV vaccine in patients <26 years of age	Consider HPV vaccine in patients <26 years of age	Consider HPV vaccine in patients <26 years of age	Consider HPV vaccine in patients <26 years of age
Laboratory monitoring	CBC and LFT every 2 weeks for 1 month *then* CBC & LFT at week 8 *then* CBC & LFT every 3 months	CBC and LFT every month for 4 months *then* CBC & LFT every 3months	CBC and CMP every 3–6 months	CBC and CMP every 3–6 months	See individual recommendations
Dermatologic	Annual or semi-annual skin exam		Annual or semi-annual skin exam		See anti-TNF and thiopurine recommendations
	Avoid prolonged sun exposure, use sunscreen (≥SPF 15), and/or wear sun-protective clothing		Avoid prolonged sun exposure, use sunscreen (≥SPF 15), and/or wear sun-protective clothing		
Tuberculosis			Determine status (PPD/ Mantoux or QuantiFERON Gold) prior to initiating therapy and annually thereafter		See anti-TNF-α recommendations
Hepatitis B[†]	Vaccinate if not immune	Vaccinate if not immune	Vaccinate if not immune Refer to hepatologist prior to initiating therapy if HBsAg or HBcAb positive	Vaccinate if not immune	See anti-TNF-α and thiopurine/MTX recommendations
Pneumocystis jirovecii prophylaxis[‡]	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Cervical dysplasia	Annual Pap smear		Annual Pap smear		Annual Pap smear

[†]All patients should be screened for hepatitis B (HBsAg, hepatitis B surface antibody, HBcAb) at diagnosis.

[‡]May be considered in patients on high-dose corticosteroids, patients on triple immune suppression, patients with lymphopenia or leukopenia, patients with multiple comorbidities particularly chronic obstructive pulmonary disease, patients older than 55 years of age [179].

CBC: Complete blood count; CMP: Comprehensive metabolic panel; HBcAb: Hepatitis B core antibody; HBsAg: Hepatitis B surface antigen; HPV: Human papillomavirus; LFT: Liver function tests; MTX: Methotrexate; PPD: Purified protein derivative; SPF: Sun protection factor; TdaP: Tetanus, diphtheria and pertussis.

Table 3

Risk of lymphoma in patients exposed to thiopurines.

Age (years)	Annual incidence rate		
	Continuing	*Discontinued*	*Never received*
<50	0.37	0	0
50–65	2.58	0.66	0.40
>65	5.41	1.88	1.68

Modified from [52].

Table 4

Risk of non-melanoma skin cancer in inflammatory bowel disease patients who continue, discontinue or never received thiopurines.

Age (years)	Annual incidence rate		
	Continuing	*Discontinued*	*Never received*
<50	0.66	0.38	0
50–65	2.59	1.96	0.60
>65	4.04	5.70	0.84

Modified from [47].

Table 5

Risk of malignancy in patients exposed to immune suppressant, methotrexate or biologic therapy.

	AZA/6MP [45,47,52,93,159]	MTX [93]	Anti-TNF-α [46,49,93,140]	Anti-integrin† [7]	Combination [46,49,93,159]
Melanoma	0	0	+	ID	ID
NMSC	+	0	0	ID	+‡
Lymphoma	+	0	ID	ID	+
HSTCL	+	0	0	ID	+§
Cervical dysplasia	+	ID	+	ID	+

†Natalizumab only.

‡Greater risk than in patients treated with immune suppressant alone [46].

§Greater risk than in patients treated with immune suppressant alone (1:45,000 vs 1:21,945) [159].

6MP: 6-mercaptopurine; AZA: Azathioprine; HSTCL: Hepatosplenic T-cell lymphoma; ID: Insufficient data; MTX: Methotrexate; NMSC: Non-melanoma skin cancer.

Table 6

Risk of infection in Crohn's disease patients treated with combination therapy versus corticosteroid, immune suppressant or anti-TNF-α monotherapy.

	HR (95% CI)	
	Monotherapy	***Combination therapy***
Tuberculosis	2.7 (1.0–7.3)	7.4 (2.1–26.3)
Candidiasis	2.7 (1.8–4.0)	3.8 (2.0–7.6)
Herpes zoster	1.7 (1.0–2.7)	3.7 (1.8–7.5)

HR: Hazard ratio.

Adapted from [93].

Table 7

Risk of progressive multifocal leukoencepholopathy in John Cunningham virus antibody-positive patients exposed to natalizumab.

Exposure (months)	No prior IS use	Prior IS use
1–24	0.5/1000	1.5/1000
25+	3.9/1000	10.6/1000

IS: Immune suppressant.

Data taken from [151].