Understanding the Cautions and Contraindications of Immunomodulator and Biologic Therapies for Use in Inflammatory Bowel Disease

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Abstract: Ulcerative colitis and Crohn's disease are chronic inflammatory bowel diseases for which there are no cures. These diseases are immunopathogenic, and medical treatment is centered on the temperance of a dysregulated immune response to allow mucosal healing and prevent the sequelae of fistulation and stenosis. Accordingly, the armamentarium of medications, which has expanded immensely in recent history, is not without significant infectious and neoplastic risks. Many of these untoward effects can be mitigated by screening and avoidance of contraindicated medications. This review seeks to highlight the cautions for use of immunomodulators, anticytokine, and α4-integrin antagonists. The potential adverse events are further complicated by substantial heterogeneity in disease phenotype in the inflammatory bowel disease population. Large patient registries and databases provide considerable experience and knowledge to calculate the incidence of safety outcomes. To identify rarer outcomes after prolonged therapy, more prospective studies and continued adverse event reporting will aid safe application and minimize potential harms.

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Crohn's disease (CD) and ulcerative colitis (UC), the 2 principle subtypes of inflammatory bowel disease (IBD), are chronic disorders likely caused in part by an inappropriate immune response to commensal bacteria[1] affecting approximately 1.4 million individuals in the United States and 2.2 million in Europe.[2] IBD has significant effects on quality of life, educational performance, and workplace participation,[3] and results in small increases in mortality.[4] Although it can manifest at any age, IBD primarily presents between the ages of 20 and 40 years,[5] often peak years of career productivity and fertility. The current paradigm for medical therapy is to induce remission by alleviating symptoms, promoting mucosal healing, and preventing intestinal complications to avoid surgical resection.[6]

Beginning with Truelove and colleagues who reported treatment success of UC with cortisone in the *British Medical Journal* in 1955,[7] tempering the immune response with corticosteroids, 5-aminosalicylates, immunomodulators, and manufactured antibodies has been the mainstay of IBD medical therapy. The medications in our armamentarium are not without significant risks of adverse events, and for innumerable reasons, not the least of which is the phenotypic heterogeneity of the diseases, optimizing a patient's disease course continues to be challenging. The following is a review of the cautions and contraindications of clinically used immunomodulatory and biologic medical therapies widely used today for the treatment of IBD.

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IMMUNOMODULATORS

Thiopurines

The thiopurines, 6-mercaptopurine (6-MP) and azathioprine (AZA), were developed in the 1950s by Nobel laureates Hitchings and Elion and initially used for the treatment of leukemic children (Table 1).[8] The first reported use for IBD was in 1962 by Bean[9] using 6-MP for UC treatment, and a landmark study published in 1980 by Present and coworkers

TABLE 1. Summary of Contraindications, Pregnancy, and Lactation Cautions and Notable Drug Interactions for Immunomodulators

Drug	Absolute Contraindications	Relative Contraindications	Pregnancy/ Lactation	Drug Interactions	Comments
Thiopurines (AZA/6-MP)	• Hypersensitivity, e.g., TIP	• Men <35 yr[a]	• Low risk in monotherapy	5-ASA, ACEi, allopurinol,[a] furosemide, metronidazole, TMP-SFX, thiazides	• Consider checking EBV IgG in men <35 yr (risk of HPS)
	• TPMT deficiency	• Men >65 yr	• Avoid initiating during pregnancy		• Risk of HSTCL in young men
	• Active or chronic infections	• Recurrent cervical dysplasia	• Breastfeeding safe after 4 h of dose		• Increased risk of NMSC
		• Prolonged sun exposure			• Increased risk of lymphoma
		• Negative anti-EBV IgG			• Consider UTC screening with CT or US in male smokers >65 yr
MTX	• Hypersensitivity, e.g., MIP	• Obesity (BMI >30 kg/m^2)	• Teratogenic	Hepatotoxic drugs, NSAIDs (may potentiate BMS, aplastic anemia, GI toxicity) sulfonamides, tetracyclines	• Alternative to thiopurines for combination therapy in men <35 yr
	• Pregnancy	• DM, HLD	• Abortifacient		• Discontinue 6 mo before conception for women; consider 3 mo for males
	• Active or chronic infections	• Hypoalbuminemia	• Breastfeeding not advised		• Possible risk of reversible oligospermia
	• CrCl <20 mL/min	• Premenopausal women			
	• Chronic liver disease	• Hematologic abnormality			
	• Alcoholism				
	• HBV, HCV				

Pregnancy and lactation from Mahadevan U, McConnell RA, Chambers CD. Drug Safety and Risk of Adverse Outcomes for Pregnant Patients With Inflammatory Bowel Disease. *Gastroenterology*. 2017;152:451–462 e452.

[a]Consistent with the Study of Biological and Immunomodulator Naive Patient in Crohn's Disease (SONIC trial), in young men who are at high-risk of disease progression and complications, the senior author still prescribes combination therapy with thiopurines.

ACEi, angiotensin-converting enzyme inhibitor; ASA, aminosalicylate; BMI, body mass index; BMS, bone marrow suppression; CrCl, creatinine clearance; CT, computed tomography; DM, diabetes mellitus; HLD, hyperlipidemia; HSTCL, hepatosplenic T-cell lymphoma; IgG, immunoglobulin G; MIP, MTX-induced pneumonitis; NSAID, nonsteroidal anti-inflammatory drug; TIP, thiopurine-induced pancreatitis; TMP-SFX, trimethoprim-sulfamethoxazole; US, ultrasound; UTC, urinary tract cancer.

reported the efficacy of 6-MP in active CD.[10] Current American Gastroenterological Association guidelines for treatment of CD recommend thiopurines to be used along with a corticosteroid or biologic for remission induction.[11] AZA is the prodrug and is converted to 6-MP through a nonenzymatic reaction.[12] Thereafter, 6-MP is enzymatically metabolized through several competitive pathways yielding at least 2 clinically significant metabolites, 6-thioguanine (6-TGN) and 6-methylmercaptopurine ribonucleotides (6-MMPR).[13] 6-TGN has proapoptotic effects on activated T lymphocytes through indirect activation of a cell cycle arresting guanosine triphosphatase, 6-MMPR has antimetabolic effects by inhibiting purine synthesis, and thiopurine s-methyl transferase (TPMT) maintains a balance between these metabolities.[13]

TPMT Deficiency

In an environment of decreased or absent TMPT activity, the metabolism of the drug to 6-MMPR cannot occur adequately or at all, and catabolism is directed toward the overproduction and accumulation of 6-TGN metabolites. Although elevated levels of these metabolites are associated with 3-fold increased likelihood of clinical remission, an overabundance leads to myelotoxicity.[14] Measurement of pretreatment TPMT activity and metabolites while on treatment reduces the risk of adverse events and

improves efficacy by up to 7% and 30%, respectively.[15] Approximately 1 in 300 are missing the genes to produce any TPMT, approximately 11% are heterozygous for the wild type, and nearly 89% are homozygous for the wild type who produce high levels of TPMT. Although there are reports of AZA treatment success in TPMT-deficient leukemic children whose serum levels were intensely monitored, thiopurines are best avoided in the homozygous mutant population to avoid potentially lethal myelosuppression.[16]

Drug Interactions

Apart from genetics, serum levels of TPMT are subject to several factors including age, sex, and cigarette smoking status (higher serum levels in younger, male, nonsmoking patients), and its production is primed using thiopurines.[12] 5-aminosalicylates agents should be used with some caution with thiopurines, as the 5-aminosalicylates agents are known weak inhibitors of TPMT, causing increased 6-TGN levels and consequent leukopenia; however, this effect is not as pronounced with balsalazide.[16–18] TPMT activity seems to also be negatively affected by several thiazide diuretics and furosemide.[16] Caution is also needed with concomitant warfarin, because of thiopurine weakening of its anticoagulant effect.[16]

Concomitant allopurinol use is "contraindicated" but with an asterisk. Because allopurinol inhibits xanthine oxidase, another key enzyme in the thiopurine metabolic pathway, the production of 6-TGN is consequently increased, again potentially leading to myelosuppression.[16] Many experienced prescribers routinely use allopurinol to capitalize on this effect, as shown by Sparrow and colleagues, who described thiopurine treatment success by the addition of allopurinol to thiopurine nonresponders.[19] Moreover, concomitant allopurinol can be used in the 24% of patients who develop dose-dependent hepatotoxicity secondary to increased levels of 6-MMPR.[20] The addition of allopurinol results in shunting away from the hepatotoxic 6-MMPR and increases levels of 6-TGN. This method requires close monitoring of the complete blood count and a thiopurine dose reduction to 25% to 33% of normal weight-based dosing.[21] Previous interaction concerns with angiotensin-converting enzyme inhibitors, trimethoprim-sulfamethoxazole, and metronidazole were likely due more to the myelosuppressive effects of their own.[12]

Fertility Uncertainties

Fertility issues in the IBD patient population are of particular concern, as these are diseases that more often affect the young. In fact, individuals with IBD are less fertile than their healthy counterparts, 17% to 44% and 18% to 50% for nonsurgically-treated women and men, respectively, according to a recent systematic review by Tavernier et al.[22] This decrease is attributed more to a "voluntary childlessness" stemming from IBD-centric fears and not to actual reproductive capacity, although active disease likely increases the risk of poor pregnancy outcomes.[23,24] It is also worth noting that there is a well-established reversible negative impact on spermatogenesis caused by sulfasalazine.[25–27]

Fertility concerns surrounding thiopurine use have been a source of scientific debate over the last 2 decades. AZA and 6-MP were previously classified by the United States Food and Drug Administration (FDA) category D (as an aside, such categorizations have been eliminated and replaced with the Pregnancy and Lactation Labeling Rule [PLLR][28]), and although neither drug is known to cross the placenta, their metabolites, 6-TGN and 6-MMP, do.[23,29] Thought to be secondary to gestational changes in hepatic metabolism, maternal serum concentrations of 6-TGN decrease and 6-MMP increase with no apparent consequence to the mother. Still, Jharap et al[29] found 60% of neonates born to mothers on thiopurines during pregnancy to be anemic at birth. Thiopurines are clearly teratogenic in animals,[30] but the same effect of maternal exposure in humans has rarely been demonstrated.[31,32] Although the risk of teratogenicity in humans is not entirely clear, most recent studies are reflective that they are indeed safe[29,33–36] and possibly protective (odds ratio [OR], 0.6; 95% confidence interval [CI], 0.4–0.9; $P = 0.02$) for a favorable global pregnancy outcome as demonstrated by Casanova et al.[37] Nonetheless, most authors agree that thiopurines should not be commenced during pregnancy because of the risk of drug-induced pancreatitis.[23]

Rajapaske et al reported in 2000 of an increased risk of congenital anomalies in children whose fathers were treated with 6-MP within 3 months of conception.[38] In their study, 57 men who fathered 140 pregnancies and their wives were interviewed. Pregnancies were divided into 3 groups: (1) 13 pregnancies where the father had taken 6-MP within 3 months before conception; (2) 37 where the father had discontinued 6-MP use 3 or more months before conception, and (3) 90 pregnancies where the father had never taken 6-MP before conception. They reported a statistically significant increased risk of pregnancy complications (spontaneous abortions or congenital anomalies [limb and digital abnormalities in these cases]). In groups 1 and 2 (the recent and remote 6-MP user groups), there was a 16-fold increased risk of such complications (95% CI, 1.6–161; $P < 0.013$) and nearly a 20-fold increased risk comparing the recent and never users (95% CI, 3.1–122; $P < 0.002$). Strangely, there was no statistically significant increased risk when comparing all 6-MP users (recent and remote users) and never users ($P < 0.097$). Although this study was congruent with older animal studies and a Danish human study that suggested a similar trend,[39] this study was fiercely criticized for its low statistical power and wide CIs.[40] More importantly, more recent studies failed to duplicate these concerning findings,[41–43] and recent ECCO guidelines on reproduction and pregnancy do not recommend the periconception discontinuation of thiopurines.[44]

Hypersensitivity and Pancreatitis

A primary contraindication to thiopurines is a known hypersensitivity to the drug class. The hypersensitivity allergic reaction is neither common (occurs in 1% of patients[45]), nor TPMT-related, nor dose-dependent, as in the cases of myelosuppression and hepatotoxicity.[46] These unpredictable

hypersensitivity reactions typically occur during the first weeks of treatment or after the patient has been weaned from steroids.[46] True hypersensitivity comprises most commonly of fever, myalgias and arthralgias, flu- and sepsis-like manifestations, and rash.[46] The rash can be as banal as urticaria,[47] to more severe erythema nodosum-like eruptions[48] or Sweet's syndrome[49] as detailed in case reports. Such reactions will soon reappear within hours of resuming the medication.

Nausea, a nonhypersensitivity reaction, is the most common AZA-induced adverse event,[45] and in some patients, this can be circumvented by a switch to 6-MP. Some prescribers have reported successes after hypersensitivity reactions using the same AZA-to-6-MP change,[47,50] up to a 61% success rate in 1 study,[51] leading some authors to conclude that the nitroimidazole molecule (a product of the nonenzymatic metabolism of AZA to 6-MP) is culpable for both adverse events.[52] Still, a more recent study demonstrated that an AZA-to-6-MP switch in the setting of adverse reactions was successful in two-thirds of cases, although this was much less likely in patients who experienced a flu-like illness or pancreatitis.[53]

Thiopurine-induced pancreatitis is often thought of as part of the spectrum of a similar allergic response, but it is better classified as an idiosyncratic reaction. Thiopurine-induced pancreatitis has an incidence of 4%[45] to 12%[54] and is the most common cause of pancreatitis in patients with IBD, accounting for 63% (52%–73%)[55] of cases. It occurs more commonly in female (OR, 3.4; 95% CI, 1.3–9.3; $P = 0.012$) and CD (OR 5.8; 95% CI, 1.6–20.6; $P = 0.007$) patients.[55] Although there have been several cases of successful desensitization for both hypersensitivity[46] and thiopurine-induced pancreatitis,[56] outside a controlled setting and in an era with more available alternatives, it is advised to avoid this medication class in such cases.

Reactive Hemophagocytic Syndrome

Hemophagocytic syndrome (also known as hemophagocytic lymphohistiocytosis or macrophage activation syndrome), first described in 1939,[57] is a rare and potentially lethal (29% mortality[58]) consequence of immunosuppressive use, especially thiopurines, particularly in young male patients with CD with primary Epstein-Barr virus (EBV) infection.[58,59] This condition, better described as reactive hemophagocytic syndrome (RHS) to distinguish it from the primary or familial disorders, though the hereditary forms can be triggered by the same infectious agents, is a severe immune overreaction to intracellular pathogens such as *Mycobacterium tuberculosis*, spirochetes, and viruses, most often of the herpes family. The underlying autoimmune dysfunction and impairment of cytotoxic regulatory pathways in IBD, coupled with pharmaceutical immunosuppression that further compromises the expulsion of the igniting pathogen, cause a cytokine storm with massive macrophage activation and consequent hemophagocytosis. Patients present with fever, cytopenia, severe hyperferritinemia (≥10,000 ng/mL), and organ infiltration, resulting in splenomegaly, hepatomegaly, and lymphadenopathy.[58] Such patients should undergo bone marrow biopsy, which allows for malignancy evaluation and culture. Patients are treated with supportive care, discontinuation of immunosuppressive agents, pathogen-directed treatment and intravenous immunoglobulin.[58]

Primary EBV infection or reactivation is the most common cause of RHS.[60] Although cytomegalovirus (also a common cause[61]) can be treated with ganciclovir, there is no effective treatment for EBV, making this syndrome especially lethal, although there have been some small successes with the chemotherapeutic agent etoposide.[60] For causes unclear, the incidence of RHS is increased for males and those with CD.[58] Thus, for this reason and the increased risk for hepatosplenic T-cell lymphoma (not associated with EBV, discussed below), the risks and benefits of thiopurines must be weighed more cautiously in the treatment of young male patients. Some have advocated checking EBV serologies in young male patients before starting a thiopurine because of this increased risk of RHS.[62] In fact, Lam et al proposed an algorithm in their narrative review of 2015 that focused attention on mitigating EBV-associated lymphoproliferative disorders in patients with IBD, wherein they argued to avoid starting thiopurines in EBV seronegative patients if possible, and to repeat EBV serological testing (EBV IgG viral capsid antigen, IgG EBV-determined nuclear antigen [EBNA], and IgM viral capsid antigen) every 3 to 6 months while on any immunosuppression.[63] Moreover, they recommended monitoring the EBV viral load in those who become seropositive, changing therapy to a biologic if on a thiopurine, and reducing the biologic dose if already on a biologic.[63] However, there are no societal guidelines addressing this concern. The senior author currently does not routinely check EBV serologies among patients with IBD in his practice.

Malignancy

There are few things more likely to concern a patient about a medication's adverse reactions than the possibility of an increased risk of cancer, no matter how remote. Thiopurines are indeed mutagenic, an effect that increases with increased dose and treatment duration.[64] Through the generation of reactive oxygen species, thiopurines enhance the negative effects of ultraviolet light on DNA, consequently increasing the risk of nonmelanoma skin cancer (NMSC), a risk that may continue through the lifetime of the patient, even after the drug is discontinued.[65] Long et al[66] demonstrated an 85% increased risk of NMSC in patients with IBD treated with a thiopurine (OR, 1.85; 95% CI, 1.66–2.05). Generally, these cancers—basal cell carcinoma and squamous cell carcinoma—are rarely fatal, although they can be disfiguring and have negative impacts on patients' quality of life. Patients with a past or current history of increased sun exposure should be considered for alternative treatment.[67]

A recent meta-analysis by Allegretti et al[68] demonstrated an increased risk of high-grade cervical dysplasia and cervical cancer in patients with IBD on immunosuppressive medications with steroids, immunomodulators, or biologics (OR, 1.34; 95% CI, 1.23–1.46), with an OR of 3.45 for immunomodulator use specifically. This is congruent with recent findings from a large Danish retrospective cohort study that revealed an 8% increased

risk of high-grade intraepithelial cervical lesions per prescription of AZA redeemed (incidence rate ratio [RR] 1.08; 95% CI, 1.04–1.13).[69] It is thus recommend that special attention must be paid to women with cervical abnormalities, and strong consideration given to thiopurine discontinuance in the setting of advancing dysplasia or recurrence after eradication.[70]

It is the increased risk of lymphoma associated with thiopurine use that is most concerning to provider and patient alike[71]—the risk interestingly compared with a 1/1112 lifetime's risk of "dying by drowning" in a recent review article.[67] Although the absolute risk is small, the increased relative risk of lymphoma while taking a thiopurine is irrefutable. Thiopurine-associated lymphomas are most often due to reactivation of EBV caused by immunosuppression, and the risk rapidly returns to baseline on cessation of the drug, as opposed to DNA damage seen in NMSC.[72] A recent meta-analysis by Kotlyar et al[72] reported in population-based studies a standardized incidence ratio for lymphoma of 2.80 (95% CI, 1.82–4.32) in patients with IBD who use thiopurines. An increased relative risk was especially high for patients younger than 30 years (standardized incidence ratio, 6.99; 95% CI, 2.99–16.4), but patients older than 50 years had the highest absolute risk (1:350 per year).[72] Men younger than 35 years are at risk for the very rare lymphoma variant hepatosplenic T-cell lymphoma (a minority of IBD and non-IBD cases were EBV-positive in a systematic review).[73] The risk is less than 1:20,000 person-years (PY), but is seen only rarely in women, is quickly fatal, and associated with thiopurines used for a duration of greater than 2 years either as monotherapy or in combination with antibodies to tumor necrosis factor-alpha (anti-TNF-α).[74]

Congruent with the Danish IBD population study by Pasternak and coworkers that showed an association between thiopurine use and urinary tract cancer (RR, 2.40; 95% CI, 1.24–6.54),[75] from the large French prospective IBD cohort Cancers Et Surrisue Associé aux Maladies inflammatories intestinales En France (CESAME), Bourrier et al[76] also demonstrated the same increased risk. In the CESAME study, this risk was greatest in men older than 65 years, where the standardized incidence ratio was 3.70 (95% CI, 1.48–7.23; $P = 0.007$), although they were not completely able to adjust for smoking status. Because of the "accelerating effect" thiopurines have on tumor growth, Bourrier et al proposed that prescribers consider urinary tract cancer screening with CT or ultrasound in men older than 65 with a tobacco use history before starting a thiopurine, a practice suggested in the transplant literature.[76,77]

There is a paucity of data available to guide initiating or restarting a thiopurine in the setting of a cancer history, and the question has been addressed in several recent reviews.[67,78,79] Of course, such a decision should be made in conjunction with an oncologist, and current expert opinion recommends the patient free of cancer for at least 2 and up to 5 years.[80] Much of the data are from the transplant literature, and an oft-cited older study reported that a history of urinary tract cancers and myeloma have the highest risk of recurrence at greater than 25%.[81] Fortunately, the CESAME cohort showed no difference in recurrence rates between patients treated with thiopurines and those who were not.[82] A recent meta-analysis by Shelton et al,[79] pooling 16 studies (including CESAME) that included both patients with IBD and those with rheumatologic conditions, bolstered these findings and provided some reassurance that the use of immunomodulators in patients with a history of cancer may be safer than we had previously believed. Last, a retrospective study comprising of 333 patients with IBD with a history of cancer across 8 academic medical centers conducted by Axelrad et al[83] found that those who were subsequently exposed to thiopurines, methotrexate (MTX), or anti-TNF-α medications were at no increased risk of incident cancer than those patients with IBD who received no such treatment.

Infection Concerns

Akin to all immunosuppressive medications, thiopurines are associated with an increased risk of opportunistic infections, as demonstrated by Toruner et al,[84] where thiopurines were associated with a 3-fold increased risk (OR, 3.1; 95% CI, 1.7–5.5). Thiopurines should not be initiated in the setting of active untreated infection. This is particularly true for viral infections, to which thiopurine users are particularly vulnerable for both primary infection or reactivation.[67] The most effective means of prevention is a defense-as-offense approach, with judicious vaccination where available and applicable. Treatment need not be held in the setting of mild presentations of herpes simplex virus or cytomegalovirus; however, if cytomegalovirus disease is detected in the colon, cessation of the medication may be required. Acute varicella, although now rare in the United States because of routine vaccination, is of grave concern in patients with IBD on any type of immunosuppression, including corticosteroids, immunomodulators, and biologics, as there is risk of severe and fatal outcomes due to nondermatologic organ involvement, death being most commonly associated with varicella pneumonia.[85]

Methotrexate

MTX is an antifolate drug that was developed by biochemist Yellapragada SubbaRow in concert with Sidney Farber to replace the more toxic aminopterin as treatment for leukemic children in the 1940s.[86] Despite the drug's long history, its precise mechanism of action is not entirely clear. High-dose MTX, as used in oncologic treatments, functions a bit differently than the lower-dose formulations used in immune-mediated conditions such as rheumatoid arthritis and CD. At these high doses, MTX inhibits dihydrofolate reductase (among others), causing the synthesis inhibition of nucleotides, consequently disturbing antiproliferative effects.[87] In lower doses, it is believed that other folate-dependent enzymes are negatively affected, leading to the accrual of adenosine, which has immunosuppressive and anti-inflammatory effects through lymphotoxicity, causing blockade of numerous cytokines and chemokines.[87,88]

MTX-induced Pneumonitis

MTX hypersensitivity anaphylactoid reactions are rare, even in the oncology literature where the doses used are

significantly higher and where rechallenge or desensitization to treat osteosarcoma might be necessary.[89,90] MTX-induced pneumonitis (MIP) is an idiosyncratic hypersensitivity reaction that is significantly more common, with some case series reporting prevalence as high as 12%, although this is chiefly in the rheumatoid arthritis literature.[87,91,92] The prevalence of MTX hypersensitivity pneumonitis in patients with CD is more likely between 0.3% and 0.7%,[92] although a recent meta-analysis found that MTX use in rheumatologic and IBD was not associated with an increased risk of adverse respiratory events (RR, 1.03; 95% CI, 0.9–1.17).[93] MIP is potentially fatal, presenting with fever, tachypnea, dyspnea, alveolar and interstitial infiltrates, nonproductive cough, hypoxia, and hypoxemia.[91,92] MTX should be withdrawn in this setting and not restarted.

Renal, Hepatic, and Hematologic Cautions

MTX is metabolized by the liver and excreted in the urine. In circulation, it is albumin-bound; thus, hypoalbuminemia or the presence of concomitant medications that competitively bind albumin (e.g., tetracyclines) cause the accumulation of free MTX in the serum, increasing the risk of the hepatic, hematological, and the aforementioned pulmonary toxicity.[94,95] A creatinine clearance less than 20 mL/min is a contraindication to MTX treatment,[96] as are medications that competitively inhibit the renal excretion of MTX (e.g., sulfonamides and commonly used nonsteroidal anti-inflammatory drugs).[95]

MTX is associated with an increased incidence of negative liver events (RR, 2.19; 95% CI, 1.73–2.77)[97] through oxidative stress,[98] and thus hepatotoxic drugs and preexisting liver disease are contraindications to MTX use. This includes suspected or undiagnosed liver disease, as in patients who are heavy alcohol users and obese (body mass index >30 kg/m^2), diabetic, and hyperlipidemic patients, of whom the latter 3 are at increased risk of nonalcoholic fatty liver disease.[94,98] Known chronic liver diseases, particularly chronic viral hepatitis B (HBV) and C (HCV) are also contraindications. Although rare and more often associated with anti-TNF-α agents, reactivation of resolved HBV infection in MTX-treated patients has been reported,[99] although a recent report claimed no reactivation in an HBV-infected population with rheumatological diseases in Thailand.[100] Liver damage associated with HCV does not seem to be synergistic with MTX, although it should generally be avoided in such situations.[101] For MTX-treated psoriasis patients, current guidelines recommend a surveillance liver biopsy after a cumulative dose of 1000 to 1500 mg in patients with a baseline risk of liver disease and 3500 to 4000 mg for those without such risk factors.[94] No similar guidelines exist for patients with IBD. Moreover, Dawwas et al[98] report that because MTX-induced hepatotoxicity is so rarely associated with need for liver transplant, in the absence of the above-mentioned risk factors, the use of MTX should not be discouraged.

Fertility Concerns

A retrospective French study of 28 cases of first trimester MTX-exposed pregnancies showed that only 1 child had minor anomalies who was exposed to MTX until 8.5 weeks' postconception, leading the authors to conclude that a low dose of MTX does not pose a strong teratogenic risk if the medication is discontinued as soon as possible.[102] Nevertheless, MTX is FDA category X,[95] as MTX is a folic acid analog and antagonist, consequently making it teratogenic, an abortifacient, and thus is strongly contraindicated during pregnancy and in women of childbearing age who are generally nonadherent or without reliable contraception.[103] This is especially imperative between 6 and 8 weeks after conception.[95,102] MTX concentrates heavily in the liver, spleen, and kidneys, and traces can remain in the liver for up to 4 months. It is recommended that women discontinue the medication 6 months before conception for an adequate washout period.[103] Most experts consider breastfeeding a strong contraindication to MTX use due to increased risk of immunosuppression in the infant,[23,104,105] but MTX secretion into breast milk is minimal,[103] and was not discouraged in a recent study of MTX-treated mothers with lupus.[106]

MTX is not mutagenic but is toxic to dividing cells.[95] Consequently, based in large part on animal studies, it has been believed that MTX causes a reversible oligospermia, and it has been recommended that men withhold MTX for 12 weeks (enough time for a cycle of spermatogenesis to occur) before conception. Human studies are mixed, but there have been no reports of abnormal births to fathers on MTX, and cessation of MTX in this population is likely not necessary.[107]

Infection Concerns

Active and chronic infections are likely to be worsened with MTX and are a contraindication. A systematic review from Portugal addressing MTX management during active infections in the MTX-treated rheumatoid arthritis population showed no increased risk of complications with common respiratory infections, including rhinovirus and influenza infections and community acquired pneumonia.[108] Only patients with *Pneumocystis jirovecii* pneumonia had an increased risk of mortality when taking MTX.[108] Current expert opinion dictates that mild infections not requiring antibiotics are not a contraindication to continuation of MTX.[109] The development of nonsevere infections necessitating antibiotics should prompt temporary discontinuation of MTX until the antibiotic course has completed and the clinical symptoms have resolved. Severe infections (i.e., those requiring intravenous antibiotics and/or hospitalization) should also prompt the discontinuation of MTX, and MTX should not be restarted until the antibiotic course has been completed, the clinical symptoms are resolved, and markers of severe infection return to baseline.[109]

BIOLOGICS

TNF-α-antagonists

TNF-α is a pleiotropic cytokine with multiple roles fundamental to the inflammatory response of the innate immune system and the pathogenesis of IBD.[110] Largely produced by monocytes,

macrophages, and T lymphocytes, TNF-α binds to receptors on lymphoid cells, transducing activation signals to said cells and the nuclear factor κB (NFκB) therein.[110,111] Consequently, NFκB causes the upregulation of many cytokines (e.g., interleukin [IL]-1, IL-6) that both induce inflammation and promote cell survival. NFκB is strongly activated in the gut tissue of patients with IBD, causing a runaway cytokine upregulation and secretion in the inflamed gut.[110] Although studies show contradictory data, and the mechanism has yet to be fleshed out fully, it seems also that anti-TNF-α agents are effective in treating IBD by blocking production of proinflammatory cytokines such as IL-6 and intensified adhesion molecule expression causing leukocyte migration.[110] Moreover, anti-TNF-α agents can also induce a reverse signaling mechanism in a cytokine-producing cell, dampening the cell's ability to produce and secrete more cytokines.[110] Last, anti-TNF-α agents can induce cell death by antibody-dependent cellular cytotoxicity, where the Fc portion of the molecule binds an effector cell whose degranulation lyses the TNF-α-receptor-expressing target cell, and via the complement cascade, complement-dependent cytotoxicity occurs.[110] Although theoretical, this may help explain the deleterious effects of anti-TNF-α agents in patients with congestive heart failure.

In the United States, there are currently 4 anti-TNF-α medications that are FDA approved for IBD. Infliximab (IFX) was the first to be approved in 1998, followed by adalimumab, certolizumab pegol (CZP), and golimumab, each varying in molecular structure, binding affinities, and effectiveness (Table 2).[112] In 2 recent meta-analyses, versus placebo they have all been shown to be effective in the induction of remission with a RR of 1.66 (95% CI, 1.17–2.36) and 2.45 (95% CI, 1.72–3.47) for CD and UC, respectively.[113,114] Similarly, anti-TNF agents were 1.78 times more likely to maintain remission (95% CI, 1.51–2.09) in CD and twice as likely in UC (95% CI, 1.52–2.62).

Heart Failure

Akin to many maladies, heart failure is associated with inflammation. In fact, an elevated serum level of TNF-α can be found in patients in decompensated heart failure, stable systolic dysfunction, and stable heart failure with a preserved ejection fraction. Similar to the renin-angiotensin-aldosterone overstimulation, this inflammation was seen as part of a system trying to restore cardiovascular homeostasis. Preclinical data in animal models of acute myocardial infarction suggested that TNF-α blockade preserved cardiac function and prevented remodeling[115] and was followed by human studies that demonstrated improvement in quality of life and 6-minute walk distance.[116] This prompted multicenter clinical trials, Randomized Etanercept Worldwide Evaluation (RENEWAL, which was actually the pooled results of 2 similar trials)[117] and Anti-TNF Therapy Against Congestive Heart Failure (ATTACH),[118] which examined the effect of TNF-α antagonism (etanercept and IFX, respectively) in patients with moderate-to-severe heart failure.

Surprisingly, these studies demonstrated etanercept and IFX were not effective in the setting of congestive heart failure, and seemed to increase the risk of heart failure exacerbations and death.[116–118] The reasons for these outcomes have been recurrently questioned since these failed trials, and in a recent review article, the lead author of the RENEWAL study posed some intriguing hypotheses to explain the unsettling results. One explanation is that although IFX works well in CD through its binding of tmTNF-α expressed by T cells causing complement fixation and subsequent cell lysing, which ultimately destroys inappropriately activated clones of T cells in the gut, in a similar mechanism, IFX could bind to tmTNF-α expressed on the membrane of an already compromised cardiac myocyte, stimulating complement fixation and thus apoptosis.[116] Simply put, this theory proposes the cardiac myocyte is dying, and IFX is making sure of it.

Thus, the presence of New York Heart Association class III and IV symptoms are contraindications to anti-TNF therapy, and caution should be taken in patients with mild heart failure. Based on the results of the ATTACH trial, a general cutoff of a left ventricular ejection fraction of ≤35% can be considered, but conferring with the patient's cardiologist would be most prudent.[118] Moreover, special attention to this comorbidity should be paid with elderly patients, in whom cardiovascular disease might be occult.[119]

Hypersensitivity

A history of an acute severe infusion or injection reaction is a contraindication to TNF-α antagonists. Infusion reactions to IFX are not uncommon and are divided into 2 general categories, acute and delayed, and further refined to mild, moderate, and severe.[120] Acute reactions occur in 10% to 40% of patients, and 2% experience delayed reactions.[120] The latter is a serum sickness that can include rash, arthralgias, and fever and can occur anytime from 1 day to 2 weeks after infusion. Severe delayed reactions can be life-threatening; a case of IFX-induced acute respiratory distress syndrome has been reported.[121]

Acute reactions occur during the infusion. Mild-to-moderate reactions cause fairly innocuous symptoms such as nausea, pruritus, headache, and fever, typically self-resolving with stopping or slowing of the infusion, or administration of antihistamines. Acute severe reactions occur in 5% of patients,[120] and warrant discontinuation of the medication. Acute severe reactions are described as anaphylactoid and can include hypotension, bronchospasm, and laryngeal edema. Although clinically identical, true IgE-mediated anaphylactic hypersensitivity reactions to anti-TNFα agents have been reported but are quite rare.[122] Still not fully understood, the anaphylactoid reactions likely occur through a mechanism of IgG antibodies to IFX[120] or through direct mast cell degranulation by IFX itself.[123]

Demyelinating Diseases

Patients with IBD are at increased risk of neurological sequelae.[124] In fact, a cross-sectional study found increased ORs for multiple sclerosis (MS) and/or optic neuritis of 1.54 (95% CI, 1.03–2.32) and 1.75 (95% CI, 1.28–2.39) for CD and UC, respectively.[125] Moreover, a study from 1995 showed that both patients

TABLE 2. Summary of Contraindications, Pregnancy, and Lactation Cautions and Notable Drug Interactions for Biologics

Drug	Absolute Contraindications	Relative Contraindications	Pregnancy/Lactation	Drug Interactions	Comments
Anti-TNF-α	• Hypersensitivity	• History of melanoma or NMSC	• Low risk in monotherapy	Anakinra, abacept	• Increased risk of melanoma
IFX	• CHF	• Recurrent cervical dysplasia	• Breastfeeding probably safe		• Avoid live vaccines in patient infants up to 12 mo
Adalimumab	• Active or chronic infections, especially LTBI and invasive fungal infections	• HBV, HIV	• ADA: time last dose 3–4 wk before delivery		
Certolizumab pegol	• Demyelinating diseases (e.g., MS, optic neuritis)		• GOL: time last dose 4–6 wk before delivery		
Golimumab	• History of HSTCL		• IFX: time last dose 8–10 wk before delivery		
			• CZP: does not cross placenta, no dose adjustment		
Anti-integrins	• Hypersensitivity	• Positive anti-JCV IgG (NAT)	• Low risk in monotherapy		• Taper CS within 6 mo (NAT)
Natalizumab	• Known or suspected PML (NAT)	• Recent abdominal surgery (VDZ)	• NAT: time last dose 4–6 wk before delivery		• Consider checking iATP
Vedolizumab	• Active, severe infections		• VDZ: time last dose 8–10 wk before delivery		• Avoid live vaccines
	• Rising transaminases		• Breastfeeding probably safe, limited data		
UST	• Hypersensitivity	• Known history or increased risk of CV disease	• Low risk in monotherapy, limited data		• Avoid live vaccines
	• Active, severe infections		• Time last dose 8–10 wk before delivery		

Pregnancy and lactation from Mahadevan U, McConnell RA, Chambers CD. Drug Safety and Risk of Adverse Outcomes for Pregnant Patients With Inflammatory Bowel Disease. *Gastroenterology*. 2017;152:451–462 e452.

ADA, adalimumab; CHF, congestive heart failure; CS, corticosteroids; CV, cardiovascular; CZP, certolizumab; GOL, golimumab; HBV, hepatitis B virus; HIV human immunodeficiency virus; HSTCL, hepatosplenic T-cell lymphoma; iATP, intracellular CD4+ATP; IgG, immunoglobulin G; JCV, john cunningham virus; LTBI, latent tuberculosis infection; PEG, pegol; TNF, tumor necrosis factor.

with CD and UC had focal white matter lesions in the brain on magnetic resonance imaging (MRI), 46% and 42%, respectively, versus only 16% in their age-matched controls.[126]

It is known that TNF-α plays a pathophysiologic role in diseases such as MS, and one could reasonably hypothesize that TNF-α antagonists could slow or arrest the disease process. Yet, a study published in 1999 testing this hypothesis using lenercept, an anti-TNF-α drug whose production has since been terminated, showed the opposite, with patients experiencing MS exacerbations and worsening of symptoms.[127] The true reason is unknown, but it has been speculated that anti-TNF-α agents disturb an immunoregulatory function of TNF-α, resulting in the propagation of autoreactive T cells, enhancing a myelin-specific T-cell response, thus accelerating autoimmune tissue destruction.[128] Accordingly, coexisting demyelinating diseases are a strong contraindication to TNF-α antagonism, and prescribers need be aware this medication class can potentially unmask previously occult neurological disease.

Fertility and Pregnancy Concerns

There are far fewer data available about the safety of anti-TNF agent use in those trying to conceive (women and men) and in pregnancy, as compared with immunomodulators that have more than a half-century of history. Initially, there was concern about the effects on gestation that anti-TNF-αs might have, possibly related to the anti-TNF-α properties of thalidomide.[129] All anti-TNF-α agents used for IBD are FDA category B. The prospective Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) study has only showed an increased risk of infant infections at 12 months (RR, 1.50; 95% CI, 1.08–2.09)

born to mothers with UC on immunomodulatory and anti-TNF-α combination therapy.[130] This supports current expert consensus, notably the London Position Statement of the World Congress of Gastroenterology[104] and the European Crohn's and Colitis Organisation (ECCO),[44] both of whom feel that IFX, adalimumab, and CZP are low risk and can be continued in the first 2 trimesters of pregnancy, although ECCO recommends withholding anti-TNF-α therapy at 24 to 26 weeks of gestation. A recent meta-analysis found no difference in unfavorable pregnancy outcomes in those who used anti-TNFα agents as compared to those who did not.[131]

It is worth noting that both IFX and adalimumab cross the placenta and are detectable in the infant's serum in the first 6 to 12 months of life; CZP also crosses the placenta but only at very low levels because of its structure.[23,132] This is the reason for the ECCO recommendation of withholding the anti-TNF-α agent after the second trimester.[44] However, more recent data from Julsgaard et al[132] showed that despite a more than 2-fold increased relative risk of infection in infants born to mothers treated with an anti-TNF-α agent and thiopurines as compared to mothers treated with anti-TNF-α agents alone, these infections were benign childhood illnesses. More importantly, continuation of the anti-TNF-α agent beyond 30 weeks of gestation did not increase infection risk in the infant.[132] Still, live vaccines should be avoided in these infants in their first 12 months because of an increased risk of disseminated infection, as in one case report of an infant who died at 4½ months from disseminated Bacillus Calmette-Guérin (BCG) infection after having received the vaccine at 3 months.[132,133]

The effect of anti-TNF-α agents on male fertility has been fraught with conflicting reports. Several earlier studies in the IBD literature reported negative effects on sperm and semen.[27,107,134] Still, further studies in the rheumatological literature have found that anti-TNF-α agents have no negative effects on male fertility and can be continued in patients trying to conceive.[135–137]

Infection Concerns

It is well established that anti-TNF-α agents leave patients susceptible to opportunistic infections.[138] Because of the public health concern of tuberculosis, it receives much attention, but it is important to highlight that common bacterial infections, such as pneumococcal pneumonia, are far more common and can be especially severe in patients who are receiving anti-TNF-α therapy.[139] That said, because TNF-α is essential for the sequestration of mycobacteria in the formation of granulomas, tuberculosis infection, either active or latent, is a relative contraindication to anti-TNF-α therapy, one that can be mitigated with appropriate precautions.[138] There is no interspecialty societal consensus as to the duration of antitubercular therapy before starting anti-TNF-α therapy in a patient diagnosed with latent tuberculosis infection, but isoniazid for at least 2 weeks (and up to 6–9 months) before anti-TNF-α initiation is common practice.[67,140] It is recommended that an infectious disease specialist be involved at the outset.

An active infection with opportunistic, invasive fungal species, such as candidiasis, aspergillosis, histoplasmosis, blastomycosis, and coccidioidomycosis is a contraindication to anti-TNF-α therapy, but the medication can be safely initiated or restarted after successful eradication of the infection.[67] The latter 3 infections tend to be geographically dependent.

Caution must be used in patients with a history of hepatitis B (HBV) infection and prophylaxis considered in patients at moderate or high risk of HBV reactivation.[141] Anti-TNF-α agents can cause reactivation of the virus. In one report, not unlike several others, a patient with chronic HBV who was being treated with corticosteroids, AZA, and IFX experienced fulminant hepatic failure and subsequent death on withdrawal of these agents.[142] On the therapy, his viral load dramatically increased, and the withdrawal of the drugs caused an immune reconstitution and resultant destruction of HBV-infected hepatocytes.[142] Similarly, HIV infection is not a contraindication to anti-TNF-α therapy, but does necessitate caution and awareness that the immunosuppressive effects of anti-TNF-α agents have been attributed to increased viral replication and may enhance the severity of HIV-related infections.[143] Hepatitis C (HCV) infection, however, does not seem to carry the same risks as the former 2.[144]

Malignancy

Whether anti-TNF-α monotherapy increases malignancy risk has been a contested issue, but there is mounting evidence that suggests this has at least been overstated.[145] An association among immunosuppression, consequent diminished tumor surveillance, and cancer would in many ways be expected. Several earlier retrospective studies using large health care and insurance databases did fuel such concerns, showing statistically significant increased risks of lymphoma, melanoma, and nonmelanoma skin cancer.[66,146,147] Conversely, the prospectively collected Crohn's Therapy, Resource, and Evaluation Assessment Tool (TREAT) Registry showed no difference in overall malignancy incidence between IFX treated and general populations.[148] Moreover, Nyboe Anderson and colleagues demonstrated similar findings from a nationwide Danish cohort that included over 56,000 patients with IBD who were followed for 489,433 PY.[149] This study highlighted the significance of thiopurine use history as a confounder in many of these studies.[145] Last, whether a cancer history precludes anti-TNF therapy has been well addressed in a recent meta-analysis by Shelton et al,[79] where they found no increased risk of cancer recurrence in patients exposed to anti-TNF-α agents with 31,258 PY of follow-up.

Issues surrounding cervical dysplasia and its relation to IBD have too been inconsistent. A recent Danish study found a small increased risk for low-grade squamous intraepithelial lesion and high-grade squamous intraepithelial lesion in patients with UC and CD.[69] The low-grade squamous intraepithelial lesion incidence RR was 1.15 (95% CI, 1.00–1.32) and 1.26 (95% CI, 1.07–1.48), and the high-grade squamous intraepithelial lesion 1.12 (95% CI, 1.01–1.25) and 1.28 (95% CI, 1.13–1.45) for UC and CD, respectively. Anti-TNF-α agents were associated with an increased risk of high-grade squamous intraepithelial lesion in patients with CD (incidence RR, 1.85; 95% CI, 1.12–3.04).

Anti-integrins

Another class of medications recently FDA approved for treatment in moderate-to-severe IBD is the anti-integrins. Integrins are glycoprotein cell surface receptors found on circulating lymphocytes. In IBD, the lymphocytes home to the inflamed intestines where the α4β7 integrin interacts with mucosal addressin adhesion molecule-1 (MAdCAM-1) on endothelial cells in the gut vasculature.[150] Anti-integrin monoclonal antibodies bind to the integrin, preventing its interaction with the inflamed mucosa, hence reducing the migration of effector lymphocytes into gut tissue and reducing the inflammatory process.[151]

Natalizumab

Natalizumab (NAT), approved by the FDA in 2004 for use in MS and in 2008 for CD, is a recombinant IgG4 monoclonal antibody that binds α4 integrins, impairing the lymphocytes' ability to further damage the inappropriately inflamed tissue.[152,153] Importantly, NAT is not selective for the gut-specific α4β7, also binding α4β1.[153,154] This possibly accounts for its efficacy in MS, but it is also the source of its association with progressive multifocal leukoencephalopathy (PML), caused by reactivation of latent John Cunningham virus (JCV).

Progressive Multifocal Leukoencephalopathy

JCV is thought to exist in 50% of the general population, and until the AIDS epidemic in the 1980s, its primary sequelae were seldom seen.[155] JCV normally is harbored in the kidney, but in an immunosuppressed state or in the presence of drugs that impair lymphocyte surveillance across the blood-brain barrier, the virus can spread to the central nervous system. PML is an opportunistic, fatal infection of the brain that led to the voluntary recall of NAT in 2005.[156] It was reintroduced the following year with a global risk management program, and it continues be unavailable for use in treatment of IBD in Europe.

As reported by Bloomgren et al,[155] the overall incidence rate of PML among patients treated with NAT is 2.1 cases per 1000 patients. Factors associated with an increased risk, besides positive anti-JCV antibodies, are a history of immunosuppressant use before NAT and extended NAT use (25–48 months). The incidence of PML with all 3 risk factors present is 11.1 per 1000 (95% CI, 8.3–14.5). Thus, the presence of anti-JCV antibodies is a relative contraindication to NAT use, but current and previous immunosuppression treatment is as well.[157] To mitigate the latter risk, steroids must be tapered within 6 months, and it has been suggested to check for intracellular CD4+ATP (iATP) as a marker of immune system function.[158] Biogen, the drug's manufacturer recommends to periodically monitor patients on NAT for the development of anti-JCV antibodies and to consider discontinuation of NAT in those who become antibody-positive.[157] They also recommend obtaining a baseline brain MRI in patients with CD to distinguish preexisting from newly developed lesions.[157]

Fertility

Unlike all other biologics, NAT is FDA category C in pregnancy. Like all anti-TNF agents, save CZP, NAT actively crosses the placenta in the third trimester. In a study where monkeys were given more than twice the human dose of NAT, offspring were noted to have hematological (anemia and thrombocytopenia), splenic, hepatic, and thymic abnormalities.[159] There is a paucity of data in humans, most of which comes from the neurology literature. One observational study from 2011, which followed the outcomes of 35 accidental pregnancies in patients with MS who were treated with NAT at the time of conception, resulted in 1 elective abortion, 5 early spontaneous abortions, and 28 healthy infants, one of whom was born with hexadactyly.[160] A report of 2 cases in neonates born to mothers exposed to NAT, found the neonates to have T lymphocytes that were significantly slower to respond to the most potent chemoattractant.[161] A more recent case series of patients with MS exposed to NAT in their third trimester described 10 of the 13 infants having anemia and thrombocytopenia, most of which resolved after 4 months of life, and 1 case of subclinical intracranial hemorrhage.[162] A much larger prospective observational study of 101 German women with MS exposed to NAT in the first trimester demonstrated no difference in pregnancy outcomes as compared to diseased matched controls.[163] Thus, definitive data do not exist, but NAT seems to be of minimal risk in pregnancy. Expert opinion recommends administering the last dose at 36 to 38 weeks of gestation, to mitigate the immunization risk to the mother.[23]

The effects of NAT on male fertility are unknown. A study in guinea pigs failed to show any differences in reproductive capacity as compared to the untreated group.[164] Still, some recommend withholding the medication 2 months before conception.[165]

Vedolizumab

Vedolizumab (VDZ) was approved by the FDA in mid 2014 for the treatment of moderate-to-severe UC and CD.[166] Of course, we have not yet amassed the body of data analogous to the older biologics, but VDZ seems to be exceptional within this special class of medications. Remarkably, VDZ seems to generally have the same safety profile as the placebo to which it has been compared.[167]

The first key distinction is that unlike its anti-integrin cousin NAT, VDZ is gut selective for the α4β7 integrin and consequently does not seem to harbor the dreaded JCV concern; to date, there have been no cases of VDZ-associated PML.[151,167] A recently published study by Colombel et al observed the long-term safety of VDZ across 6 trials, 2830 patients with 4811 PY of follow-up, and in this population, if treated with NAT, 6 to 7 cases of PML would have been expected. Again, when compared with placebo, there was no increased risk of any infection. Moreover, they found that exposure-adjusted incidence rates were lower with VDZ than placebo for all adverse events. Most infections were upper respiratory infections and the incidence was again lower in VDZ-treated patients than those who received

placebo. Of note, 4 cases of tuberculosis were observed, all of whom were exposed to VDZ, considered primary infections but were from endemic areas. Overall, the authors did not report any increased risk of disseminated opportunistic infections that have been reported with other biologic therapies. Notwithstanding, the cautions recommended regarding latent tuberculosis infection and active or recurrent infections should similarly be observed in this medication class.[168–171] Recent data published by Lightner et al[172] found a signal for an increased incidence of postoperative complications within 30 days of abdominal surgery in those who have received VDZ within 12 weeks of the operation (53% versus 33% for anti-TNF-α agents versus 28% for nonbiologic therapy, $P < 0.001$). Specifically noted were surgical site infections, which were seen in 37% in the VDZ cohort, versus 10% and 13% for the other 2 groups, respectively ($P < 0.001$).[172] Last, Colombel et al[167] did not observe a relationship between VDZ exposure and malignancy in their long-term safety of 6 clinical trials.

Fertility

There are even fewer data regarding the safety of VDZ in pregnancy than NAT. Dubinsky et al[173] followed study subjects who became pregnant during the study and were consequently dismissed from the study per the protocol. Twenty-seven female subjects were followed, 25 with IBD and 2 healthy volunteers. Outcomes from 20 pregnancies fathered by the male subjects were also reported. In the female group, there were 11 live births, 2 of which were premature, and 1 congenital anomaly was reported in a healthy volunteer. The male group produced 9 live births, 2 spontaneous and 2 elective abortions, and 3 were lost to follow-up. The findings of this study are intriguing, but few conclusions can be drawn.

Ustekinumab

The drug most recently approved by the FDA for use in moderate-to-severe CD is ustekinumab (UST), an anti-p40 antibody that blocks the binding of proinflammatory cytokines IL-12 and IL-23 to T cells, natural killer cells, and antigen-presenting cells.[174] These cytokines are involved in the disease processes of CD, MS, and psoriasis.[175] Compared with patients with UC and controls, an increase in IL-12 production has been observed in mononuclear cells of the lamina propria of patients with CD.[175]

Because UST was only recently introduced into the IBD arena, most of the safety data come from the psoriasis literature. The most significant safety concern for UST has been an increased risk for a major adverse cardiovascular event (MACE), which was reported as early as 2007 by Krueger et al.[176] A meta-analysis by Ryan et al, which the authors concede may have been underpowered, revealed no increased MACE risk in psoriasis patients receiving anti-IL12/IL-23 or anti-TNF-α agents.[177] However, Papp et al published a long-term safety study for use in psoriasis patients who included 3117 patients with nearly 9000 PY of follow-up, in which their most concerning finding was an increased risk of MACE with 0.44 MACEs per 100 PY (95% CI, 0.32–0.61); however, the authors reported this rate was similar to anti-TNF-α drugs and nonbiologic treated psoriasis patients.[178] More long-term studies are needed in patients with IBD addressing this issue.

Papp's large long-term safety study did not report any latent tuberculosis infection reactivation or systemic fungal infections.[178] The only opportunistic infection noted was disseminated VZV with no evidence of visceral involvement. There was an increased incidence of NMSCs that was comparable to other biologics, but one must consider that many in this patient population had also received carcinogenic ultraviolet light therapy. Overall, available long-term safety data have not shown increased serious adverse events in either the psoriasis or CD populations.[175] The recent multicenter international clinical trials UNITI-1, UNITI-2, and IM-UNITI, as reported by Feagan et al[179] support this theme, finding no difference in rates of adverse events between UST and placebo. In a subset of 276 patients in the aforementioned psoriasis safety registry who self-reported a history of IBD as well, the incidence of serious infections was significantly lower (1.4 per 100 PY) in those receiving UST compared with those patients on IFX (5.75 per 100) or other biologics (4.32 per 100).[180] Regarding safety in pregnancy and lactation, the data are limited but have not shown an increased risk of spontaneous abortions or a clinically significant concentration in breast milk.[28]

CONCLUSIONS

After decades of relatively stagnant advancement in the medical treatment of IBD, a recent eruption of creativity and serendipity has produced many more treatment options to subdue an immune dysregulation. Coupled with the heterogeneity of IBD presentation, this influx of new medicines and new uses of old medicines presents new challenges and potential harms, thus making appropriate application of paramount importance. Fleshing out these important details has best been and continues to be through population-based studies. Because of studies from databases such as the Danish national health system, Olmsted County, Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID), and TREAT, we gain considerable experience and knowledge to calculate the incidence of safety outcomes. For rarer outcomes after prolonged therapy, we need more of such studies—post marketing surveillance where patients are followed over a long period. Such clinical informatics will aid the safe application and minimize potential harms.

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