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INFLAMMATORY BOWEL DISEASE (S HANAUER, SECTION EDITOR)

Managing Risks with Biologics

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Abstract

Purpose of Review With a rapidly evolving complement of advanced targeted therapies in inflammatory bowel disease, additional safety and side effect concerns emerge. It is the purpose of this review to consider various risks with biologic therapies in inflammatory bowel disease and discuss mitigating strategies.

Recent Findings Two recently approved monoclonal antibodies (vedolizumab and ustekinumab) and a Janus kinase inhibitor small molecule (tofacitnib) have introduced a number of novel safety and risk considerations. We review the clinical trial and real-world safety data to date on these agents as well as review new data and considerations with anti-tumor necrosis factor agents. New vaccines for varicella zoster virus, hepatitis B virus, and high-dose influenza have been studied, and we discuss the clinical importance of these findings. Lastly, we make management recommendations in the event of particular side effects or complications.

Summary Understanding the risks of new agents in inflammatory bowel disease, potential mitigating strategies, and management considerations is important to achieving and maintaining clinical outcomes in IBD patients.

Keywords Crohn's disease · Ulcerative colitis · Biologics · Infection · Safety

Introduction

The last several years have seen rapid growth in the inflammatory bowel disease (IBD) therapeutic armamentarium. In the last few years, three agents with novel mechanisms of action have been FDA approved. The selective anti-integrin monoclonal antibody, vedolizumab, the anti-interleukin 12/23 antibody, ustekinumab, and the orally administered Janus kinase inhibitor small molecule, tofacitinib, have brought new safety, immunologic, and side effect considerations.

In this article, we review some key treatment aspects of these newer agents including efforts to prevent adverse events, minimize risks, and address side effects or complications should they arise. The authors readily acknowledge the lack of evidence-based guidance, and make expert opinion recommendations for the management of complications that arise. The authors also recognize that efficacy and safety are not mutually exclusive, that all treatment considerations should be individualized accounting for the benefits of therapy along with the risks. Active IBD can be considered an adverse event, and thus deserves consideration when balancing these risks.

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Infection Risk

Due to the modification of immune system effect with biologics, infections—both common and opportunistic—remain a key safety consideration. It has been recognized that IBD patients are at increased risk of infectious complications compared to the non-IBD population including influenza, pneumonia, herpes zoster, *Clostridium difficile*, and others [1–4]. Concurrent immunosuppressive therapy alters this risk. For anti-TNFs, studies have demonstrated conflicting findings on potential common infection risk (e.g., pneumonia) and this topic continues to be debated [5–8]. Differences in study design, disease type and severity, comorbid steroid and narcotic use, and patient age may explain some of the contrast.

Opportunistic infections, on the other hand, are definitively associated with anti-TNFs, and include both bacterial (e.g., tuberculosis, listeriosis) and fungal (e.g., histoplasmosis, coccidioidomycosis) etiologies [9–11]. The risk of opportunistic infection increases with age (odds ratio [OR] 1.1 per 5 years

95% CI 1.1–1.2) with patients over 50 years carrying three times (95% CI 1.2–7.2) increased risk of opportunistic infection [12].

Molecularly, TNF is key for the containment of viral infections. Anti-TNF therapy has been associated with increased risk of herpes zoster and hepatitis B virus (HBV) reactivation and fulminant HBV hepatitis [3, 13–15]. This has occurred in both HBV surface antigen-positive patients, but also in surface antigen negative/core antibody positive, though recent studies have estimated this latter rate between 0 and 3% [16–19].

Due to its gut-selective mechanism of action, the anti-integrin vedolizumab carries an appealing infectious safety profile. In pooled post hoc analysis of the vedolizumab clinical trials, there was no overall increased risk of infection or serious infection compared to placebo [20•]. Rates of gastrointestinal infections (mostly gastroenteritis), clostridial infections (including *Clostridium difficile*), and TB were higher in vedolizumab-treated patients compared to placebo, though the TB infections were largely felt to be primary infection in hyperendemic areas. Risk factors for serious infection were younger age, concurrent corticosteroids, and opiate use. While a concern limiting the use of its nonselective anti-integrin predecessor, natalizumab, there have been no reported cases of progressive multifocal leukoencephalopathy related to the JC virus with vedolizumab.

Similarly, ustekinumab seems to offer a favorable infectious safety profile. Randomized clinical trials demonstrated no increased infection frequency compared to placebo (2.3% vs 2.3%) [21] with ustekinumab and the Psoriasis Longitudinal Assessment and Registry (PSOLAR), which monitors ustekinumab for psoriasis, demonstrated an infection rate of 1.3 per 100 PY with ustekinumab compared to 5.75/100 with infliximab and 4.3/100 with other biologics [22]. Furthermore, there is a lower rate of TB reactivation with ustekinumab than anti-TNFs (0.02 per 100 person years; infliximab 0.39; golilumab 0.24) though it should be noted that lower doses (45–90 mg) and longer intervals (every 12 weeks) are used in psoriasis. In the UNITI trials of ustekinumab for Crohn's disease, there was one subject on concurrent 30 mg prednisone that developed listeria meningitis. Consequently, longer term monitoring is needed of these potential signals, but overall, the infection data is encouraging.

Conversely, tofacitinib seems to carry additional dose-related infectious risk. In ulcerative colitis clinical trials, tofacitinib-treated participants had higher prevalence of all-cause infections compared to placebo (39.8% 10 mg BID and 35.9% 5 mg BID vs. 24.2% placebo in OCTAVE Sustain), though the majority were mild or moderate [23]. Furthermore, participants receiving tofacitinib demonstrated increased rates of herpes zoster virus (HZV) reactivation compared to placebo (7.6 per 100 person years; adjusted hazard ratio 1.4; 95% CI 1.09–1.81) [24] with nearly 5% of participants in the higher dose maintenance arms experiencing HZV reactivation. However, all HZV reactivations were in one or two dermatomes, nonserious, and did not require tofacitinib discontinuation. Thus, the infection risk must be considered when entertaining the use of tofacitinib.

The Best Defense Is a Good Offense

Infection Risk Assessment

Assessing an individual patient's risk of therapeutic complications is the first step to improving safety with biologic agents. Clinicians should carefully assess for age and comorbidities that would further increase susceptibility to infections (e.g., diabetes, renal disease, respiratory disorders) as well as consider concomitant medications that increase infection risk such as corticosteroids and immunomodulators [12, 25].

TB status should be evaluated prior to therapy with interferon-gamma release assays (Quantiferon-TB Gold and T-SPOT) as the preferred mechanism, with chest X-ray to follow if positive, and referral to Infectious Disease for latent TB treatment. False negatives can occur with concomitant corticosteroids.

HBV serology including HBV surface antibody (HBsAb), surface antigen (HBsAg), and core antibody (HBcAb) should be obtained prior to therapy [14]. The 2015 American Gastroenterological Association guidelines recommend risk stratification based on HBV serology and the proposed therapy [26]. In general, HBsAg-positive patients should receive suppressive antiviral therapy alongside monoclonal antibody therapy, while HBsAg-negative/HBcAb-positive patients should receive prophylactic HBV antiviral treatment if being placed on a monoclonal antibody or > 4-week corticosteroid therapy. However, 2018 AASLD guidelines offer the option of careful observation in the select HBsAg-negative/HBcAb-positive population given the overall lower rates of reactivation [27]. Currently, there are no recommendations for HBV treatment in tofacitinib therapy as clinical trials excluded patients with evidence of HBV infection, though this risk may be similar to monoclonal antibodies [28].

Vaccinations

Vaccinations are a key mitigating strategy of the infectious risk of biologics. Unfortunately, immunization rates in IBD patients fall below expectations [29]. A recommended list of items to review, vaccination status to assess, and immunizations to provide derived from American College of Gastroenterology (ACG) guidelines [30•] is provided in Table 1. As gastroenterologists can often be the only physician IBD patients routinely see, many of the preventative health

Table 1 Infection risk assessment, vaccination status, and recommended vaccination doses for inflammatory bowel disease patients. Adapted from "ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease" [30•]

	Patient population	Titer check pre-immunization	Dosing regimen
Inactivated vaccine available			
Corynebacterium diphtheria, *Clostridium tetani*, *Bordetella pertussis* (Tdap)	All patients if not given in the last 10 years or Td ≥ 2 years	No	Single dose of Tdap recommended at age 11 through 64 years; Td booster every 10 years
Hepatitis A	All patients	Yes HAV Ab	2 doses at 0 and 6 months
Hepatitis B	All patients	Yes HBVsAb, HBVsAg, HBVcAb	3 doses at 1, 1–2, and 4–6 months; check titers 1 month after the last dose; if no response, 3 options: revaccinate, double dose HBV vaccination or combined HAV/HBV vaccine
Human papilloma virus	Male and female, aged 11–26	No	3 doses at 0, 2, and 6 months
Influenza	All patients	No	Annual immunization with trivalent inactivated influenza vaccine; "high dose" vaccine for patients 65 and older; live attenuated intranasal influenza vaccine is contraindicated in immunosuppressed patients
Neisseria meningitidis	All patients aged 11–19 high risk (military, college, splenectomy, endemic area, HIV)	No	Two or three doses depending on vaccine
Streptococcus pneumonia	All patients	No	If no previous vaccination, PCV13 followed by a dose of PPSV23 after 2–12 months; if received 1 or more doses of PPSV23 should receive PCV13 one or more years after PPSV23; another dose of PPSV23 should be administered 5 years after the initial PPSV23 dose and at age 65 years or older if at least 5 years have elapsed since their previous PPSV23 dose
Herpes zoster	Age > 50 years? Starting tofacitinib	No	Shingrix—2 doses (2–6 mo apart). Shingrix now preferred herpes zoster vaccine.
Live vaccine available			
Measles, mumps, rubella	If unknown vaccination history; do not give to immunosuppressed patients	Yes	Two doses (> 28 days apart) at least 4 weeks before starting immunosuppressive therapy
Varicella	If unknown vaccination history or prior infection OK to administer on "low dose" immunosuppression[a]	Yes VZV IgG	2 doses (4–6 weeks apart) at least 1 month before starting immunosuppressive therapy
Herpes zoster	Age > 50 yrs. ? Starting tofacitinib	No	Zostavax—1 dose. No longer preferred herpes zoster vaccine.

[a] Low-dose immunosuppression defined by the Infectious Disease Society of America as prednisone ≤ 20 mg/day, azathioprine ≤ 3.0 mg/kg/day, mercaptopurine ≤ 1.5 mg/kg/day, methotrexate ≤ 0.4 mg/kg/week [31]

considerations with immunosuppressive therapy should be managed by the treating gastroenterologist [32–35].

Generally, nonlive vaccinations are safe for administration, even in immunosuppressed individuals. While live vaccinations are contraindicated in patients already on higher dose immunosuppressive therapy or anti-TNF agents, Infectious Disease Society of America guidelines allow for live vaccines in those on low dose immunosuppression (prednisone ≤ 20 mg/day, azathioprine ≤ 3.0 mg/kg/day, mercaptopurine ≤ 1.5 mg/kg/day, methotrexate ≤ 0.4 mg/kg/week) [31]. Similarly, the vedolizumab package insert states that patients may receive live vaccines if the benefits outweigh the risks (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125476s000lbl.pdf) and some early data confirms this approach [36].

Recent developments since the publication of ACG guidelines include the FDA approval of an inactivated recombinant HZV vaccination (Shingrix) [37]. With increased efficacy in immunocompetent participants compared to Zostavax, including in the elderly (> 70 years old), and no reports of immune-mediated disease exacerbation, Shingrix is now the Centers for Disease Control preferred HZV vaccination over Zostavax [38]. However, Shingrix has not yet been tested in immunosuppressed individuals, so efficacy and safety in this cohort is currently unknown.

Additional vaccine developments include a new two-dose HBV vaccine, HEPLISAV-B, that was recently recommended by the Advisory Committee on Immunization Practices, but the clinical utility in IBD remains unknown. High-dose influenza vaccination has also recently received attention, and

studies of organ transplant populations suggest the high-dose influenza vaccination (FluZoneHD) may impart improved serologic efficacy compared to standard dose vaccination [39]. A recent single-center study suggested improved seroprotection with the high-dose influenza vaccine in IBD patients receiving immunomodulators, but other immunosuppressive regimens were not studied [40].

Managing Infections

If a patient develops an infectious complication during therapy, we recommend stratification by infection severity. We classify severe infections as those requiring admission to the intensive care unit, multiple organ dysfunction, or fulfilling systemic inflammatory response criteria. For viral illnesses, in patients experiencing either a severe primary infection or reactivation, we recommend holding anti-TNF agents, ustekinumab, and tofacitinib (Table 2) until appropriate therapy is instituted and clinical improvement is observed. With mild infections, we would continue these medications if biologic dosing is due. Given the gut selective nature of vedolizumab, with the exception of severe CMV colitis, we continue this agent during viral infections. If HZV is identified in a patient receiving tofacitinib, we would recommend holding until resolution. If the infection is severe or disseminated, we would consider switching to alternative therapy if available until if or when proper HZV vaccination with Shingrix can occur. Fortunately, given the small molecule nature of tofacitinib, interruptions of therapy do not carry the same immunogenic potential as monoclonal antibodies.

Similarly, with bacterial infections, we recommend severity stratification, holding anti-TNFs, ustekinumab, and tofacitinib in severe infections and continuing vedolizumab if dosing is due (Table 2). Conversely, in the setting of *Clostridium difficile* (*C. diff*) infection, we recommend holding vedolizumab during *C. diff* treatment with restarting therapy after *C. diff* resolution. If a patient receiving an anti-TNF, ustekinumab, or tofacitinib is diagnosed with *C. diff* and dosing of the biologic is due, we initiate *C. diff* therapy, delay (or hold for tofacitinib) the biologic for 5–7 days and ensure symptomatic improvement and clinical stability before dosing or restarting the biologic along with completion of *C. diff* therapy. This approach helps balance the risk of an IBD relapse with concurrent infection treatment.

Given the well-documented risk of opportunistic infections with anti-TNF agents, we recommend stopping anti-TNF therapy once an opportunistic organism is suspected or identified (Table 2). Further dosing should be held until the infection is completely treated and resolved and even then, consideration should be given to switching to alternative therapies. As an extension given the paucity of guiding data, we recommend stopping ustekinumab and tofacitinib during evaluation and treatment with potential to restart after infection is cleared. With the safety data to date and lack of increased opportunistic infectious risk in post hoc studies [20•, 43], we continue vedolizumab in this setting, unless the GI tract is the primary site of infection.

It should be noted that while we recommend holding certain monoclonal antibodies with the theory of restoring the blocked mechanism amidst an infectious complication, the half-life of the monoclonal antibodies ranges from 9.5 days (infliximab) to 25.5 days (vedolizumab) and the immunologic effect may be even longer. Thus, for complete drug clearance and functional restoration, a 6- to 8-week period of drug abstinence would be required. Complete treatment and resolution of infectious complications generally necessitate shorter time periods. Therefore, clinical interpretation of this recommendation is necessary and must weigh the risk of IBD exacerbation or immunogenicity upon withholding biologics with the rare risk of progression of infection by continued immunosuppression.

Malignancy Risks

Noncutaneous Malignancy Risk

There have long been malignancy concerns with biologic agents, but data was indirect and controversial. There was historical concern of hepatosplenic T cell lymphoma risk in patients receiving anti-TNFs, particularly young males; however, this has now been attributed to thiopurines [44]. While prior studies have not demonstrated increased lymphoma risk with anti-TNFs for RA, a recent large French population cohort study concluded that anti-TNFs were associated with increased risk of lymphoma in both monotheraphy (adjusted hazard ratio [AHR] 2.41; 95% CI 1.60–3.64) and combination therapy with thiopurines (AHR 6.11; 95% CI 3.46–10.8) [45•, 46, 47]. The most common lymphoma type in anti-TNF monotherapy was nonfollicular (28%) and in combination therapy was Hodgkin lymphoma (43%). The median age at diagnosis was 60 years, suggesting that similar to infectious risk, advanced age may predispose to the lymphomatous risk with anti-TNFs. To date, anti-TNFs have not been associated with the development of other primary noncutaneous malignancies.

Data from the vedolizumab GEMINI studies did not demonstrate an increased malignancy risk compared to expected population rates [43]; however, in the pooled post hoc analysis, all noncutaneous malignancies occurred in vedolizumab-treated participants, including several gastrointestinal cancers (colorectal, appendiceal carcinoid, and hepatic neoplasm). These findings necessitate longer follow-up data.

In the UNITI studies of ustekinumab, there were reports of prostate, colorectal and breast cancer in patients

Table 2 Recommended management of infections, malignancy, immunologic complications, and metabolic issues encountered during the course of biologic therapy

	Anti-TNF	Vedolizumab	Ustekinumab	Tofacitinib
Infections				
Viral	Continue (hold if severe)[a]	Continue, unless primary GI tract	Continue (hold if severe)[a]	Stop Treat Restart?
Bacterial	Continue (hold if severe)[a]	Continue	Continue (hold if severe)[a]	Continue (hold if severe)[a]
Opportunistic	Stop Treat Restart?	Continue, unless primary GI tract	Stop Treat Restart	Stop Treat Restart
C. difficile	Brief hold Treat Resume	Hold dose? Treat Restart	Brief hold Treat Resume	Brief hold Treat Resume
Noncutaneous malignancy				
Solid tumor	Continue Stop if cytotoxic chemo or metastatic[b,c]	Continue[c]	Continue Stop if cytotoxic chemo or metastatic[b]	Continue Stop if cytotoxic chemo or metastatic[b]
Lymphoma	Stop-treat, then individualize: restart vs switch to non-anti-TNF	Continue, unless primary GI tract	Continue Stop if cytotoxic chemo[b]	Continue Stop if cytotoxic chemo[b]
Cutaneous malignancy				
Nonmelanoma	Continue	Continue	Continue	Continue, but monitor
Melanoma	Stop-treat Switch to non-anti-TNF	Continue	Hold if chemo[b]	Hold if chemo[b]
Immunologic complications				
Anti-drug antibodies	High Ab[d]: stop Low Ab: add IMM and/or increase drug	High Ab: stop Low Ab: add IMM and/or increase drug	Continue, add IMM	N/A
Lupus-like	Stop Switch to a non-anti-TNF	N/A	N/A	N/A
Demyelinating	Stop Switch to a non-anti-TNF	N/A	Continue, but monitor	N/A
Psoriasis	Mild[e]: continue anti-TNF, Treat topically, ± methotrexate Severe: stop and treat, ± methotrexate, switch to non-anti-TNF	Continue	Effective treatment for anti-TNF psoriasis	Continue
Metabolic issues				
Transaminase elevation	Continue: if < 2× ULN Stop: > 2× ULN or (+) Hepatitis B or autoimmune hepatitis	Continue, but monitor	Continue	Continue
Lipids	Continue	Continue	Continue	Continue, but monitor

TNF tumor necrosis factor, *IMM* immunomodulator, *ULN* upper limit normal, *Ab* antibody

[a] Severe infections include those requiring intensive care, multiple organs affected, or meeting systemic inflammatory response criteria

[b] If stopping biologic during chemotherapy, we recommend monitoring for rebound IBD flare once the chemotherapy is stopped

[c] For checkpoint inhibitors, in patients without preexisting IBD, anti-TNFs and vedolizumab have been successfully used for treatment of checkpoint inhibitor-induced colitis. It is currently unknown how checkpoint inhibitors will influence underlying IBD, and thus, we recommend discussion with the treating oncologist and close clinical observation during therapy. In IBD patients not yet receiving biologics who develop worsening inflammation on checkpoint inhibitors, we recommend anti-TNF or vedolizumab therapy

[d] Antibody concentration interpretation depends on the assay utilized (ELISA vs radioimmune vs mobility shift) and no standard criteria have been defined. A cutoff of < 8 μg/mL for low and ≥ 8 μg/mL for ELISA has been described for infliximab antibodies [41]. The authors recommend providers utilize a single laboratory consistently and become familiar with the range and interpretation of results

[e] Mild dermatologic reactions defined as those encompassing < 5% total body surface area, tolerable to patient, and not rapidly expanding. Severe reactions involve ≥ 5% body surface, are intolerable to the patient, or quickly enlarging [42]

receiving ustekinumab, but the rates were not different from the general US population expected types and rates [21]. Data from the clinical trials of ustekinumab in psoriasis and PSOLAR have not suggested any increased malignancy risk in patients receiving ustekinumab compared to controls [48–50].

In the clinical trials of tofacitinib for ulcerative colitis, no tofactinib-treated patients developed noncutaneous malignancies. Pooling data from the rheumatoid arthritis clinical trials demonstrated no increase in age- and sex-adjusted standardized incidence rate (SIR) of malignancies (excluding nonmelanoma skin cancer) compared to Surveillance, Epidemiology, and End Results (SEER) expected rates (SIR 1.0; 95% CI 0.8–1.1) [51, 52]. However, there may be emerging malignancy signals within the long-term extension studies that will require additional monitoring [53].

Regarding recurrence of prior noncutaneous malignancy, studies to date have demonstrated no significant increased risk of recurrence with anti-TNFs [54]. Long-term data on vedolizumab, ustekinumab, and tofacitinib is pending.

Cutaneous Malignancy Risk

In IBD patients, anti-TNF therapy has been associated with an increased risk of melanoma (OR 1.88; 95% CI 1.08–3.29) [55]; however, other studies, including from rheumatoid arthritis, have not confirmed this association [56]. There is no significant increased risk of nonmelanoma skin cancer (NMSC) with anti-TNFs (OR 1.14; 95% CI 0.95–1.36) [55].

In the pooled post hoc study of vedolizumab safety, 5 out of 2884 vedolizumab-treated patients developed cutaneous malignancies (2 melanoma, 3 NMSC). Those who developed melanoma previously received anti-TNF therapies and those with NMSC were previously or concurrently treated with thiopurines, suggesting that the malignancies may have been related to previous therapies rather than vedolizumab. All dermatologic malignancies were reported as resolved. Longer term follow-up is underway.

Clinical trials of ustekinumab in IBD have not demonstrated any increased cutaneous malignancies compared to placebo (21) and the long-term follow-up studies of ustekinumab in treatment of psoriasis [48].

In the OCTAVE induction and maintenance trials of tofacitinib for ulcerative colitis, six patients developed NMSC compared to one placebo. There were no reports of melanoma in either group. In rheumatoid arthritis, the tofacitinib follow-up studies demonstrated no increased risk of NMSC compared to expected rates. Interestingly, one study observed an increase in the NMSC incidence rate in higher dosing groups (10 mg BID vs 5 mg BID) [52], but other reports contradict this finding [51].

Managing Malignancy

Given the malignancy concerns with biologic agents, prior to therapy a meticulous malignancy history including the malignancy type, timing, treatment, and last follow-up should be sought. Specific attention should be paid to skin (melanoma and nonmelanoma), hematologic (lymphoma), and cervical cancer histories given the increased risk of these cancers in various biologic (and thiopurine) regimens.

Noncutaneous Malignancy Management

For all cases of malignancy (cutaneous and noncutaneous) during therapy, we recommend a multidisciplinary approach involving the gastroenterologist and dermatologic or oncologic specialties with direct and open communication regarding the balance of IBD therapies with malignancy treatment. For noncutaneous solid tumors, we recommend continuation of the biologic agents unless concurrent cytotoxic chemotherapy is administered or there is metastatic involvement (Table 2). We recommend holding anti-TNF, ustekinumab, and JAK inhibitor therapy with cytotoxic chemotherapy, to avoid excessive immunosuppression. Vedolizumab can be continued regardless of the chemotherapy, unless the GI tract is the primary site in which case, discussion with oncology a shared decision is advised. We recommend close clinical follow-up for rebound IBD activity after chemotherapy.

Similarly, if an individual receiving ustekinumab or tofacitinib is diagnosed with lymphoma, we recommend withholding these biologics if concurrent cytotoxic chemotherapy is administered, otherwise continue therapy. Given the associated lymphoma risk with anti-TNFs, we advocate for cessation of therapy during treatment and consideration of transitioning to an alternative mechanism of action upon diagnosis. We continue vedolizumab unless the GI tract is the primary site of involvement.

In patients with a history of prior malignancy in remission, we do not withhold any particular biologic therapy except in the case of metastatic melanoma given this malignancy's propensity for delayed recurrence. In this situation, we avoid anti-TNF therapy extrapolating the increased risk of melanoma with this antibody class. In patients with prior history of lymphoma in sustained oncologic remission, if all biologic classes are potential options, we tend to favor a non-anti-TNF mechanism; however, if anti-TNF therapy is indicated, the combination of anti-TNF with methotrexate is a reasonable option. We avoid the combination of anti-TNF and thiopurines given the potential additive lymphoma risk with this combination [45•].

Cutaneous Malignancy Management

If a patient develops NMSC, we recommend continuing all biologics so long as local excision and control is feasible. Given the possible NMSC signal with tofacitinib, we continue therapy but recommend close monitoring of clinical outcomes and development of additional lesions with a low threshold to alter therapy. If systemic chemotherapy is advised for NMSC, we follow similar recommendations to solid tumors as above.

In the setting of melanoma, we discontinue anti-TNFs during treatment and switch mechanism of action after completion of melanoma therapy. Similarly, we hold ustekinumab and tofacitinib if chemotherapy is being administered. We recommend continuing vedolizumab throughout diagnosis and treatment.

Immunologic Issues and Risks

Anti-TNFs have been associated with a wide array of immunologic entities including but not limited to humoral immunogenicity, psoriatic and lupus-like reactions, and demyelinating processes. With the wealth of existing literature, we will not extensively review the humoral immunogenicity aspects of anti-TNFs. Vedolizumab studies to date estimate the immunogenicity at 4% after 52 weeks of treatment without a significant rate increase over exposed time, but increases to 10% 16 weeks after last dose [20•]. Concomitant immunomodulator reduced vedolizumab anti-drug antibody formation from 4 to 3%. Ustekinumab may have lower immunogenicity potential as rates of anti-drug antibody formation in the IM-UNITI trial were 2.3% at week 44 [21]. In contrast to monoclonal antibodies, tofacitinib is a small molecule, and immunogenicity with tofacitinib has not been described.

Psoriatic lesions with anti-TNFs have been well described, with an estimated incidence of 0.6–5.3% with a slight predilection for CD [57]. The most commonly affected areas are hands and feet (palmoplantar), scalp, and ears. Timing of onset is variable and can occur at any point during therapy. The complication appears to be a class-effect, with frequent recurrence reported when another anti-TNF is attempted [58]. No psoriatic reactions to vedolizumab, ustekinumab, or tofacitinib have been reported. In fact, ustekinumab is FDA approved for use in plaque psoriasis and psoriatic arthritis while tofacitinib carries an FDA indication for psoriatic arthritis, making these agents potentially appealing therapeutic alternatives.

Rates of drug-induced lupus reactions with anti-TNFs are estimated at < 1% and have been reported for all anti-TNF agents [59, 60]. The exact etiology of anti-TNF lupus reaction is unknown, but proposed hypotheses include anti-TNF-induced cellular apoptosis releasing DNA and lupus auto-antigens, disinhibition of TNF-mediated auto-antibody regulation, increased B cell activity due to susceptibility to infections, and promotion of T-helper 2 immune responses in anti-TNF patients. One vedolizumab-treated participant developed cutaneous lupus in the GEMINI trials. Similarly, a single case of ustekinuamb-induced cutaneous lupus with recurrence upon rechallenge has been reported [61]. Drug-induced lupus has not been reported with tofacitinib to date. Long-term follow-up is necessary to estimate the real-world incidence of this complication in the newer agents.

Likewise, the exact incidence and cause of demyelinating processes with anti-TNFs is unknown. These demyelinating reactions predominantly affect the central nervous system and typically resolve after drug discontinuation; however, progressive clinical courses have also been described and highlight the potential severity of this complication [62, 63]. A single case of ustekinumab-induced central nervous system demyelination has been reported in CD patient previously treated with three anti-TNFs [64]. No cases of demyelinating conditions have been reported with vedolizumab or tofacitinib to date.

Immunologic Assessment

A history of prior biologic treatment and antibody formation should be elicited. Comorbid immunologic disease such as psoriasis, lupus, or multiple sclerosis or any demyelinating condition should also be noted as this can inform potential contraindications or possible multi-beneficial approaches.

Immunologic Issue Management

If a patient develops anti-drug antibodies to a monoclonal antibody, we recommend stratifying by the concentration of antibody into high and low concentrations (Table 2); however, this stratification has not been standardized and varies depending on the type of anti-drug antibody assay utilized (ELISA vs radioimmune vs mobility shift) and laboratory performing the testing. A cutoff of < 8 μg/mL for low concentration and ≥ 8 μg/mL for high concentration using an ELISA anti-drug antibody assay for infliximab has been proposed [41]. We recommend that providers utilize a single laboratory when feasible for drug and antibody testing and become familiar with results and interpretation. In the setting of low antibody concentration, we add concomitant immunomodulator if not previously prescribed, and if already receiving an immunomodulator, we either increase the biologic dose or decrease the dosing interval in an attempt to overcome the anti-drug antibodies with close observation and repeat drug and antibody levels 3–6 months later.

Lupus-like reactions and de novo demyelinating responses to anti-TNFs should precipitate withholding therapy during evaluation and treatment of the complication (Table 2). Discontinuation of the offending medication alone may result in improvement in a period of weeks to 6 months. However, involvement of appropriate specialty assistance (e.g., rheumatology for lupus, neurology for demyelination) should be considered promptly as concurrent immunosuppression may need to be manipulated to treat the reaction and the potential severity of demyelinating processes. Both lupus-like and demyelinating reactions require a change in mechanism to non-anti-TNF therapy given the class effect of these entities.

Treatment of psoriatic lesions secondary to anti-TNFs includes topical steroids depending on the extent and location, vitamin D analogues, keratolytics, and UV phototherapy (Table 2). Those with lesions involving < 5% total body surface area are tolerable to the patient, and not rapidly expanding can be treated topically in collaboration with dermatology [42]. Unfortunately, topical therapy alone is effective in a minority of cases. Severe (≥ 5% total body surface area, intolerable, or rapidly expanding) or refractory psoriasis may require discontinuation of anti-TNF therapy with a transition to alternative mechanism of action. In this setting, we favor ustekinumab given its dermatologic use in psoriasis [65].

Metabolic and Hematologic Complications

All biologic medications have been associated with at least one metabolic or hematologic side effect or derangement. Liver enzyme abnormalities with anti-TNFs are typically asymptomatic and discovered incidentally, though anti-TNFs have also been associated with autoimmune hepatitis [66, 67]. Excluding autoimmune hepatitis, liver enzyme abnormalities with anti-TNFs are usually self-limited [68]. Neutropenia is the most commonly reported anti-TNF hematologic complication, with incidence ranging 0.6–5.7% patients. Classically mild and transient, anti-TNF-induced neutropenia rarely requires discontinuation [69, 70].

Hepatobiliary events were observed more frequently in vedolizumab-treated participants (0.3 per 100 PY [95% CI 0.2–0.5]) compared to placebo (0.0 per 100 PY [95% CI 0.0–1.4]) in the clinical trials, with hepatic steatosis the most common hepatobiliary event (0.2 per 100 PY [95% CI 0.1–0.3]) [20•]. There was no difference in isolated abnormal liver enzymes in vedolizumab (2.1 [95% CI 1.6–2.5]) compared to placebo (2.8 [95% CI 0.6–5.1]) and isolated liver enzyme abnormalities did not lead to vedolizumab discontinuation. No hematologic abnormalities were observed in the clinical trials of vedolizumab [71, 72].

No significant liver enzyme abnormalities have been observed in ustekinumab or tofacitinib-treated patients. In the OCTAVE trials of tofacitinib, two tofacitinib-treated patients developed absolute lymphopenia [23].

In clinical trials, more participants receiving tofacitinib had abnormal lipid profiles with higher total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) compared to placebo [23]. This same effect was seen in the rheumatoid arthritis tofacitinib clinical trials where they observed a dose-dependent mean increase in LDL and HDL by approximately 10–20%, with lipid increases correlating to reduction in inflammation [73]. These increases were generally seen in the first 4 weeks of therapy, stabilized after 3 months of therapy, and have not been associated with cardiovascular events. Several mechanisms including lower baseline levels of LDL and HDL in autoimmune patients compared to healthy controls and tofacitinib-induced altered cholesterol ester metabolism have been suggested [74]. There were also higher rates of creatine kinase elevation in tofacitinib participants, but no patients experienced concurrent myopathy or rhabdomyolysis.

Metabolic and Hematologic Assessment

Preexisting metabolic and hematologic abnormalities should be evaluated and discussed. Baseline labs prior to therapy should include a complete blood count, renal, and liver functions in all patients. A baseline lipid panel in patients starting tofacitinib should be obtained. We do not routinely check creatine kinase levels.

Metabolic Condition Management

During routine therapy, we recommend at least annual hematologic, renal, and liver function labs or more frequent as directed by specific therapies (e.g., thiopurines) or patient symptoms.

If a patient receiving anti-TNF therapy develops isolated abnormal liver transaminases less than twice the upper limit of normal, we will continue therapy with ongoing observation (Table 2). If the transaminases are greater than this cutoff, we will evaluate for autoimmune hepatitis (along with other common causes of elevated transaminases) and withhold therapy. If autoimmune hepatitis is confirmed, we discontinue therapy with that particular agent. Otherwise, we recommend continuation of other biologics and small molecules with ongoing observation and consultation with a hepatologist if liver function tests worsen.

For tofacitinib, we recommend monthly monitoring of lipid panel for the first 3–6 months or until stabilized given the early and rapid time course delineated in clinical studies. Continued elevation after 12 weeks should prompt further evaluation and consideration of adjunctive statins or alternative therapies.

Conclusions

With a rapidly evolving IBD armamentarium targeting a variety of mechanisms, the complexity of management has simultaneously intensified. Understanding the risks of side effects, reactions, and complications of the new agents is pivotal to informed therapeutic decision making and patient counseling. Along with risk assessments, vaccination strategies, and active monitoring, we propose several management strategies to optimize patient outcomes in the early period of these newer agents.

Compliance with Ethical Standards

Conflict of Interest Miguel Regueiro reports personal fees from Abbvie, Janssen, UCB, Takeda, Pfizer, Seres, and Allergan, outside the submitted work. Miguel Regueiro serves as a consultant and advisory boards for Abbvie, Janssen, UCB, Takeda, Miraca, Pfizer, Celgene, and Amgen. He also receives research support from Abbvie, Janssen, and Takeda.

Benjamin Click declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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