Safety Considerations with the Use of Corticosteroids and Biologic Therapies in Mild-to-Moderate Ulcerative Colitis

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Background: The risk of corticosteroid-associated adverse events can limit the use of systemic corticosteroids. Oral, topically acting, second-generation corticosteroids that deliver drug to the site of inflammation, and biologic therapies, are effective treatment alternatives. The aim of this review was to evaluate the safety and tolerability of topically acting corticosteroids and biologic therapies versus oral systemic corticosteroids for ulcerative colitis (UC).

Methods: The PubMed database was searched for clinical and observational trials, systematic reviews, and case reports/series published between January 1950 and September 30, 2016. Search terms used included "corticosteroids," "beclomethasone dipropionate," "budesonide," "infliximab," "adalimumab," "golimumab," and "vedolizumab" in combination with "ulcerative colitis" or "inflammatory bowel disease."

Results: A total of 582 studies were identified from PubMed searches. Only 1 direct comparative trial for oral topically acting corticosteroids and systemic corticosteroids was available, and no comparative trials versus biologic therapies were identified. In patients with mild-to-moderate UC, short-term (4–8 wk) oral beclomethasone dipropionate or oral budesonide multimatrix system demonstrated safety profiles comparable with placebo with few corticosteroid-related adverse events reported. Based on long-term data in patients with moderate-to-severe UC, biologics have a generally tolerable adverse event profile, although infections, infusion reactions, and autoimmune disorders were frequently reported.

Conclusions: Second-generation corticosteroids, beclomethasone dipropionate and budesonide multimatrix system, exhibited a favorable safety profile in patients with mild-to-moderate UC. For biologics, which are only indicated in moderate-to-severe UC, additional studies are needed to further ascertain the benefit to risk profile of these agents in patients with mild-to-moderate disease (see Video Abstract, Supplemental Digital Content, http://links.lww.com/IBD/B653).

(Inflamm Bowel Dis 2017;23:1689–1701)

Key Words: biologics, inflammatory bowel disease, large intestine, ulcerative colitis

Ulcerative colitis (UC) is a chronic, relapsing disease, and traditionally, management of UC has depended on disease severity (mild, moderate, or severe), classified according to a patient's clinical symptoms (e.g., daily number of stools, amount of blood in the stool, systemic symptoms, and anemia), inflammatory indices (e.g., erythrocyte sedimentation rate), and the endoscopic extent and severity of the disease.[1,2] However, the updated UC clinical decision support tool acknowledges that these indices may not accurately reflect disease severity and future disease course and suggest that colectomy risk also be considered when determining appropriate treatment (Table 1).[3] For patients with UC and low colectomy risk, topical and oral formulations of 5-aminosalicylic acid (5-ASA) are generally a first-line therapy.[3] Corticosteroids may also be considered for patients refractory to 5-ASA, but the corticosteroid class has a broad adverse event (AE) profile and should be tapered during the maintenance phase.[3] Patients with UC who have an increased risk of colectomy (e.g., patients who are younger than 40 years or those with high C-reactive protein and erythrocyte sedimentation rate or steroid-requiring disease) may benefit from induction of remission with corticosteroids combined with thiopurine or biologic therapies (e.g., anti–tumor necrosis factor [TNF] medications, vedolizumab); however, as with patients at low risk of colectomy, corticosteroids require tapering and replacement with a different therapy (e.g., a biologic) to maintain UC remission.[3]

Ultimately, the treatment plan for an individual patient must take into account multiple factors, including patient preference[1] and overall health concerns (e.g., drug AE profile).[1,2] The adverse consequences of oral systemic corticosteroids (e.g., prednisone) are generally well known, but health care providers may be less

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ibdjournal.org).

Received for publication March 3, 2017; Accepted June 23, 2017.

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Technical editorial and medical writing support was provided, under the direction of the author, by Mary Beth Moncrief, PhD, and Jillian Gee, PhD, Synchrony Medical Communications, LLC, West Chester, PA. Funding for this support was provided by Salix Pharmaceuticals, Raleigh, NC. Salix Pharmaceuticals did not actively contribute to the content of this article but reviewed for scientific accuracy.

R. K. Cross, receives fees for consulting and participation in advisory boards from AbbVie Inc., Janssen, Takeda, and UCB, and receives research funding from AbbVie Inc.

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DOI 10.1097/MIB.0000000000001261

Published online 8 September 2017.

TABLE 1. UC Care Pathway Treatment Summary

Patient Risk of Colectomy	Induction	Maintenance	No Remission or Disease Relapse
Low[a]	Oral 5-ASA Rectal 5-ASA Oral budesonide or prednisone Rectal steroids May be used alone or in combination	Oral or rectal 5-ASA; taper steroids over 60 d	Consider as high-risk patient
High[b]	Short course of steroids and thiopurine	Taper steroids over 60 d and initiate anti-TNF or vedolizumab with/without thiopurine or methotrexate	Consider as high-risk patient not in remission
	Anti-TNF with/without thiopurine	Continue with anti-TNF with/without immunomodulator	
	Vedolizumab with/without immunomodulator	Continue with vedolizumab with/without immunomodulator	
High—not in remission	Anti-TNF with/without thiopurine	NA	Anti-TNF or vedolizumab for patients who do not respond to prednisone
	Thiopurine		Increase dose or add immunomodulator or switch to a different biologic in patients who lose response to anti-TNF therapy
	Vedolizumab with/without immunomodulator		Increase thiopurine dose or switch to anti-TNF or vedolizumab in patients who fail to maintain remission with steroids and thiopurine treatment
	Proctocolectomy		Increase dose or switch to anti-TNF therapy with/without thiopurine for patients who lose response to vedolizumab

[a]Patients with limited anatomical extent and mild endoscopic disease.
[b]Patients with extensive colitis, deep ulcers, age <40 years, high C-reactive protein and erythrocyte sedimentation rate, steroid dependence, history of hospitalization, *Clostridium difficile* infection, or cytomegalovirus infection.
NA, not applicable.
Data from Dassopoulos T et al. *Gastroenterology*. 2015;149:238–245.[3]

aware of the safety of oral topically acting corticosteroids (e.g., budesonide multimatrix system [MMX]) and biologic therapies. Indeed, studies that examined infliximab prescribing patterns suggest that gastroenterologists are not familiar with potentially serious AEs related to biologic therapies (e.g., serious infection and demyelinating syndrome).[4,5] Because health care providers are in the position to consider biologic therapies in place of traditional corticosteroids for patients with mild-to-moderate disease at high risk of colectomy, this narrative review discusses the safety and tolerability profile of oral systemic and oral topically acting corticosteroids and biologic therapies for the treatment of UC. The objective of this descriptive review is to provide health care providers with an understanding of potential safety and tolerability profiles when initiating these therapies, so they can better inform patients of the potential benefits and risks of each therapeutic option.

METHODS

Clinical and observational trials, systematic reviews, and case reports/series with publication dates between January 1950 and September 30, 2016 were identified through PubMed. Search terms used to identify publications related to corticosteroids included "corticosteroids" in combination with "ulcerative colitis" or "inflammatory bowel disease." Because safety data were limited in clinical studies of corticosteroids in inflammatory bowel disease (IBD), additional searches using "corticosteroids" and specific corticosteroid-related AEs (e.g., "cardiovascular") were

performed. To identify literature on topical corticosteroids, search terms "beclomethasone dipropionate" and "budesonide" were combined with "ulcerative colitis" or "inflammatory bowel disease." Publication searches for biologic therapies were performed using "infliximab," "adalimumab," "golimumab," and "vedolizumab" in combination with "ulcerative colitis" or "inflammatory bowel disease." Bibliographies of the publications identified from the PubMed search were reviewed to identify additional trials of interest. Trials that were conducted in pediatric populations or did not provide safety data were excluded.

RESULTS

A total of 582 studies were identified from initial PubMed searches for review, and a further 31 studies were selected from publication bibliographies. Most (85%) of the identified studies were excluded because they did not evaluate the efficacy and safety of corticosteroids or safety parameters of interest, did not provide adequate efficacy and safety data specifically for patients with UC, or were review articles.

SAFETY AND TOLERABILITY OF SYSTEMIC CORTICOSTEROIDS

Oral systemic corticosteroids are typically reserved for induction of remission in patients with mild-to-moderate UC (at low or high risk of colectomy) who do not achieve remission with 5-ASA or who experience relapse while on 5-ASA maintenance therapy.[1,2] However, systemic corticosteroids are not recommended for long-term treatment to maintain UC remission[1] because of their adverse safety profile. Overall, most (>90%) patients receiving systemic corticosteroids for an inflammatory condition will experience at least 1 corticosteroid-related AE.[6,7]

Systemic corticosteroids may impact multiple organ systems and therefore are associated with a diverse set of AEs.[1] Dermatologic (skin bruising/thinning), psychologic and behavioral disturbances (e.g., minor mood and sleep disturbances), neurologic disorders (e.g., headache and vertigo), infections, gastric conditions, and fracture have been associated with systemic corticosteroid use in multiple patient populations.[6,8,9] In patients with IBD, gastrointestinal (GI; 21% of all AEs), neurologic (17%), and endocrine and metabolic (15%) AEs were the most commonly reported.[9] Single-case reports and case-controlled studies in various patient populations (e.g., patients with rheumatoid arthritis or IBD) have indicated that systemic corticosteroids increase the risk of secondary medical conditions (e.g., memory impairment,[10] lipodystrophy,[11] pancreatitis,[12] atrial fibrillation,[13,14] arterial dysfunction [e.g., increased frequency of plaques and reduced compressibility],[15] venous thromboembolism,[16] pulmonary embolism,[17] tendon rupture,[18] opportunistic infections,[19–21] ocular hypertension,[22] infections,[21,23] and suicide[24]) and mortality,[23] but it is unclear whether there is an actual causative relationship between these conditions and corticosteroid use. However, a meta-analysis of 47 publications demonstrated a 5-fold increase in incidence of several AEs (e.g., bruising, cataracts, epistaxis, gastric lesions or ulcers, lethal infection, muscle weakness tuberculosis, hip, femoral, and vertebral fracture) with the use of corticosteroids (excluding topical intranasal or inhaled formulations) across various patient populations.[8]

The risk and incidence of corticosteroid-related AEs increase with longer duration of treatment,[7,25] likely because of

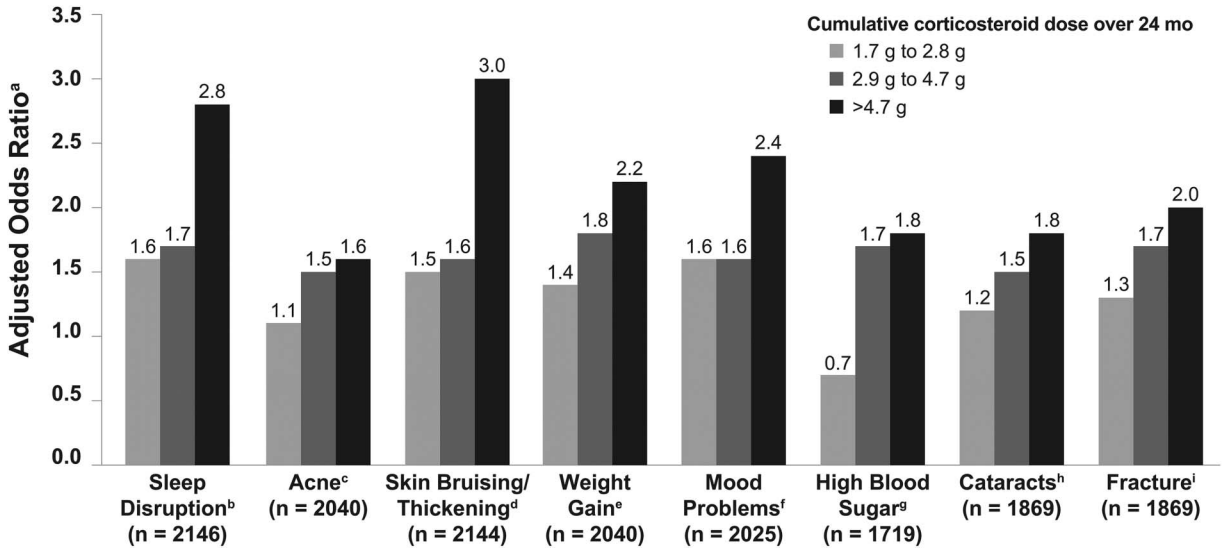

FIGURE 1. Dose-related risk of systemic corticosteroid-related AEs. [a]Relative to corticosteroid doses <1.7 g. [b]Adjusted for age, sex, and number of comorbid diseases. [c]Adjusted for age, sex, and ethnicity. [d]Adjusted for age, sex, new user, and number of comorbid diseases. [e]Adjusted for age, sex, new user, ethnicity, and number of comorbid diseases. [f]Adjusted for age, sex, ethnicity, and number of comorbid diseases. [g]Among nondiabetic patients, adjusted for ethnicity and number of comorbid diseases. [h]Adjusted for age, ethnicity, number of comorbid diseases, and income. [i]Adjusted for age, sex, income, and number of comorbid diseases. Data from Curtis JR et al. *Arthritis Rheum*. 2006;55:420–426.[6]

the higher daily and cumulative doses.[6,13,26] A population-based claims database analysis in patients who used corticosteroids for treatment of a variety of medical conditions demonstrated up to a 3-fold increased risk of some AEs with higher cumulative corticosteroid doses (between 1.7 and >4.7 g) as compared to doses <1.7 g (Fig. 1).[6] Use of corticosteroids in combination with other immunomodulatory and biologic agents (e.g., thiopurines and infliximab) also increases the risk of serious AEs (e.g., opportunistic infection), with greatest risk occurring when 3 immunosuppressive agents are combined.[21] Because of the various and potentially serious AEs associated with corticosteroid use, health care providers should be wary of prescribing corticosteroids long term.[27]

SAFETY AND TOLERABILITY OF ORAL TOPICALLY ACTING CORTICOSTEROIDS

Unlike conventional oral corticosteroids, GI topical corticosteroids facilitate delivery of active medication directly to the site of inflammation, either through direct application (e.g., enema) or targeted delivery of active drug (beclomethasone dipropionate [BDP] and budesonide MMX).[28–31] Topical targeting can provide local anti-inflammatory action within the GI tract with potentially reduced systemic levels of corticosteroid.[31] Oral topically acting therapies are second-generation corticosteroids that use various drug delivery technologies (e.g., multiple methacrylic polymer coatings) to ensure GI targeting,[30–34] which may potentially reduce the incidence of AEs associated with conventional systemic corticosteroids. However, although several active comparator trials of oral topically acting corticosteroids versus prednisone have been reported,[32,34] few head-to-head studies with the oral topically acting corticosteroids have been conducted, making it difficult to determine the most favorable benefit-risk profile within this drug class.[71]

BDP

Oral BDP is indicated in Europe as add-on therapy for treatment of active mild or moderate UC that is unresponsive to 5-ASA. Oral BDP uses a gastroresistant film coating to deliver active medication to the distal small bowel and throughout the colon.[35] Although efficacy results from several clinical trials in patients with UC are available, published safety data from these trials are somewhat limited.[35–37] In short-term clinical trials (e.g., 4 wk), the AE profile of BDP was similar to that of placebo and 5-ASA[35,36] but was not substantially more favorable than prednisone because of the continued occurrence of corticosteroid-related AEs.[37] However, more patients achieved clinical response without corticosteroid-related AEs with BDP (51.2%) than with prednisone taper (37.8%), suggesting a more favorable benefit-risk profile.[37] Unlike prednisone, clinically significant reductions in plasma cortisol concentrations have not been observed with short-term BDP treatment in most patients.[35–37] Long-term safety and tolerability data for oral BDP have not been published, but a retrospective study of patients with active UC who received BDP for a mean of 6.2 weeks did not identify any difference in safety parameters among short-term (e.g., 4 wk) versus long-term (5–18 wk) treatment.[38]

Budesonide MMX

Two formulations of oral budesonide are available, including pH-dependent release formulations and budesonide extended-release tablets, which uses a Multi-Matrix System (MMX) technology to achieve targeted delivery throughout the colon[39,40]; however, only budesonide MMX is indicated in the United States for induction of remission in patients with mild-to-moderate UC. Data from multiple short-term (≤8 wk) clinical trials of budesonide MMX are available.[41] In a pooled analysis of safety data from 5 clinical trials (2 double-blind, placebo- and active-comparator phase 3 trials [CORE I and CORE II]; 2 placebo-controlled phase 2 trials; and 1 phase 3, open-label study), budesonide MMX 3 to 9 mg (the approved dose) for up to 8 weeks was well tolerated.[41] In this analysis, the rate of any AE was similar between budesonide MMX and placebo (3 mg, 35.3%; 6 mg, 60.6%; 9 mg, 54.5%; placebo, 50.5% [in placebo-controlled trials] to 50.6% [in open-label studies]) and was not substantially impacted by higher budesonide MMX doses (6 versus 9 mg). In double-blind studies, the most common AEs (>3% of patients) with budesonide MMX 9 mg were UC exacerbation (12.5%), headache (11.8%), nausea (4.5%), decreased blood cortisol concentrations (4.2%), and abdominal pain

TABLE 2. Summary of Prespecified Glucocorticoid-related AEs with Budesonide MMX

	Randomized, Double-blind Studies		Open-label Studies
AE, n (%)	Budesonide MMX, 9 mg/d (n = 270)[a]	Placebo (n = 293)	Budesonide MMX, 9 mg/d (n = 60)[a]
Any[b]	26 (9.6)	27 (9.8)	5 (8.3)
Mood changes	9 (3.3)	11 (4.0)	0
Sleep changes	7 (2.6)	12 (4.4)	0
Acne	6 (2.2)	5 (1.8)	1 (1.7)
Insomnia	6 (2.2)	8 (2.9)	1 (1.7)
Moon face	3 (1.1)	4 (1.5)	3 (5.0)
Fluid retention	2 (0.7)	3 (1.1)	1 (1.7)
Hirsutism	1 (0.4)	0	0
Flushing	0	3 (1.1)	0
Striae rubrae	0	2 (0.7)	0

[a]AEs potentially related to the use of glucocorticoids were not prespecified in study CRO-03-53, and thus, this population was not included in the analysis.
[b]Potential glucocorticoid-related AEs presented in descending order of frequency for budesonide MMX 9-mg group, then alphabetically for AEs with equal frequency.
Reproduced and adapted from Lichtenstein GR et al. Budesonide MMX for the induction of remission of mild-to-moderate UC: a pooled safety analysis. *J Crohn's Colitis.* 2015;9:738–746.[41] Published by Oxford University Press on behalf of the European Crohn's and Colitis Organisation online at http://ecco-jcc.oxfordjournals.org/content/9/9/738.article-info.

(3.5%). Although corticosteroids are known to suppress the immune system, thereby potentially increasing infection risk, the incidence of infections was generally similar with budesonide MMX 9 mg (12.7%) and placebo (8.5%). Serious AEs were reported by 2.0% to 5.9% of patients who received budesonide MMX in randomized trials and 2.2% in open-label studies. Prespecified corticosteroid-related AEs occurred in fewer than 10% of patients who received budesonide MMX (Table 2) and plasma cortisol concentrations remained within normal limits for most patients.[41]

The safety of budesonide MMX compared with other medications for induction of remission in patients with mild-to-moderate UC (e.g., 5-ASA and pH-dependent budesonide [indicated for induction of remission in Crohn's disease [CD]) has been evaluated in 2 clinical trials (5-ASA [mesalamine] delayed-release tablets in the CORE I trial[42] and pH-dependent budesonide in CORE II[39]). Results from CORE I (8 wk of treatment) showed that the incidence of any AE was similar with budesonide MMX 9 mg (57.5%) and delayed-release mesalamine 2.4 g (63.0%).[42] The most frequent AEs with budesonide MMX 9 mg versus delayed-release mesalamine, respectively, were UC (11.0% versus 10.2%), headache (6.3% versus 9.4%), pyrexia (2.4% for both), and insomnia (3.9% versus 2.4%). Rates of infection were not reported. Budesonide MMX was associated with a slightly higher number of any potential corticosteroid-related AE (11.8%) compared with delayed-release mesalamine (7.9%), including sleep disturbance (3.2% versus 0.8%), mood (4.0% versus 1.6%), and insomnia (4.0% versus 1.6%). Severe AEs were reported in a similar percentage of patients in the budesonide MMX 9 mg (6.3%) and delayed-release mesalamine (5.5%), and both were less than that reported with placebo (12.4%). No increase in the percentage of patients who experienced serious AEs was reported with budesonide MMX 9 mg (2.4%) compared with delayed-release mesalamine (3.1%).[42] Based on these data, budesonide MMX seems to have a safety profile generally similar to that of delayed-release mesalamine, which is often prescribed for induction of remission in patients with mild-to-moderate disease. Health care providers and patients should be aware of the potential for corticosteroid-related AEs such as mood changes and insomnia; however, corticosteroid-related AEs occurred with similar frequency with budesonide MMX (5.9%–9.6% of patients) and placebo (9.8%) in clinical trials.[41] Although pH-dependent budesonide is not currently indicated for induction of remission in patients with mild-to-moderate UC, an 8-week, active comparator (CORE II) study was performed with the 2 budesonide formulations.[39] Overall, the percentage of patients who reported any AE was similar for budesonide MMX 9 mg (55.5%) and pH-dependent budesonide 9 mg (54.8%), but budesonide MMX 9 mg was associated with fewer corticosteroid-related AEs (6.3% versus 11.1%, respectively). Most patients reported mild-to-moderate AEs in both groups (21.1%–25.0% with budesonide MMX versus 23.0%–23.8% with pH-dependent budesonide). The incidence of serious treatment-related AEs was similar in budesonide MMX 9 mg and pH-dependent budesonide 9 mg treatment groups (0.8%), and no infections were reported during the study.[39]

Long-term data (>8 wk) for the use of oral topically acting corticosteroids as a class for treatment of UC are limited. A meta-analysis of six 12-month studies of budesonide (either MMX or pH-dependent) in patients with CD reported no significant difference in corticosteroid-related AEs versus placebo (budesonide, 23% versus placebo, 19%; odds ratio 1.3; $P = 0.3$).[43] These findings combined with evidence from short-term trials[39,42,72] suggest that GI topical therapies might have a generally favorable long-term safety profile, especially when compared with systemic corticosteroids.

SAFETY AND TOLERABILITY OF BIOLOGIC THERAPIES

Several biologic therapies are indicated for induction and maintenance of remission in patients with moderate-to-severe UC refractory to conventional therapy with corticosteroids. However, the current UC Clinical Care Pathway suggests that biologics (with or without immunomodulators) may be used as a first-line therapy for induction and maintenance of remission in patients with mild-to-moderate disease who have a high risk of colectomy.[3] Because clinical trials have evaluated biologic therapies for both induction and maintenance of remission combined, the overall lengths of the trials have been longer than those conducted with systemic and oral topically acting corticosteroids; therefore, the comparative safety of biologics versus corticosteroids is difficult to ascertain. It should also be noted that biologic therapies have typically been examined in patients with moderate-to-severe UC that was steroid dependent or refractory to other therapies (e.g., immunomodulators).[44–48] Thus, the patient populations included in clinical trials of biologics represent a less healthy subset of patients than those included in trials of corticosteroids. In addition, most trials allowed concomitant use of corticosteroids and purine antimetabolites (e.g., azathioprine or 6-mercaptopurine) during the studies, making distinction between biologic and corticosteroid and purine antimetabolite effects difficult.[44,47,48] However, it is clear that biologic therapies, such as systemic corticosteroids, are immunosuppressive, a characteristic associated with increased risk of malignancy (when combined with thiopurines)[49] and infections (e.g., tuberculosis[23,49–51] and opportunistic infections).[49–51] Biologics exert no effects on endogenous cortisol concentrations and are not associated with the corticosteroid-related AEs that deter corticosteroid tolerability, but unlike oral agents, biologics may be associated with infusion-related reactions and an increased risk of autoimmunity (e.g., lupus and demyelinating disease).[49,52] Biologics may also stimulate production of antidrug antibodies, which may reduce efficacy[53] and can result in infusion-related reactions.[54] Data from head-to-head studies of different biologic therapies are not currently available, but indirect comparisons among agents reveal similar short-term (Table 3)[44,47,48,55] and long-term (Table 4) safety profiles.

Infliximab

Short-term safety data for infliximab compared with corticosteroids are limited, given that the pivotal clinical trials have typically combined their safety analyses for induction and maintenance periods (e.g., >30 wk). However, in the UC SUCCESS randomized, double-blind trial which examined the safety and efficacy of azathioprine alone, infliximab alone, or infliximab in combination with azathioprine (n = 231) during a 16-week period, 33% of patients who received infliximab 5 mg/kg (3 infusions; n = 78) had ≥1 AE by week 8 (Table 3).[44] The most common AEs after 8 weeks of therapy with infliximab were pyrexia (6%), headache (5%), abdominal pain (4%), and anemia (4%). No patients in the infliximab alone group experienced a serious AE, versus 8% of patients who received azathioprine and 4% who received combination treatment. Serious infections (1%) and alterations in liver test results (e.g., alanine aminotransferase World Health Organization [WHO] classification ≥2; 4%) occurred with infliximab, but the incidence was lower than that reported with azathioprine (1% versus 16%, respectively). There were no between-group differences in the incidence of malignancy or lymphoma. Anti-infliximab antibodies were observed in 19% (7/37) of patients in the infliximab group and occurred less frequently when infliximab was combined with azathioprine (3%; 1/31). No deaths occurred during the study.[44]

Two randomized studies of infliximab also demonstrated a relatively favorable safety profile.[46] After 54 weeks (Active Ulcerative Colitis Trial [ACT] I, 54 wk; ACT II, 30 wk) of infliximab 5 mg/kg (approved dose for UC) or 10 mg/kg given at weeks 0, 2, and 6 for induction and every 8 weeks for maintenance, the incidence of any AE was not significantly different with infliximab versus placebo ($P \geq 0.1$; Table 4).[56] Events of infection ($P \geq 0.2$), serious infections ($P \geq 0.7$), acute infusion reactions ($P > 0.4$), and hypersensitivity reactions ($P > 0.6$) were not significantly higher in the combined infliximab group versus

TABLE 3. Safety of Biologic Therapies for Induction of Remission in UC

	UC SUCCESS[44]; 8-week Induction		M06-826[47]; 8-week Induction		PURSUIT-SC[45]; 6-week Induction		GEMINI 1[48]; 6-week Induction	
	Infliximab	Azathioprine	Adalimumab		Golimumab		Vedolizumab	
	5 mg/kg[a]	2.5 mg/kg	160/80 mg[b]	Placebo	200/100 mg[c]	Placebo	300 mg[d]	Placebo
AE, n (%)	(n = 78)	(n = 79)	(n = 223)	(n = 223)	(n = 331)	(n = 330)	(n = 746)	(n = 149)
Any AE	26 (33.3)	41 (51.9)	112 (50.2)	108 (48.4)	124 (37.5)	126 (38.2)	337 (45.2)	69 (46.3)
AE leading to discontinuation	2 (2.6)	6 (7.6)	12 (5.4)	12 (5.4)	1 (0.3)	3 (0.9)	NR	NR
Any serious AE	0	6 (7.6)	9 (4.0)	17 (7.6)	9 (2.7)	20 (6.1)	25 (3.4)	10 (6.7)
Any infection	NR	NR	32 (14.3)	35 (15.7)	39 (11.8)	40 (12.1)	104 (13.9)	22 (14.8)
Serious infection	1 (1.3)	1 (1.3)	0	3 (1.3)	1 (0.3)	6 (1.8)	4 (0.5)	3 (2.0)
Infusion/injection-related reaction	0	1 (1.3)	13 (5.8)	7 (3.1)	11 (3.3)	5 (1.5)	3 (0.4)	1 (0.7)
Most common AEs								
Abdominal pain	3 (3.8)	4 (5.1)	NR	NR	NR	NR	NR	NR
Upper abdominal pain	0	4 (5.1)	NR	NR	NR	NR	NR	NR
Anemia	3 (3.8)	4 (5.1)	NR	NR	9 (2.7)	7 (2.1)	NR	NR
Fatigue	0	4 (5.1)	NR	NR	NR	NR	NR	NR
Headache	4 (5.1)	8 (10.1)	NR	NR	10 (3.0)	17 (5.2)	57 (7.6)	7 (4.7)
Nasopharyngitis	NR	NR	NR	NR	11 (3.3)	11 (3.3)	NR	NR
Nausea	1 (1.3)	10 (12.7)	NR	NR	3 (0.9)	7 (2.1)	NR	NR
Pyrexia	5 (6.4)	3 (3.8)	NR	NR	6 (1.8)	7 (2.1)	NR	NR
UC	NR	NR	NR	NR	7 (2.1)	13 (3.9)	20 (2.7)	8 (5.4)
Vomiting	0	6 (7.6)	NR	NR	NR	NR	NR	NR
Tuberculosis	0	0	0	0	0	0	NR	NR
Malignancies	0	0	0	2 (0.9)[e]	NR	NR	0	0

[a]Intravenous infliximab 5 mg/kg at weeks 0, 2, 6, and 14; safety data from a placebo-controlled induction study were not available. The UC-SUCCESS trial evaluated azathioprine, infliximab, and azathioprine and infliximab combination for the induction of UC remission.
[b]Subcutaneous adalimumab 160 mg at week 0, 80 mg at week 2, and 40 mg at weeks 4 and 6.
[c]Subcutaneous golimumab 200/100 mg at weeks 0 and 2.
[d]Intravenous vedolizumab 300 mg at days 1 and 15.
[e]Basal cell carcinoma (n = 1); and breast cancer (n = 1).
NR, not reported.

TABLE 4. Safety of Biologic Therapies for Maintenance of Remission in UC

	ACT-1[56]; 54 Weeks		ULTRA 2[59]; 52 Weeks		PURSUIT-M[55]; 52 Weeks		GEMINI 1[48]; 52 Weeks	
	Infliximab		Adalimumab		Golimumab		Vedolizumab	
	5 mg/kg[a]	Placebo	160/80 mg[b]	Placebo	100 mg[c]	Placebo	300 mg[d]	Placebo
AE, n (%)	(n = 121)	(n = 121)	(n = 257)	(n = 260)	(n = 154)	(n = 156)	(n = 122)	(n = 126)
Any AE	106 (87.6)	103 (85.1)	213 (82.9)	218 (83.8)	113 (73.4)	103 (66.0)	100 (82.0)	106 (84.1)
Leading to discontinuation	10 (8.3)	11 (9.1)	23 (8.9)	34 (13.1)	14 (9.1)	10 (6.4)	NR	NR
Serious AE	26 (21.5)	31 (25.6)	31 (12.1)	32 (12.3)	22 (14.3)	12 (7.7)	10 (8.1)	20 (15.9)
Any infection	53 (43.8)	47 (38.8)	116 (45.1)	103 (39.6)	60 (39.0)	44 (28.2)	87 (71.3)	89 (70.6)
Serious infection	3 (2.5)	5 (4.1)	4 (1.6)	5 (1.9)	5 (3.2)	3 (1.9)	3 (2.5)	4 (3.2)
Infusion/injection-related reaction	12 (9.9)	13 (10.7)	31 (12.1)[e]	10 (3.8)	11 (7.1)	3 (1.9)	7 (5.7)	2 (1.6)
Most common AEs								
Abdominal pain	11 (9.1)	16 (13.2)	NR	NR	11 (7.1)	4 (2.6)	NR	NR
Anemia	4 (3.3)	12 (9.9)	NR	NR	NR	NR	NR	NR
Arthralgia	21 (17.4)	18 (14.9)	NR	NR	8 (5.2)	12 (7.7)	NR	NR
Bronchitis	NR	NR	NR	NR	NR	NR	7 (9)	7 (5.6)
Cough	NR	NR	NR	NR	9 (5.8)	5 (3.2)	NR	NR
Fatigue	14 (11.6)	11 (9.1)	NR	NR	NR	NR	NR	NR
Gastroenteritis	NR	NR	NR	NR	NR	NR	3 (2.5)	5 (4.0)
Headache	22 (18.2)	27 (22.3)	NR	NR	12 (7.8)	14 (9.0)	NR	NR
Influenza	NR	NR	NR	NR	NR	NR	8 (6.6)	3 (2.4)
Nasopharyngitis	NR	NR	NR	NR	21 (13.6)	11 (7.1)	19 (15.6)	15 (11.9)
Nausea	14 (11.6)	14 (11.6)	NR	NR	NR	NR	NR	NR
Pain	14 (11.6)	19 (15.7)	NR	NR	NR	NR	NR	NR
Pharyngitis	12 (9.9)	10 (8.3)	NR	NR	5 (3.2)	4 (2.6)	NR	NR
Pyrexia	14 (11.6)	10 (8.3)	NR	NR	NR	NR	NR	NR
Sinusitis	8 (6.6)	4 (3.3)	NR	NR	NR	NR	2 (1.6)	6 (4.8)
Rash	14 (11.6)	16 (13.2)	NR	NR	7 (4.5)	3 (1.9)	NR	NR
UC	23 (19.0)	40 (33.1)	NR	NR	24 (15.6)	29 (18.6)	NR	NR
URTI	20 (16.5)	28 (23.1)	NR	NR	9 (5.8)	4 (2.6)	12 (9.8)	13 (10.3)
UTI	NR	NR	NR	NR	NR	NR	5 (4.1)	6 (4.8)
Antibodies against study drug	9/116 (7.8)	NR	7/245 (2.9)	NR	32/1103 (2.9)	NR	23/620 (3.7)	NR
Tuberculosis	0	0	NR	NR	3 (1.9)	1 (0.6)	NR	NR
Malignancies	2[f]	0	2 (0.8)[g]	0	3 (1.9)[h]	1 (0.6)[i]	1 (0.8)[j]	2 (1.6)[k]
Neurologic disorder	1[l]	0	NR	NR	NR	NR	NR	NR
Lupus-like syndrome	0	0	1 (0.4)	0	NR	NR	NR	NR
Any hematologic-related AE	NR	NR	5 (1.9)[m]	0	NR	NR	NR	NR

[a]Intravenous infliximab 5 mg/kg at weeks 0, 2, 6 and then every 8 weeks through week 46.
[b]Subcutaneous adalimumab 160 mg at week 0, 80 mg at week 2, and 40 mg at week 4 and every other week thereafter.
[c]Subcutaneous golimumab 100 mg every 4 weeks.
[d]Intravenous vedolizumab 300 mg every 8 weeks.
[e]$P < 0.001$ versus placebo.
[f]Prostatic adenocarcinoma (n = 1); and colonic dysplasia (n = 1).
[g]Squamous cell carcinoma (n = 1); and gastric cancer (n = 1).
[h]Rectal cancer (n = 1); thyroid cancer (n = 1); and lung adenocarcinoma (n = 1).
[i]Breast cancer (n = 1).
[j]Colon cancer (n = 1).
[k]Colon cancer (n = 1); and transitional cell carcinoma (n = 1).
[l]Optic neuritis (n = 1).
[m]Mostly leukopenia in patients receiving concomitant immunosuppressants; $P = 0.030$ versus placebo.
NR, not reported; URTI, upper respiratory tract infection; UTI, urinary tract infection.

placebo.[56] Anti-infliximab antibodies were observed in patients receiving infliximab 5 and 10 mg/kg in the ACT I (7.8% and 4.4%, respectively) and ACT II (9.5% and 3.2%) studies, and their presence was associated with increased incidence of infusion reactions.[56]

Extension phases of the 2 trials, which followed patients for approximately 3 years, provided further data on infliximab safety, with few patients (<5 patients per 100 patient-years of exposure) discontinuing infliximab because of AEs and no patients who received infliximab 5 mg/kg requiring colectomy.[46] The number of infections was relatively high (99/100 patient-years), and many required antimicrobial therapy (41/100 patient-years). Only 4.3% of patients experienced a serious infection, but 1 patient died of histoplasmosis pneumonia. Infusion reactions occurred in 15.6% of patients (7.25/100 patient-years). Anti-infliximab antibodies were detected in up to 14% of patients, with particularly high titers of anti-infliximab antibodies in patients who had stopped and restarted infliximab therapy.[46]

Despite the generally positive tolerability profile during these clinical trials, it is always of concern that studies may not reflect clinical practice because of restricted patient enrollment criteria. However, retrospective assessments of clinical practice largely confirmed the safety profile of infliximab for IBD.[57,58] In a 10-year follow-up in an IBD population (n = 271; approximately 8 infliximab infusions per patient), 13% of patients discontinued treatment because of an AE,[57] including infections in 1.8% of patients. One patient developed extrapulmonary tuberculosis. Infusion reactions occurred in 9% of patients and 0.7% of patients developed possible demyelination. There have been reports of malignancy with infliximab (and other anti-TNF agents)[46,52,57]; however, a meta-analysis did not identify an increase in the risk of malignancy with infliximab.[50]

Adalimumab

In a randomized, placebo-controlled trial in patients with moderate-to-severe UC (Ulcerative Colitis Long-Term Remission and Maintenance with Adalimumab [ULTRA] 1), subcutaneous adalimumab 160/80 mg (approved induction dose; Table 3) or adalimumab 80/40 mg for 8 weeks had a favorable safety and tolerability profile compared with that of placebo.[47] The percentage of patients who reported serious AEs was lower with adalimumab 160/80 (4.0%) and 80/40 (3.8%) versus placebo (7.6%). Opportunistic infections were reported in 1 patient in the adalimumab 160/80 mg group (esophageal candidiasis) and none in the 80/40 mg group. During this short-term study, no malignancy, lupus-like syndrome, or mortality was reported; the presence of antiadalimumab antibodies was not evaluated.[47]

In the ULTRA 2 trial, patients treated with adalimumab 160 mg at week 0 and 80 mg at week 2 followed by 40 mg every 2 weeks had a numerically higher incidence of infectious AEs (45.1%) compared with placebo (39.6%) (Table 4).[59] In addition, the incidence of injection-site–related AEs ($P < 0.001$) and hematologic-related AEs ($P < 0.03$) was significantly higher with adalimumab versus placebo. The incidence of serious infections and opportunistic infections with adalimumab was low (1.6% and 1.9%, respectively) and was similar to that of placebo (1.9% and 1.2%). In the adalimumab group, 1 patient (0.4%) had lupus-like syndrome and 2 patients had a malignancy (0.8%; squamous cell carcinoma, gastric cancer; n = 1 each) versus none in the placebo group. No cases of demyelinating disease or lymphomas were reported. A total of 2.9% of patients developed antiadalimumab antibodies during 52 weeks of treatment.[59]

In the ULTRA 3 trial with up to 4 years of adalimumab treatment (2338 patient-years), the rate of serious infection and opportunistic infection (excluding tuberculosis) was fairly low (3.4 and 0.3 events per 100 patient-years, respectively).[60] Three patients each (0.1 events/100 patient-years) developed lymphoma or demyelinating disease. All patients with lymphoma had previous or concomitant azathioprine use. Twenty-three events (1.0 events/100 patient-years) of malignancy (including lymphoma) were reported; the incidence of malignancy was generally stable over time. Two deaths (0.1%) occurred in the adalimumab group, both were cardiac related.[60]

In some cases, patients may experience primary nonresponse or loss of response with infliximab and may be transitioned to another biologic therapy. Adalimumab seems to be well tolerated in anti-TNF–experienced patients with UC.[61–63] In a 1-year, prospective study of 73 patients with active UC, 49 of whom were transitioned from infliximab to adalimumab, no serious infections or malignancies were reported and previous infliximab therapy did not affect the incidence of AEs.[62] An uncontrolled, retrospective open-label study assessed the safety of transitioning from infliximab to adalimumab in patients with UC (n = 30). Twelve patients required infliximab discontinuation because of acute infusion reaction (n = 8), delayed hypersensitivity reaction (n = 3), or lupus-like syndrome (n = 1).[61] When patients received adalimumab 160 mg at week 0 and 80 mg at week 2 followed by 40 mg every other week for a mean of 48 weeks, 6 patients experienced AEs (fatigue and mild rash, transient fever, arthralgia, psoriasis exacerbation, and treatment-refractory cough [n = 1 for each]).[61] These data suggest that patients who lost responsiveness to or developed AEs associated with infliximab could be safely transitioned to treatment with adalimumab.

Golimumab

The efficacy and safety of 6-week induction therapy with golimumab 200 mg at week 0 and 100 mg at week 2 (200/100 mg, the approved dose) or 400/200 mg was evaluated in the randomized, double-blind, placebo-controlled Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment-Subcutaneous (PURSUIT-SC) trial (n = 774). Overall, the safety and tolerability of golimumab 200/100 mg was generally comparable with that of placebo (Table 3).[45] No occurrences of active tuberculosis, delayed hypersensitivity or anaphylactic reactions, demyelinating disorders, or serious opportunistic infections were observed during the study, and only 0.4% of patients developed antigolimumab antibodies.[45] In a long-term

maintenance study, patients received golimumab 50 or 100 mg every 4 weeks or placebo for 52 weeks; the safety profile of golimumab 100 mg (the approved maintenance dose) at week 54 was somewhat less favorable than placebo (Table 4).[45] Three deaths were reported with golimumab (malnutrition and sepsis [with golimumab 2 mg/kg intravenous induction], cardiac failure [golimumab 400/200 mg], and disseminated tuberculosis [golimumab 200/100 mg, n = 1 for each]). The incidence of serious AEs, malignancies, and injection-site reaction with golimumab 100 mg was greater than that observed with placebo. The incidence of AEs overall and infections was more frequent with golimumab 100 mg versus placebo.[55] Four patients developed tuberculosis, with 1 mortality. Antibodies against golimumab were observed in 2.9% of patients, and most of these (67.7%; 21/31) were neutralizing.[55] When patients in the PURSUIT-IV or PURSUIT-SC clinical trials were followed for approximately 3 years (about 15.5 golimumab administrations, a mean of 1.3 yr since the 1-year trial), the overall safety profile was similar to that of the 52-week maintenance study.[64] The rate of infections (89.1/100 patient-years at 2 yr versus 95.7/100 patient-years at 1 yr) and serious infections (4.5/100 versus 5.2/100 patient-years), malignancy (0.6/100 versus 0.5/100 patient-years), demyelination (0.1/100 versus 0.1/100 patient-years), hypersensitivity reactions (2.5/100 versus 2.1/100 patient-years), and serum sickness/anaphylactic reactions (0/100 versus 0.1/100 patient-years) were not increased with continued golimumab exposure.[64]

Vedolizumab

Vedolizumab was developed with the goal of minimizing the risk of demyelinating diseases, such as progressive multifocal leukoencephalopathy, which have been observed with the first-generation anti-integrin antibody natalizumab.[65] In a phase 3, randomized, double-blind, 6-week induction trial in patients with moderate-to-severe UC, intravenous vedolizumab 300 mg at days 1 and 15 had an AE profile similar to that of placebo (Table 3).[48] The most common AEs were headache (8%) and UC exacerbation (3%). Serious infections and infusion reactions occurred in <1% of patients, and no malignancies were reported. During the long-term extension trial, patients who responded to induction therapy with vedolizumab received vedolizumab 300 mg every 4 weeks or every 8 weeks (approved maintenance dose regimen) or placebo for 52 weeks. The overall safety of vedolizumab with every 8-week (Table 4) and every 4-week dosing was similar to that of placebo. No cases of progressive multifocal leukoencephalopathy were reported, and no increases in peripheral blood total lymphocyte counts occurred. Infusion reactions were slightly more frequent with vedolizumab (6% with 8-wk and 11% with 4-wk dosing) than those with placebo (2%). Malignancies occurred in a similar percentage of patients who received vedolizumab every 8 weeks (<1%; colon cancer, n = 1) and placebo (2%; colon cancer and transitional cell carcinoma, n = 1 each). Only 3.7% of patients had antivedolizumab antibodies.[48]

Safety for approximately 3 years of vedolizumab therapy was analyzed in a pooled analysis of patients with UC or CD (N = 894) in which patients received vedolizumab 300 mg every 4 weeks.[66] The most common AEs were UC exacerbation (24%) and nasopharyngitis (23%). Serious infections occurred in 5% of patients and caused study discontinuation in 4% of patients. Infusion reactions occurred in 3% of patients. Mortality and malignancy (melanoma [n = 2] and breast cancer, metastases to peritoneum/colon cancer, renal cancer, and malignant lung neoplasm [n = 1 each]) occurred in <1% of patients.[66] No cases of progressive multifocal leukoencephalopathy were reported.[66]

The safety of vedolizumab for the induction and maintenance of remission of IBD (including CD and UC) was further substantiated by a meta-analysis of 6 clinical trials (N = 2815).[67] No significant difference was observed with vedolizumab in patients with UC compared with placebo in terms of serious AEs (relative risk [RR] 1.0; 95% confidence interval [CI], 0.7–1.4), serious infection (RR 0.9; 95% CI, 0.2–3.2), and nasopharyngitis (RR 1.3; 95% CI, 0.8–2.0). In addition, in patients with IBD (UC or CD), the risk of mortality (RR 1.4; 95% CI, 0.2–8.7), any cancer (RR 0.5; 95% CI, 0.0–4.6), and disease exacerbation (RR 0.8; 95% CI, 0.5–1.3) was similar between vedolizumab and placebo.[67]

Comparative Safety Among Biologics

Direct comparisons of the safety profile of the various approved biologic therapies are difficult because of the absence of prospective head-to-head clinical trials. The overall safety and tolerability profile of adalimumab (in terms of AE profile, hospitalizations, steroid use after initiation of anti-TNF therapy, and incidence of serious infections) seems to be similar to that of infliximab.[68–70] An analysis of data from randomized clinical trials of adalimumab (n = 685) and infliximab (n = 728) suggested that infliximab was similar to adalimumab in terms of serious AEs (odds ratio of infliximab to adalimumab, 1.2; 95% CI, 0.4–3.5) and AE-related discontinuations (odds ratio 0.7; 95% CI, 0.2–2.5).[70] This was supported by a retrospective analysis of a medical and pharmacy claims database of prescriptions for adalimumab (n = 288) and infliximab (n = 1112).[68] Another analysis of these data from an anti-TNF–naive population showed no difference in all-cause hospitalization (hazard ratio [HR] 1.1; 95% CI, 0.8–1.4; $P = 0.74$), UC-related hospitalization (HR 1.0; 95% CI, 0.7–1.5; $P = 0.85$), serious infections (HR 0.6; 95% CI, 0.3–1.3; $P = 0.22$), or steroid use >60 days after initiation of biologic therapy (HR 0.9; 95% CI, 0.7–1.1; $P = 0.16$) for those treated with infliximab versus adalimumab.[68] A meta-analysis that examined the risk of infection and malignancy with biologic therapies as both a group and individually reported no significant between-drug effect for serious infections ($P = 0.8$), opportunistic infections ($P = 0.4$), or any infection ($P = 0.6$).[50] However, in another meta-analysis of randomized, controlled trials in patients with IBD, the RR of developing opportunistic infection seemed greatest for infliximab (RR 2.5; 95% CI, 0.9–7.0) and golimumab (RR 2.03; 95% CI, 0.2–18.0), but these were not significantly different versus adalimumab (RR 1.6; 95% CI, 0.5–5.3).[51] No direct comparative trials have been performed for golimumab or

vedolizumab in patients with UC; however, a head-to-head trial of vedolizumab and other biologics (infliximab, adalimumab, and golimumab) in patients with IBD is underway.

DISCUSSION

This review has described the AE profile of systemic and targeted corticosteroids and biologics; however, the data for these agents from clinical trials are difficult to compare given differences in disease severity, patient populations, and length of follow-up. Medical guidelines traditionally recommend step-up therapy for induction of remission in mild-to-moderate UC, with 5-ASA administered as a first-line therapy followed by corticosteroids (systemic and topical) as necessary.[1,2] Because systemic corticosteroids, even during a short exposure, have been associated with numerous AEs (e.g., adrenocortical insufficiency, increased fracture risk, susceptibility to infection, metabolic alterations, gastric conditions, nervous system effects [e.g., mood changes and sleep disruption],[8] and anecdotal accounts of other disorders [e.g., atrial fibrillation]),[10–22,24] topical corticosteroids should be used in place of systemic formulations when possible. Both BDP and budesonide MMX have a favorable benefit to risk profile[37,41,73–75]; however, longer-term data (beyond 8 wk) on the use of these agents are currently not available in patients with UC. Thus, similar to conventional formulations, nonsystemic corticosteroids are not recommended for maintenance of remission, and patients must be transitioned to an alternative therapy (i.e., thiopurine or a biologic). Because of this and their favorable efficacy and safety profile, biologics are beginning to be recommended as an alternative first-line therapy for induction of remission in patients with mild-to-moderate UC.[3] However, the efficacy and safety profile of biologics for patients with mild UC has not been established. In addition, the lack of head-to-head comparative trials and the focus of clinical trials of biologics on patients with

TABLE 5. AEs Associated with Corticosteroids and Biologics

Drug Category	Common AEs	Rare AEs
Systemic corticosteroids	Acne	Avascular necrosis
	Adrenocortical insufficiency	Bone fracture
	Bone loss	Cardiovascular AEs (e.g., atrial fibrillation)
	Bruising	Serious infections
	Fluid retention	
	Hirsutism	
	Hypertension	
	Insomnia/sleep changes	
	Leukocytosis	
	Metabolic alterations/weight gain	
	Mood changes	
	Moon face	
	Muscle weakness	
	Ophthalmic AEs (e.g., cataracts and ocular hypertension)	
	Striae rubrae	
Nonsystemic corticosteroids	Acne	Adrenal insufficiency
	Bruising	Fluid retention
	Headache	Flushing
	Moon face	Hirsutism
		Insomnia/sleep changes
		Leukocytosis
		Metabolic alterations/weight gain
		Mood changes
		Striae rubrae
		Visual disturbance
Biologics	Dermatologic disorders (e.g., psoriasis and eczema)	Hematologic-related AEs (e.g., leukopenia)
	Development of antidrug antibodies	Hepatitis
	Headache	Lupus-like syndrome
	Infusion/injection-related reactions	Malignancies
		Neurologic disorders
		Serious infections

moderate-to-severe disease,[45–48,55,56,59,77] without subanalysis of efficacy and safety by disease severity (i.e., efficacy and safety specifically in patients with moderate disease), make it difficult to determine the benefit to risk of biologic therapies for patients with moderate UC.

Ultimately, the decision to initiate topically acting second-generation corticosteroids, systemic corticosteroids, or a biologic in patients with mild-to-moderate UC depends on patients' willingness to accept the risk of common and infrequent AEs associated with each type of medication (Table 5) and several patient-related factors. Of key importance, patients should be queried about their comorbid medical conditions, history of malignancy, previous history of infection, vaccination status, future travel plans, and potential for interaction with individuals with active communicable infections, such as tuberculosis.[51] All patients should be evaluated for Hepatitis B virus and latent tuberculosis before starting steroid or biologic therapy.[51] According to the UC Clinical Care Pathway, consideration should be given to earlier use of a thiopurine and/or biologic agent in patients at increased risk of colectomy, particularly patients with more than 1 risk factor (e.g., patients with extensive disease, deep ulcers, age <40 yr, high C-reactive protein levels, elevated erythrocyte sedimentation rate, *Clostridium difficile* and cytomegalovirus infection, and requirement for corticosteroids).[3,78] Whenever possible, patients should share in the decision making on which therapy to initiate, as they may have strong preferences on treatment (e.g., avoidance of systemic corticosteroids secondary to concerns of short-term cosmetic side effects and aversion to thiopurine secondary to fear of lymphoma). Cost and patient access to treatment are also important factors to consider, particularly given that patients with UC incur greater treatment costs compared with individuals without UC.[79] Clearly, immunomodulators and biologic agents, either as monotherapy or in combination with one another, are more expensive than conventional therapy.[80] Payers may not permit patients to "skip" to biologic therapy, despite a higher risk of colectomy.

CONCLUSIONS

Treatment for patients with mild-to-moderate UC has historically relied on systemic corticosteroids to induce remission in patients not responding to 5-ASA; however, with the availability of oral, topically acting, second-generation corticosteroids and increasing understanding of the safety profile of biologic agents, this paradigm is shifting.[1–3,76] The direct targeting of medication to the GI tract with topically acting corticosteroids decreases the risk of corticosteroid-related AEs and provides a favorable benefit to risk profile versus systemic corticosteroids.[37,41] Use of these agents, however, is limited to the short term to induce, not maintain, remission. Biologic agents have traditionally been reserved for patients with moderate-to-severe UC who are steroid dependent or refractory to other therapies[1,2]; however, they are increasingly used earlier in clinical practice. Another obvious advantage of biologic use is that they can both induce and maintain remission in patients with mild-to-moderate UC. Although biologics are likely efficacious in patients with mild-to-moderate UC,[81] data on the overall benefit to risk of biologics in this patient population are limited. The new American Gastroenterological Association UC Clinical Care Pathway emphasizes consideration of factors other than symptoms to initiate immune suppressant or biologic therapy such as the patient's individual risk factors for colectomy; this approach is likely to result in earlier use of immune suppressants and/or biologic therapy in patients with mild-to-moderate UC.

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