CME

A Review of Available Medical Therapies to Treat Moderate-to-Severe Inflammatory Bowel Disease

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The treatment armamentarium for inflammatory bowel disease has expanded rapidly in the past several years with new biologic and small molecule-agents approved for moderate-to-severe ulcerative colitis and Crohn's disease. This has made treatment selection more challenging with limited but evolving guidance as to where to position each medication. In this review, we discuss the efficacy data for each agent approved in the United States by reviewing their phase 3 trial data and other comparative effectiveness studies. In addition, safety considerations and use in special populations are summarized with proposed algorithms for positioning therapies. The aim is to provide a synopsis of high-impact data and aid in outpatient treatment decision-making for patients with inflammatory bowel disease.

KEYWORDS: ulcerative colitis; Crohn's disease; biologic; small molecule; IBD; drug positioning

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INTRODUCTION

The treatment armamentarium for inflammatory bowel disease (IBD) keeps expanding. Multiple biologic and small-molecule agents with novel mechanisms of action have revolutionized the management of ulcerative colitis (UC) and Crohn's disease (CD).

Disease severity is typically dichotomized into mild and moderate to severe based on clinical symptoms, laboratory values, biomarkers, and endoscopic findings (1–3). Treatment decisions for UC and CD are made considering not only current disease activity and severity but also risk tolerance, concomitant conditions, potential for treatment-related complications, and payer input. The goal for treatment is to control symptoms and diminish inflammation to prevent disease progression and complications.

Whereas positioning of biologics was previously a matter of choosing which anti–tumor necrosis factor (anti-TNF) biologic to use next, the current process is more nuanced. There are limited head-to-head trials available, and comparative efficacy network meta-analyses (NMA) have inherent limitations due to varied study designs. In this review, we will summarize the available data to aid in treatment decisions for outpatients with moderate-to-severe UC and CD and provide treatment algorithms for reference (Figures 1 and 2).

ULCERATIVE COLITIS

Anti-TNF

Anti-TNF monoclonal antibodies were the first biologics approved for use in IBD. For this review, biosimilars are considered equal to their originator product for positioning. Three anti-TNF are approved by the US Food and Drug Administration (FDA) for treatment of UC refractory to conventional therapy (4–8). Infliximab (IFX) is delivered intravenously, while adalimumab (ADA) and golimumab (GOL) are subcutaneous injections (Table 1). Anti-TNF drug clearance is affected by factors including gender, body size, concomitant use of immunosuppressive agents, disease type, serum albumin concentration, and degree of systemic inflammation (9,10).

In the ACT 1 randomized controlled trial (RCT) of IFX, biologic-naive patients with UC treated with 5 mg/kg during induction and maintenance achieved significantly higher clinical remission (week 54: 35% vs 17%, $P = 0.001$) and mucosal healing rates (week 54: 46% vs 18%, $P < 0.001$) compared with those treated with placebo (8). In ULTRA 1, biologic-naive patients treated with standard induction ADA (160 mg/80 mg) achieved higher clinical remission (week 8: 19% vs 9%; $P = 0.031$) and endoscopic remission rates compared with those treated with placebo (4). In ULTRA 2, more biologic-naive patients achieved clinical remission (week 52: 22% vs 12%, $P = 0.029$) and endoscopic remission rates (week 52: 31% vs 19%, $P = 0.018$) with ADA over those treated with placebo. Anti-TNF–experienced patients treated with ADA had higher clinical remission rates compared with those treated with placebo (week 52: 10% vs 3%, $P = 0.039$) (Table 2) (4). In response to a concern for ADA underdosing, the SERENE UC trial compared high-dose induction and maintenance to standard dosing (11). Overall clinical remission rates during induction and maintenance were similar. However, during the SERENE maintenance study, patients with more severe disease had higher efficacy with weekly dosing compared with that with biweekly dosing ($P < 0.05$) (11).

In the UC SUCCESS trial, combination therapy of 5 mg/kg of IFX with 2.5 mg/kg of azathioprine (AZA) achieved 40%

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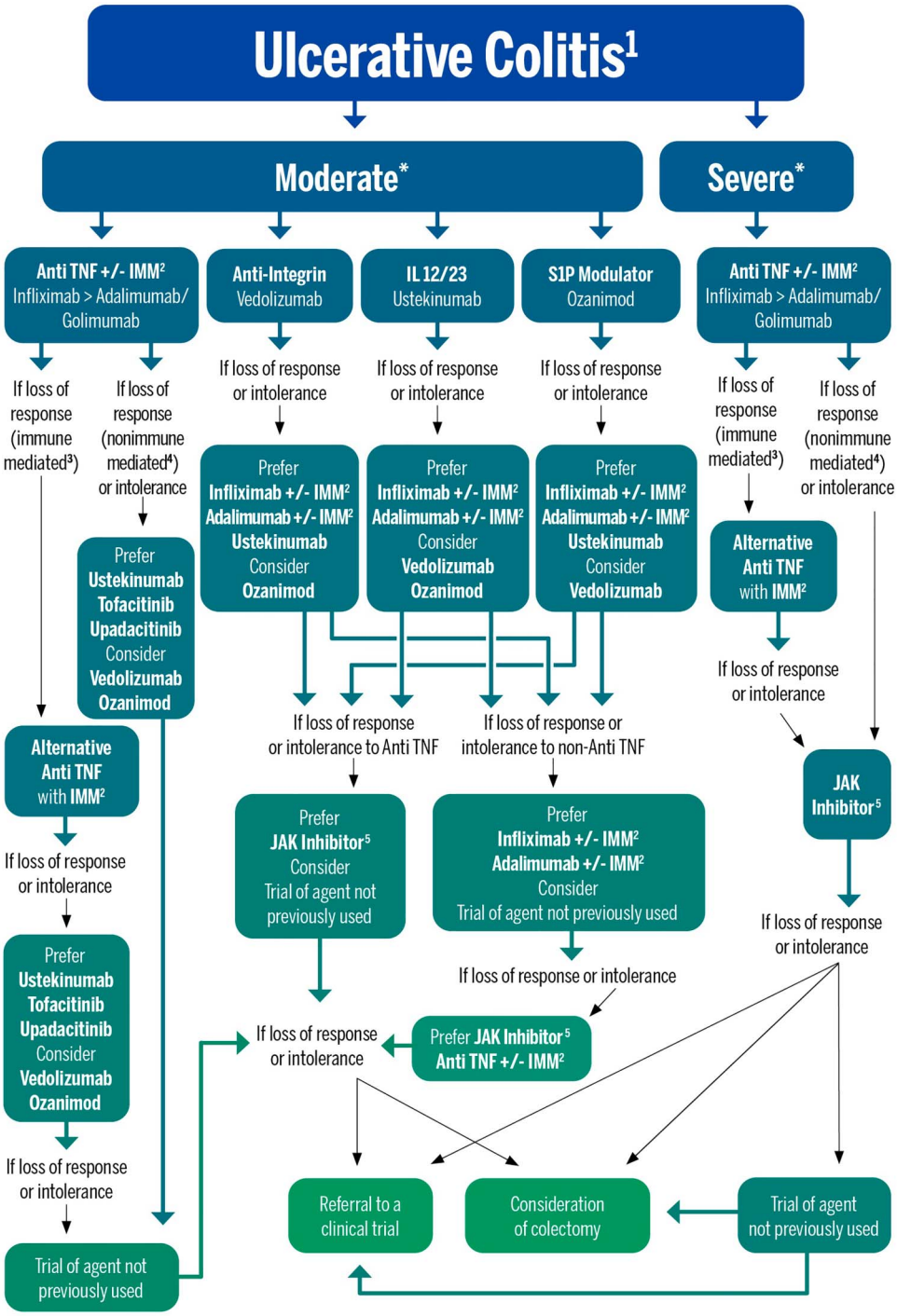

Figure 1. Proposed treatment algorithm for outpatient moderate-to-severe ulcerative colitis. Moderate disease: May Score 4-6; Severe Disease: Mayo Score >/=7 (3). [1]At any time based on patient's clinical presentation, disease severity, disease activity or shared decision making, consideration of colectomy is reasonable. [2]IMM, immunomodulator [3]Immune mediated: Development of antidrug antibodies, levels vary based on assay [4]Non-immune mediated: Loss of clinical response without development of antidrug antibodies [5]Must have prior failure of anti-TNF to use JAK inhibitors due to US black box warnings https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-boxed-warning-about-increased-risk-blood-clots-and-death-higher-dose-arthritis-and; access date June 1, 2023.

corticosteroid-free remission rate at week 16 compared with IFX (22%; $P = 0.017$) or AZA monotherapy (24%; $P = 0.032$). Mucosal healing rates with IFX (with or without AZA) were significantly higher when compared with AZA monotherapy (12).

Vedolizumab

Vedolizumab (VDZ) is a gut-specific, leukocyte antitrafficking monoclonal antibody targeting the α4β7 integrin that prevents migration of leukocytes to the bowel (Table 1). In the GEMINI 1

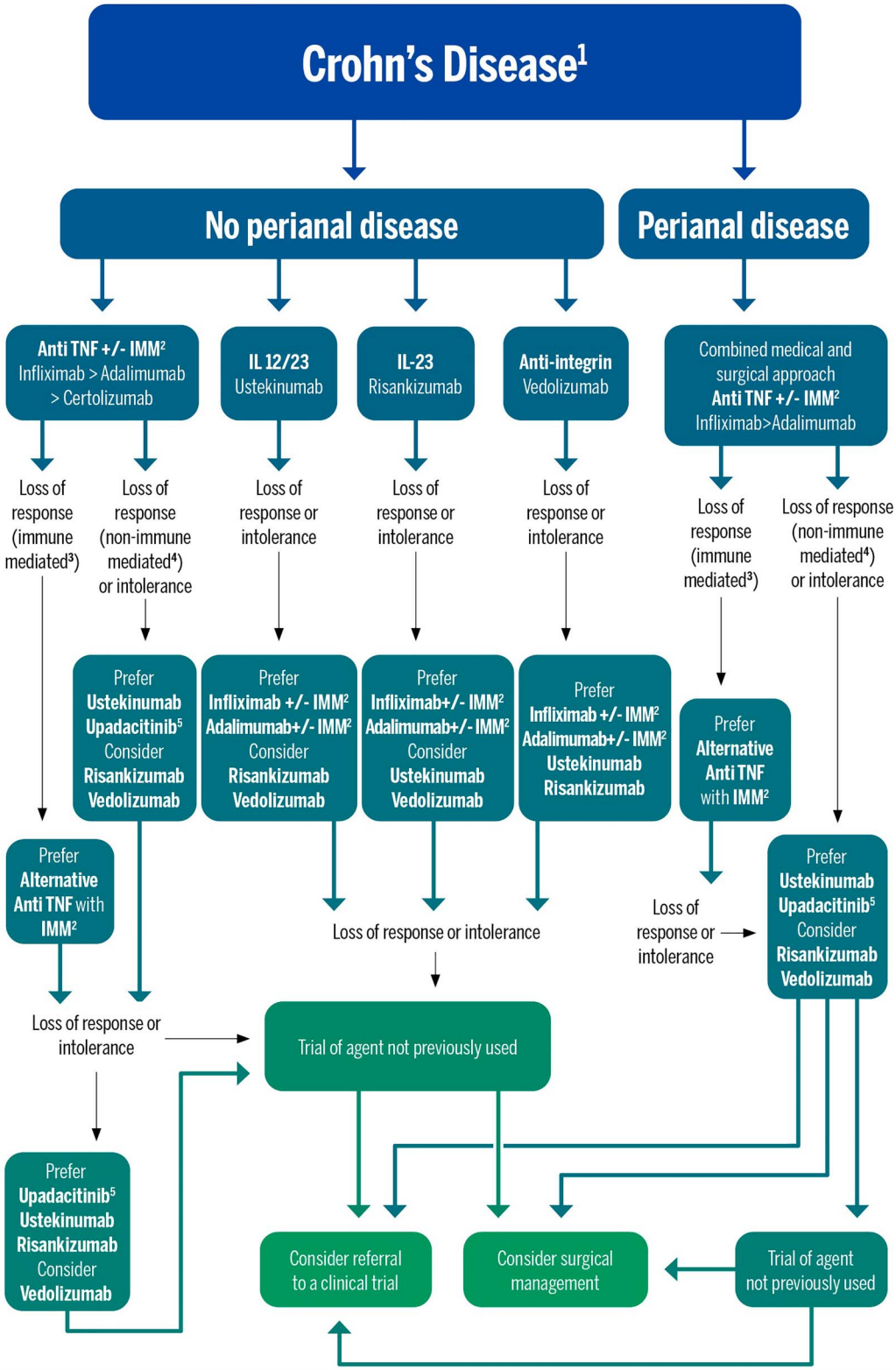

Figure 2. Proposed treatment algorithm for outpatient moderate-to-severe Crohn's disease. [1]At any time based on patient's clinical presentation, disease severity, disease activity or shared decision making, consideration of surgical management is reasonable. [2]IMM, immunomodulator [3]Immune mediated: Development of antidrug antibodies, level dependent on assay [4]Non-immune mediated: Loss of clinical response without development of antidrug antibodies [5]Must have prior failure of anti-TNF to use JAK inhibitors due to US black box warnings (https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death; access date June 1, 2023).

Table 1. Standard induction and maintenance dosing of medications approved for IBD in current US formulations

Drug	Induction dose	Induction route	Maintenance dose	Maintenance route	Condition treated
Infliximab	5 mg/kg at 0, 2, 6 wk	IV	5 mg/kg q8 weeks	IV	UC/CD
Adalimumab	160 mg day 1, 80 mg day 15	SQ	40 mg q2 weeks	SQ	UC/CD
Certolizumab	400 mg 0, 2, 4 wk	SQ	400 mg q4 weeks	SQ	CD
Golimumab	200 mg day 1, 100 mg day 15	SQ	100 mg q4 weeks	SQ	UC
Vedolizumab	300 mg at 0, 2, 6 wk	IV	300 mg q8 weeks	IV	UC/CD
Ustekinumab	<55 kg: 260 mg 55–85 kg: 390 mg >85 kg: 520 mg	IV	90 mg q8 weeks	SQ	UC/CD
Risankizumab	600 mg at 0, 4, 8 wk	IV	180 mg or 360 mg q8 weeks	SQ	CD
Tofacitinib	10 mg BID for 8 wk	PO	5 mg or 10 mg BID; XR dosing 11 mg or 22 mg daily	PO	UC
Upadacitinib	45 mg daily for 8 wk (UC), 12 wk (CD)	PO	15 mg or 30 mg daily	PO	UC/CD
Ozanimod	0.23 mg daily day 1–4 0.46 mg daily day 5–7	PO	0.92 daily	PO	UC

BID, twice daily; CD, Crohn's disease; IBD, inflammatory bowel disease; IV, intravenous; PO, per oral; SQ, subcutaneous; UC, ulcerative colitis.

trial, including biologic-naive patients and biologic-experienced patients with UC, clinical remission at week 6 was achieved in 17% and 5% in the VDZ and placebo arms, respectively ($P = 0.001$) (13). At 52 weeks, clinical remission rates for maintenance infusions every 4 (45%) and 8 weeks (42%) were superior to placebo (16%; $P < 0.001$ for both) (Table 2). Mucosal healing at week 52 was superior with VDZ compared with that with placebo (every 4 weeks: 56%, every 8 weeks: 52%, placebo 20%; $P < 0.001$ for both). Dose escalation to every 4 weeks may be beneficial in patients with loss of response to VDZ (14,15).

Anti-IL12/23

Ustekinumab (UST) is an anti-interleukin 12/23 (IL 12/23) that binds to the p40 subunit common to IL12 and IL23 (Table 1). In the UNIFI trial, biologic-naive and biologic-experienced (51% of the cohort) patients treated with 6 mg/kg of UST achieved higher week 8 clinical remission rates (16% vs 5%, $P < 0.001$) and endoscopic improvement (27% vs 14%, $P < 0.001$) compared with those treated with placebo. UST clinical remission rates at week 8 were lower in biologic-experienced patients (13% vs 1% placebo) (16). During the maintenance trial, at week 44, more patients treated with 90 mg every 8 weeks vs placebo achieved clinical remission (44% vs 24%; $P < 0.001$) and endoscopic improvement (51% vs 29%, $P < 0.001$) (Table 2) (16). In the UNIFI 3-year extension, dose escalation from every 12 weeks to every 8 weeks (current standard dosing) achieved symptomatic remission in 58.8% of patients with loss of response (17).

Janus kinase inhibitors

Two oral Janus kinase inhibitors (JAKi), tofacitinib (TOFA) and upadacitinib (UPA), are approved for UC (Table 1). TOFA preferentially inhibits JAK1 and JAK3, whereas UPA exclusively inhibits JAK1. In the United States, JAKi are approved for patients who did not respond to 1 or more anti-TNF (18,19).

In the OCTAVE 1 and 2 induction trials, patients receiving 10 mg of TOFA twice daily achieved clinical remission 19% and 17% vs 8% and 4% for those treated with placebo, respectively ($P = 0.007$ and $P < 0.001$). The treatment effect was similar in TNF-naive vs TNF-exposed patients (18). In the OCTAVE Sustain maintenance trial, clinical remission rates at week 52 were 34% (5 mg group), 41% (10 mg group), and 11% (placebo) ($P < 0.001$ for both, P values comparing drug with placebo). Endoscopic remission was higher for 10 mg of TOFA (46%) and 5 mg of TOFA (37%) compared with that for placebo (13%; $P < 0.001$ for both, P values comparing drug with placebo) (Table 2) (18).

In the U-ACHIEVE and U-ACCOMPLISH induction trials, more patients treated with 45 mg of UPA daily achieved clinical remission compared with those treated with placebo (26% and 33% vs 5% and 4%, respectively; $P < 0.0001$ for both). At 52 weeks, more patients treated with 15 mg of UPA (42%) and 30 mg of UPA (52%) achieved clinical remission compared with those treated with placebo (12%) ($P < 0.0001$ for both) (Table 2) (19). On subgroup analysis, clinical remission was lower in biologic-experienced patients with UC (18% with UPA vs <1% in placebo). Endoscopic remission was higher with 15 mg of UPA and 30 mg of UPA compared with that with placebo (19% and 26% vs 6%, $P < 0.001$ for both). Post hoc analyses of induction studies for TOFA and UPA showed improvement in rectal bleeding, stool frequency, and fecal urgency within days (20,21).

Ozanimod

Ozanimod (OZN) is an oral sphingosine-1-phosphate receptor modulator that selectively binds to sphingosine-1-phosphate receptors 1 and 5, thereby limiting egress of lymphocytes from lymph nodes (Table 1). In the TRUE NORTH trial, more OZN patients achieved clinical remission compared with those treated with placebo at week 10 (18% vs 6%, $P < 0.001$) and week 52 (37% vs 19%, $P < 0.001$) (Table 2). At week 52, mucosal healing was achieved in 30% of OZA patients vs 14% of patients on placebo ($P < 0.001$). At least 30% and 17% of patients enrolled had prior anti-TNF and VDZ exposure, respectively (22). In a post hoc analysis of TRUE NORTH, biologic-naive patients

Table 2. Summary of phase 3 trial data of US FDA–approved therapies in the United States for ulcerative colitis

					Efficacy end points														
					Clinical response		Clinical remission		Mucosal healing		Unique findings								
Study	Agent (MOA)	Study design	Study period	Substudy	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Mucosal healing end point	Histoendoscopic mucosal healing endpoint	Glucocorticoid free end point	Primary end points	Secondary end points
ACT 1 and ACT 2 (8)	Infliximab (anti-TNF monoclonal antibody)	Randomized to receive 5 mg/kg or 10 mg/kg or placebo at standard dosing (0, 2, 6 then q8 weeks)	Induction (week 8)	ACT 1	37.2%	5 mg/kg: 69.4% 10 mg/kg: 61.5%	14.9%	5 mg/kg: 38.8% 10 mg/kg: 32.0%	33.9%	5 mg/kg: 62% 10 mg/kg: 59%			Decrease from baseline in total Mayo score of at least 3 points and at least 30% with accompanying decrease in subscore for rectal bleeding or absolute subscore for rectal bleeding 0 or 1	Total Mayo score of 2 points or lower with no individual subscore >1 point	Mayo endoscopy subscore of 0 or 1		Clinical remission and corticosteroid free	Clinical response at 8 wk	Clinical response or clinical remission with discontinuation of steroids at week 30 and week 54, clinical remission and mucosal healing at weeks 8, 30, and 54, clinical response at week 8 in patients refractory to steroids
				ACT 2	29.3%	5 mg/kg: 64.5% 10 mg/kg: 69.2%	5.7%	5 mg/kg: 33.9% 10 mg/kg: 27.5%	30.9%	5 mg/kg: 60.3% 10 mg/kg: 61.7%									
			Maintenance (week 30)	ACT 1	29.8%	5 mg/kg: 52.1% 10 mg/kg: 50.8%	15.7%	5 mg/kg: 33.9% 10 mg/kg: 36.9%	24.8%	5 mg/kg: 50.4% 10 mg/kg: 49.2%	Corticosteroid free: 10.1%	Corticosteroid free: 5 mg/kg: 24.3% 10 mg/kg: 19.2%							
				ACT 2	26.0%	5 mg/kg: 47.1% 10 mg/kg: 60.0%	10.6%	5 mg/kg: 25.6% 10 mg/kg: 35.8%	30.1%	5 mg/kg: 46.3% 10 mg/kg: 56.7%	Corticosteroid free: 3.3%	Corticosteroid free: 5 mg/kg: 18.3% 10 mg/kg: 27.3%							
			Maintenance (week 54)	ACT 1	19.8%	5 mg/kg: 45.5% 10 mg/kg: 44.3%	16.5%	5 mg/kg: 34.7% 10 mg/kg: 34.4%	18.2%	5 mg/kg: 45.5% 10 mg/kg: 46.7%	Corticosteroid free: 8.9%	Corticosteroid free: 5 mg/kg: 25.7% 10 mg/kg: 16.4%							
ULTRA 1 (4)	Adalimumab (anti-TNF monoclonal antibody)	Randomized to receive ADA 160/80 mg induction followed by 40 mg q14 d vs ADA 80/40 mg induction followed by 40 mg q14 d vs placebo	Induction (week 8)		44.6%	160/80 mg: 54.6% 80/40 mg: 51.5%	9.2%	160/80 mg: 18.5% 80/40 mg: 10%	41.5%	80/40 mg: 37.7% 160/80 mg: 46.9%			Decrease from baseline in total Mayo score of at least 3 points and at least 30% with accompanying decrease in subscore for rectal bleeding or absolute subscore for rectal bleeding 0 or 1	Total Mayo score of 2 points or lower with no individual subscore >1 point	Mayo endoscopy subscore of 0 or 1			Proportion of patients in each treatment group in remission per Mayo score at week 8	Proportion of patients with clinical response per Mayo score at week 8, proportion of patients with mucosal healing at week 8, proportion of patients with subscore indicators of mild disease (rectal bleeding subscore <1, physicians global assessment <1, stool frequency <1)

Table 2. (*continued*)

					Efficacy end points													
					Clinical response		Clinical remission		Mucosal healing		Unique findings							
Study	Agent (MOA)	Study design	Study period	Substudy	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Mucosal healing end point	Histoendoscopic mucosal healing endpoint	Glucocorticoid free end point	Primary end points	Secondary end points
ULTRA 2 (5)	Adalimumab (anti-TNF monoclonal antibody)	Randomized to receive induction with 160/80 mg and then 40 mg q14 d vs placebo. Bio-naive and bio-exposed patients	Induction (week 8)		All: 34.6% Bio-naive: 38.6% Bio-exposed: 28.7%	All: 50.4% Bio-naive: 59.3% Bio-exposed: 36.7%	All: 9.3% Bio-naive: 11% Bio-exposed: 6.9%	All: 16.5% Bio-naive: 21.3% Bio-exposed: 9.2%	All: 31.7% Bio-naive: 35.2% Bio-exposed: 26.7%	All: 41.1% Bio-naive: 49.3% Bio-exposed: 28.6%			A decrease from baseline in the total Mayo score by at least 3 points and at least 30% with an accompanying decrease in rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1	Total Mayo score of 2 points or lower with no individual subscore >1 point	Mayo endoscopy subscore of 0 or 1		Discontinued steroids before week 52 and achieved remission by week 52	Proportion of patients in each treatment group in remission per Mayo score at week 8 and week 52	Patients with clinical remissions at weeks 8 and 52 (sustained), patients with clinical response per Mayo score at week 8, week 52, and weeks 8 and 52, proportion of patients with mucosal healing at week 8, week 52, and weeks 8 and 52 (sustained) proportion of patients with subscore indicators of mild disease (rectal bleeding subscore <1, physicians global assessment <1, stool frequency <1), patients who achieved remission at week 52 and discontinued steroids before week 52, IDBQ responders at week 8 and 52
			Maintenance (week 52)		All: 18.3% Bio-naive: 24.1 Bio-exposed: 9.9%	All: 30.2% Bio-naive: 36.7% Bio-exposed: 20.4%	All: 8.5% Bio-naive: 12.4% Bio-exposed: 3%	All: 17.3% Bio-naive: 22% Bio-exposed: 10.2%	All: 15.4% Bio-naive: 19.3% Bio-exposed: 9.9%	All: 25% Bio-naive: 31.3% Bio-exposed: 15.3%	Corticosteroid free: 5.7%	Corticosteroid free: 13.3%							
			Sustained response (weeks 8 and 52)		All: 4.1% Bio-naive: 16.6% Bio-exposed: 5.9%	All: 8.5% Bio-naive: 29.3% Bio-exposed: 15.3%	All: 12.2% Bio-naive: 6.2% Bio-exposed: 1.0%	All: 23.8% Bio-naive: 10.7% Bio-exposed: 5.7%	All: 10.6% Bio-naive: 13.8% Bio-exposed: 5.9%	All: 18.5% Bio-naive: 24.0% Bio-exposed: 10.2%								

Table 2. (*continued*)

					Efficacy end points													
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Study	Agent (MOA)	Study design	Study period	Substudy	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Mucosal healing end point	Histoendoscopic mucosal healing endpoint	Glucocorticoid free end point	Primary end points	Secondary end points
PURSUIT SC (6)	Golimumab (anti-TNF monoclonal antibody)	Randomized to receive 200/100 mg vs 400/200 mg at weeks 0, 2 vs placebo	Induction (week 6)		30.30%	200/100 mg: 51% 400/200 mg: 54.9%	6.4%	200/100 mg: 17.8% 400/200 mg: 17.9%	28.70%	200/100 mg: 42.3% 400/200 mg: 45.1%			Decrease from baseline in the Mayo score 30% and 3 points, accompanied by either a rectal bleeding subscore of 0 or 1 or a decrease from baseline in the rectal bleeding subscore	Total Mayo score of 2 points or lower with no individual subscore >1 point	Mayo endoscopy subscore of 0 or 1			Week 6 clinical response	Week 6 clinical remission, mucosal healing, and IBDQ score change
PURSUIT-M (7)	Golimumab (anti-TNF monoclonal antibody)	Patients who responded to induction randomized to placebo vs 50 mg vs 100 mg q4 weeks	Maintenance (week 30)				22.70%	50 mg: 35.8% 100 mg: 39.7%					Decrease from baseline in the total Mayo score by at least 3 points and at least 30% with an accompanying decrease in rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1	Total Mayo score of 2 points or lower with no individual subscore >1 point	Mayo endoscopy subscore of 0 or 1		Maintained clinical response through week 54 and corticosteroid free at week 54	Clinical response maintained through week 54	Clinical remission at both weeks 30 and 54, mucosal healing at both weeks 30 and 54, corticosteroid-free remission at week 54
			Maintenance (week 54)		31.2%	50 mg: 47.0% 100 mg: 49.7%	22.1%	50 mg: 33.1% 100 mg: 33.8%			Corticosteroid free: 20.7%	Corticosteroid free: 50 mg: 38.5% 100 mg: 30.5%							
			Sustained response (weeks 30 and 54)				15.60%	50 mg: 23.2% 100 mg: 27.8%	26.60%	50 mg: 41.7% 100 mg: 42.4%									

Table 2. (*continued*)

					Efficacy end points														
					Clinical response		Clinical remission		Mucosal healing		Unique findings								
Study	Agent (MOA)	Study design	Study period	Substudy	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Mucosal healing end point	Histoendoscopic mucosal healing endpoint	Glucocorticoid free end point	Primary end points	Secondary end points
GEMINI I (13)	Vedolizumab (anti-α4β7 integrin)	Cohort 1 randomized to 300 mg vedolizumab at weeks 0, 2 vs placebo. Cohort 2 open-label vedo induction. Those who responded to induction at week 6 randomly assigned to receive vedolizumab 300 mg at q4 or q8 weeks or placebo. Bio-naive and bio-exposed patients	Induction (week 6)		25.5%	47.10%	5.4%	16.9%	24.8%	40.9%			Decrease from baseline in the total Mayo score by at least 3 points and at least 30% with an accompanying decrease in rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1	Total Mayo score of 2 points or lower with no individual subscore >1 point	Mayo endoscopy subscore of 0 or 1			Clinical response at 6 wk, clinical remission at 52 wk	Clinical remission at week 6, mucosal healing at week 6, durable clinical response (week 6 and week 52), mucosal healing week 52, glucocorticoid-free remission at week 52 in patients receiving steroids at baseline
			Maintenance (week 52)		23.8%	q4 weeks: 52% q8 weeks: 56.6%	15.9%	q4 weeks: 44.8% q8 weeks: 41.8%	19.8%	q4 weeks: 56% q8 weeks: 51.6%	Corticosteroid free: 13.9%	Corticosteroid free: q4 weeks: 45.2% q8 weeks: 31.4%							
UNIFI (16)	Ustekinumab (anti-interleukin 12/23)	Patients randomized to receive 130 mg vs 6 mg/kg weight-based induction dosing. Those with response to therapy by week 8 randomized to receive SQ 90 mg every 8 wk vs 12 wk vs placebo. Bio-naive and bio-exposed patients	Induction (week 8)		31.3%	130 mg: 51.3% 6 mg/kg: 61.8%	5.3%	130 mg: 15.6% 6 mg/kg: 15.5%	13.8%	130 mg: 26.3% 6 mg/kg: 27%	Histoendoscopic mucosal healing: 8.90%	Histoendoscopic mucosal healing: 130 mg: 20.3% 6 mg/kg: 18.4%	Decrease from baseline in the total Mayo score by at least 3 points and at least 30% with an accompanying decrease in rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1	Total Mayo score of 2 points or lower with no individual subscore >1 point	Mayo endoscopy subscore of 0 or 1	Histologic improvement (defined as neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue) and endoscopic improvement		Clinical remission at week 8, clinical remission at week 44	Endoscopic improvement at week 8, clinical response, histo-endo mucosal healing at week 8, maintenance of clinical response through week 44, endoscopic improvement at week 44, corticosteroid free remission at week 44, maintenance of clinical response

Table 2. (*continued*)

					Efficacy end points													
					Clinical response		Clinical remission		Mucosal healing		Unique findings							
Study	Agent (MOA)	Study design	Study period	Substudy	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Mucosal healing end point	Histoendoscopic mucosal healing endpoint	Glucocorticoid free end point	Primary end points	Secondary end points
UNIFI (16)			Maintenance (week 44)		44.6%	q12 wk: 68% q8 weeks: 71%	24%	q12 wk: 38.4% q8 weeks: 43.8%	28.6%	q12 wk: 43.6% q8 weeks: 51.1%	Corticosteroid free: 23.4%	Corticosteroid free: q12 wk: 37.8% q8 weeks: 42%							
OCTAVE 1 and 2 (18)	Tofacitinib (JAKi)	Randomly assigned to receive tofacitinib 10 mg BID vs placebo for 9 wk. Those with response to therapy randomized to receive 5 mg BID vs 10 mg BID vs placebo. Bio-naive and bio-exposed patients	Induction (week 8)	OCTAVE 1	32.8%	59.90%	8.2% TNF exp.: 1.5% TNF naive: 15.8%	18.5% TNF exp.: 12.6% TNF naive: 25.2%	15.6% TNF exp.: 6.2% TNF naive: 26.3%	31.3% TNF exp.: 24% TNF naive: 39.6%			Decrease from baseline in the total Mayo score by at least 3 points and at least 30% with an accompanying decrease in rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1	Total Mayo score of 2 points or lower with no individual subscore >1 point and rectal bleeding subscore 0	Mayo endoscopy subscore of 0 or 1		No administration of glucocorticoid for >4 wk before assessment		
				OCTAVE 2	28.6%	55%	3.6% TNF exp.: 0% TNF naive: 8.5%	16.6% TNF exp.: 12% TNF naive: 22.1%	11.6% TNF exp.: 6.2% TNF naive: 19.1%	28.4% TNF exp.: 21.8% TNF naive: 36.4%								Clinical remission at 8 wk, clinical remission at 52 wk	Mucosal healing at 8 wk, mucosal healing at 52 wk, glucocorticoid free among patients in remission at maintenance trial entry 52 wk
			Maintenance (week 52)	OCTAVE SUSTAIN	20.2%	5 mg: 51.5% 10 mg: 61.9%	11.1%	5 mg: 34.3% 10 mg 40.6%	13.1%	5 mg: 37.4% 10 mg: 45.7%	Corticosteroid free: 5.1%	Corticosteroid free: 5 mg: 35.4% 10 mg: 47.3%							

Table 2. (*continued*)

					Efficacy end points														
					Clinical response		Clinical remission		Mucosal healing		Unique findings								
Study	Agent (MOA)	Study design	Study period	Substudy	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Mucosal healing end point	Histoendoscopic mucosal healing endpoint	Glucocorticoid free end point	Primary end points	Secondary end points
UACHIEVE and UACCOMPLISH (19)	Upadacitinib (JAK-1 selective inhibitor)	In induction studies (UC1 and UC2), patients were randomly assigned (2:1) to receive oral upadacitinib (45 mg once daily) or placebo for 8 wk. For maintenance (UC3), those who achieved clinical response were randomly assigned (1:1:1) to receive upadacitinib 15 mg, upadacitinib 30 mg, or placebo once daily in the UC3 maintenance study. Bio-naive and bio-exposed patients	Induction (week 8)	UC1	27.0%	73.0%	5.0%	26.0%	7%	36%	Histoendoscopic mucosal healing: 7%	Histoendoscopic mucosal healing: 30%	Adapted Mayo score: a decrease in adapted Mayo score of ≥2 points and ≥30% from baseline, and a decrease in the rectal bleeding score of ≥1 point or an absolute rectal bleeding score of ≤1	Adapted Mayo score ≤2, with stool frequency score ≤1 and not greater than baseline, RBS = 0, and endoscopic subscore ≤1 without friability	Mayo endoscopy subscore of 0 or 1	Endoscopic score ≤1 without friability and Geboes score ≤3 · 1	Clinical remission at week 52 and were corticosteroid-free for ≥90 d before week 52 in those who achieved clinical remission at the end of the induction studies	Clinical remission at week 8, clinical remission at week 52	Endoscopic improvement at week 8, endoscopic remission at week 8, clinical response per Adapted Mayo score at week 8, clinical response per partial adapted Mayo score at week 2, histological-endoscopic mucosal improvement (HEMI) at week 8, no bowel urgency at week 8, no abdominal pain at week 8, histological improvement at week 8, change from baseline in IBDQ score at week 8, mucosal healing at week 8, endoscopic improvement at week 52, maintenance of clinical remission at week 52, corticosteroid-free clinical remission at week 52, maintenance of endoscopic improvement at week 52, endoscopic remission at week 52, maintenance of clinical response per adapted Mayo score at week 52, HEMI at week 52, change from baseline in IBDQ score at week 52, mucosal healing at week 52, no bowel urgency at week 52, no abdominal pain at week 52

Table 2. (*continued*)

					Efficacy end points														
					Clinical response		Clinical remission		Mucosal healing		Unique findings								
Study	Agent (MOA)	Study design	Study period	Substudy	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Mucosal healing end point	Histoendoscopic mucosal healing endpoint	Glucocorticoid free end point	Primary end points	Secondary end points
UACHIEVE and UACCOMPLISH (19)				UC2	25.0%	74.0%	4.0%	33.0%	8%	44%	Histoendoscopic mucosal healing: 6%	Histoendoscopic mucosal healing: 37%							
			Maintenance (week 52)	UC3	19.0%	15 mg: 63% 30 mg: 77%	12.0%	15 mg: 42% 30 mg: 52%	14%	15 mg: 49% 30 mg: 62%	Histoendoscopic mucosal healing: 12% Corticosteroid free: 22%	Histoendoscopic mucosal healing: 15 mg: 35% 30 mg: 50% Corticosteroid free: 15 mg: 57% 30 mg: 68%							
TRUENORTH (22)	Ozanimod (selective sphingosine-1-phosphate receptor modulator)	10-week induction period, patients in cohort 1 were assigned to receive oral ozanimod at 1 mg (equivalent to 0.92 mg of ozanimod) or placebo once daily in a double-blind manner, and patients in cohort 2 received open-label ozanimod at the same daily dose. At 10 wk, patients with clinical response underwent randomization again to receive double-blind ozanimod or placebo through week 52. Bio-naive and bio-exposed patients	Induction (week 10)		25.9%	47.8%	6.0%	18.4%	11.6%	27.3%	Histoendoscopic mucosal healing: 3.7%	Histoendoscopic mucosal healing: 12.6%	Reduction in the total Mayo score of ≥3 points and ≥30% from baseline or in the 3-component Mayo score of ≥2 points and ≥35% from baseline and a reduction in the rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of ≤1 point	Rectal bleeding subscore of 0; a stool frequency subscore of 1 or less, with a decrease of at least 1 point from baseline; and an endoscopy subscore of 1 or less	Defined as a mucosal endoscopy subscore of ≤1 without friability	Endoscopic improvement plus histologic remission, defined as a mucosal endoscopy score of ≤1 and a Geboes score of <2.0		Percentage of patients with clinical remission at week 10 and 52	Percentage of patients with clinical response at week 10, endoscopic improvement at week 10, and mucosal healing at week 10, percentage of patients with clinical response at week 52, endoscopic improvement, maintenance of clinical remission (remission at week 52 in the subgroup of patients with remission at week 10), glucocorticoid-free remission (remission with no glucocorticoid use for ≥12 wk), mucosal healing, and durable clinical remission (remission at weeks 10 and 52, assessed in all patients in the maintenance period)

Table 2. (*continued*)

Study	Agent (MOA)	Study design	Study period	Substudy	Efficacy end points											
					Clinical response		Clinical remission		Mucosal healing		Unique findings					
					Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Mucosal healing end point	Histoendoscopic mucosal healing endpoint	Glucocorticoid free end point	Primary end points	Secondary end points
TRUENORTH (22)			Maintenance (week 52)		41.0%	60.0%	18.5%	37.0%	26.4%	45.7%	Corticosteroid free: 16.70% Histoendoscopic mucosal healing: 14.1%	Corticosteroid free: 31.7% Histoendoscopic mucosal healing: 29.6%							

ADA, adalimumab; BID, twice daily; CDAI, Crohn's Disease Activity Index; CD, Crohn's disease; IBDQ, Inflammatory Bowel Disease Questionnaire; JAKi, Janus kinase inhibitor; SQ, subcutaneous; TNF, tumor necrosis factor; UC, ulcerative colitis.

had higher rates of clinical remission (biologic naive: 29%, 1 biologic failure: 22%, 2 or more biologic failures: 5%) and mucosal healing (biologic naive: 15%, 1 biologic failure: 16%, 2 or more biologic failures: 2%) compared with biologic-exposed patients (23).

CROHN'S DISEASE

Anti-TNF

Three anti-TNF are approved for CD by the US FDA: IFX, ADA, and certolizumab (CTZ) (Table 1) (24–28). In ACCENT 1, more patients receiving maintenance IFX (5 mg/kg and 10 mg/kg) achieved clinical remission in 39% ($P = 0.003$) and 45% ($P = 0.0002$), respectively, compared with 21% with placebo at week 30 (Table 3) (29). The SONIC trial demonstrated that combination IFX with AZA is more likely than IFX or AZA monotherapy to lead to corticosteroid-free clinical remission (30). Endoscopic remission rates were 44%, 30%, and 17% for combination IFX with AZA, IFX, and AZA, respectively. In a post hoc analysis of the SONIC trial, efficacy of combination therapy was noted to be related to improved IFX levels (31). IFX is the only biologic with specific labeling for perianal CD, with 36% of patients on maintenance IFX with complete cessation of draining fistulas at week 54 compared with 19% of patients on placebo ($P = 0.009$) (32).

In CLASSIC I, standard ADA induction (160 mg/80 mg) induced clinical remission in 36% compared with 12% on placebo ($P = 0.001$) at week 4 (25). For ADA responders who were re-randomized in CLASSIC II, 79% of patients receiving maintenance 40 mg biweekly and 83% receiving 40 mg weekly achieved clinical remission compared with 44% on placebo ($P < 0.05$) (Table 3) (27). Similar to the SERENE UC trial, SERENE CD compared high-dose ADA with standard induction ADA followed by randomization to clinically adjusted dosing vs therapeutic drug monitoring (level greater than 5 μg/mL) during maintenance. Clinical remission rates at week 4 were 44% for both high-dose and standard groups. Endoscopic response at week 12 (43% vs 39%, $P = 0.462$) and week 56 (45% vs 44%, $P = 0.824$) and clinical remission (71% vs 66%, $P = 0.497$) were similar between groups (33).

Vedolizumab

In GEMINI II, patients with CD (50% with prior exposure to anti-TNF) receiving VDZ achieved clinical remission rates higher than placebo (15% vs 7%; $P = 0.02$) at week 6. At week 52, patients receiving VDZ every 4 and 8 weeks achieved higher clinical remission rates (36% and 39%, respectively) compared with those on placebo (22%; $P = 0.004$ and $P < 0.001$) (34). GEMINI III, composed of patients with CD with prior anti-TNF failure, week 10 results showed 27% of VDZ and 12% of placebo patients were in clinical remission ($P = 0.001$) (Table 3) (35). There are mixed results regarding efficacy of VDZ for treating perianal disease (36,37).

Anti-IL12/23 and Anti-IL23

UST (anti-IL12/23) and risankizumab (RISA) (anti-IL23) are approved for CD treatment (Table 1). In the UNITI 1 and 2 trials, more patients receiving induction with 6 mg/kg infusion of UST achieved clinical remission by week 8 compared with those on placebo (21% and 40% compared with 7% and 20%; $P \leq 0.001$ for both). Patients receiving subcutaneous maintenance injections of 90 mg every 8 weeks achieved clinical remission in 53% compared with 36% for placebo ($P = 0.04$) (Table 3) (38). In a meta-analysis, 58% of patients with loss of response to UST benefited from dose

Table 3. Summary of phase 3 trial data of US FDA–approved therapies in the United States for Crohn's disease

					Efficacy end points													
					Clinical response		Clinical remission		Unique findings									
Study	Agent (MOA)	Study design	Study period	Substudy	Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Loss of response end point	Endoscopic response end point	Stool frequency and abdominal pain score clinical remission end point	Deep remission end point	Primary end points	Secondary end point
Targan (24)	Infliximab (anti-TNF monoclonal antibody)	Patients randomly assigned to receive a single infusion of 5 mg/kg, 10 mg/kg, 20 mg/kg or placebo	Induction (week 4)		17%	5 mg/kg: 81% 10 mg/kg: 50% 20 mg/kg: 64%	4%	Composite: 33%			Reduction of 70 or more points in the CDAI at 4 wk that was not accompanied by change in concomitant medications	CDAI <150					Clinical response	Clinical remission, IBDQ, CRP (normal <8)
			Maintenance (week 12)		12%	5 mg/kg: 48% 10 mg/kg: 29% 20 mg/kg: 46%	8%	5 mg/kg: 30% 10 mg/kg: 18% 20 mg/kg: 25%										
ACCENT (29)	Infliximab (anti-TNF monoclonal antibody)	Patients received a 5 mg/kg infusion of infliximab at week 0 and after week 2 response assessment, randomized to (1) placebo at weeks 2, 6, then q8 weeks, (2) 5 mg/kg at week 2, 6 and then q8 week, (3) 5 mg/kg at week 2, 6 followed by 10 mg/kg q8 weeks	Maintenance (week 30)				21%	Group 2: 39% Group 3: 45%			Decrease in CDAI by 70 points or more from baseline value and at least 25% reduction in total score	CDAI <150	A CDAI of at least 175, a CDAI increase of at least 35% and a CDAI at least 70 points more than the week 2 CDAI for 21 d or longer				Proportion of patients who responded at week 2 and in remission by week 30, time to loss of response up to week 54	IBDQ, corticosteroid free, antibodies to infliximab
			Maintenance (week 54)						Corticosteroid free: 9% Time to loss of response: 19 wk	Corticosteroid free: Composite: 29% Time to loss of response: Composite: 46 wk								
CLASSIC 1 (25)	Adalimumab (anti-TNF monoclonal antibody)	Patients randomized to receive SQ injection at week 0, 2 with adalimumab 40 mg/20 mg, 80 mg/40 mg, 160 mg/80 mg or placebo	Induction (week 4)		25%	40/20 mg: 34% 80/40 mg: 40% 160/80 mg: 50%	12%	40/20 mg: 18% 80/40 mg: 24% 160/80 mg: 36%			Decrease in CDAI by >100 points	CDAI <150					Difference in rates of remission at week 4 (defined at CDAI <150)	IBDQ, CRP (normal <0.8), 100-point response at week 4

Table 3. (*continued*)

Study	Agent (MOA)	Study design	Study period	Substudy	Efficacy end points												
					Clinical response		Clinical remission		Unique findings							Primary end points	Secondary end point
					Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Loss of response end point	Endoscopic response end point	Stool frequency and abdominal pain score clinical remission end point	Deep remission end point	
CLASSIC II (27)	Adalimumab (anti-TNF monoclonal antibody)	Patients from CLASSIC 1 with response randomized to receive 40 mg q2 weeks, 40 mg weekly or placebo	Maintenance (week 56)		56%	q2 weeks: 79% Weekly: 89%	44%	q2 weeks: 79% Weekly: 83%			Decrease in CDAI by >100 points from week 0 of CLASSIC 1	CDAI <150					Maintenance of remission through week 56 (CDAI <150)	IBDQ, CRP, 70- and 100-point decrease in CDAI
PRECISE 1 (26)	Certolizumab (anti-TNF monoclonal antibody)	Patients randomly assigned to receive SQ certolizumab pegol 400 mg at week 0, 2, 4 and then q4 vs placebo. Randomization stratified by serum CRP (<10, >10), use of concurrent steroids and use of concurrent immunosuppressive drugs. Bio-naive and bio-exposed patients	Induction (week 6)		CRP >10: 26% Overall: 27%	CRP >10: 37% Overall: 35%	CRP >10: 17% Overall: 17%	CRP >10: 22% Overall: 22%			Decrease in CDAI by >100 points from baseline	CDAI <150					Induction of response (decrease in CDAI by 100 points) at week 6 and response at both week 6 and 26	IBDQ, clinical remission at week 6 and 26 with baseline serum of >10 and a decrease in CDAI by 100
PRECISE 2 (28)	Certolizumab (anti-TNF monoclonal antibody)	After induction with certolizumab, patient with clinical response stratified by their CRP randomized to receive certolizumab 400 mg every 4 wk vs placebo	Maintenance (week 26)		CRP >10: 34% Overall: 36%	CRP >10: 62% Overall: 63%	CRP >10: 26% Overall: 29%	CRP >10: 42% Overall: 48%	Fistula closure: 43%	Fistula closure: 54%	Decrease in CDAI by >100 points from baseline	CDAI <150					Clinical response at week 26 for those with baseline CRP >10	Overall response at week 26, remission at week 26
GEMINI II (34)	Vedolizumab (anti-α4β7 integrin)	Patients randomly assigned to receive 300 mg of IV vedolizumab at weeks 0, 2 vs placebo. If clinical response at week 6, randomized to receive Vedo q8 weeks, q4 weeks, or placebo. Bio-naive and bio-exposed patients	Induction (week 6)		25.70%	31.40%	6.80%	14.50%			Decrease in CDAI by >100 points from week 0	CDAI <150					Clinical remission and CDAI-100 response at week 6, clinical remission at week 52	Mean change in CRP from baseline to week 6, CDAI-100 at 52 wk, glucocorticoid steroid-free remission, durable clinical remission

Table 3. (*continued*)

					Efficacy end points													
					Clinical response		Clinical remission		Unique findings									
Study	Agent (MOA)	Study design	Study period	Substudy	Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Loss of response end point	Endoscopic response end point	Stool frequency and abdominal pain score clinical remission end point	Deep remission end point	Primary end points	Secondary end point
GEMINI II (34)			Maintenance (week 52)		30.10%	q8w: 43.5% q4w: 45.5%	21.60%	q8w: 39% q4w: 36.4%	Corticosteroid free: 15.9%	Corticosteroid free: q8w: 31.7% q4w: 28.8%								
GEMINI III (35)	Vedolizumab (anti-α4β7 integrin)	Patients randomly assigned to receive Vedo 300 mg IV at weeks 0, 2, 6 vs placebo. Bio-naive and bio-exposed patients	Induction (week 6)		TNF failure: 22.3% TNF naive: 24% Overall: 22.7%	TNF failure: 39.2% TNF naive: 39.2% Overall: 39.2%	TNF failure: 12.1% TNF naive: 12.0% Overall: 12.1%	TNF failure: 15.2% TNF naive: 31.4% Overall: 19.1%			Decrease in CDAI by >100 points from week 0	CDAI <150					Clinical remission (CDAI <150) at week 6	CDAI-100 at week 6 and clinical remission (CDAI <150) at week 10 in TNFi failure population and on remission at week 6 and 10 in overall population
			Induction (week 10)		TNF failure: 24.8% TNF naive: 22.0% Overall: 24.2%	TNF failure: 46.8% TNF naive: 51.0% Overall: 47.8%	TNF failure: 12.1% TNF naive: 16.0% Overall: 13.0%	TNF failure: 26.6% TNF naive: 35.3% Overall: 28.7%										
UNITI (38)	Ustekinumab (anti-interleukin 12/23)	Patients who had clinical response after receiving receive single induction dose of UST (130 mg or 6 mg/kg) or placebo (UNITI1 [prior TNF failure] and UNITI 2 [bio-naive and bio-exposed]) randomly assigned to receive SQ maintenance at every 8 wk vs 12 wk vs placebo. Bio-naive and bio-exposed patients	Induction (week 6)	UNITI 1	21.50%	130 mg: 34.3% 6 mg/kg: 33.7%	8.90%	130 mg: 16.3% 6 mg/kg: 18.5%										

Table 3. (*continued*)

Study	Agent (MOA)	Study design	Study period	Substudy	Efficacy end points												
					Clinical response		Clinical remission		Unique findings								
					Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Loss of response end point	Endoscopic response end point	Stool frequency and abdominal pain score clinical remission end point	Deep remission end point	Primary end points	Secondary end point
UNITI (38)				UNITI 2	28.70%	130 mg: 51.7% 6 mg/kg: 55.5%	17.70%	130 mg: 28.7% 6 mg/kg: 34.9%										
			Induction (week 8)	UNITI 1	20.2%	130 mg: 33.5% 6 mg/kg: 37.8%	7.30%	130 mg: 15.9% 6 mg/kg: 20.9%			Decrease in CDAI from baseline of >100 points	CDAI <150					Clinical response at week 6, clinical remission at week 44	Clinical remission at week 8 and 44, clinical response at week 8 and 44, decrease in baseline CDAI of at least 70 points, change in CRP, normalization of CRP, change in fecal calpro, glucocorticoid-free remission
				UNITI 2	32.10%	130 mg: 47.4% 6 mg/kg: 57.9%	19.60%	130 mg: 30.6% 6 mg/kg: 40.2%										
			Maintenance (week 44)	Overall	44.30%	q8: 59.4% q12: 58.1%	35.90%	q8: 53.1% q12: 48.8%	Corticosteroid free: 29.80%	Corticosteroid free: q8: 46.9% q12: 42.6%								
				UNITI 1			26.20%	q8: 41.1% q12: 38.6%										
				UNITI 2			44.30%	q8: 62.5% q12: 59.6%										

Table 3. (*continued*)

					Efficacy end points													
					Clinical response		Clinical remission		Unique findings									
Study	Agent (MOA)	Study design	Study period	Substudy	Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Loss of response end point	Endoscopic response end point	Stool frequency and abdominal pain score clinical remission end point	Deep remission end point	Primary end points	Secondary end point
ADVANCE and MOTIVATE (42)	Risankizumab (anti-interleukin 23 p19 inhibitor)	Patients randomized to receive a single dose of IV risankizumab (600 mg or 1,200 mg) or placebo at weeks 0, 4, 8. ADVANCE included inadequate response to conventional therapy or biologics, MOTIVATE included inadequate response to biologics. Bio-naive and bio-exposed patients	Induction (week 4)	ADVANCE	25%	600 mg: 41% 1,200 mg: 37%	10%	600 mg: 18% 1,200 mg: 19%	Stool frequency and abdominal pain score clinical remission: 9%	Stool frequency and abdominal pain score clinical remission: 600 mg: 21% 1,200 mg: 21%	Decrease in CDAI from baseline of >100 points	CDAI <150 (in US) and in non-US, average daily liquid or very soft stool frequency of 2–8 or less plus average daily abdominal pain score <1 and both not worse than baseline		>50% decrease in SES-CD from baseline (or for isolated ileal disease and baseline SES-CD of 4, at least 2 pt reduction from baseline)	Average daily liquid or very soft stool frequency of 2.8or less plus average daily abdominal pain score <1 and both not worse than baseline		Clinical remission at week 12 and endoscopic response at week 12	CDAI-100 at week 4 and 12, CDAI clinical remission at week 4, enhanced stool frequency and abdominal pain score at week 12, stool frequency and abdominal pain score clinical remission at week 4, endoscopic remission at week 12, ulcer-free endoscopy at week 12, composite end point of clinical response and endoscopic response at week 12
				MOTIVATE	21%	600 mg: 37% 1,200 mg: 32%	11%	600 mg: 21% 1,200 mg: 19%	8%	600 mg: 17% 1,200 mg: 18%								

Table 3. (*continued*)

Study	Agent (MOA)	Study design	Study period	Substudy	Efficacy end points												
					Clinical response		Clinical remission		Unique findings							Primary end points	Secondary end point
					Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Loss of response end point	Endoscopic response end point	Stool frequency and abdominal pain score clinical remission end point	Deep remission end point	
ADVANCE and MOTIVATE (42)			Induction (week 12)	ADVANCE	37%	600 mg: 60% 1,200 mg: 65%	24.60%	600 mg: 45.2% 1,200 mg: 41.6%	Endoscopic response: 12% Stool frequency and abdominal pain score clinical remission: 21.71%	Endoscopic response: 600 mg: 40.2% Stool frequency and abdominal pain score clinical remission: 600 mg: 43.5% 1,200 mg 41%							
ADVANCE and MOTIVATE (42)				ADVANCE (biofailure)			25.8%	600 mg: 42.6% 1,200 mg: 37.7%	Endoscopic response: 11.3% Stool frequency and abdominal pain score clinical remission: 22.7%	Endoscopic response: 600 mg: 32.8% 1,200 mg: 23.6% Stool frequency and abdominal pain score clinical remission: 600 mg: 40.5% 1,200 mg: 38.7%							
				ADVANCE (no biofailure)			23.10%	600 mg: 48.9% 1,200 mg: 47.1%	Endoscopic response: 12.8% Stool frequency and abdominal pain score clinical remission: 20.5%	Endoscopic response: 600 mg: 50.3% 1,200 mg: 43.6% Stool frequency and abdominal pain score clinical remission: 600 mg: 44.3% 1,200 mg: 47.5%							

Table 3. (*continued*)

					Efficacy end points													
					Clinical response		Clinical remission		Unique findings									
Study	Agent (MOA)	Study design	Study period	Substudy	Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Loss of response end point	Endoscopic response end point	Stool frequency and abdominal pain score clinical remission end point	Deep remission end point	Primary end points	Secondary end point
ADVANCE and MOTIVATE (42)				MOTIVATE	30%	600 mg: 60% 1,200 mg: 61%	19.80%	600 mg: 41.9% 1,200 mg: 40.3%	Endoscopic response: 11.20% Stool frequency and abdominal pain score clinical remission: 19.30%	Endoscopic response: 600 mg: 28.8% 1,200 mg: 34% Stool frequency and abdominal pain score clinical remission: 600 mg: 34.6% 1,200 mg: 39.8%								
FORTIFY (43)	Risankizumab (anti-interleukin 23 p19 inhibitor)	Patients with clinical response to MOTIVATE or ADVANCE at week 12 or 24 randomized to receive 180 mg, 360 mg, or placebo SQ every 8 wk. Bio-naive and bio-exposed patients	Maintenance (week 52)	Overall	48%	180 mg: 67% 360 mg: 62%	40.80%	180 mg: 55.4% 360 mg: 52.5%	Endoscopic response: 21.90% Stool frequency and abdominal pain score clinical remission: 39.6% Deep remission: 10%	Endoscopic response: 180 mg: 47.1% 360 mg: 46.8% Stool frequency and abdominal pain score clinical remission: 180 mg: 46.5% 360 mg: 51.8% Deep remission: 180 mg: 25% 360 mg: 29%	Decrease in CDAI from baseline of >100 points	CDAI <150 (in US) and in non-US, average daily liquid or very soft stool frequency of 2–8 or less plus average daily abdominal pain score <1 and both not worse than baseline		>50% decrease in SES-CD from baseline (or for isolated ileal disease and baseline SES-CD of 4, at least 2 pt reduction from baseline)	Average daily liquid or very soft stool frequency of 2.8or less plus average daily abdominal pain score <1 and both not worse than baseline	Complete clinical and endoscopic remission	Clinical remission and endoscopic response at week 52	Stool frequency and abdominal pain score clinical remission, CDAI clinical response, enhanced stool frequency and abdominal pain clinical response, ulcer-free endoscopy, endoscopic remission, CDAI deep remission at 52 wk

Table 3. (*continued*)

Study	Agent (MOA)	Study design	Study period	Substudy	Efficacy end points												
					Clinical response		Clinical remission		Unique findings								
					Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Loss of response end point	Endoscopic response end point	Stool frequency and abdominal pain score clinical remission end point	Deep remission end point	Primary end points	Secondary end point
FORTIFY (43)				Biofailure			34.90%	180 mg: 48.7% 360 mg: 48%	Endoscopic response: 20.3% Stool frequency and abdominal pain score clinical remission: 34.1%	Endoscopic response: 180 mg: 40.7% 360 mg: 44.1% Stool frequency and abdominal pain score clinical remission: 180 mg: 40.7% 360 mg: 48.0%							
FORTIFY (43)				No biofailure			58.50%	180 mg: 72.7% 360 mg: 64.1%	Endoscopic response: 26.8% Stool frequency and abdominal pain score clinical remission: 56.1%	Endoscopic response: 180 mg: 63.6% 360 mg: 53.8% Stool frequency and abdominal pain score clinical remission: 180 mg: 61.4% 360 mg: 61.5%							

Table 3. (*continued*)

					Efficacy end points													
					Clinical response		Clinical remission		Unique findings									
Study	Agent (MOA)	Study design	Study period	Substudy	Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Loss of response end point	Endoscopic response end point	Stool frequency and abdominal pain score clinical remission end point	Deep remission end point	Primary end points	Secondary end point
UEXCEL, UEXCEED and UENDURE (44)		Patients with moderate-to-severe Crohn's disease randomized to receive 12 wk of 45 mg once daily vs placebo. Those with clinical response randomized to receive 15 mg vs 30 mg vs placebo once daily. Bio-naive and bio-exposed	Induction (week 12)	UEXCEL (failure of conventional or biologic therapy)							Decrease in CDAI from baseline of >100 points	CDAI <150				Complete clinical and endoscopic remission	CDAI clinical remission and endoscopic response at week 12, 52	Clinical response (CDAI decrease >100), clinical remission by stool frequency/ abdominal pain scores, glucocorticoid-free CDAI clinical remission, endoscopic remission, IBDQ, change from baseline fatigue score, deep remission (both CDAI clinical remission and endoscopic remission), maintenance of CDAI clinical remission
UEXCEL, UEXCEED and UENDURE (44)	Upadacitinib (JAK-1 selective inhibitor)				37.30%	56.60%	29.10%	49.50%	Endoscopic response: 13.1%	Endoscopic response: 45.5%				>50% decrease in SES-CD from baseline (or for isolated ileal disease and baseline SES-CD of 4, at least 2 pt reduction from baseline)				
				UEXCEED (failure of biologic therapy)														

Table 3. (*continued*)

Study	Agent (MOA)	Study design	Study period	Substudy	Efficacy end points												
					Clinical response		Clinical remission		Unique findings							Primary end points	Secondary end point
					Placebo	Drug	Placebo	Drug	Placebo	Drug	Clinical response end point	Clinical remission end point	Loss of response end point	Endoscopic response end point	Stool frequency and abdominal pain score clinical remission end point	Deep remission end point	
UEXCEL, UEXCEED and UENDURE (44)			Maintenance (week 52)		17.70%	29.60%	21.10%	38.90%	Endoscopic response: 3.5%	Endoscopic response: 34.6%							
						15 mg: 41.4%		15 mg: 37.3%	Endoscopic response: 7.3%	Endoscopic response: 15 mg: 27.6%							
						30 mg: 51.2%		30 mg: 47.6%	Deep remission: 3.7%	30 mg: 40.1%							
										Deep remission: 15 mg: 14.8%							
										30 mg: 23.2%							
				UENDURE	15.20%		15.10%										

CDAI, Crohn's Disease Activity Index; JAKi, Janus kinase inhibitor; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumor necrosis factor.

escalation (39). In a post hoc analysis of patients with CD with perianal fistulas treated with UST in the SEAVUE and STARDUST trials, 54% and 47%, respectively, had complete resolution of fistula drainage at 1 year (40). In a meta-analysis of 9 studies with 346 patients, pooled UST fistula response and remission were 56% and 17%, respectively (41).

RISA induction trials (ADVANCE and MOTIVATE) demonstrated superiority of 600 mg of RISA over placebo for all coprimary end points of clinical remission and endoscopic response at week 12 ($P < 0.0001$ for all end points) (42). Approximately 20% of patients enrolled had failed UST. In ADVANCE (failure of conventional therapy or biologics), clinical remission rates were 45% for RISA vs 25% for placebo ($P < 0.001$). Endoscopic response rates were 40% for RISA vs 12% for placebo ($P < 0.0001$). In ADVANCE, clinical remission rates were similar regardless of biologic exposure status, but endoscopic response was numerically higher in biologic-naive patients compared with that in biologic failures (50% vs 33%, respectively). In MOTIVATE (biologic failures only), clinical remission rates were 42% for RISA vs 19% for placebo ($P < 0.0001$). Endoscopic response rates were 29% for RISA vs 11% for placebo ($P < 0.0001$) (42). In the FORTIFY follow-up maintenance trial, the clinical remission (52% vs 41%, $P = 0.005$) and endoscopic response rates (47% vs 22%, $P < 0.001$) for 360 mg maintenance every 8 weeks were superior to placebo (Table 3) (43).

Upadacitinib

Upadacitinib was approved by the US FDA in May 2023 for CD. In CD, induction is for 12 weeks with 45 mg daily. Maintenance dosing is 15 mg or 30 mg daily (Table 1). In U-EXCEL (biologic experienced and conventional treatment failures), there were superior week 12 clinical remission rates (50% vs 29%, $P < 0.0001$) and endoscopic response rates (46% vs 13%; $P < 0.0001$) compared with those with placebo. In U-EXCEED (biologic experienced only), compared with U-EXCEL, there were lower week 12 clinical remission (39% vs 21%; $P < 0.0001$) and endoscopic response rates (35% vs 4%; $P < 0.0001$). In the U-ENDURE maintenance trial, there was a dose-dependent improvement in clinical remission rates (30 mg 48%, 15 mg 24% vs placebo 14%; $P < 0.0001$ for both) and endoscopic response rates (30 mg 40%, 15 mg 28%, vs placebo 7%; $P < 0.0001$ for both) (Table 3) (44). In a subgroup analysis of U-ENDURE patients with CD with perianal fistulas and fissures, UPA patients at 1 year had significantly more external closure of fistulas compared with those on placebo (30 mg 21%, 15 mg 17%, vs 0% placebo; $P = 0.036$ and 0.029) and complete resolution of fissures compared with those on placebo (30 mg 76%, 15 mg 33%, vs placebo 0%) (45).

COMPARATIVE EFFECTIVENESS

Selecting a medical therapy should be a shared decision-making process after discussing risks, efficacy, mode of delivery, safety, and other special patient considerations. Comparing biologics and small molecules across trials is difficult due to varied trial designs and studied patient populations. Though there are several head-to-head trials such as VARSITY and SEAVUE, most comparative effectiveness studies evaluating first-line and second-line therapies are retrospective. Traditional meta-analyses and NMA may assist with indirectly comparing treatment efficacy.

Ulcerative colitis

In VARSITY, the only head-to-head biologic trial in UC, standard dosing of VDZ was compared with ADA. Twenty-one percent of

Special Population	Anti- TNF[61,65,74]	VDZ[75]	Anti-IL12/23[76–79]	Jaki [66,67]	S1P[22,70,80]
Older adult patient*[62,81]	✓ ✓	✓ ✓ ✓	✓ ✓ ✓	✓ ✓	✓ ✓
Pregnant patient[22,82]	✓ ✓ ✓	✓ ✓ ✓	✓ ✓ ✓	X	X
Patient with prior malignancy[63,83]	✓ ✓	✓ ✓ ✓	✓ ✓ ✓	✓ ✓	✓ ✓
Patient with presence of dermatologic EIM**,^ [84]	✓ ✓ ✓	✓	✓ ✓ ✓	✓ ✓	✓
Patient with presence of rheumatologic EIM**,^ [84]	✓ ✓ ✓	✓	✓ ✓	✓ ✓ ✓	✓

✓ = Less favorable ✓✓ = Moderately favorable ✓ ✓ ✓ = Preferred therapy X = Not currently recommended

Figure 3. Special considerations for inflammatory bowel disease therapeutic decision-making. *Favor treatment with appropriate treatment rather than undertreatment due to the risks of unopposed inflammation. **EIM, extraintestinal manifestation. ^If EIM secondary to bowel inflammation, choose the most appropriate bowel therapy. IL, interleukin; JAKi, Janus kinase inhibitor; S1P, sphingosine-1-phosphate; TNF, tumor necrosis factor; VDZ, vedolizumab.

patients were previously exposed to an anti-TNF other than ADA. VDZ had significantly higher rates of clinical remission (31 vs 23%; $P = 0.006$) and endoscopic improvement (40% vs 28%; $P < 0.001$) at week 52 compared with ADA. However, ADA had higher rates of corticosteroid-free clinical remission compared with VDZ (22% vs 13%; 95% confidence interval [CI] −18.9 to 0.4) (46).

The retrospective multicenter EVOLVE study including 1,095 biologic-naive patients (604 UC, 491 CD) found similar rates of clinical remission and mucosal healing when comparing VDZ with anti-TNF (47). In VDZ-exposed patients, second-line anti-TNF remained effective in UC and CD. In a prospective Dutch registry of anti-TNF–experienced patients, TOFA had higher rates of steroid-free clinical remission compared with VDZ (week 12: odds ratio [OR] 6.33, 95% CI 3.81–10.50; week 52: OR 1.86, 95% CI 1.15–2.99) (48).

From the aforementioned phase 3 trials in anti-TNF–experienced patients, induction with ADA, VDZ, and OZN had lower clinical remission rates, whereas UPA, TOFA, and UST clinical remission rates remained similar (5,13,16,18,19,23,46). Indirect treatment comparisons through NMA provide some direction on treatment selection. In TNF-naive patients, IFX has been found to be superior to other anti-TNF for clinical response (ADA: OR 2.01, 95% CI 1.36–2.98; GOL: OR 1.67, 95% CI 1.08–2.59) and mucosal healing (ADA: OR 1.87, 95% CI 1.26–2.79; GOL: OR 1.75, 95% CI 1.13–2.73) (49). In an NMA comparing VDZ with other advanced therapies, IFX was associated with more clinical remission (OR 1.67, 95% CI 1.16–2.42) and ADA with less clinical remission (OR 0.69, 95% CI 0.54–0.88) (50).

In an NMA from 2020, in biologic-naive patients, IFX ranked highest for induction of clinical remission and endoscopic improvement. In TNF-experienced patients, UST and TOFA ranked highest for induction of clinical remission (superior to ADA and VDZ) and endoscopic improvement (51).

A more recent NMA of phase 3 RCT reported that UPA was superior to all other biologic and small molecules available for induction of clinical remission in UC (compared with IFX, OR 2.7, 95% CI 1.18–6.20; ADA, OR 4.64, 95% CI 2.47–8.71; VDZ, OR 3.56, 95% CI 1.84–6.91; UST, OR 2.92, 95% CI 1.31–6.51; TOFA, OR 2.84, 95% CI 1.28–6.31; OZN OR 2.70, 95% CI 1.18–6.20) (52). In biologic-naive patients, IFX and OZN ranked highest for induction of clinical remission (52). In biologic-exposed patients, TOFA and UST ranked highest for induction of clinical remission (52).

Crohn's disease

The SEAVUE trial, the only head-to-head biologic trial in CD, found that biologic-naive patients had similar rates of clinical remission at 1 year with ADA vs UST (65% vs 61%; $P = 0.42$). Endoscopic remission rates were also similar (31% vs 29%; $P = 0.63$) (53). In an NMA composed of 15 phase 2 and 3 RCT, in biologic-naive patients, IFX combination with AZA ranked highest for induction of clinical remission, followed in decreasing odds by IFX, ADA, UST, RISA, VDZ, and CTZ (54). After IFX failure, RISA (OR 2.10, 95% CI 1.12–3.92) had higher odds for inducing clinical remission compared with VDZ (54). In a recent NMA from 2023 including 25 trials, IFX and RZB ranked highest for induction of remission (55).

In smaller comparative effectiveness studies, ADA was superior to CTZ for induction of remission (relative risk [RR] 2.93, 95% CI 1.21–7.75) in an NMA comparing anti-TNF (56). In a post hoc analysis of 2 clinical trials, compared with UST, patients treated with IFX were more likely to achieve endoscopic remission at 1 year (adjusted OR [aOR] 3.35, 95% CI 1.07–10.49) (57).

In the EVOLVE study, anti-TNF therapy is not significantly affected by VDZ exposure (47). In a prospective Dutch registry, patients with CD with prior anti-TNF failure had higher rates of steroid-free clinical remission with UST over VDZ (OR 2.74, 95% CI 1.23–6.09) (58). In the Study of a Prospective Adult Research Cohort with IBD registry, UST had a lower likelihood of

treatment failure compared with VDZ in patients with CD with anti-TNF failure (adjusted hazard ratio [HR] 0.66, 95% CI 0.54–0.86) (59). Examining efficacy solely with phase 3 endoscopic remission rates, UST and RISA are not significantly affected by prior anti-TNF exposure, whereas ADA and VDZ endoscopic remission rates are diminished (34,35,38,43,53).

Performance of certain biologics may be location specific. In a pooled analysis from 4 clinical trials comparing endoscopic healing at 1 year, IFX was superior to VDZ in patients with ileal ulcers (aOR 5.39, 95% CI 1.03–28.05, $P = 0.045$). For colonic disease, compared with UST, endoscopic healing at 1 year was significantly increased with ADA (aOR 3.97, 95% CI 1.45–10.90; $P = 0.007$) (60).

SAFETY

Before starting treatment, there should be a careful assessment of a patient's medical history and comorbid conditions (Figure 3). The benefits of treatment must outweigh risks, and the patient should be included in the shared decision-making process.

Anti-TNF are associated with an increased risk of infection. From the Therapy, Resource, Evaluation and Assessment Tool registry, the most common serious infection with IFX was pneumonia, followed by sepsis and herpes zoster. The rates of malignancy and mortality were similar between IFX and non-IFX groups. Notably, the dose of IFX was not associated with increased rates of adverse events (61). In a meta-analysis of 15 observational studies, combination anti-TNF with thiopurines increased the risk of serious infection compared with anti-TNF monotherapy (RR 1.19, 95% CI 1.03–1.37) (62). Anti-TNF have also been associated with an increased risk of lymphoma and melanoma (61,63). Conversely, in a Danish nationwide registry-based cohort study, lymphoma and melanoma risk has not been found to be increased in TNF when adjusted for AZA exposure (64). Compared with anti-TNF monotherapy, combination therapy with a thiopurine increased the risk of lymphoma (HR 2.53, 95% CI 1.35–4.77) (65).

The JAKi are associated with a dose-dependent increase in risk of infections (18,19). The relative risk of serious infections was 1.03 (95% CI 0.76–1.40). Herpes zoster is increased in patients treated with JAKi (RR 1.57, 95% CI 1.04–2.37), and the recombinant zoster vaccine is recommended (66). In the ORAL surveillance study of patients with rheumatoid arthritis aged 50 years and older with 1 or more cardiac risk factors, there were higher rates of major adverse cardiovascular events (3.4% vs 2.5%, HR 1.33, 95% CI 0.91–1.94) and cancers (4.2% vs 2.9%, HR 1.48, 95% CI 1.04–2.09), particularly lung cancer in patients with a history of smoking, with TOFA when compared with anti-TNF (67). By contrast, the OCTAVE open-label, long-term extension trial in UC with up to 7 years treatment, there were no signals for higher rates of major adverse cardiovascular events, thrombosis, or malignancy (68).

OZN is contraindicated in patients with cardiac arrhythmias, history of myocardial infarction, monoamine oxidase inhibitor use, and untreated, severe sleep apnea (69). Bradycardia was increased with OZN during TRUE NORTH induction, but no new safety signals were seen in the 3-year open-label extension study (70). Confirmation of varicella immunity is recommended before starting OZN.

Several NMA have indirectly compared safety of available therapies. Rates of serious adverse events in patients with UC were increased with IFX but decreased with VDZ compared with placebo (49,52). In UC, VDZ and UST had the lowest rates of infection in maintenance trials (51). In a recent NMA, compared with anti-TNF, VDZ was associated with a lower risk of serious infections (OR 0.68, 95% CI 0.56–0.83) in UC. In CD, UST was associated with a lower risk of serious infections compared with anti-TNF (OR 0.49, 95% CI 0.25–0.93) and VDZ (OR 0.40, 95% CI 0.17–0.93) (71).

In an administrative claims study comparing UST with VDZ, UST was associated with lower all-cause hospitalization including nonsurgical CD hospitalization and infections (72). Reported incidence rates of opportunistic infections per 100 person-years in patients with IBD were highest with anti-TNF (0.83) and JAKi (0.55) and lowest with anti-integrins (0.05) and OZN (0) (73).

DISCUSSION

Sorting through the data examined in this review article, we have carefully considered the currently available high-impact studies on the US FDA–approved therapies for moderate-to-severe IBD and proposed treatment algorithms (Figures 1 and 2). With a goal of mucosal healing to reduce disease progression and downstream complications, we favor a personalized approach, taking into consideration current disease activity, severity, comorbid conditions including extraintestinal manifestations, safety, patient preference, and cost. Selecting a first-line, second-line, or third-line agent requires a careful review of the aforementioned factors in conjunction with analysis of the available data applied to each patient, given the limited available comparative effectiveness trials currently available.

In UC, we favor anti-TNF (or combination therapy) as a first-line therapy for severe disease, while for moderate disease, it is reasonable to consider starting with VDZ, UST, or OZN. Second-line and third-line treatment decisions are dependent on evaluation of the reason for loss of response and consideration for the use of an alternative agent within class or switching classes especially in the setting of medication intolerance (Figure 1).

In CD, we favor anti-TNF (or combination therapy) as a first-line therapy for perianal disease, while for moderate-to-severe CD, UST, RISA, or VDZ can be considered. If loss of response occurs due to antibody formation, consider using an alternative anti-TNF (or combination therapy). In the setting of intolerance to an anti-TNF, switch out of class to UST, UPA, RISA, or VDZ for second-line or third-line treatment. If the first-line agent was a non–anti-TNF, consider a trial of an anti-TNF (or combination therapy) or another mechanism of action not previously used (Figure 2). We look forward to additional comparative and real-world data on the current treatments, future approvals, novel therapeutics, and use of combination biologics.

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CONFLICTS OF INTEREST

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