Dual Advanced Therapies and Novel Pharmacotherapies for Moderately to Severely Active Crohn's Disease

Chung Sang Tse, MD*, Parambir S. Dulai, MBBS

KEYWORDS

• Dual biologic therapies • Combination biologics and small molecules • Clinical trials

KEY POINTS

- Dual advanced therapies (combination of biologics and/or small molecule therapies) have been used to treat refractory Crohn's disease and/or concomitant rheumatologic extraintestinal manifestations with a 30-60% efficacy, although adverse events (particularly infectious complications) can occur in nearly two-thirds of patients.
- Risankizumab demonstrated promising results for inducing and maintaining clinical and endoscopic response in phase 2 clinical trials, and its safety and efficacy are further explored in phase 3 placebo-controlled induction (completed, preliminary results reported) and maintenance studies (underway).
- Phase 2 induction studies of mirikizumab, ozanimod, and guselkumab have demonstrated varying degrees of efficacy in inducing clinical and/or endoscopic response with an acceptable safety profile; phase 3 trials of these agents are currently underway with anticipated study completion over the next 2-5 years.

INTRODUCTION

Over the past 2 decades, there have been tremendous advancements in the number of pharmacotherapies with increasingly specific therapeutic targets for patients with moderately to severely active Crohn's disease (CD).[1] Nevertheless, less than 50% of patients with CD have sustained benefit from existing Food and Drug Administration (FDA)-approved anti-TNF antagonists, anti-integrin, and anti-interleukin therapies[2,3]

Division of Gastroenterology, University of California, San Diego, 9500 Gilman Drive, MC 0956, La Jolla, CA 92093-0956, USA
* Corresponding author.
E-mail address: cstse@ucsd.edu
Twitter: @CSTseMD (C.S.T.)

Gastroenterol Clin N Am 51 (2022) 283–298
https://doi.org/10.1016/j.gtc.2021.12.005
gastro.theclinics.com

and greater than 20% have refractory CD despite treatments with multiple biologic agents.[4]

In this review, we will explore the available evidence for the safety and efficacy of dual advanced therapies (DATs) that combine biologic (intravenous [IV] or subcutaneous [SQ]) and/or oral small molecule therapies in patients with CD, some of whom have concomitant rheumatologic disease/extraintestinal manifestation (EIM), based on published case series and small cohort studies.[5–9] We will also review the available data for emerging pharmacologic therapies in phase 2 or 3 clinical trials in patients with moderately to severely active CD. We intend to inform readers of novel treatments for CD that are of the most interest within the realm of clinical practice in treating refractory CD ± active rheumatologic symptoms.

DUAL ADVANCED THERAPY

Antitumor necrosis factor (TNF) antagonists (infliximab, adalimumab, and certolizumab pegol), anti-integrin (vedolizumab), and anti-interleukin (ustekinumab) were approved by the FDA between 1998 and 2016 for the treatment of adults with moderately to severely active CD. Golimumab, an anti-TNF antagonist, and tofacitinib, an oral pan-Janus kinase (JAK) inhibitor, are approved for the treatment of moderately to severely active ulcerative colitis (UC), but not for CD. Apremilast is an oral small molecule phosphodiesterase 4 used to treat psoriasis and psoriatic arthritis.[10] Off-label use of concomitant biologic and/or small molecule therapies has been reported in case series/small cohort studies of patients with refractory CD after inadequate response to multiple biologic therapies[5–9,11,12] or active rheumatologic symptoms[6,7,9] (**Table 1**).In a systematic review and meta-analysis of 10 studies (each with a study sample of ≥10 patients) of 211 patients with CD who had 279 trials of combination advanced therapy, the pooled clinical and endoscopic remission rates were 59% and 34%, respectively.[13] In the largest cohort study of patients with IBD treated with DAT, Glassner and colleagues[8] report 50 patients with IBD (31 CD, 18 UC, 1 indeterminate IBD) treated with 53 combinations of DAT at the Houston Methodist Hospital (see **Table 1**). Thirty-one patients with CD 34 were treated with 34 combinations of DAT (in 4 classes of biologic/small molecule therapies): vedolizumab and ustekinumab (n = 23), vedolizumab and anti-TNF (n = 5), tofacitinib and anti-TNF (n = 2), tofacitinib and ustekinumab (3), and adalimumab and apremilast (n = 1). One-fifth (20%, 6/31) of the patients with CD had concomitant rheumatologic disease (4 psoriasis, 2 psoriatic arthritis, and 2 ankylosing spondylitis). Before the initiation of DAT, 17% (n = 5) were in remission, 31% (n = 9) mild disease, 38% (n = 11) moderate disease, and 14% (n = 4) severe disease (by the Harvey-Bradshaw Index [HBI]). For the 5 patients with CD in remission at baseline, DAT was initiated for persistent rheumatologic symptoms from psoriatic arthritis or ankylosing spondylitis. The median duration of DAT was 8 months (interquartile range [IQR] 5.5–13 months) for the entire cohort of 50 patients with IBD (without specification by IBD subtype). Although on DAT, 16% (5/31) of patients with CD underwent surgery. Otherwise, the efficacy (clinical, endoscopic, biochemical response) and adverse events (AEs) rates were reported as an agglomerate for all the study patients without delineation by IBD subtype. As a cohort of IBD patients, there were increases in the rates of clinical remission (50% vs 14%, $P = .0018$; median follow-up 4 months, IQR 3–6 months), endoscopic remission (34% vs 6%, $P = .0039$; median follow-up 8 months, IQR 6–12 months), and decrease in C-reactive protein (CRP; 5.0 mg/dL to 2.4 mg/dL, $P = .002$; median follow-up 3 months, IQR 2–5 months) after the initiation of DAT compared with baseline.[8] A total of 26% (13/50) of patients with IBD experienced 23 AEs, the most common of which were enteric and sinopulmonary infections (14 cases), while on DAT after a mean duration of

Table 1
Dual advanced therapies (biologic or small molecules) for Crohn's disease in case series and cohort studies published from January 2018 to July 2021

Publication	Biologic/Small Molecule Combinations	Efficacy & Safety
Glassner et al,[8] 2020	50 patients with IBD (31 CD, 18 UC, 1 indeterminate IBD), for which the CD patients were treated with 34 combinations of DAT: • Vedolizumab and ustekinumab (n = 23) • Vedolizumab and anti-TNF (n = 5) • Tofacitinib and anti-TNF (n = 2) • Tofacitinib and ustekinumab (3) • Adalimumab and apremilast (n = 1)	• Efficacy: 5 patients with CD underwent surgery while on DAT. Otherwise, the efficacy of DAT for the cohort of 50 patients without delineation by IBD subtype: clinical remission increased from 14% to 50% (P = .0018), endoscopic remission increased from 6% to 34% (P = .0039), and CRP decreased from 5 mg/dL to 2.4 mg/dL (P = .002) from baseline to follow-up (median 8 mo, IQR 5.5–13 mo) • Safety: 23 AEs, of which 8 were serious AEs (no deaths) were reported in the cohort of 50 IBD patients (CD not specified)
Yang et al,[5] 2020	22 patients with refractory CD treated with 23 combinations of DAT: • Vedolizumab and ustekinumab (n = 8) • Vedolizumab and anti-TNF (n = 13) • Ustekinumab and anti-TNF (n = 3)	• Efficacy: 50% (12/24) had clinical response and 41% (10/24) had clinical remission, 43% had endoscopic improvement and 26% had endoscopic remission (by SES-CD). Mean CRP decreased from mean 17.0–9.0 (P = .02) across the study • Safety: 3 patients had AEs, drug-induced lupus, pneumonia, and 1 patient had recurrent basal cell skin cancer and infections (prior history of these conditions before DAT)
Kwapisz et al,[11] 2021	15 patients (14 CD, 1 UC) with medically refractory luminal disease: • Vedolizumab and anti-TNF (n = 8) • Ustekinumab and anti-TNF (n = 2) • Vedolizumab and ustekinumab (n = 5)	• Efficacy (not delineated between CD/UC): 73% (11/15) symptomatic improvement, 67% (10/15) corticosteroid dose reduction, and 20% (3/15) disease progression requiring surgery • Safety: 20% (n = 3) hospitalized for infections; 1 patient discontinued vedolizumab for postinfusion arthralgia

(*continued on next page*)

Table 1
(*continued*)

Publication	Biologic/Small Molecule Combinations	Efficacy & Safety
Privitera et al,[6] 2021	11 patients with active CD (n = 5) or active rheumatologic symptoms (n = 6): • Ustekinumab and anti-TNF (n = 5) • Ustekinumab and vedolizumab (n = 2) • Vedolizumab and anti-TNF (n = 3) • Vedolizumab and apremilast (n = 1)	• Efficacy: Of the patients with moderately active CD, 20% (1/5) had remission and 80% (4/5) had mild CD activity. Of the patients with severe psoriatic/spondyloarthritic symptoms, 50% (3/6) had remission and 50% (3/6) had mild rheumatologic symptoms. • Safety: 2 AEs, perianal abscess and drug-induced liver injury
Burer et al,[12] 2018	4 patients with CD treated with vedolizumab and anti-TNF: • Vedolizumab and infliximab (n = 2) • Vedolizumab and adalimumab (n = 2)	• Efficacy: All patients had clinical remission at the end of follow-up (range 12–20 mo); 50% (2/4) endoscopic remission and 25% (1/4) endoscopic improvement after a median of 14 mo • Safety: 1 patient (25%) had recurrence of polyarthritis after discontinuation of adalimumab
Mao et al,[7] 2018	4 patients with active CD (1 with active AS): • Vedolizumab and anti-TNF (n = 3) • Vedolizumab and ustekinumab (n = 1)	• Efficacy: 75% (3/4) achieved clinical remission; 25% (1/4) had esophageal CD flare despite resolution of AS symptoms • Safety: 1 patient with 2 episodes of uncomplicated *C difficile* infections; another patient with hand-foot-mouth disease and influenza
Fumery et al,[9] 2020	7 patients with IBD, including 5 CD (2 AS, 2 psoriasis): • Vedolizumab and anti-TNF (n = 1) • Ustekinumab and anti-TNF (n = 4)	• Efficacy: no clinical or endoscopic response in one patient with luminal and perianal CD (12 mo of golimumab and vedolizumab); clinical-biochemical remission with endoscopic response in another with CD and AS (30 mo of golimumab and ustekinumab); deep remission and improvement of AS in one patient (12 mo of etanercept and vedolizumab); CD deep remission without improvement of psoriasis in 2 patients (3–4 mo of ustekinumab and adalimumab/infliximab) • Safety: No adverse events reported

Abbreviations: AS, ankylosing spondylitis; CD, Crohn's disease; CD-PRO/SS, Crohn's Disease-Patient Reported Outcome Signs and Symptoms; CRP, C-reactive protein; DAT, dual biologic therapy; EIM, extraintestinal manifestation; HBI, Harvey-Bradshaw Index; IBD-U, indeterminate inflammatory bowel disease; IQR, interquartile range; PRO-2, two-item patient-reported outcome; SES-CD, Simplified Endoscopic Score-Crohn's disease; TNF, tumor necrosis factor; UC, ulcerative colitis.

Key: *Efficacy and safety outcomes were reported for all patients with IBD without delineation of response by IBD subtype.

5.1 ± 4.8 months.[8] Although no deaths were reported, 8 serious AEs requiring hospitalization (all related to infections/abscesses) were reported in 6 patients with IBD after a mean duration of DAT of 4.1 ± 3.6 months (see **Table 1**).[8] Overall, this retrospective cohort study suggests that combination biologic or small molecule therapy for IBD in patients with persistent CD or rheumatologic disease activity can be effective although side-effects, particularly infectious complications, can occur.

Yang and colleagues[5] describe the largest cohort study of patients with CD treated with DAT where clinical, biochemical, and endoscopic responses are reported (see **Table 1**). At the University of California, San Diego, and University of Calgary, 22 patients with refractory CD (phenotype 59% stricturing, 36% penetrating, and 50% with perianal fistulas; 91% had IBD-related surgeries) with treatment failure to 4 single biologic therapies ± immunomodulators previously were treated with 24 trials of DAT with 3 combinations of biologic therapy agents/classes (no small molecules): vedolizumab and ustekinumab (n = 8), vedolizumab and anti-TNF (n = 13), and ustekinumab and anti-TNF (n = 3). The median duration of DAT treatment was 274 days (IQR 191–365 days) with up to 1-year of follow-up. Half (50%) of the DAT trials had clinical improvement and 41% had clinical remission (by the 2-item patient-reported outcome [PRO2] measure); 43% had endoscopic improvement and 26% had endoscopic remission (by the Simple Endoscopic Score for Crohn's Disease [SES-CD] or explicitly stated); and the mean CRP decreased from 17.0 (IQR 11.0–24.0) to 9.0 (IQR 4.0–14.0) (P = .02) (see **Table 1**). Three patients had adverse experienced: drug-induced lupus (vedolizumab with adalimumab; adalimumab was discontinued), pneumonia (vedolizumab with ustekinumab), and a patient had basal cell skin cancer, recurrent *Clostridium difficile* infection, and Acinetobacter bacteremia (this patient had all 3 diseases before the initiation of vedolizumab and an anti-TNF agonist). Overall, dual biologic therapy was associated with clinical, biochemical, and endoscopic improvements in a subset of patients with refractory CD in this cohort.

Privitera and colleagues[6] describe the third largest cohort of patients with IBD (11 CD, 5 UC) treated with DAT at 9 Italian IBD referral centers (see **Table 1**). In the 11 patients with CD, DAT were initiated in 5 patients for treatment of moderately active CD (by HBI) and in 6 patients for severe EIM symptoms (by clinical judgment). Four combinations of DAT were used: anti-TNF with either ustekinumab (n = 5) or vedolizumab (n = 3); ustekinumab and vedolizumab (n = 2); and vedolizumab and apremilast (n = 1). Of the 5 patients for which DAT was initiated for moderately active CD, 2 did not have rheumatologic disease/symptoms and 3 had mild/inactive psoriatic disease at baseline, the DAT treatment ranged from 2 to 8 months, and after DAT induction (2 months), 4 of 5 patients had mild CD symptoms and 1 achieved remission. Of the 6 patients for which DAT was initiated for severe rheumatologic symptoms (5 spondyloarthritis and 1 psoriatic disease; baseline CD activity were equally distributed between remission, mild, moderate disease), the DAT treatment ranged from 5 to 19 months, and all patients achieved CD remission and had mild/remission of psoriatic/spondyloarthritic symptoms (equally divided) after 2 months of DAT. AEs were reported in 2 patients: perianal abscess (4 months of certolizumab ustekinumab) and drug-induced liver injury (19 months of apremilast and vedolizumab). Overall, in this cohort, DAT rapidly improved both intestinal and extraintestinal symptoms with few AEs in patients with CD ± concomitant rheumatologic symptoms (see **Table 1**).[6]

Kwapisz and colleagues, 2021,[11] describe the fourth largest cohort study of patients with IBD (14 CD, 1 UC) treated with DAT for the management of refractory luminal disease at the Mayo Clinic, Rochester (see **Table 1**). In this cohort, 3 combinations of dual biologic therapy classes were used (no small molecule agents): vedolizumab and anti-TNF (n = 8); ustekinumab and anti-TNF (n = 2); and vedolizumab and ustekinumab

(n = 5). The median duration of dual biologic treatment was 6 months; the median follow-up time was 24 months. Most patients (73%, 11/15) had symptomatic improvement (by the Crohn's disease-patient reported outcome signs and symptoms [CD-PRO/SS] or partial Mayo score for UC) and 67% (10/15) had corticosteroid dose reduction, but 20% (3/15) had disease progression that required surgical management. There were 3 serious AEs that required hospitalization (Salmonella gastroenteritis, *C difficile* infection, and malnutrition), 4 infections treated with antibiotics, and vedolizumab was discontinued in a patient for postinfusion arthralgia (see **Table 1**).

Three additional published case series each with less than 10 patients are summarized in **Table 1**. Overall, DAT were associated with improved CD and/or rheumatologic disease activity in ~29% to 50% of patients, though infectious complications can occur in ~15% to 25% of patients.

NOVEL PHARMACOLOGIC THERAPIES IN PHASE 2 AND 3 CLINICAL TRIALS

Mirikizumab

Mirikizumab is a humanized IgG4 monoclonal antibody that targets IL-23p19 (p19 subunit of the IL23 cytokine).[14,15] The efficacy and safety of mirikizumab was evaluated in SERENITY, a phase 2, randomized, parallel-arm, placebo-controlled trial of 191 patients with moderately-to-severely active CD,[14,15] and VIVID, an ongoing phase 3 trial (ClinicalTrials.gov: NCT03926130) (**Table 2**).

In SERENITY, 191 patients were randomized 2:1:1:2 to dose-ranging IV mirikizumab (200 mg, 600 mg, or 1000 mg) or placebo at weeks 0, 4, and 8.[15] Clinical improvements were observed in patients treated (at all doses for CDAI, 42%–56%, $P<.03$; mirikizumab 600 mg and 1000 mg by PRO-2, 22%–28%, $P<.05$) as compared with placebo (23% and 6%, respectively) from baseline to week 12 (see **Table 2**).[14] Endoscopic response (SES-CD 50% reduction from baseline) rates were significantly higher ($P<.01$) at week 12 for patients treated with mirikizumab 600 mg (38%; 95% confidence interval [CI], 21–54) and 1000 mg (44%; 95% CI, 32–56) as compared with placebo (11%; 95% CI, 3–19).[14] Similarly, endoscopic remission (SES-CD <4 for ileocolonic CD or <2 for isolated ileal CD and no subscore >1) was statistically higher at week 12 for patients treated with mirikizumab 600 mg (15.6%, $P = .03$) and 1000 mg (20%, $P = .009$) as compared with placebo (1.6%).[14]

With regards to safety, treatment-emergent AEs rates were similar across all mirikizumab dose-ranging groups (58%–66%) and placebo (70%) (see **Table 2**). Similarly, serious AEs were similar across all mirikizumab-treated (3%–10%) and placebo (11%) groups.[14]

Overall, induction with mirikizumab had higher rates of overall clinical and endoscopic from baseline to week 12 as compared with placebo in the phase 2 SERENITY study. A phase 3 randomized placebo-active controlled trial with an estimated enrollment of 1150 patients is currently underway in the VIVID trial with an estimated completion date in April 2023 (ClinicalTrials.gov: NCT03926130).

Guselkumab

Guselkumab is a humanized IgG1 monoclonal antibody with selective antagonistic binding to IL-23.[16–19] The efficacy and safety of guselkumab was evaluated in GALAXI 1, a phase 2, multicenter, placebo-controlled dose-ranging study (200 mg, 600 mg, and 1200 mg IV at weeks 0, 4, and 8, respectively) of 250 patients with moderately to severely active CD with inadequate response to intolerance to corticosteroids, immunosuppressants, and/or biologic therapies (anti-TNF antagonists, vedolizumab) (see **Table 2**).[16–18]

Table 2
Updates on pharmacologic therapies in phase 2 or 4 clinical trials for moderate to severely active Crohn's disease published from January 2018 to July 2021

Class	Pharmacotherapy	Trials, Phases	Mechanism; Administration	Updates
Anti-Interleukin	Mirikizumab[14,15]	SERENITY (phase 2), VIVID (phase 3, ongoing)	Humanized IgG4 monoclonal antibody with selective binding to the p19 subunit of IL-23; IV and SQ	• Efficacy (clinical): Clinical improvements (CDAI and PRO-2) were observed in the mirikizumab 600 mg (35%–53%) and 1000 mg (22%–28%) groups as compared with placebo (6%–23%; *P*<.05) from baseline to week 12.[14,15] • Efficacy (endoscopic): A higher portion of patients achieved 50% reduction in SES-CD scores at week 12 (from baseline) in the mirikizumab 600 mg (38%) and 1000 mg (44%) groups compared with placebo (11%; *P*<.01). Similarly, endoscopic remission were observed in 16% and 20% of patients in the mirikizumab 600 mg and 1000 mg groups, respectively, compared with 2% in the placebo group (*P* = .03).[14] • Safety: Similar frequencies of treatment-emergent AEs (58%–66%) and serious AEs (0%–9%) were observed across mirikizumab treatment groups and in the placebo group (70% and 11%, respectively)[14]
	Guselkumab[16–18]	GALAXI 1 (phase 2)	Humanized IgG1 monoclonal antibody with selective binding to IL-23; IV	• Efficacy (clinical): Guselkumab-treated patients had higher rates of clinical remission (CDAI score < 150; 20%, 42%, and 54%) at weeks 4, 8, and 12, respectively, as compared with placebo (12%, 16%, 16%; *P* = .001)[16,17] • Efficacy (biochemical): Reductions in CRP (median −2.2 mg/L) and fecal calprotectin (median −176 μg/g) were numerically greater in guselkumab-treated patients compared with the placebo group (0.0 mg/L and 20 μg/g) from baseline to week 12 (*P*-values not presented)[17]

(*continued on next page*)

Table 2
(*continued*)

Class	Pharmacotherapy	Trials, Phases	Mechanism; Administration	Updates
				• Efficacy (endoscopic): Numerically more guselkumab-treated patients had reductions in SES-CD ((LS mean −4.6 vs −0.5), endoscopic healing (17% vs 4%) and endoscopic remission (14% vs 4%) from baseline to week 12 as compared with placebo (*P*-values not presented).[19] • The early trend for achievement of clinical,[17] biochemical,[18] and endoscopic[19] response were observed in the overall guselkumab-treated population, as well as subgroups with refractory disease to biologic or conventional therapies (corticosteroid, immunosuppressant). • Safety: In the guselkumab 200, 600, 1200 mg IV, and placebo treatment groups, serious AEs occurred in 4%, 4%, 2%, and 4%, and serious infections occurred in 2%, 0%, 0%, and 0% of patients, respectively. There were no reported deaths, active tuberculosis, serious hypersensitivity reactions, or malignancies.[16]
	Risankizumab[20–23]	Phase 2 extended open-label studies; FORTIFY (phase 3); ADVANCE and MOTIVATE (phase 3)	Humanized IgG1 monoclonal antibody with selective binding to the p19 subunit of IL-23; IV induction and SQ maintenance	• Efficacy (clinical): In the extended open-label study (up to 206 wk), 77% (23/30 of responders; 35%, 23/65, with nonresponder imputation) had clinical remission (CDAI <150).[21] In the phase 3 studies, significantly more (all *P*<.05) of risankizumab-induced patients (17%–21%, 28%–38%, and 35%–45%) had clinical remission at weeks 4, 8, and 12, respectively, as compared with the placebo group (8%–11%, 13%–17%, 19%–25%).[22] • Efficacy (endoscopic): In the extended open-label study (up to 206 wk), 59% (23/39 of responders; 35%, 23/39, with nonresponder imputation) had endoscopic remission (CDEIS ≤4, or ≤2 for isolated

				Crohn's ileitis).[21] In the phase 3 studies, significantly more patients achieved endoscopic remission in the risankizumab-treated groups compared with placebo (20%–24% vs 4%–9%, *P*<.001).[23] • Safety: Serious AEs and discontinuations due to AEs were observed/occurred in 35% (23/65) and 32% (21/65) of patients in the extended open-label study.[21] The most common AEs (20%–31%) were nasopharyngitis, gastroenteritis, and fatigue.[21] There were no reported tuberculosis infections, malignancies, or death.[20–23]
Sphingosine-1-Phosphate	Ozanimod[2]	STEPSTONE (phase 2, uncontrolled)	S1P subtype 1 and 5 receptor modulator; oral capsule	• Efficacy: Clinical remission (CDAI <150 points) was achieved in 39% (27/69) of patients after 12 wk of ozanimod, as well as decreases in SES-CD, CDAI, PRO2, GHAS, and RHI scores in an uncontrolled trial (n = 69).[2] • Safety: Discontinuation of ozanimod due to AEs occurred in 16% (11/69) of patients. The most common AEs were CD flare (26%, 18/69) and abdominal pain (15%, 10/69) of patients.[2]

(*continued on next page*)

Table 2
(*continued*)

Class	Pharmacotherapy	Trials, Phases	Mechanism; Administration	Updates
Janus Kinase Inhibitor	Upadacitinib[27,28]	CELEST (phase 2)	Oral JAK kinase inhibitor with JAK1 selectivity; oral	• Efficacy (induction, week 12/16): Dose-response endoscopic remission was observed in upadacitinib-treated patients, with the highest rates observed in patients who received upadacitinib 24 mg twice-daily (22%, *P*<.01), compared with placebo (0%). Clinical remission rates did not differ between patients who received upadacitinib (11%–27%) and placebo (14%, *P*>.4). A transcriptomics substudy found that upadacitinib reversed the overexpression of inflammatory fibroblasts after 12–16 wk. • Efficacy (maintenance, week 52): a higher proportion of patients who received upadacitinib 12 mg twice-daily were in clinical remission as compared with those who received upadacitinib 3 mg twice-daily (52%–73% vs 29%–41%, *P*<.1), but the rates of endoscopic remission were not different between the dose-ranging groups. • Safety: AEs were the most common in the upadacitinib 12 mg twice-daily group (81% any AEs, 28% serious AEs, and 25% AEs that led to discontinuation of treatment). Significantly higher increases in the total cholesterol, high-density lipoprotein, and low-density lipoprotein levels were observed in patients who received upadacitinib 12 mg and 24 mg twice-daily as compared with placebo from baseline to week 16. There were no deaths or tuberculosis infections reported.

Abbreviations: AE, adverse event; CDAI, Crohn's disease activity index; CRP, C-reactive protein; FACIT, Functional Assessment of Chronic Illness Therapy; GHAS, Geboes Histology Activity Score; IgG, immunoglobulin; IL, interleukin; IV, intravenous; JAK, Janus kinase; LS, least square; MAdCAM-1, mucosal addressin cell adhesion molecule-1; PRO-2, two-item patient-reported outcome; RHI, Robart's Histopathology Index; SES-CD, Simple Endoscopic Score for Crohn's Disease; S1P, sphingosine 1-phosphate; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease; SQ, subcutaneous.

A higher proportion of guselkumab-treated patients achieved clinical remission (CDAI score < 150; 20%, 42%, and 54%) at weeks 4, 8, and 12, respectively, as compared with placebo (12%, 16%, 16%; $P = .001$) (see **Table 2**).[17] A higher and increasing proportion of guselkumab-treated patients had clinical response (CDAI decrease by ≥100 from or CDAI <150), from 44.0% to 56.0% to 66.0% at weeks 4, 8, and 12, respectively, as compared with placebo (26%, 26%, 24%; $P<.001$).[16,17]

Similarly, a higher proportion of guselkumab-treated patients had clinical-biomarker response (clinical response and CRP/fecal calprotectin reduced by ≥50% from baseline) that increased from weeks 4, 8, and 12 (26% to 43% to 48%) as compared with placebo (14%, 10%, 8%; $P<.001$).[17] Guselkumab-treated patients, as compared with placebo, had greater reductions in CRP (median −2.2 mg/L vs 0.0 mg/L; normalization in 35% vs 19%) and fecal calprotectin (median −176 μg/g vs 20 μg/g; normalization in 33% vs 27% placebo) from baseline to week 12 (*P*-values not reported) (see **Table 2**).[18]

A higher proportion of guselkumab-treated patients achieved endoscopic response (SES-CD decrease by ≥50% from baseline or SES-CD ≤2), endoscopic healing (absence of mucosal ulcerations), and endoscopic remission (SES-CD≤2), 37%, 17%, and 14%, respectively, as compared with placebo (12%, 4%, 4%) at week 12 based on video ileocolonoscopies read by masked central readers (*P*-values not presented) (see **Table 2**).[19] Guselkumab-treated patients had numerically greater reductions in SES-CD scores compared with the placebo group from baseline to week 12 (least square [LS] mean −4.6 vs −0.5); however, a dose-response relationship with guselkumab was not demonstrated for the clinical or endoscopic outcomes.[19]

With regards to safety, guselkumab-treated patients had similar rates of overall AEs (40%–52%) and serious AEs (2%–4%) as compared with the placebo group (57% and 4%, respectively) through week 12.[16] The overall discontinuation rate through week 12 was low (4%).[16] There were no reported deaths, tuberculosis, or serious hypersensitivity reactions.[16]

Overall, induction with guselkumab had higher rates of overall clinical remission, clinical-biomarker response, and clinical response as early as week 4 that continued to increase in proportion through week 12 as compared with placebo; however, a dose-response relationship was not apparent within the range of doses tested. A small phase 3, open-label study (estimated enrollment of 25 patients) is currently underway with anticipated completion in 2025 (ClinicalTrials.gov: NCT04397263).

Risankizumab

Risankizumab is a humanized monoclonal IgG1 antibody targeting the IL-23 p19 subunit that received FDA approval for the treatment of moderate-to-severe plaque psoriasis in April 2019.[20–23] The efficacy and safety of risankizumab in patients with moderately to severely active CD was evaluated in a phase 2 open-label extension study[20] and three phase 3 trials, FORTIFY, ADVANCE, and MOTIVATE (see **Table 2**).[21–23]

In the phase 2 open-extension trial of risankizumab, 101 patients who did not achieve deep remission by week 12 of the original phase 2 study[24] (33 from the placebo group, 23 from the risankizumab 200 mg group, and 34 from the risankizumab 600 mg group) received an additional 12 weeks of open-label risankizumab 600 mg, then patients who achieved deep remission/clinical remission by week 26 proceeded to the 52-week maintenance trial (risankizumab 180 mg SQ every 8 weeks).[20] In this open-extension trial at week 26, 54% (55/101) were in clinical remission (CDAI <150) and 6% (6/101) had clinical-endoscopic remission (see **Table 2**). Of the 62 patients who remained in the maintenance trial (including 1 patient who did not achieve clinical remission but continued to maintenance trial due to protocol deviation) at week

52, 71% achieved clinical remission, 35% endoscopic remission (CDEIS ≤4, or ≤2 for isolated Crohn's ileitis), 29% clinical-endoscopic remission, and 24% mucosal healing (absence of mucosal ulceration) (see **Table 2**).[20] Endoscopic outcomes were assessed by masked central reading of ileocolonoscopies.[20,21]

In the final results from the open-label extension phase 2 study, which continued till the closure of Study M15-898 at week 206, 65 patients who achieved clinical response (reduction of CDAI ≥100 from baseline) without clinical remission (CDAI <150) at week 26/52 proceeded to receive risankizumab 180 mg SQ every 8 weeks (4 patients received reinduction of risankizumab 600 mg IV every 4 weeks for 3 doses at week 26/52).[21] At week 206, clinical remission was observed in 77% (23/30; 35%, 23/65, with nonresponder imputation) and endoscopic remission in 59% (23/39; 35%, 23/39, with nonresponder imputation) of patients (see **Table 2**).[21] Overall, the open-label extension study of risankizumab supported the efficacy of selective IL-23 blockade for the treatment of moderately to severely active CD.[21]

ADVANCE and MOTIVATE are active phase 3, double-blind, randomized, placebo-controlled trials with 850 and 569 patients, respectively, with moderately to severely active CD with inadequate response or intolerance to conventional and/or biologic treatments. Patients were randomized to 2:2:1 or 1:1:1 of risankizumab 600 mg IV, 1200 mg IV, or placebo as induction therapy in ADVANCE and MOTIVATE, respectively.[22,23] At weeks 4, 8, and 12, significantly more (all $P<.05$) patients achieved clinical remission in the risankizumab 600 mg (17%–21%, 28%–35%, 35%–45% by CDAI <150 or PRO-2 stool frequency subscore [SFS] ≤2.8 and abdominal pain subscore [APS] ≤1 with neither worse than baseline) and 1200 mg groups (18%–21%, 30%–38%, 39%–42% by CDAI or PRO-2 criteria) as compared with placebo (8%–11%, 13%–17%, 19%–25%) (see **Table 2**).[22] At week 12, 19% to 24% ($P<.001$) and 20% to 24% ($P<.001$) of patients in the risankizumab 600 mg and 1200 mg groups, respectively, achieved endoscopic remission (SES-CD≤4) as compared with 4% to 9% in the placebo group (see **Table 2**).[23]

FORTIFY is a phase 3 placebo-controlled induction study of risankizumab in 931 patients with moderately to severely active CD that was completed in April 2021. Preliminary results are available from the sponsor's center news center.[25]

With regards to safety, overall AEs and serious AEs were reported in 92% (60/65) and 35% (23/65) in the phase 2 extended open-label study.[21] In the extended open-label study, 32% (21/65) patients prematurely discontinued risankizumab, including 9% (6/65) that were AE-related (see **Table 2**).[21] The most common AEs were nasopharyngitis (31%), gastroenteritis (23%), and fatigue (20%).[21] No tuberculosis infections, malignancies, or death were observed in the risankizumab open-label study or extended open-label study.[20,21]

Overall, phase 2 and 3 trials support the efficacy of risankizumab induction therapy for clinical and endoscopic response, and phase 3 trials maintenance trials are completed/underway to provide additional data on its safety and efficacy in patients with moderately to severely active CD.

Ozanimod

Ozanimod is an oral agent that selectively binds sphingosine-1-phosphate (S1P) receptor subtypes 1 and 5[2] that was recently approved by the FDA for treatment of patients with moderately to severely active UC in May 2021.[2,26] For CD, the safety and efficacy of ozanimod 1 mg oral capsule was evaluated in STEPSTONE, a phase 2, uncontrolled, multicenter trial of 69 patients with moderately to severely active CD[2] (see **Table 2**). Ozanimod was administered in a 7-day escalation protocol (0.25 mg daily for 4 days and then 0.5 mg daily for 3 days) then 1 mg daily.[2]

Clinical, endoscopic, and histologic improvement were observed based on decreases in the mean SES-CD (−2.2, SD 6.0), CDAI (−130, SD 104), PRO2 (−66, SD 65), global histologic disease activity score (GHAS; −5.9, SD 11.0), and Robarts histologic index (RHI; −10.6, SD 25.1) scores from baseline to week 12[2] (see **Table 2**). Clinical remission (CDAI <150 points) was achieved in 39% (27/69) of patients.[2]

With regards to safety in the phase 2 uncontrolled trial for ozanimod in patients with moderately to severely active CD (n = 69), the most common treatment-emergent AEs were CD flare (26%), abdominal pain (15%), lymphopenia (13%), arthralgia (13%), and nausea (12%) (see **Table 2**).[2] Ozanimod was discontinued in 16% (11/69) of patients who experienced treatment-emergent AEs.[2] There were no clinically important changes in heart rate were observed at treatment initiation.[2]

Overall, clinical, endoscopic, and histologic improvements were observed in STEPSTONE, a phase 2 uncontrolled trial of ozanimod. A phase 3 placebo-controlled induction study of ozanimod 1 mg is underway with estimated enrollment of 600 patients with moderately to severely active CD and anticipated completion in 2023 (ClinicalTrials.gov: NCT03440372). A phase 3 open-label extension study of ozanimod 1 mg × 48 weeks is underway with estimated enrollment of 1200 patients and anticipated to be completed in 2026 (ClinicalTrials.gov: NCT03467958).

Upadacitinib

Upadacitinib is an oral JAK1 inhibitor that received FDA approval for treatment of adults with moderate to severe rheumatoid arthritis in August 2019.[27,28] In CD, the efficacy and safety of upadacitinib was evaluated in CELEST, a phase 2, randomized placebo-dose ranging trial (3 mg, 6 mg, 12 mg, or 24 mg twice-daily; or 24 mg once-daily) in 220 patients with moderately to severely active CD refractory/intolerant to immunosuppressants or anti-TNF antagonists[27] (see **Table 2**).

Postinduction (week 12/16), the rates of clinical remission (average daily SFS 1.5 and APS 1.0, with neither worse than the baseline value) were not significantly different (P>.4) between upadacitinib-treated (11%–27%) and placebo 14% groups, and a dose-response association was also not observed[27] (see **Table 2**). Dose-response relationship for endoscopic remission (SES-CD ≤4 and a ≥2-point reduction from baseline, with no subscore >1) was observed in 10% (P< .1), 8% (P-value not reported), 8% (P< .1), 22% (P<.01), and 14% (P<.05) of patients treated with upadacitinib 3 mg, 6 mg, 12 mg, 24 mg twice-daily, and 24 mg once-daily, respectively, versus 0% in the placebo group (see **Table 2**).[27] A total of 180 patients completed the induction period and were rerandomized to upadacitinib 3 mg, 6 mg, 12 mg twice-daily, or 24 mg once-daily, in the maintenance period. At week 52, 52% to 73% of patients in the upadacitinib 12 mg twice-daily group were in clinical remission, as compared with 29% to 41% in the upadacitinib 3 mg twice-daily group (P<.1); clinical remission rates were not different in the other dose-ranging groups (see **Table 2**).[27] At week 52, the rates of endoscopic response were not different between the dose-ranging groups.[27]

With regards to safety, higher incidences of AEs occurred with the higher doses of upadacitinib (≥12 mg twice-daily; see **Table 2**).[27] Serious AEs occurred in 5% to 28% upadacitinib-treated patients, with the highest incidence in the 12 mg twice-daily group (28%, 10/36).[27] Similarly, 3% to 25% of patients had AEs that led to the discontinuation of upadacitinib, with highest incidence occurring in patients treated with 12 mg twice-daily (25%, 9/26) (see **Table 2**). Moreover, at week 16, patients who received upadacitinib 12 mg twice-daily and 24 mg twice-daily had significantly higher

increases in the total cholesterol (mean 0.44, SD 0.9, $P<.05$; mean 0.70, SD 0.68, $P<.001$), high-density lipoprotein (mean 0.15, SD 0.28, $P<.1$; mean 0.48, SD 0.47, $P<.001$), and low-density lipoprotein (mean 0.43, SD 0.69, $P<.01$; mean 0.42, SD 0.48, $P<.01$) cholesterol levels compared with patients in the placebo group (mean −0.10, SD 0.68; mean −0.02, SD 0.34; mean −0.01, SD 0.47, respectively). There were no deaths or tuberculosis occurred in the 52-week study.[27]

Overall, a dose-response relationship for endoscopic remission was demonstrated in the phase 2 ozanimod induction study, CELEST, though its efficacy for achieving clinical remission was not observed. A phase 3 placebo-controlled induction study is currently underway to further explore the efficacy and safety of upadacitinib induction, with estimated enrollment of 501 patients and study completion in February 2022 (ClinicalTrials.gov: NCT03345849).

A transcriptomics substudy was conducted in 74 patients from the CELEST study who had endoscopic remission but persistent mucosa inflammation at week 12 or 16 (postinduction).[28] In areas with mucosal inflammation, treatment with upadacitinib was observed to be associated with the reversal in the overexpression of inflammatory fibroblast (*SOX6*, *PTGDR2*, and *PDGFD*), interferon-γ effector (*IFNG*, *TBX21*, and *GZMH*), and acute inflammatory markers (*CHI3L1*, *OSM*, and *S100A8*) in anti-TNF refractory patients from baseline to week 12/16 (see **Table 2**).[28] Conversely, the transcriptomes of noninvolved intestinal areas did not differ between baseline and postinduction. This suggests that upadacitinib modulates mucosal inflammatory molecular pathways as a mechanism by which JAK1 inhibition may be effective in patients with CD and refractory to anti-TNF therapy.[28]

SUMMARY

In summary, in patients with refractory CD and/or active EIMs (eg, ankylosing spondylitis) or rheumatologic diseases (eg, psoriatic arthritis) despite the use of single biologic or small molecule agents may benefit from a combination of DAT. Several novel pharmacotherapies with more specific mechanistic targets (eg, interleukin-23, Janus kinase inhibitor subtypes, and sphingosine-1-phosphate) have shown promising results in phase 2 clinical trials and multiple phase 3 studies are currently underway with anticipation of completion over the next 5 years. Pharmacologic therapies with improved efficacy, safety, and tolerability are active areas for research and development to address lingering unmet needs for patients with moderately to severely active CD.

CLINICS CARE POINTS

- Dual advanced therapies (combination of biologics and/or small molecule therapies) have been used to treat refractory Crohn's disease and/or concomitant rheumatologic extraintestinal manifestations with a 30% to 60% efficacy, although adverse events (particularly infectious complications) can occur in nearly two-thirds of patients.
- Risankizumab demonstrated promising results for inducing and maintaining clinical and endoscopic response in phase 2 clinical trials, and its safety and efficacy are further explored in phase 3 placebo-controlled induction (completed, preliminary results reported) and maintenance studies (underway).
- Phase 2 induction studies of mirikizumab, ozanimod, and guselkumab have demonstrated varying degrees of efficacy in inducing clinical and/or endoscopic response with an acceptable safety profile; phase 3 trials of these agents are currently underway with anticipated study completion over the next 2 to 5 years.

DISCLOSURE

P.S. Dulai: Consulting and/or grant support from Takeda, Abbvie, Janssen, Pfizer, Gilead, BMS, Lily, Novartis, Scipher, and Prometheus. C.S. Tse has nothing to disclose.

REFERENCES

1. Feuerstein JD, Ho EY, Shmidt E, et al. AGA clinical practice guidelines on the medical management of moderate to severe luminal and perianal fistulizing crohn's disease. Gastroenterology 2021;160(7):2496–508.
2. Feagan BG, Sandborn WJ, Danese S, et al. Ozanimod induction therapy for patients with moderate to severe Crohn's disease: a single-arm, phase 2, prospective observer-blinded endpoint study. Lancet Gastroenterol Hepatol 2020;5(9): 819–28.
3. Rutgeerts P, Gasink C, Chan D, et al. Efficacy of Ustekinumab for Inducing Endoscopic Healing in Patients With Crohn's Disease. Gastroenterology 2018;155(4): 1045–58.
4. Shi HY, Ng SC. The state of the art on treatment of Crohn's disease. J Gastroenterol 2018;53(9):989–98.
5. Yang E, Panaccione N, Whitmire N, et al. Efficacy and safety of simultaneous treatment with two biologic medications in refractory Crohn's disease. Aliment Pharmacol Ther 2020;51(11):1031–8.
6. Privitera G, Onali S, Pugliese D, et al. Dual Targeted Therapy: A Possible Option for the Management of Refractory Inflammatory Bowel Disease. J Crohn's Colitis 2020;15(2):335–9.
7. Mao EJ, Lewin S, Terdiman JP, et al. Safety of dual biological therapy in Crohn's disease: a case series of vedolizumab in combination with other biologics. BMJ Open Gastroenterol 2018;5(1):e000243.
8. Glassner K, Oglat A, Duran A, et al. The use of combination biological or small molecule therapy in inflammatory bowel disease: A retrospective cohort study. J Dig Dis 2020;21(5):264–71.
9. Fumery M, Yzet C, Brazier F. Letter: combination of biologics in inflammatory bowel diseases. Aliment Pharmacol Ther 2020;52(3):566–7.
10. Fala L. Otezla (Apremilast), an oral PDE-4 inhibitor, receives FDA approval for the treatment of patients with active psoriatic arthritis and plaque psoriasis. Am Health Drug benefits 2015;8(Spec Feature):105.
11. Kwapisz L, Raffals LE, Bruining DH, et al. Combination Biologic Therapy in Inflammatory Bowel Disease: Experience From a Tertiary Care Center. Clin Gastroenterol Hepatol 2021;19(3):616–7.
12. Buer LCT, Høivik ML, Warren DJ, et al. Combining Anti-TNF-α and Vedolizumab in the Treatment of Inflammatory Bowel Disease: A Case Series. Inflamm Bowel Dis 2018;24(5):997–1004.
13. Ahmed W, Galati J, Kumar A, et al. Dual Biologic or Small Molecule Therapy for Treatment of Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2021. https://doi.org/10.1016/j.cgh.2021.03.034.
14. Sands BES WJ, Peyrin-Biroulet L, Higgins P, et al. OP108 Efficacy and Safety of Mirikizumab After 52-Weeks Maintenance Treatment in Patients with Moderate-To-Severe Crohn's Disease. Gastroenterology 2021. Nov 5;S0016-5085(21) 03725-2.
15. Sandborn WJ, Sands BE, Hindryckx P, et al. S0705Evaluationof Symptom Improvement During Induction in Patients With Crohn's Disease Treated With Mirikizumab. Am Coll Gastroenterol 2020;115:S354.

16. Sandborn WJ, Chan DJ J, Lang G, et al, on behalf of the GALAXI 1 Investigators. OP089 The efficacy and safety of guselkumab induction therapy in patients with moderately to severely active Crohn's disease: week 12 interim analyses from the phase 2 GALAXI 1 study. United European Gastroenterology Journal 2020;Vol. 8(8S):8–142.
17. Danese S, Sandborn WJ, Feagan BG, et al. OP28 The effect of guselkumab induction therapy on early clinical outcome measures in patients with Moderately to Severely Active Crohn's Disease: Results from the phase 2 GALAXI 1 study. J Crohn's Colitis 2021;15(Supplement_1):S027–8.
18. Sands BE, Danese S, Andrews JM, et al. Fr532 The effect of guselkumab induction therapy on inflammatory biomarkers in patients with moderately to severely active crohn's disease: week 12 results from the phase 2 GALAXI 1 Study. Gastroenterology 2021;160(6, Supplement). S-350-S-351.
19. D'Haens G, Rubin DT, Panes J, et al. 455 The effect of guselkumab induction therapy on endoscopic outcome measures in patients with moderately to severely active crohn's disease: week 12 results from the phase 2 GALAXI 1 Study. Gastroenterology 2021;160(6, Supplement):S-91.
20. Feagan BG, Panes J, Ferrante M, et al. Risankizumab in patients with moderate to severe Crohn's disease: an open-label extension study. Lancet Gastroenterol Hepatol 2018;3(10):671–80.
21. Ferrante M, Feagan BG, Panés J, et al. OP27 Long-term safety and efficacy of risankizumab treatment in patients with Crohn's disease: Final results from the Phase 2 open-label extension study. J Crohn's Colitis 2020;14(Supplement_1): S024–5.
22. Schreiber S, Ferrante M, Panaccione R, et al. OP26 Risankizumab induces early clinical remission and response in patients with Moderate-to-Severe Crohn's Disease: Results from the phase 3 ADVANCE and MOTIVATE studies. J Crohn's Colitis 2021;15(Supplement_1):S026–7.
23. Bossuyt P, Ferrante M, Baert F, et al. OP36 Risankizumab therapy induces improvements in endoscopic endpoints in patients with Moderate-to-Severe Crohn's Disease: Results from the phase 3 ADVANCE and MOTIVATE studies. J Crohn's Colitis 2021;15(Supplement_1):S033–4.
24. Feagan BG, Sandborn WJ, D'Haens G, et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. Lancet 2017;389(10080):1699–709.
25. AbbVie. Phase 3 Maintenance Results Show Patients with Crohn's Disease Receiving Risankizumab (SKYRIZI®) Achieved Endoscopic Response and Clinical Remission at One Year. AbbVie Inc. Updated 2 June 2021. 2021. Available at: https://news.abbvie.com/news/press-releases/phase-3-maintenance-results-show-patients-with-crohns-disease-receiving-risankizumab-skyrizi-achieved-endoscopic-response-and-clinical-remission-at-one-year.htm. Accessed September 11, 2021.
26. Bristol-Myers Squibb Company. Zeposia Prescribing Information. Zeposia U.S. Product Information. Princeton, N.J.: Bristol-Myers Squibb Company; 2021.
27. Sandborn WJ, Feagan BG, Loftus EV Jr, et al. Efficacy and Safety of Upadacitinib in a Randomized Trial of Patients With Crohn's Disease. Gastroenterology 2020; 158(8):2123–38.e8.
28. Aguilar D, Revilla L, Garrido-Trigo A, et al. Randomized Controlled Trial Substudy of Cell-specific Mechanisms of Janus Kinase 1 Inhibition With Upadacitinib in the Crohn's Disease Intestinal Mucosa: Analysis From the CELEST Study. Inflamm Bowel Dis 2021. https://doi.org/10.1093/ibd/izab116.