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A SPECIAL MEETING REVIEW EDITION

Highlights in Ulcerative Colitis From the American College of Gastroenterology Annual Scientific Meeting

A Review of Selected Presentations From ACG 2022

• October 21-26, 2022 • Charlotte, North Carolina

Special Reporting on:

- Duration of Response to Ozanimod After Treatment Withdrawal: Results From the Phase 3 True North Study
- Post Hoc Analyses of the True North Study Evaluating Ozanimod in Patients with Ulcerative Colitis
- Benefits of High Versus Low Dose Upadacitinib as Maintenance Treatment in Ulcerative Colitis Patients Who Were Responders to 8-week Induction With Upadacitinib: Results From the U-ACHIEVE Phase 3 Maintenance Trial
- Efficacy and Safety of Upadacitinib in Patients With Moderate to Severe Active Ulcerative Colitis Receiving 16 Weeks' Extended Induction Treatment Followed by 52 Weeks' Maintenance Treatment in the U-ACHIEVE/U-ACCOMPLISH Trials
- One-Year Comparative Effectiveness of Ustekinumab Versus Tofacitinib for Ulcerative Colitis After Anti-Tumor Necrosis Factor Failure
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- The Effect of Guselkumab Induction Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: QUASAR Phase 2b Induction Results at Week 12 by Prior Inadequate Response or Intolerance to Advanced Therapy

PLUS Meeting Abstract Summaries

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Duration of Response to Ozanimod After Treatment Withdrawal: Results From the Phase 3 True North Study

Ozanimod is an orally available sphingosine-1-phosphate (S1P) receptor modulator that selectively targets S1P1 and S1P5.[1] Ozanimod leads to lymphocyte retention in the peripheral lymphoid organs, thereby preventing their access to sites of chronic inflammation.[2] It is US Food and Drug Administration (FDA) approved with an indication for the treatment of adults with moderately to severely active ulcerative colitis (UC).[3]

This approval was based on results from the True North study, a phase 3, randomized, double-blind, placebo-controlled trial that enrolled 2 cohorts of patients with moderately to severely active UC.[4] In cohort 1, 645 patients were randomized 2:1 to treatment with ozanimod 0.92 mg or placebo. In cohort 2, 367 patients received open-label ozanimod 0.92 mg. Clinical remission was defined as a complete Mayo score of 2 or lower with no individual subscore greater than 1 point, and clinical response was defined as a decrease from baseline of at least 3 points and at least 30% in the complete Mayo score and a decrease of at least 1 point in the rectal bleeding subscore (RBS) or an absolute RBS of 0 or 1.

Significantly more patients treated with ozanimod achieved the primary endpoint of clinical remission than patients in the placebo arm, both in the induction (18.4% vs 6.0%; *P*<.001) and maintenance (37.0% vs 18.5%; *P*<.001) phases. Rates of clinical response were also higher with ozanimod than with placebo at both induction (47.8% vs 25.9%; *P*<.001) and maintenance (60.0% vs 41.0%; *P*<.001) timepoints. These response rates were found to be durable and maintained for an additional 94 weeks in an open-label extension (OLE) study.[5]

In clinical practice, temporary discontinuation of biologic treatments, including ozanimod, can occur for a variety of reasons.[6] A better understanding of the duration of response following discontinuation of ozanimod may assist clinicians in clinical decision making. A post hoc analysis of the True North study examined the time to disease relapse in patients who had discontinued ozanimod and switched to placebo during the maintenance phase.[7] Disease relapse was defined as a partial Mayo score increase of 2 or more points vs week 10 with an absolute partial Mayo score of at least 4 points, an endoscopic subscore of at least 2 points, and exclusion of other causes of increased disease activity unrelated to underlying UC. This analysis compared all clinical responders on ozanimod at week 10 who were randomized to continuous ozanimod (OZA/OZA) or placebo (OZA/PBO) during the maintenance period.

Results from this post hoc analysis showed a distinction between the 2 groups by week 8, with 96.1% of the OZA/OZA patients considered nonrelapsers, compared with 90.6% of OZA/PBO patients (Figure 1). This divergence was more apparent by week

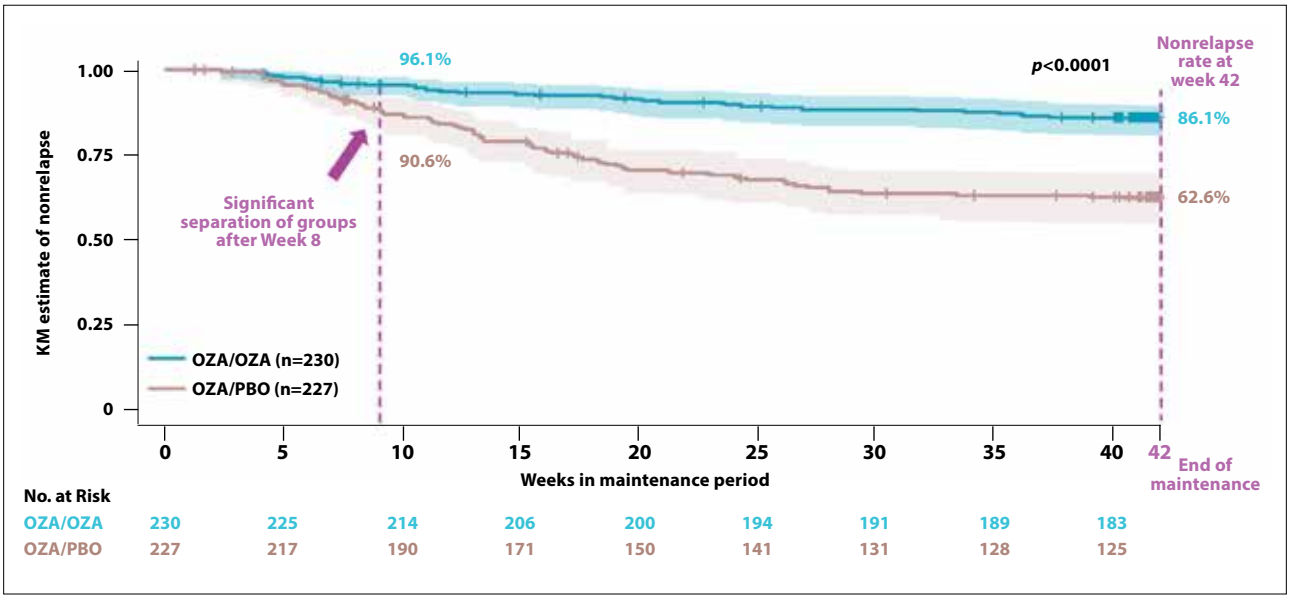

Figure 1. Time to disease relapse during the True North maintenance phase. The shaded areas represent the 95% CI. Data are shown up to week 42, the end of the maintenance period. No relapses occurred after week 39.1 in the ITT population. ITT, intention-to-treat; KM, Kaplan-Meier; OZA/OZA, continuous ozanimod; OZA/PBO, ozanimod followed by placebo. Adapted from Sands BE et al. ACG abstract 62. *Am J Gastroenterology*. 2022;117(suppl 105).[7]

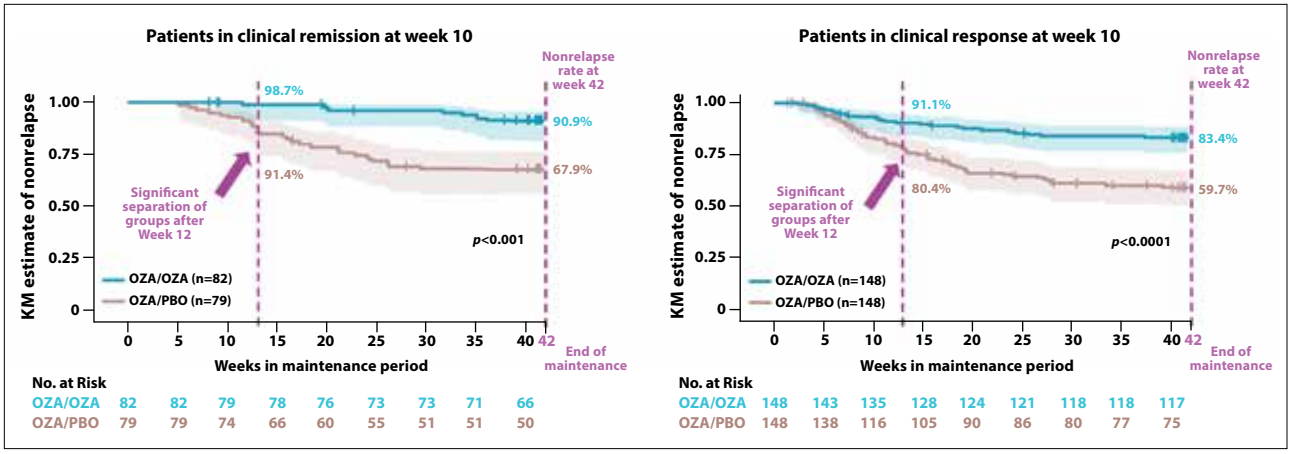

Figure 2. Impact of disease response on time to disease relapse during the True North maintenance phase. The shaded areas represent the 95% CI. Data are shown up to week 42, the end of the maintenance period. No relapses occurred after week 39.1 in the ITT population. ITT, intention-to-treat; KM, Kaplan-Meier; OZA/OZA, continuous ozanimod; OZA/PBO, ozanimod followed by placebo. Adapted from Sands BE, et al. ACG abstract 62. *Am J Gastroenterology*. 2022;117(suppl 105).[7]

42 (end of maintenance), with 86.1% of patients in the OZA/OZA group considered nonrelapsers, compared with 62.6% in the OZA/PBO group (*P*<.0001).

The degree of disease activity at the start of maintenance therapy impacted the subsequent rates of disease relapse (Figure 2). Clinical remission at week 10 was associated with improved outcomes at week 42 compared with clinical response at week 10. Among patients in clinical remission at week 10, the nonrelapse rate at week 42 was 90.9% for patients in the OZA/OZA group compared with 67.9% for patients in the OZA/PBO group (*P*<.001). For patients who were in clinical response at week 10, the week 42 nonrelapse rate was 83.4% in the OZA/OZA group vs 59.7% in the OZA/PBO group (*P*<.0001).

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Post Hoc Analyses of the True North Study Evaluating Ozanimod in Patients with Ulcerative Colitis

Several post hoc analyses of the True North study, which demonstrated ozanimod efficacy and safety in patients with moderately to severely active UC, were presented.[1]

Two analyses focused on the impact of endoscopic disease on ozanimod effectiveness. The first assessed the impact of baseline endoscopic disease activity on clinical outcomes with ozanimod treatment in patients.[2] Among the 1012 patients in the True North study, a higher proportion of patients had severe disease (60.2%) than moderate disease (39.8%) at baseline. Compared with placebo, ozanimod demonstrated significantly superior efficacy in most clinical outcomes in patients with moderate and severe endoscopic disease, regardless of disease activity at baseline. The treatment effects of ozanimod were similar for all evaluated efficacy endpoints at week 10 in patients with moderate and severe US, regardless of baseline endoscopic disease activity. At week 52, ozanimod efficacy was similar for most evaluated endpoints regardless of baseline endoscopic disease activity.

The second post hoc analysis focused on endoscopic disease and evaluated the association of baseline endoscopic disease distribution (left-sided colitis vs extensive colitis) on clinical outcomes with ozanimod.[3] This analysis found that ozanimod was more effective than placebo in patients with left-sided and extensive colitis at weeks 10 and 52 for all evaluated endpoints, and this efficacy was similarly effective regardless of disease distribution. Some data suggested that patients with extensive disease at baseline may require a longer treatment time to robustly achieve more stringent histo-

logic endpoints, but these endpoints were achieved by week 52.

A third post hoc analysis examined the safety and efficacy of ozanimod in patients according to their age group (<60 years or ≥60 years).[4] Ozanimod efficacy was similar between these 2 age groups and superior to placebo regardless of age group across several efficacy endpoints, including clinical remission, clinical response, endoscopic improvement, and mucosal healing, both at week 10 and week 52. Placebo response rates were higher in older than in younger patients across all efficacy endpoints at both timepoints. As a result, the adjusted treatment differences for ozanimod vs placebo for most endpoints were lower for the older age group and none achieved statistical significance. Among older patients, ozanimod treatment was not associated with any new safety signals, and there was no evidence of higher rates of serious adverse events. The authors noted that the study had relatively few participants aged 60 years or older, so larger real-world studies may be useful.

Two post hoc analyses examined the efficacy of ozanimod according to prior treatment history. One examined ozanimod efficacy in patients who were previously exposed to vedolizumab.[5] This analysis demonstrated that ozanimod was effective in patients with prior vedolizumab exposure, including those who failed vedolizumab alone, or following other advanced therapies. After 52 weeks, a significantly higher proportion of vedolizumab-exposed patients who were rerandomized to ozanimod achieved symptomatic remission, clinical response, clinical remission, corticosteroid-free remission, and endoscopic improvement compared with vedolizumab-exposed patients rerandomized to placebo.

The second post hoc analysis that focused on prior treatment history examined the efficacy of ozanimod at week 10 with or without concomitant corticosteroids among immunomodulator- and biologic-naive patients as well as patients with prior 5-aminosalicylic acid (5-ASA) exposure.[6] Ozanimod was efficacious as an induction therapy in immunomodulator- and biologic-naive patients regardless of corticosteroid use at baseline. Further, ozanimod was also shown to have efficacy as induction therapy in patients with 5-ASA exposure at baseline. The incidence of adverse events was similar between placebo and ozanimod cohorts, regardless of prior corticosteroid exposure.

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Benefits of High Versus Low Dose Upadacitinib as Maintenance Treatment in Ulcerative Colitis Patients Who Were Responders to 8-week Induction With Upadacitinib: Results From the U-ACHIEVE Phase 3 Maintenance Trial

Upadacitinib is an oral, reversible Janus kinase (JAK) inhibitor designed with selectivity for JAK1 over JAK2, JAK3, and tyrosine kinase 2. Upadacitinib was previously demonstrated to induce and maintain clinical response and remission in patients with active UC in a phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial program comprising 2 replicate induction studies (U-ACHIEVE induction and U-ACCOMPLISH) and a single maintenance study (U-ACHIEVE maintenance).[1] The recommended maintenance dose of upadacitinib is 15 mg once daily; however, a dosage of 30 mg once daily may be considered for patients with refractory, severe, or extensive disease, and the lowest effective dosage needed to maintain response should be used.[2] However, the benefits of high (30 mg) vs low (15 mg) dose upadacitinib as maintenance treatment in UC remain to be established.

The U-ACHIEVE maintenance study randomized 1:1:1 patients who achieved clinical response following 8-week upadacitinib induction to maintenance treatment with upadacitinib 15 mg, upadacitinib 30 mg, or placebo for 52 weeks.[3] A clinical response was defined as a decrease from baseline in the Adapted Mayo score of 2 or more points and at least 30% from baseline, plus a decrease in RBS of at least 1 or an absolute RBS of 0 or 1. Two major outcomes were reported: the percentage of patients in each treatment group with mild (Adapted Mayo score <5), moderate (Adapted Mayo score 5 to ≤7), or severe (Adapted Mayo score >7) disease at weeks 0 and 52, and the percentage of patients with clinical remission per partial Adapted Mayo score (defined as an RBS of 0 and a stool frequency

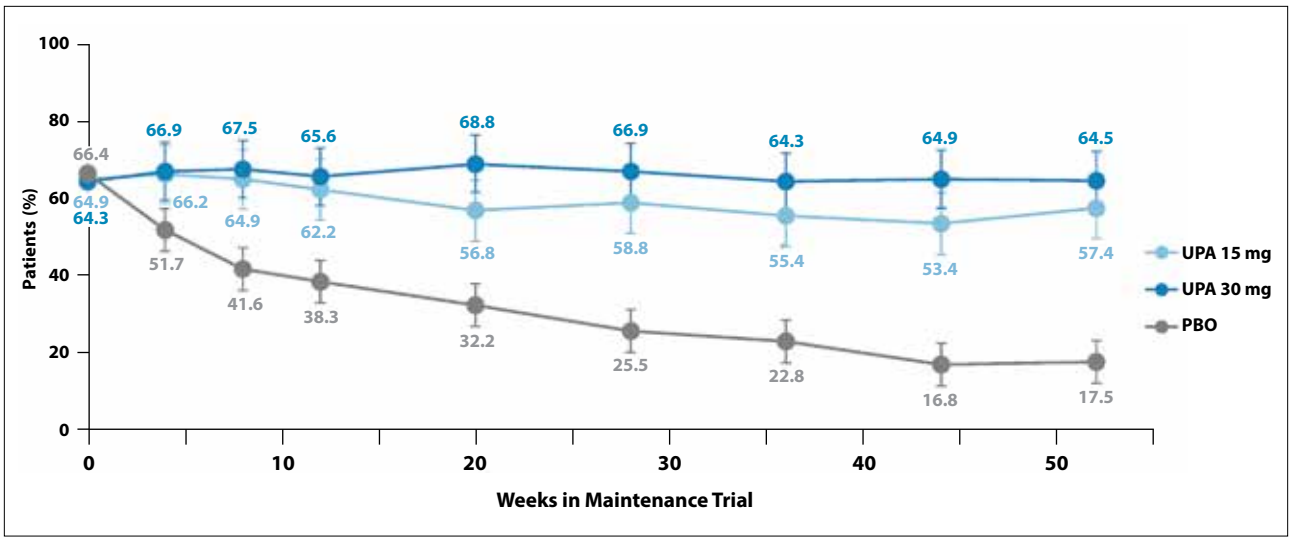

Figure 3. Proportion of patients achieving clinical remission per partial Adapted Mayo score in the U-ACHIEVE maintenance trial.
PBO, placebo; UPA, upadacitinib. Adapted from Feagan B et al. ACG abstract 1. *Am J Gastroenterology*. 2022;117(suppl 105).[3]

subscore [SFS] of 0 or 1) over time in each treatment group.

After 1 year, patients who received maintenance treatment with upadacitinib 30 mg had less severe UC than those treated with upadacitinib 15 mg. At week 0 of the maintenance trial, approximately 92% of patients had mild disease (91.9% randomized to upadacitinib 15 mg, 91.6% randomized to upadacitinib 30 mg, and 92.0% randomized to placebo). The remaining patients had moderate disease (7.4%, 8.4%, and 8.0%, respectively). No patients had severe disease at the beginning of the maintenance period. By week 52, nearly 20% more patients in the upadacitinib 30 mg group were in a less severe disease state than patients in the upadacitinib 15 mg group (P<.0001 for upadacitinib 15 mg vs upadacitinib 30 mg based on chi-squared test). In the upadacitinib 30 mg group, 74.0%, 15.6%, and 9.7% had mild, moderate, or severe disease, respectively, at week 52 vs 63.5%, 16.9%, and 18.9% in the upadacitinib 15 mg group. Both upadacitinib groups had more patients in a less severe disease state (22.8%, 47.0%, and 30.2%, with mild, moderate, and severe disease, respectively) than in the placebo group.

During 1 year of maintenance treatment, clinical remission was sustained in 57.4% of patients treated with upadacitinib 15 mg and in 64.5% of patients treated with upadacitinib 30 mg, compared with 17.5% of patients treated with placebo (Figure 3). Notably, the difference in efficacy between patients treated with upadacitinib and patients receiving placebo was apparent as early as week 4 of the maintenance phase. Patients receiving upadacitinib 30 mg maintenance treatment experienced 3.8 additional weeks of clinical remission compared with patients receiving upadacitinib 15 mg (mean of 34.4 weeks, 30.5 weeks, and 15.8 weeks) for patients treated with upadacitinib 30 mg, upadacitinib 15 mg, and placebo, respectively.

The same outcomes were assessed specifically among patients under the age of 65 years. Among these patients, 26.1% more patients in the upadacitinib 30 mg group were in a less severe disease state than the upadacitinib 15 mg group at week 52 (P<0.0001 for upadacitinib 15 mg vs upadacitinib 30 mg based on chi-squared test). Among patients less than 65 years of age in the upadacitinib 30 mg group, 75.5%, 15.8%, and 8.6% had mild, moderate, or severe disease, respectively, at week 52 vs 61.5%, 17.0%, and 20.7% in the upadacitinib 15 mg group. Both upadacitinib groups had more patients in a less severe disease state than patients in the placebo group (21.9%, 47.4%, and 30.7% with mild, moderate, and severe disease, respectively).

In patients less than 65 years of age who received 1 year of maintenance treatment, clinical remission was sustained in 54.1% of patients treated with upadacitinib 15 mg and in 64.1% of patients treated with upadacitinib 30 mg, compared with 14.7% of patients treated with placebo. These patients less than 65 years of age who were treated with upadacitinib 30 mg maintenance treatment experienced 4.2 additional weeks of clinical remission compared with patients receiving upadacitinib 15 mg (mean of 34.6 weeks, 30.4 weeks, and 16.0 weeks) for patients treated with upadacitinib 30 mg, upadacitinib 15 mg, and placebo, respectively.

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Efficacy and Safety of Upadacitinib in Patients With Moderate to Severe Active Ulcerative Colitis Receiving 16 Weeks' Extended Induction Treatment Followed by 52 Weeks' Maintenance Treatment in the U-ACHIEVE/U-ACCOMPLISH Trials

In the pivotal trials investigating upadacitinib in UC, patients in the 2 replicate induction studies (U-ACHIEVE induction and U-ACCOMPLISH) who achieved clinical response following 8-week upadacitinib induction were randomized to maintenance treatment with upadacitinib 15 mg, upadacitinib 30 mg, or placebo for 52 weeks in a single maintenance study (U-ACHIEVE maintenance).[1] Patients with UC who do not respond to an initial 8-week induction therapy may subsequently achieve a clinical response following extended 16-week induction therapy, as demonstrated with another JAK inhibitor, tofacitinib.[2] This current analysis investigated the efficacy and safety of an extended induction regimen with upadacitinib, in which patients who did not achieve a clinical response following the initial 8-week, blinded upadacitinib induction regimen were eligible to receive an additional 8 weeks of open-label, extended induction treatment with upadacitinib 45 mg.[3] Those patients in a clinical response following the 16 weeks of induction treatment became eligible for randomization into the U-ACHIEVE maintenance study.

Among the 664 patients randomized to receive upadacitinib 45 mg during the induction trials, 125 patients did not achieve a clinical response and received a further 8 weeks of induction therapy with upadacitinib 45 mg. Of these patients, 73 (58.4%) patients achieved a clinical response at week 16 and were rerandomized to maintenance treatment.

The results of this subanalysis demonstrated that an extended induction regimen of 16 weeks with upadacitinib 45 mg led to achievement of the primary endpoint of clinical remission at week 52 in 26.5% of patients treated with upadacitinib 15 mg and in 43.6% of patients treated with upadacitinib 30 mg as maintenance therapy (Figure 4).

Patients who received an extended induction regimen of 16 weeks with upadacitinib 45 mg and proceeded to maintenance treatment also achieved clinically meaningful rates of several secondary endpoints (Figure 5). These included maintenance of clinical response, no abdominal pain, no bowel urgency, endoscopic improvement, endoscopic remission, histologic-endoscopic mucosal improvement, and mucosal healing. These benefits were observed at both upadacitinib maintenance doses; however, upadacitinib 30 mg provided a greater benefit than upadacitinib 15 mg across most clinical, endoscopic and histologic endpoints assessed.

Among patients who received the extended upadacitinib induction regi-

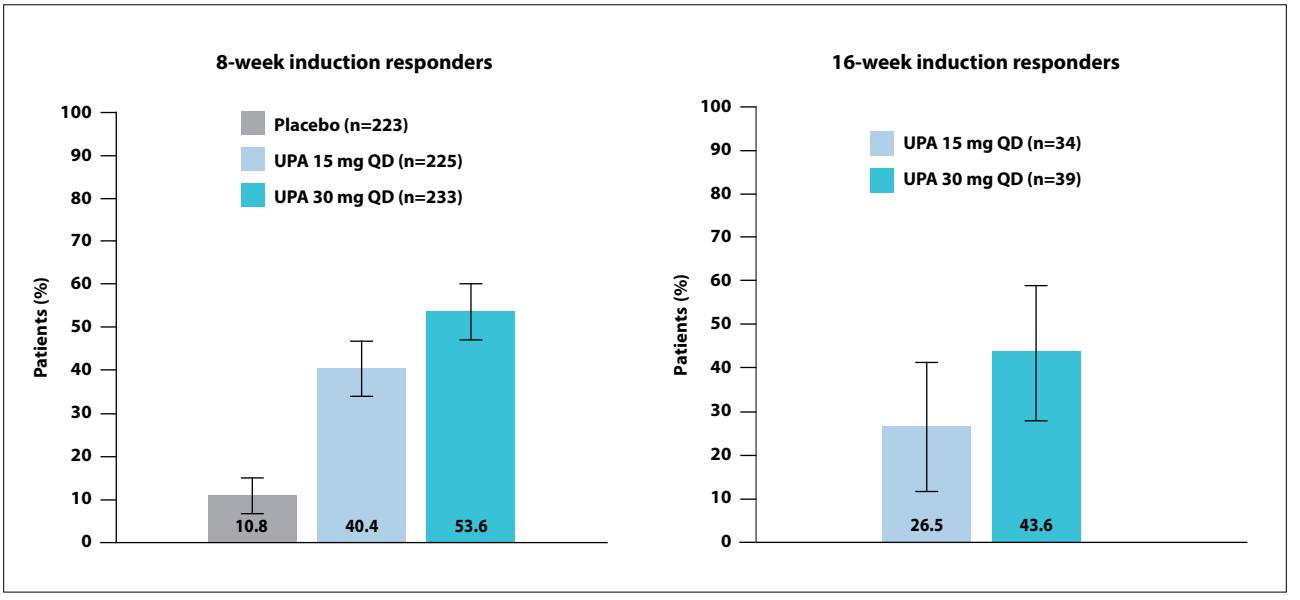

Figure 4. Clinical remission at week 52 after maintenance therapy among patients responding after the planned 8-week (left) or extended 16-week (right) upadacitinib induction regimen. Error bars denote 95% CI. QD, once daily; UPA, upadacitinib. Adapted from Panaccione R, et al. ACG abstract 61. *Am J Gastroenterology*. 2022;117(suppl 105).[3]

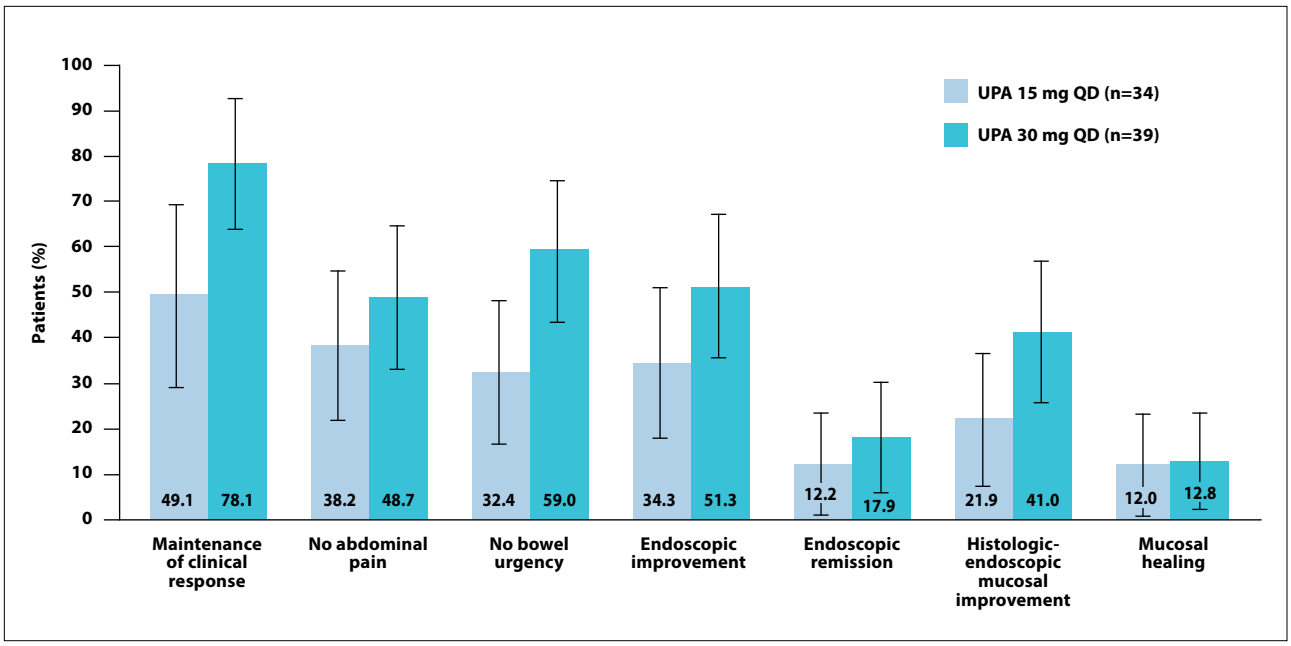

Figure 5. Key secondary efficacy endpoints achieved at week 52 after maintenance therapy among patients responding after the extended 16-week upadacitinib induction regimen. Error bars denote 95% CI. QD, once daily; UPA, upadacitinib. Adapted from Panaccione R, et al. ACG abstract 61. *Am J Gastroenterology*. 2022;117(suppl 105).[3]

men, the maintenance therapy showed no new safety signals.

Selected adverse events of special interest were reported infrequently with both maintenance doses, but more often with the 30 mg dosage. These included serious infection (2 cases in the 30 mg arm vs 1 case in the 15 mg arm), herpes zoster (2 cases in the 30 mg arm vs no cases in the 15 mg arm), anemia (3 cases in the 30 mg arm and 2 cases in the 15 mg arm), neutropenia (2 cases in the 30 mg arm and no cases in the 15 mg arm), nonmelanoma skin cancer (1 case in the 30 mg arm and no cases in the 15 mg arm), and an adjudicated major adverse cardiovascular event (1 case in the 30 mg arm and no cases in the 15 mg arm).

Two patients discontinued treatment owing to an adverse event in the 30 mg maintenance arm, compared with 1 patient in the 15 mg maintenance arm. Serious adverse events were reported among 4 patients in the 30 mg arm and 1 patient in the 15 mg arm.

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One-Year Comparative Effectiveness of Ustekinumab Versus Tofacitinib for Ulcerative Colitis After Anti-Tumor Necrosis Factor Failure

Tofacitinib is a small molecule JAK inhibitor FDA approved for the treatment of adult patients with moderately to severely active UC who have an inadequate response or intolerance to one or more tumor necrosis factor (TNF) blockers. Use of tofacitinib in combination with biologic therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.[1] Ustekinumab is a monoclonal antibody that binds to the p40 protein subunit shared by both the interleukin (IL)-12 and IL-23 cytokines. Ustekinumab is FDA approved for the treatment of adult patients with moderately to severely active UC.[2]

The efficacy of induction and maintenance therapy with tofacitinib and ustekinumab vs placebo in patients with UC has been demonstrated in phase 3 trials.[3,4] However, these agents have not been directly compared in head-to-head trials. A recent meta-analysis positioned both of these agents as equivalent after failure with anti-

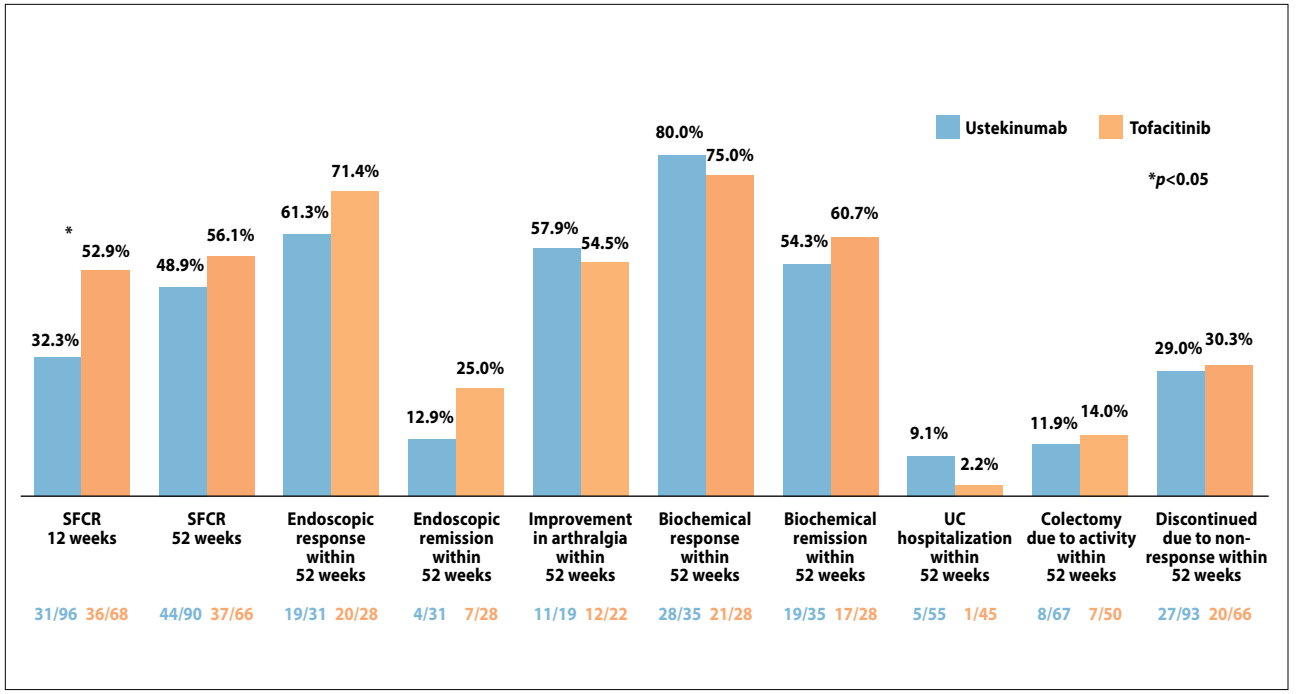

Figure 6. Outcomes among patients with ulcerative colitis and more than 1 prior anti–tumor necrosis factor failure who initiated tofacitinib or ustekinumab. SFCR, steroid-free clinical remission; UC, ulcerative colitis. Adapted from Dalal RS, et al. ACG abstract 42. *Am J Gastroenterology*. 2022;117(suppl 105).[7]

TNF inhibitor therapies.[5] Further, a recent real-world comparative effectiveness analysis conducted in patients with both anti-TNF and vedolizumab failure demonstrated no difference in steroid-free remission rates between tofacitinib and ustekinumab at 12 to 16 weeks.[6]

This retrospective cohort study was a comparative efficacy analysis that evaluated real-world outcomes reported with tofacitinib vs ustekinumab up to 52 weeks after treatment initiation in patients with UC who had failed anti-TNF agents.[7] At baseline, patients treated with tofacitinib had a higher median C-reactive protein level than ustekinumab-treated patients (5.1 mg/L vs 2.8 mg/L, respectively). Also at baseline, tofacitinib-treated patients more commonly had a Mayo endoscopic subscore of 2 or 3 (54% and 28%) vs ustekinumab-treated patients (33% and 36%).

Both ustekinumab and tofacitinib were effective in achieving a steroid-free clinical remission at 12 weeks (32.3% and 52.9%, respectively) and 52 weeks (56.1% and 48.9%, respectively). After adjustment for confounding, there were no significant differences in the rates of steroid-free clinical remission with tofacitinib vs ustekinumab at either 12 weeks (odds ratio, 1.94; 95% CI, 0.96-3.92; *P*=.064) or 52 weeks (odds ratio, 1.16; 95% CI, 0.58-2.31; *P*=.681). There was also no significant difference in the rate of drug survival with tofacitinib vs ustekinumab (hazard ratio, 1.26; 95% CI, 0.74-2.15; *P*=.399).

Week 52 rates of endoscopic response were higher than rates of endoscopic remission but were similar between the 2 agents. Several other outcomes were reported, all of which showed similar rates between ustekinumab and tofacitinib (Figure 6).

The rate of treatment discontinuation because of adverse events were low and similar between tofacitinib (3.3%) and ustekinumab (2.6%). One patient discontinued ustekinumab owing to nausea and arthralgia, and another patient discontinued tofacitinib owing to elevated liver enzymes.

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Maternal and Neonatal Outcomes in Vedolizumab and Ustekinumab Exposed Pregnancies: Results From the PIANO Registry

Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) is a national study of women with inflammatory bowel disease (IBD) and their children evaluating the safety of IBD medications on pregnancy and on short- and long-term outcomes in children. Previous data from the PIANO registry have demonstrated the safety of biologics and thiopurines in pregnant women and their children, but only a small number of patients had been treated with vedolizumab or ustekinumab.[1]

Safety concerns regarding the biologic agent vedolizumab during pregnancy involve mucosal vascular addressin cell adhesion molecule 1, which has been identified in human placental vessels and may play a role in placenta development.[2] Ustekinumab targets IL-12, which functions in uterine angiogenesis, and IL-23, which regulates the function of human decidual immune cells.[3,4] Dysregulated levels of these cytokines are associated with spontaneous abortion.[5,6]

Outcomes measured in the PIANO registry include spontaneous abortion, preterm birth, small for gestational age birth weight, low birth weight, intrauterine growth restriction, cesarean section, and requirement for neonatal intensive care at birth, placental disorders, congenital malformations, and infant infections.[7] Questionnaires were administered at study intake, throughout pregnancy, and after delivery. Patients were grouped into 2 cohorts: an exposure cohort treated with an IBD medication (vedolizumab, ustekinumab, anti-TNF agents, thiopurines, or a combination of these agents) and a control cohort with no exposure to these medicines.

Among the 1642 patients with completed pregnancies, there were 1581 live births. Most baseline demographics were relatively similar. For example, the mean maternal age at delivery was 32.0 years in vedolizumab-treated patients, 32.8 years in ustekinumab-treated patients, and 32.5 years in the control cohort. Patients had a mean of 2.0 total pregnancies in the vedolizumab and

	No exposure (n = 430)	Anti-TNFs (n = 700)	Immunomodulators (n = 226)	Combination (n = 179)	UST (n = 43)	VDZ (n = 62)	p-value
Any pregnancy complication	86 / 401 (21.4%)	123 / 649 (19.0%)	42 / 208 (20.2%)	28 / 169 (16.6%)	10 / 39 (25.6%)	10 / 59 (16.9%)	0.663
SAB (gestation ages ≤140 days)	9 / 234 (3.8%)	18 / 438 (4.1%)	6 / 136 (4.4%)	2 / 109 (1.8%)	2 / 21 (9.5%)	1 / 30 (3.3%)	0.675
SAB (all gestation ages)	11 / 429 (2.6%)	18 / 697 (2.6%)	7 / 226 (3.1%)	2 / 178 (1.1%)	2 / 43 (4.7%)	1 / 62 (1.6%)	0.739
Preterm birth (<37 weeks)	38 / 391 (9.7%)	53 / 643 (8.2%)	25 / 204 (12.3%)	24 / 166 (14.5%)	**0 / 38 (0.0%)**	**7 / 55 (12.7%)**	0.037
Small for gestational age	16 / 383 (4.2%)	31 / 579 (5.4%)	5 / 202 (2.5%)	3 / 147 (2.0%)	1 / 14 (7.1%)	2 / 35 (5.7%)	0.356
LBW (<2500 g)	21 / 380 (5.5%)	38 / 635 (6.0%)	9 / 206 (4.4%)	8 / 159 (5.0%)	1 / 38 (2.6%)	6 / 55 (10.9%)	0.493
IUGR	11 / 429 (2.6%)	13 / 700 (1.9%)	1 / 226 (0.4%)	4 / 179 (2.2%)	0 / 43 (0.0%)	1 / 62 (1.6%)	0.455
C-section	154 / 394 (39.1%)	292 / 650 (44.9%)	93 / 208 (44.7%)	90 / 168 (53.6%)	**12 / 38 (31.6%)**	**26 / 55 (47.3%)**	0.024
NICU at birth	58 / 397 (14.6%)	107 / 651 (16.4%)	31 / 209 (14.8%)	29 / 168 (17.3%)	4 / 37 (10.8%)	8 / 55 (14.5%)	0.879
Congenital malformations	28 / 268 (10.4%)	61 / 581 (10.5%)	19 / 150 (12.7%)	18 / 153 (11.8%)	7 / 39 (17.9%)	8 / 59 (13.6%)	0.715

Table 1. Pregnancy events and infant outcomes according to inflammatory bowel disease drug exposure in the PIANO registry.
C-section, cesarean section; IUGR, intrauterine growth restriction; LBW, low birth weight; NICU, neonatal intensive care unit; SAB, spontaneous abortion; TNF, tumor necrosis factor; UST, ustekinumab; VDZ, vedolizumab. Adapted from Chugh R, et al. ACG abstract 43. *Am J Gastroenterology*. 2022;117(suppl 105).[7]

ustekinumab groups, and a ean of 2.2 pregnancies in the control group. However, the median duration of disease was significantly longer (*P*<.001) in the vedolizumab (9.6 years) and ustekinumab (13.7 years) groups than in the control cohort (7.2 years). Additionally, more patients treated with vedolizumab or ustekinumab had Crohn's disease (48% and 84%, respectively) compared with the control cohort (42%).

At the time of delivery, the median concentration of vedolizumab was 9.6 µg/mL (infants), 9.1 µg/mL (infants or cord blood), and 13 µg/mL (maternal). The median concentration of ustekinumab was 4.9 µg/mL (infants), 4.9 µg/mL (infants or cord blood), and 3.4 µg/mL (maternal).

There was no increase in adverse pregnancy outcomes between vedolizumab- or ustekinumab-treated patients and the control cohort, including preterm birth, spontaneous abortion, small for gestational age, intrauterine growth restriction, cesarean section, and placental complications (Table 1). There was also no increase in adverse outcomes among infants between vedolizumab- or ustekinumab-treated patients and the control cohort, including low birth weight, neonatal intensive care unit stay, or congenital malformations. The infection rates during the first 12 months of life were not significantly affected by IBD therapy compared with the control cohort. Placental disorders were also not significantly more common among vedolizumab- or ustekinumab-treated patients compared with the control cohort.

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Induction Combination Therapy With Guselkumab and Golimumab Followed by Guselkumab Monotherapy Maintenance: Results of the Phase 2a, Randomized, Double-Blind, Proof-of-Concept VEGA Study

Golimumab is a TNF-α antagonist that is FDA approved for the treatment of adult patients with moderately to severely active UC who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine.[1] The indication for golimumab includes the induction and maintenance of clinical response, improvement of endoscopic appearance of the mucosa during induction, induction of clinical remission, and achieving and sustaining clinical remission in induction responders. Guselkumab, an IL-23p19 subunit antagonist, is FDA approved for the treatment of plaque psoriasis and psoriatic arthritis, and is currently under investigation in IBD.[2] The phase 2a VEGA study was designed to compare combination induction therapy with guselkumab plus golimumab followed by guselkumab for maintenance treatment, or either guselkumab or golimumab alone for induction and maintenance treatment, in patients with moderately to severely active UC.[3]

A total of 214 patients with moderately to severely active UC were enrolled. All patients were naive to TNF-α, IL-12/23, and IL-23p19 antagonists and had an inadequate response or intolerance to conventional therapy (immunosuppressants and/or corticosteroids). Additionally, immunosuppressants must have been discontinued prior to randomization and corticosteroids (up to a dose of prednisone of 20 mg/day or equivalent) were permitted with mandatory tapering beginning at week 6. Patients were randomized 1:1:1 to the 3 treatment arms.

Patients treated with combination induction therapy consisting of guselkumab plus golimumab followed by guselkumab maintenance monotherapy achieved higher rates of several endpoints at week 38 compared with either guselkumab or golimumab alone. Rates of clinical remission (Figure 7) at week 12 after induction therapy (defined as a Mayo score ≤2 with no individual subscore >1) were 36.6% in the combination arm compared with 21.1% with guselkumab alone (*P*=.041 compared with the combination) and 22.2% with golimumab alone (*P*=.058 compared with the combination). By week 38, clinical remission rates were 43.7% in the combination and guselkumab

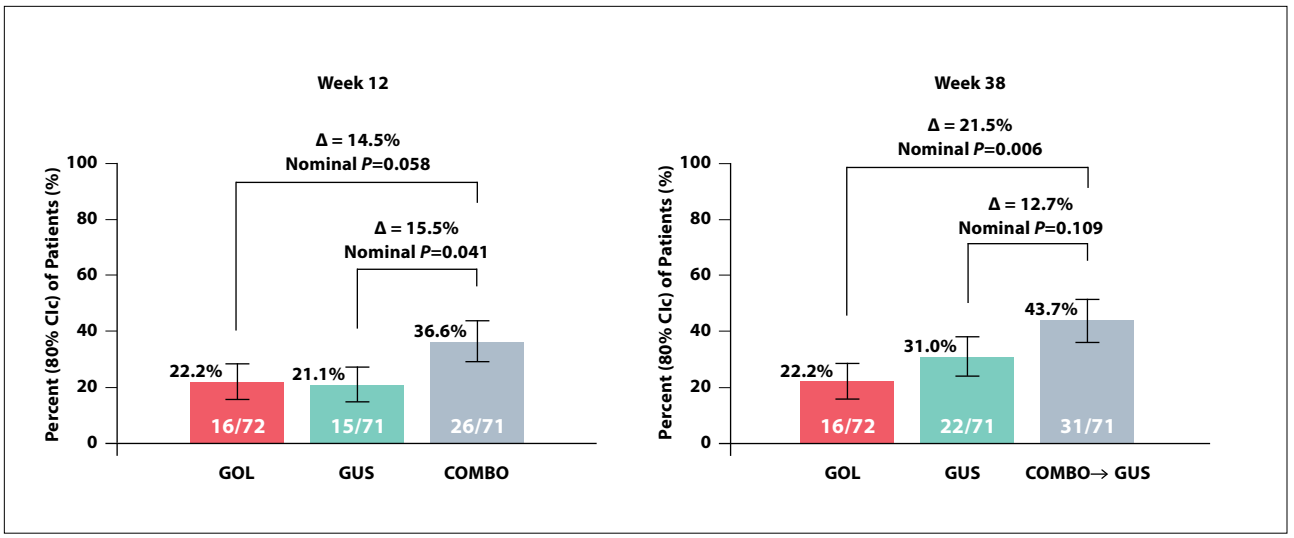

Figure 7. **Rates of clinical remission with a combination of guselkumab plus golimumab as induction therapy followed by guselkumab maintenance monotherapy, or golimumab or guselkumab alone as both induction and maintenance therapy in the VEGA study.**
COMBO, combination of golimumab plus guselkumab; GOL, golimumab; GUS, guselkumab. Adapted from Feagan BG, et al. ACG abstract 40. *Am J Gastroenterology*. 2022;117(suppl 105).[3]

maintenance arm, compared with 31.0% with guselkumab alone (*P*=.109 compared with the combination) and 22.2% with golimumab alone (*P*=.006 compared with the combination). Using the modified Mayo score (Mayo SFS of 0 or 1 and not increased from baseline, an RBS of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy), the week 38 rates of clinical remission were 47.9% with the combination compared with 31.0% with guselkumab alone (*P*=.033 compared with the combination) and 20.8% with golimumab alone (*P*<.001 compared with the combination). Symptomatic remission rates (Mayo SFS of 0 or 1 andnot increased from baseline, and an RBS of 0) at week 38 were similar across the treatment arms: 69.0% with the combination vs 69.0% with guselkumab alone and 59.7% with golimumab alone.

Endoscopic improvement was defined as an endoscopy subscore of 0 or 1 with no friability present on the endoscopy. Rates of endoscopic improvement were also higher with the combination than with the monotherapy arms. At week 12, the rates of endoscopic improvement were 49.3% in the combination arm compared with 29.6% with guselkumab alone (*P*=.016 compared with the combination) and 25.0% with golimumab alone (*P*=.003 compared with the combination). These rates at week 38 were 49.3%, 32.4% (*P*=.033), and 22.2% (*P*<.001), respectively. Endoscopic normalization was defined as an endoscopy score of 0, and at week 12 the rates were 18.3% with the combination vs 8.5% with guselkumab alone (*P*=.084 compared with the combination) and 9.7% with golimumab alone (*P*=.140 compared with the combination). These rates at week 38 were 25.4%, 15.5% (*P*=.134), and 6.9% (*P*=.002), respectively.

Similar improvements were observed for patients who achieved a composite endpoint of endoscopic improvement and histologic remission (absence of neutrophils from the mucosa [both lamina propria and epithelium], no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system) and endoscopic improvement.

Adverse event rates were comparable among the treatment groups, although more patients in the combination arm (9.9%) compared with either the guselkumab (1.4%) or the golimumab (5.6%) monotherapy arms discontinued treatment owing to an adverse event. The rates of infection were 31.0%, 23.9%, and 31.9% in the combination, guselkumab-alone, and golimumab-alone arms, respectively. Two patients in each arm (2.8% of each arm) experienced a serious infection.

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The Effect of Guselkumab Induction Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: QUASAR Phase 2b Induction Results at Week 12 by Prior Inadequate Response or Intolerance to Advanced Therapy

The IL-23p19 subunit antagonist guselkumab was evaluated in QUASAR Induction Study 1, a phase 2b study of guselkumab as induction therapy in patients with moderately to severely active UC who had an inadequate response or intolerance to either conventional therapy (thiopurines or corticosteroids) or advanced therapy (TNF-α antagonists, vedolizumab, or tofacitinib). Efficacy results compared with placebo at week 12 by prior inadequate response or intolerance to advanced therapy were reported.

The primary analysis set comprised 313 patients with moderately to severely active UC, defined as a modified Mayo score of 5 to 9 (inclusive) with a Mayo RBS of at least 1 and a Mayo endoscopy subscore of at least 2 (based on central review) at baseline. Conventional immunosuppressants and corticosteroids up to 20 mg/day of prednisone (or equivalent) were permitted. Patients were randomized 1:1:1 to treatment with guselkumab 400 mg, guselkumab 200 mg, or placebo; all doses were administered at weeks 0, 4, and 8. Randomization was stratified by a history of inadequate response or intolerance to advanced therapy, region, and concomitant use of corticosteroids at baseline.

Among the 313 patients, 47.3% had a history of inadequate response or intolerance to advanced therapy. Overall, patients with no such history showed a shorter mean duration of UC (9.08 years vs 6.17 years), a lower median C-reactive protein concentration (4.0 mg/L vs 5.1 mg/L), a slightly lower incidence of extensive UC (46.7% vs 51.4%), and a lower incidence of extraintestinal manifestations (12.1% vs 20.3%) than patients with a history of inadequate response or intolerance to advanced therapy.

Treatment with guselkumab resulted in greater improvements across key clinical and endoscopic or histologic outcome measures at week 12 compared with placebo in both patients with or without a history of inadequate response or intolerance to advanced therapy (Figure 8). The efficacy of both doses of guselkumab was also demonstrated to be comparable in patients regardless of a history of inadequate response or intolerance to advanced therapy.

Clinical response was defined as a decrease from induction baseline in the modified Mayo score by at least 30% and at least 2 points, with either a 1-point or greater decrease from baseline in the RBS or an RBS of 0 or 1. The rates of clinical response in patients with a history of an inadequate

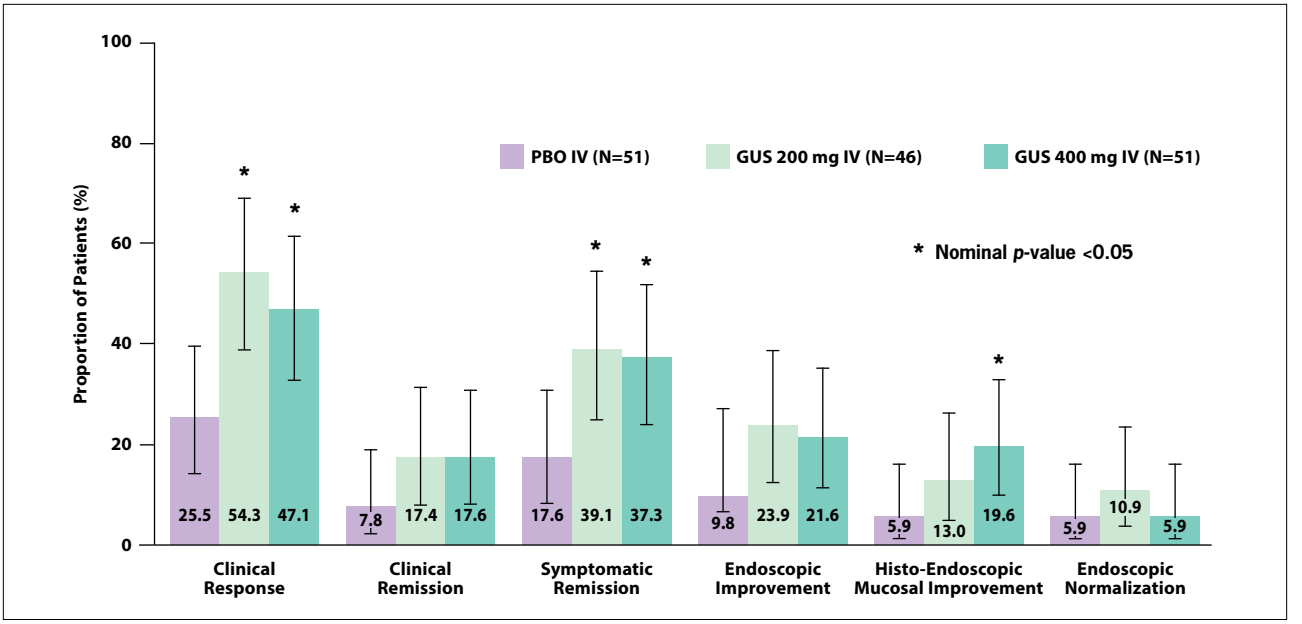

Figure 8. Key week 12 endpoints with guselkumab in the QUASAR study in patients with a history of inadequate response or intolerance to advanced therapy. Includes patients with modified Mayo score of 5-9 at induction baseline. *Nominal *P*<.05. **Nominal *P*<.001. GUS, guselkumab; IV, intravenous; PBO, placebo. Adapted from Rubin DT, et al. ACG abstract 41. *Am J Gastroenterology*. 2022;117(suppl 105).

response or intolerance to advanced therapy were 47.1% and 54.3% with guselkumab 400 mg and guselkumab 200 mg, respectively, compared with 25.5% with placebo. In patients without this history, the rates of clinical response were higher (73.2% and 67.3% with guselkumab 400 mg and guselkumab 200 mg, respectively, compared with 29.6% with placebo).

Clinical remission was defined by a SFS of 0 or 1 that has not increased from baseline, an RBS of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy. The rates of clinical remission in patients with a history of an inadequate response or intolerance to advanced therapy were 17.6% and 17.4% with guselkumab 400 mg and guselkumab 200 mg, respectively, compared with 7.8% with placebo. In patients without this history, the rates of clinical response were higher (32.1% and 32.7% with guselkumab 400 mg and guselkumab 200 mg, respectively, compared with 11.1% with placebo).

Similar trends were observed across several other endpoints, including rates of symptomatic remission, endoscopic improvement, endoscopic normalization, and a composite of histo-endoscopic mucosal improvement (Figure 8).

Reference

Rubin DT, Allegretti JR, Sands BE, et al. The effect of guselkumab induction therapy in patients with moderately to severely active ulcerative colitis: QUASAR phase 2b induction results at week 12 by prior inadequate response or intolerance to advanced therapy [ACG abstract 41]. *Am J Gastroenterology*. 2022;117(suppl 105).

Highlights in Ulcerative Colitis From the ACG Annual Scientific Meeting: Commentary

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The American College of Gastroenterology (ACG) 2022 Annual Scientific Meeting and Postgraduate Course took place in Charlotte, North Carolina in October of this year. We were glad to be back in a hybrid mix of in-person and virtual presentations. Many of these presentations provided impactful analyses of agents used in the treatment of UC.

Ozanimod is a first in class therapy available for moderate to severe UC in the United States. It is a therapy that targets the S1P receptors and is a new mechanism of action for gastroenterologists to understand.[1] By modulating the S1P receptors in lymphocytes, it prevents them from being able to follow chemokine gradients to sites of inflammation or infection. As a result, activated lymphocytes are essentially sequestered within lymph nodes and never make their way to the area of disease. This mechanism is a different type of cellular trafficking inhibition, compared to the anti-integrin therapies vedolizumab and natalizumab. Because ozanimod results in activated lymphocytes remaining in lymph nodes, there is a reduction in circulating lymphocytes that is an expected change that occurs with this therapy. However, this effect has not been associated with an increased risk of infections.

There have been a number of ongoing analyses and studies related to the use of ozanimod in moderately to severely active UC, and at ACG this year, there were some important updates that are helpful for us. The first one, presented by Dr. Bruce Sands and colleagues, focused on patients in the pivotal phase 3 True North trial of ozanimod.[2] This had a standard study design for UC, in which patients who responded to the induction phase of this study were randomized to placebo or drug in a maintenance phase. The study specifically looked at the duration of response to therapy after the treatment was withdrawn in the maintenance phase in those patients who responded to induction and then were randomized to placebo.

This is of interest to us for a number of reasons. First is to understand if ozanimod is better than placebo during maintenance, which is a standard part of managing IBD. But the second reason this is of interest is to understand whether induction carries over into maintenance phase when off therapy. It remains of great interest how we might change maintenance management in different ways, and this study provides additional insights for us. Finally, this analysis provides information to us about the benefit of restarting therapy after a treatment interruption.

Patients who were randomized to placebo had a statistically significant separation from those who were randomized to continue drug in maintenance after about 8 weeks, meaning they relapsed and had a loss of their response. It is of interest to note that

at the end of one year, the patients who had been randomized to placebo and were continuing in the study remained in response at a rate of 62.6%, and those who continued the drug in maintenance phase remained in response at a rate of 86.1%.

This analysis demonstrates the benefit of staying on drug in maintenance, and shows that some patients do have stable control after successful induction with this drug. Knowing which patients these are remains a subject of more research. It is also important to note that there were no new safety signals in the maintenance phase of this study. Placebo patients did show a higher rate of disease-related adverse events (relapse).

There were a few posters related to ozanimod that were of interest as well. Ozanimod can be positioned anywhere in the treatment algorithm for UC, including after 5-ASA or a first course of steroids as well as later in the treatment algorithm after the use of advanced therapies like immunomodulators or biological therapies. An analysis of patients who were receiving 5-ASA and who were immunomodulator and biologic naïve showed that regardless of the use of steroids, there was clear efficacy with ozanimod over placebo[3]. This is of interest because it would suggest that even when patients appear to need steroids, this drug can be used, and ultimately can be a steroid-sparing option. It also demonstrates that steroids can be avoided in many patients. I think we often jump to steroids quickly because we want to provide patients with an option while they are waiting for other therapies to get started, or steroids are used with the hope to go back to 5-ASA therapy. The truth is that by the time a patient with UC has moderate to severe disease and needs steroids, their disease is severe enough that we really should adopt the early use of a steroid-sparing therapy. These data can help to further distinguish ozanimod from the JAK inhibitors, which require failure of anti-TNF agents as a prerequisite.

Another post hoc analysis presented at ACG specifically evaluated ozanimod's efficacy and safety in patients 60 years of age or older.[4] Dr. Nabeel Khan and colleagues analyzed the older population of patients who received ozanimod in the True North study, and they found that not only was the therapy effective but that it was as safe as in patients who were younger than 60. There has been concern that as patients age they may be at higher risk for infectious complications, and this has been shown with anti-TNF therapies.[5] However, with the different mechanism of action attributed to ozanimod, it is reassuring to show that it was both effective and safe in patients from that older population.

An additional poster presented at ACG was related to the safety of ozanimod and combined patients who had received the therapy in the True North in UC as well as in the phase 3 trials of multiple sclerosis where the drug has had regulatory approval for a longer period of time.[6] This particular analysis looked at the liver enzyme elevation that occurs with this therapy, which is a well described effect of the therapy, and noted that approximately 25% of the patients with UC and as high as 42% of the patients with multiple sclerosis had mild elevation of their liver enzymes, with fewer patients having a 2- to 3-fold elevation of liver enzymes. It is well described to see this effect of the drug, but it is not thought to be a treatment-limiting adverse event, and quite interestingly these changes resolve with ongoing use of therapy. There has been no development of liver failure or drug-induced liver injury, and it is thought that this effect just reflects the induction of metabolism in the liver of this therapy.

Combining the two disease states enabled us to evaluate the safety in a large group of patients and to better understand the enzyme elevations for clinicians to know how to manage them. The current recommendation is to monitor patients' liver enzymes with this agent, and clinicians who prescribe this therapy should be aware of this as an expected change which is not associated with any long-term injury in the majority of patients and is otherwise something to monitor and to expect resolution.

Upadacitinib is an oral small molecule that was the first selective JAK1 inhibitor approved for use in moderate to severe UC. It is distinguished from the pan JAK inhibitor tofacitinib, which has been available for some time. There were two oral presentations related to upadacitinib presented at ACG.

The first one was presented by Dr. Brian Feagan and colleagues, and

ABSTRACT SUMMARY Hepatic Safety of Ozanimod in UC and Relapsing Multiple Sclerosis Phase 3 Trials

An analysis of the hepatic safety of ozanimod 0.92 mg across phase 3 trials in patients with either UC or multiple sclerosis was reported. This analysis found that elevations of AST, ALT, and bilirubin were transient and were usually asymptomatic. Additionally, liver enzyme elevations typically resolved without study drug discontinuation. The incidences of hepatic treatment-emergent adverse events were similar between treatment groups, and resulting treatment discontinuations were low. No serious hepatic events were reported, and no Hy's law cases or severe drug-induced liver injury were reported.

Reference

Rubin DT, Caldera F, Cohen J, et al. Hepatic safety of ozanimod in ulcerative colitis and relapsing multiple sclerosis phase 3 trials [ACG abstract B0368]. *Am J Gastroenterology*. 2022;117(suppl 105).

compared the different maintenance doses of upadacitinib in patients with moderate to severe UC after responding to the therapy as induction.[7]

In the pivotal trials for upadacitinib that led to its regulatory approval, there were two induction studies that demonstrated substantial benefit over placebo at a dose of 45 mg daily for eight weeks, and the maintenance study from one of these induction trials randomized patients to placebo or 15 mg or 30 mg daily of upadacitinib. The presentation at ACG specifically compared the 30 mg with the 15 mg dosing in maintenance, and demonstrated that both were substantially better than placebo at maintaining remission in these patients with moderate to severe UC. By chance, patients randomized to 30 mg daily tended to be less sick than those who had been randomized to 15 mg daily, and there was a longer sustained remission with 30 mg compared to 15 mg. Theupadacitinib prescribing information allows the use of 30 mg during the maintenance phase for patients who have refractory disease; because patients receive this therapy only after exposure to anti-TNF therapy, they are by definition, refractory. Therefore, it is important to remember that the higher dose in maintenance can and should be used on-label, and in our experience is used in the majority of patients after they have already been on one advanced therapy prior to getting to this drug. The additional evidence that it provides sustained remission and may have a more durable effect than the 15 mgdose is important to keep in mind as well. Prior published analyses demonstrated that patients in whom anti-TNF therapy fails prior to receiving upadacitinib as maintenance do better with the 30 mg dose.[8] These additional data presented at ACG demonstrate that sustained maintenance is achievable with this therapy and also that the 30 mg dose should be the preferred dose in many of our patients.

The other oral presentation related to upadacitinib at ACG was presented by Dr. Ed Loftus on behalf of his co-investigators and assessed the efficacy and safety of upadacitinib in patients who had a longer 16-week induction treatment.[9] Upadacitinib is approved for induction of moderate to severe UC for up to eight weeks, but in the clinical trials, patients who did not have a significant response by the end of eight weeks could receive an additional eight weeks of this dose. In fact, 58% of patients who did not respond during the initial eight weeks but who received the 16 weeks of therapy were captured and then were eligible in the maintenance phase, suggesting that there is a substantial number of people who might respond to this therapy in what is known as a delayed response to treatment.

The results of the study show that patients who achieve this response after 16 weeks have similar successful maintenance with the 30 mg dose of upadacitinib as those who achieved response as early as eight weeks in induction, and also demonstrated superiority of the 30 mg dose in maintenance phase compared with the 15 mg dose. Patients who have a delayed response to upadacitinib as well as those who have refractory disease or who have not responded to multiple other advanced therapies do better with the 30 mg dose in maintenance, and these results demonstrate that as well. The findings in this study are similar to reports with other therapies demonstrating that even if it takes longer for patients to respond or to achieve remission with a therapy, once they do, they have similar longer-term results as those who responded quickly. The important clinical message is to not give up too early, but certainly we should remember that patients should not be getting worse while they are on a new therapy waiting for this response.

Dr. Rahul Dalal and colleagues presented their analysis from the Massachusetts General Brigham Medical System of patients with UC who were not responding to anti-TNF therapy and who received ether ustekinumab or tofacitinib.[10] This study is of interest given our evolving understanding of how we might sequence therapies and what we can do to achieve better results. Tofacitinib is available after exposure to anti-TNF therapy, and ustekinumab is available either before or after anti-TNF therapy.

The interesting finding was that both therapies were effective and neither therapy seemed to have a greater likelihood of patients responding. It suggests that the treatment choice for a patient with moderate to severe UC who is not responding to anti-TNF therapy should perhaps be determined by other factors. For example, one consideration is our evolving understanding that IL-23 inhibitors may be preferable in patients with concomitant skin inflammation (e.g., eczema or psoriasis) while tofacitinib may be a preferable strategy in patients who have low albumin and demonstrate leaky bowels with loss of protein that might make monoclonal antibody therapies more challenging to use.

Guselkumab is a second generation monoclonal antibody targeting the p19 subunit of IL-23 for inhibition. It's distinguished from ustekinumab, which is a monoclonal antibody directed against the p40 subunit and therefore affects IL-12 and IL-23. I had the opportunity to present a post hoc analysis of the phase 2B study of guselkumab in patients with moderate to severe UC, specifically exploring the efficacy of this therapy in patients who had inadequate response or intolerance to advanced therapies.[11] We specifically looked at the 12-week induction results of guselkumab 400 mg or 200 mg administered intravenously at 0, 4, and 8 weeks compared with placebo. A subset analysis was conducted of patients based on prior exposure to other advanced therapies. This analysis demonstrated that even in difficult-to-treat patients, guselkumab was superior to placebo across most of the primary and secondary endpoints. Interestingly, the higher 400 mg dose of guselkumab was more successful at achieving the novel endpoint of histo-endoscopic mucosal improvement than the 200 mg dose. This supports

the idea that this therapy can be used after failure of advanced therapies in UC. The takeaway message continues to be that we should use effective therapies as early as we can in our patients and not wait for patients to be intolerant or failing multiple other therapies before we consider a novel mechanism or a new treatment.

Dr. Brian Feagan presented on behalf of his colleagues the 38-week follow-up of a novel combination therapy study of guselkumab and golimumab followed by guselkumab in maintenance phase.[12] This phase 2a randomized double-blind study is of great interest since we are actively exploring novel combinations of treatments to break the therapeutic ceiling in IBD. Previously presented were the successful induction results of this combination therapy study supporting that at week 12 the combination of the two drugs was superior to either drug alone with a clinical remission rate of 36.6%. Presented at ACG was the week 8 follow-up, which showed that the patients who received the combination for induction and then guselkumab in maintenance had statistically superior clinical remission rates over golimumab alone and numerically better but not statistically better remission rates compared with guselkumab alone.

Also of interest was that the combination approach followed by guselkumab achieved more histologic remission and endoscopic improvement than golimumab or guselkumab alone. The conclusion from this study demonstrates the proof of principle of this combination approach, and what I appreciate about this is the recognition that we need a more intensive therapy in induction phase with the idea of using a less systemically active and arguably safer and more convenient option in maintenance. This obviously deserves further exploration as we look for novel ways to provide better results for our patients.

The PIANO registry (Pregnancy Inflammatory bowel disease And Neonatal Outcomes) has provided invaluable information about the safety of our treatments in pregnant women with IBD, and we have learned that for the most part our therapies have been well tolerated and very safe. Dr. Rishika Chugh and colleagues presented from the well described PIANO registry of patients with IBD.[13] The analysis specifically looked at patients exposed to ustekinumab or vedolizumab, comparing them to those without that exposure. This analysis demonstrated that there was no increase in preterm birth, spontaneous abortions, small for gestational age, intrauterine growth restriction, cesarean section, or placental complications in the patients exposed to these two medications. There was also no increase in the number of neonatal ICU stays or congenital malformations, and importantly no increase in infections at one year. Both of these therapies are safe and should be continued through pregnancy, and women who are receiving these therapies should be reminded that controlling their IBD is the most important way to guarantee a successful pregnancy and pregnancy outcome.

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