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A SPECIAL MEETING REVIEW EDITION

Highlights in Ulcerative Colitis From the 18th Congress of ECCO

A Review of Selected Presentations From the ECCO Meeting

• March 1-4, 2023 • Copenhagen, Denmark

Special Reporting on:

- Analyses From the Phase 3 True North Study of Ozanimod in UC Patients
- Ozanimod in UC Patients
- Single-Cell RNAseq Temporal Analysis of Ulcerative Colitis Patients Undergoing Tofacitinib Treatment Reveals a Shift in Myeloid Cells Towards Pro-Inflammatory Phenotypes in Refractory Patients
- Efficacy of Etrasimod on Symptomatic Relief in Patients With Ulcerative Colitis: An Analysis of the Phase 3 ELEVATE UC 52 and ELEVATE UC 12 Trials
- Efficacy of Ustekinumab for Ulcerative Colitis Through 4 Years: Final Clinical and Endoscopy Outcomes From the UNIFI Long-Term Extension
- The Effects of Upadacitinib on UC Symptom Resolution and Fatigue Normalization in Patients With Moderately to Severely Acute Ulcerative Colitis: Phase 3 U-ACHIEVE and U-ACCOMPLISH Results
- Efficacy and Safety Outcomes Up to ~4 Years of Treatment With Filgotinib 200 mg Among Patients With Ulcerative Colitis: Results From the SELECTIONLTE Study
- Mirikizumab in Moderately to Severely Active Colitis

PLUS Meeting Abstract Summaries

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Analyses From the Phase 3 True North Study of Ozanimod in UC Patients

Ozanimod is a selective sphingosine-1-phosphate (S1P) receptor modulator that is approved for the treatment of adult patients with moderately to severely active ulcerative colitis (UC), according to results from the pivotal True North trial.[1,2] This multicenter, double-blind, phase 3 trial evaluated ozanimod 0.92 mg daily vs placebo as induction and maintenance therapy in patients with moderately to severely active UC.[3] The maintenance portion of the trial enrolled only patients who demonstrated a response during induction. The proportion of patients who achieved clinical remission was significantly greater with ozanimod vs placebo, both during the 10-week induction period (18.4% vs 6.0%; *P*<.001) and the 42-week maintenance period (37.0% vs 18.5%; *P*<.001). The proportion of patients who demonstrated a clinical response was also significantly greater with ozanimod vs placebo, both during the induction period (47.8% vs 25.9%; *P*<.001) and the maintenance period (60.0% vs 41.0%; *P*<.001).

An interim analysis of the True North open-label extension (OLE) study included 823 patients from the True North study.[4] Patients had a mean age of 41.7 years. Forty-one percent of patients were female, 35% had received prior therapy with a tumor necrosis factor (TNF) inhibitor, and 62% had left-sided UC. The patients represented 2219 patient-years of drug exposure. Treatment-emergent adverse events (AEs) were reported in 81.7% of patients, serious treatment-emergent AEs in 18.1%, and treatment-emergent AEs leading to discontinuation in 6.7%, with exposure-adjusted incident rate per 100 patient-years (EAIR100) values of 87.6, 7.4, and 2.5, respectively (Table 1). The most frequent treatment-emergent AEs were lymphopenia (15.6%), anemia (10.4%), and nasopharyngitis (10.3%), with EAIR100 values of 6.4, 4.2, and 4.1, respectively. Bradycardia occurred in 3 patients (0.4%; EAIR100, 0.1) and macular edema in 2 patients (0.2%; EAIR100, 0.1). Two deaths occurred, both of which were considered unrelated to study treatment. Ozanimod showed no evidence of increasing the risk of ischemic heart disease or thromboembolic events.

Table 1. The Most Frequent TEAEs for All Patients Who Entered the OLE From TN

Adverse event	All TN patients enrolled in the OLE (n=823) n (%)
TEAEs	672 (81.7)
Serious TEAEs	149 (18.1)
TEAEs leading to treatment discontinuation	55 (6.7)
Most frequent TEAEs (occurring in ≥25% of patients)	
Lymphopenia	128 (15.6)
Anemia	86 (10.4)
Nasopharyngitis	85 (10.3)
Lymphocyte count decreased	84 (10.2)
Alanine aminotransferase increased	74 (9.0)
Arthralgia	74 (9.0)
COVID-19	66 (8.0)
Headache	63 (7.7)
Upper respiratory tract infection	56 (6.8)
Gamma-glutamyl transferase increased	54 (6.6)
Hypertension	49 (6.0)
UC exacerbation	44 (5.3)
Cough	42 (5.1)

OLE, open-label extension; TEAEs, treatment-emergent adverse events; TN, True North; UC, ulcerative colitis. Adapted from Panaccione R, et al. Abstract P405. Presented at: 18th Congress of European Crohn's and Colitis Organization (ECCO); March 1-4, 2023; Copenhagen, Denmark.[4]

A second analysis examined the duration of response in patients from the True North study.[5] In the maintenance phase of True North, 230 patients continued with ozanimod therapy (82 with a clinical remission and 148 with a clinical response) and 227 patients were randomized to placebo (79 with a clinical remission and 148 with a clinical response). The subset of patients who were in clinical response without remission at week 10 were more likely to have severe disease and prior use of immunosuppressive medication than patients who had achieved a clinical remission. The time to disease relapse was significantly prolonged among patients who were randomized to maintenance therapy with ozanimod vs placebo (*P*<.0001). The difference between the 2 treatment arms became apparent as early as 8 weeks into the maintenance period. At week 42, Kaplan-Meier estimates of the proportion of patients who were relapse-free were 86.1% for patients who continued with ozanimod vs 62.6% with placebo.

A post hoc analysis investigated efficacy outcomes in 185 patients from the True North trial who had prior

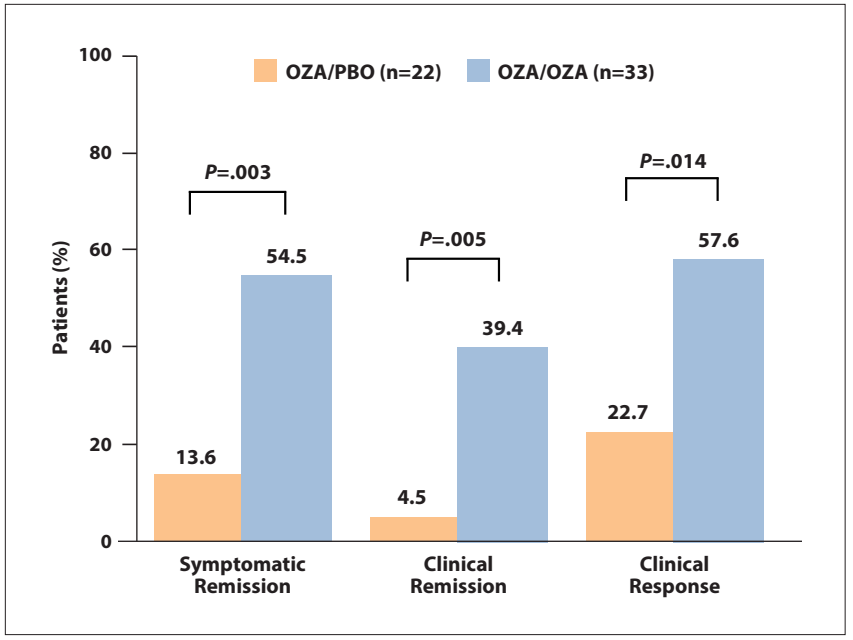

Figure 1. Remission and response outcomes of ozanimod vs placebo in vedolizumab-exposed patients with moderate to severe ulcerative colitis at week 52. OZA, ozanimod; PBO, placebo. Adapted from Sands BE, et al. Abstract P376. Presented at: 18th Congress of European Crohn's and Colitis Organistion (ECCO); March 1-4, 2023; Copenhagen, Denmark.[6]

exposure to vedolizumab.[6] This subset of patients included 35 patients randomized to placebo, 63 randomized to ozanimod, and 87 treated with open-label ozanimod. The subset of patients with prior vedolizumab exposure included 52% with extensive disease, 78% with a Mayo endoscopic score of 3, 85% with prior exposure to a TNF inhibitor, and 61% who were using corticosteroid therapy at baseline. Ozanimod therapy was superior to placebo at week 10 and week 52 according to all metrics evaluated, including symptomatic remission, clinical remission, clinical response, endoscopic improvement, and mucosal healing (Figure 1). Although the differences in outcome generally did not reach significance by week 10, the majority of outcomes were superior with ozanimod compared with placebo by week 52, including symptomatic remission (*P*=.003), clinical remission (*P*=.005), and endoscopic improvement (*P*=.017).

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Ozanimod in UC Patients

In the phase 3 True North trial, patients who completed 52 weeks of the study were eligible for entry into the OLE study, which assessed the long-term safety and efficacy of ozanimod.[1] An interim analysis of the True North trial investigated the symptomatic outcomes in patients who received approximately 3 years of continuous therapy with ozanimod.[2] The analysis included 131 patients who achieved a clinical response after 52 weeks of continuous ozanimod therapy during the True North study and subsequently entered the True North OLE study. At the time of data cutoff, 87% of patients had completed OLE week 46 and thus had received 98 weeks of continuous ozanimod therapy. Seventy-two percent of patients had completed OLE week 94, with 146 weeks of continuous ozanimod therapy. Patients had a mean age of 44 years and 48% of patients were male. Sixty-eight percent of patients had left-sided UC, 32% had received prior therapy with a TNF inhibitor, and 24% were using corticosteroids at baseline. According to observed cases, rates of symptomatic clinical response were maintained from week 5 (100%) through OLE week 94 (95.6%). Rates of clinical remission were also maintained from week 5 (84.4%) through OLE week 94 (84.4%). These same outcomes decreased slightly over time according to nonresponder imputation analysis. Reductions in rectal bleeding score and stool frequency score were maintained throughout the OLE study.

A separate study evaluated endoscopic improvement, histologic remission, and mucosal healing in the same cohort of 131 patients from the True North OLE study.[3] Among the 131 patients with a clinical response at OLE study entry, rates of endoscopic improvement were 77.9% and 73.3%, rates of histologic remission were 72.3% and 67.3%, and rates of mucosal healing were 60.2% and 56.3%, respectively, at week 46 and week 94 of the OLE study (Figure 2). The mean Mayo endoscopic score among these patients was 1.0 at the start of the OLE study and was maintained at week 46, with a mean score of 0.9, and

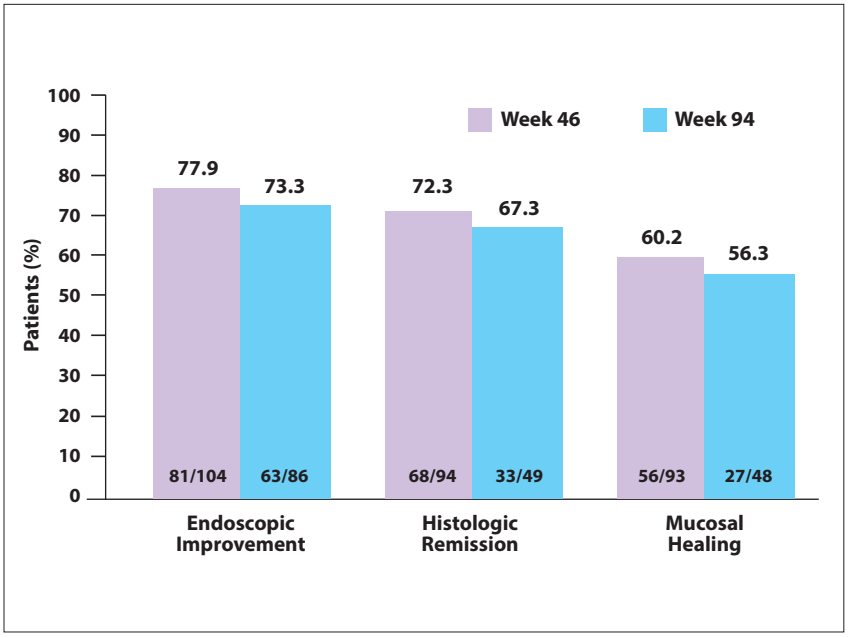

Figure 2. The efficacy of ozanimod at weeks 46 and 94 in patients with ulcerative colitis at week 52 and open-label extension entry. Adapted from Panaccione R, et al. Abstract P464. Presented at: 18th Congress of European Crohn's and Colitis Organisation (ECCO); March 1-4, 2023; Copenhagen, Denmark.[3]

at week 94, with a mean score of 1.0. The results of both studies of the True North OLE population show that continuous, long-term use of ozanimod may be associated with sustained efficacy outcomes in patients with UC.

A prospective observational cohort study at a single center evaluated the real-world safety and efficacy of ozanimod in 45 consecutive patients with moderately to severely active UC who initiated ozanimod therapy.[4] Patients had a mean age of 40.6 years and 58% of patients were male. The mean disease duration was 9.6 ± 9.2 years. At week 10, in 41 evaluable patients, 18 patients (44%) had achieved a clinical response, 24 (59%) had achieved clinical remission, and 22 (54%) had achieved a corticosteroid-free response. At week 52, among 30 evaluable patients, 5 patients (17%) demonstrated a clinical response, 5 (17%) were in clinical remission, and 4 (13%) achieved a corticosteroid-free response. Similar response rates were observed among patients who had or had not received prior advanced therapy. Two AEs led to discontinuation of treatment, including 1 case of fatigue and 1 case of hypertensive crisis in a patient with a prior diagnosis of hypertension.

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Single-Cell RNAseq Temporal Analysis of Ulcerative Colitis Patients Undergoing Tofacitinib Treatment Reveals a Shift in Myeloid Cells Towards Pro-Inflammatory Phenotypes in Refractory Patients

The introduction of targeted therapies has revolutionized the treatment of inflammatory bowel disease (IBD).[1] However, even with modern therapies, some patients fail to respond and others lose their response. AEs must also be taken into consideration. Tofacitinib is an inhibitor of the Janus kinase (JAK) family of proteins, which includes JAK1, JAK2, JAK3, and tyrosine kinase 2. Tofacitinib primarily exerts its inhibitory effects on JAK1 and JAK3.[2,3] The drug is approved for the treatment of adult patients with moderately to severely active UC who are intolerant to or failed to respond to a TNF inhibitor. Prior efforts to understand the mechanisms leading to resistance to tofacitinib in patients with UC have focused on bulk biopsy transcription analysis.

A prospective study evaluated resistance to tofacitinib in patients with UC by using single-cell RNA sequencing analysis of intestinal cells.[4] Biopsies were taken from the colon of patients with moderately to severely active UC, before and at weeks 8, 16, 24, and 48 after initiation of treatment with tofacitinib. Patients were treated with tofacitinib 10 mg twice daily for 8 weeks, followed by tofacitinib 5 mg or 10 mg twice daily thereafter. Patients who experienced a decrease of at least 1 point from baseline in the endoscopic Mayo score were classified as responders (Figure 3).[5,6] Among 31 enrolled patients, 13 demonstrated a

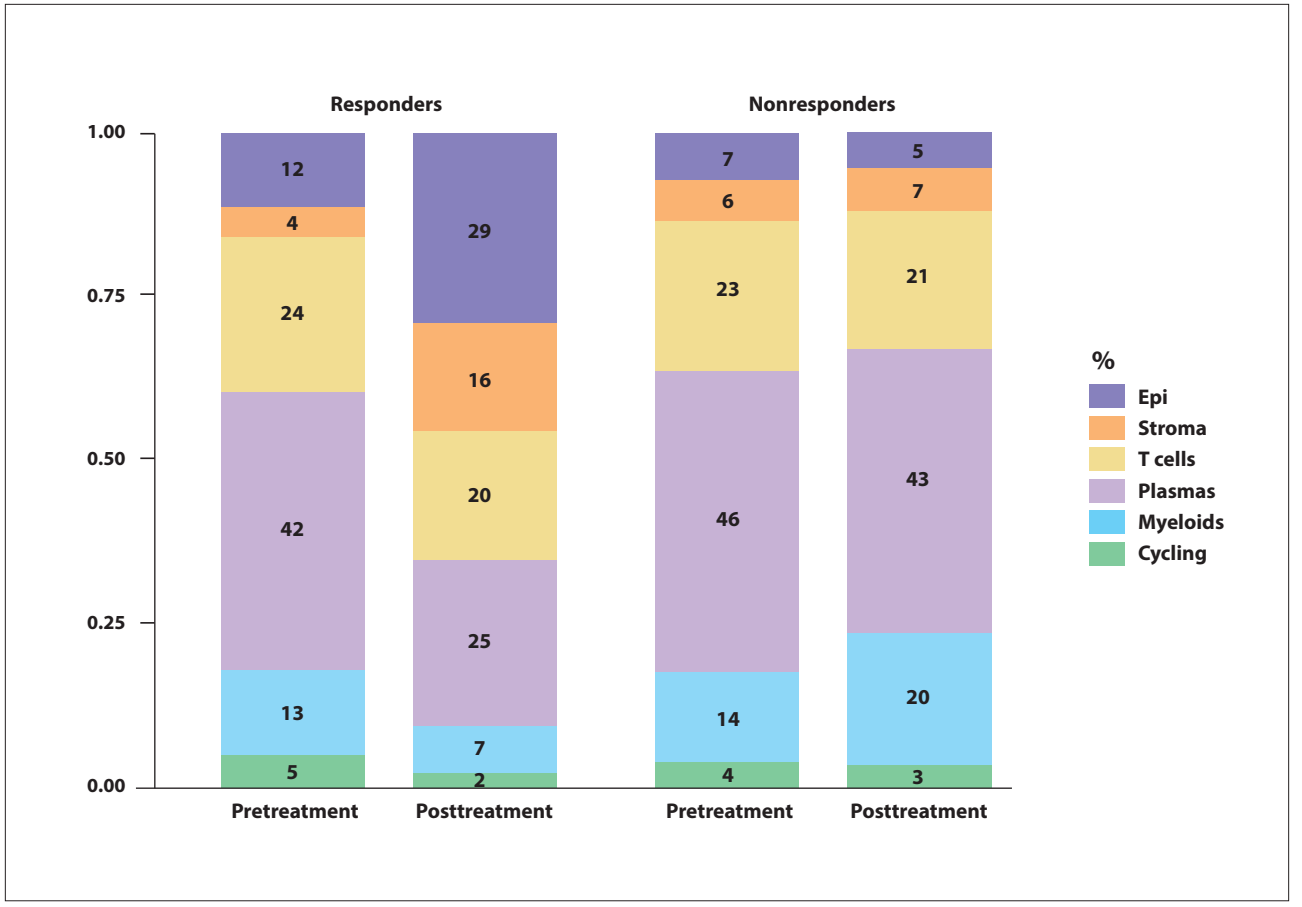

Figure 3. The cell type abundance for responder and nonresponder patients with ulcerative colitis at pretreatment and posttreatment time points. Epi, epithelium. Adapted from Melon E, et al. Abstract DOP05. Presented at: 18th Congress of European Crohn's and Colitis Organisation (ECCO); March 1-4, 2023; Copenhagen, Denmark.[4]

response to tofacitinib.

A single-cell RNA sequencing data set was generated from nearly 70,000 cells from the intestinal biopsies. According to differential expression, cells were classified into the 6 main subsets found in the colonic mucosa: plasma and B cells, T cells, stroma, cycling cells, myeloid cells, and epithelium. Patients with a response to tofacitinib showed partial recovery of the epithelium and the stroma compartment, as well as a decrease in the plasma and B cells, myeloid cells, and cycling cells. Proportions of T cells did not change. In contrast, patients who did not respond to tofacitinib showed an increase in the number of myeloid cells, including neutrophils, M1 inflammatory macrophages, and inflammatory monocytes. After treatment, M2 macrophages from patients with a response showed a gene expression profile consistent with a more tolerogenic and less inflammatory profile. In contrast, patients who did not respond to tofacitinib expressed genes that are consistent with activation of inflammatory pathways, as demonstrated by the increased expression of *MMP9*, *CLEC5A*, *INHBA*, *SPP1*, *MMP12*, *PLAUR*, and *IDO1*. The results suggest that failure to respond to tofacitinib is actively mediated by an increase in inflammatory gene activity and point to specific targeting of the inflammatory myeloid cells for future drug development.

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Efficacy of Etrasimod on Symptomatic Relief in Patients With Ulcerative Colitis: An Analysis of the Phase 3 ELEVATE UC 52 and ELEVATE UC 12 Trials

Etrasimod is a S1P receptor modulator selective for the S1P1, S1P4, and S1P5 modulators.[1] The safety and efficacy of the investigational drug were demonstrated in the double-blind, phase 3 ELEVATE UC 52 and ELEVATE UC 12 trials in patients with moderately to severely active UC.[2] In ELEVATE UC 52, 433 patients received etrasimod 2 mg or placebo for 12 weeks of induction followed by 40 weeks of maintenance therapy. In ELEVATE UC 12, 354 patients received etrasimod 2 mg or placebo for 12 weeks. A benefit with etrasimod vs placebo was observed as early as week 2. The trials demonstrated a significant improvement in the rate of complete remission after 12 or 52 weeks of treatment with etrasimod vs placebo (P<.05).

A post hoc analysis of the ELEVATE UC 52 and ELEVATE UC 12 trials investigated symptom relief as measured by stool frequency and rectal bleeding.[3] In the combined population from the ELEVATE trials, more than one-third of patients (approximately 37%) had been exposed to a biologic or JAK inhibitor. Subgroup analysis suggested that patients without prior exposure to a biologic therapy or a JAK inhibitor experienced a greater rate of symptomatic response than patients with prior exposure to those agents. In the ELEVATE UC 52 trial, among patients who were biologic and JAK-inhibitor naive, the rate of symptomatic remission was significantly improved with etrasimod vs placebo, both at week 12 (Δ29.6%; P<.001) and at week 52 (Δ30.1%; P<.001; Figure 4). In contrast, the difference elicited with etrasimod therapy was not significant among patients with prior exposure to a biologic therapy or JAK inhibitor at week 12 (Δ10.2%; P=.181) or at week 52 (Δ8.7%; P=.238). Among patients with prior exposure to 1 biologic agent

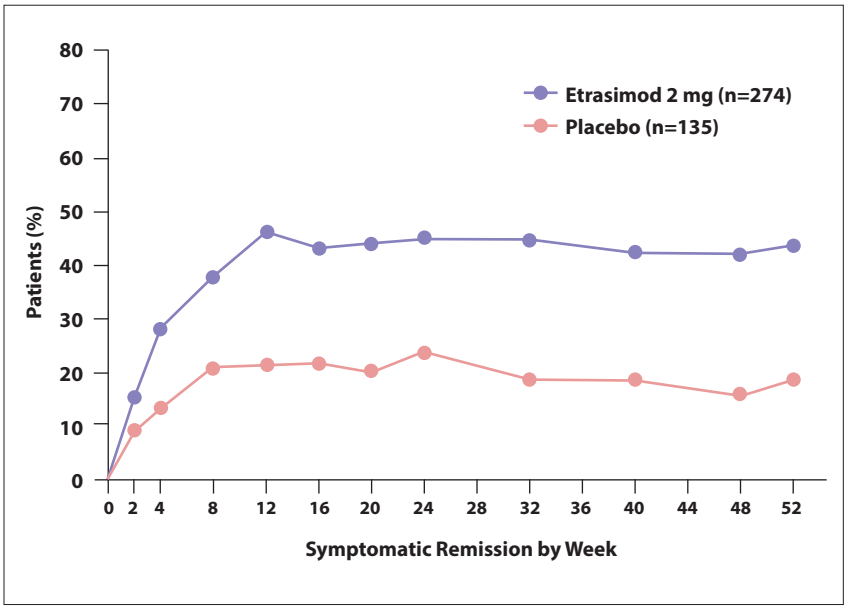

Figure 4. The achievement of symptomatic remission of patients with ulcerative colitis treated with etrasimod vs placebo in ELEVATE UC 52. Adapted from Chaparro M, et al. Abstract DOP42. Presented at: 18th Congress of European Crohn's and Colitis Organisation (ECCO); March 1-4, 2023; Copenhagen, Denmark.[3]

ABSTRACT SUMMARY Subcutaneous Infliximab (CT-P13 SC) as Maintenance Therapy for Ulcerative Colitis: A Phase 3, Randomized, Placebo-Controlled Study: Results of the LIBERTY-UC Study

CT-P13 is a subcutaneous formulation of infliximab that was developed to provide a more convenient therapeutic option for patients (Abstract P492). The LIBERTY-UC study compared open-label CT-P13 5 mg/kg vs placebo as induction therapy in patients with moderately to severely active UC. At week 10, patients with a clinical response were randomized 2:1 to receive CT-P13 120 mg or placebo, administered every 2 weeks for up to 54 weeks. Among 548 patients who were enrolled in the study, 438 exhibited a response after induction and were randomized at week 10 to CT-P13 maintenance (n=294) or placebo (n=144). The trial met its primary endpoint, demonstrating a superior rate of clinical remission with CT-P13 vs placebo at week 54 (43.2% vs 20.8%; P<.0001). The trial also met its key secondary endpoints of clinical response (53.7% vs 31.3%; P<.0001), endoscopic-histologic mucosal improvement (35.7% vs 16.7%; P<.0001), and corticosteroid-free remission (36.7% vs 18.0%; P=.0127).

or JAK inhibitor, the rate of symptomatic remission was also superior with etrasimod vs placebo, both at week 12 (Δ24.7%; *P*=.015) and at week 52 (Δ22.9%; *P*=.015). Among patients with exposure to more than 1 biologic or JAK inhibitor therapy, the rate of symptomatic remission was not significantly different with etrasimod vs placebo at week 12 or at week 52 (*P*<.05). Similar outcomes were observed in subgroups from ELEVATE UC 12.

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Efficacy of Ustekinumab for Ulcerative Colitis Through 4 Years: Final Clinical and Endoscopy Outcomes From the UNIFI Long-Term Extension

Ustekinumab is a monoclonal antibody that binds to the p40 protein subunit of interleukin (IL) 12 and IL-23—key regulators of the immune response.[1] The antibody is approved for the treatment of adult patients with moderately to severely active UC.[2,3] The placebo-controlled, phase 3 UNIFI study compared 44 weeks of maintenance therapy with ustekinumab 90 mg administered every 8 weeks or every 12 weeks, followed by a long-term extension (LTE) study that continued through 4 years.[4,5] The LTE study included 143 patients in the 8-week arm and 41 patients in the 12-week arm. Dose adjustments were allowed at week 56 and thereafter. The LTE analysis included all patients randomized to ustekinumab at the start of maintenance therapy who had Mayo score data available at week 200 or experienced treatment failure before week 200. Outcomes evaluated at the final efficacy visit at week 200 included clinical remission, endoscopic improvement, clinical response, and modified Mayo score response.

Final clinical outcomes were similar for ustekinumab 90 mg administered every 8 weeks or every 12 weeks. At week 200, using modified observed case methodology with treatment failure rules applied, 58% of patients were in clinical remission in both ustekinumab arms (Figure 5). Among patients who were in clinical remission at the start of maintenance therapy, the rate of clinical remission in the combined population was 67%, the rate of endoscopic improvement was 67%. and the rate of clinical response was 80%. The rate of response according to modified Mayo score was 80% in the combined population. No new safety signals were observed.

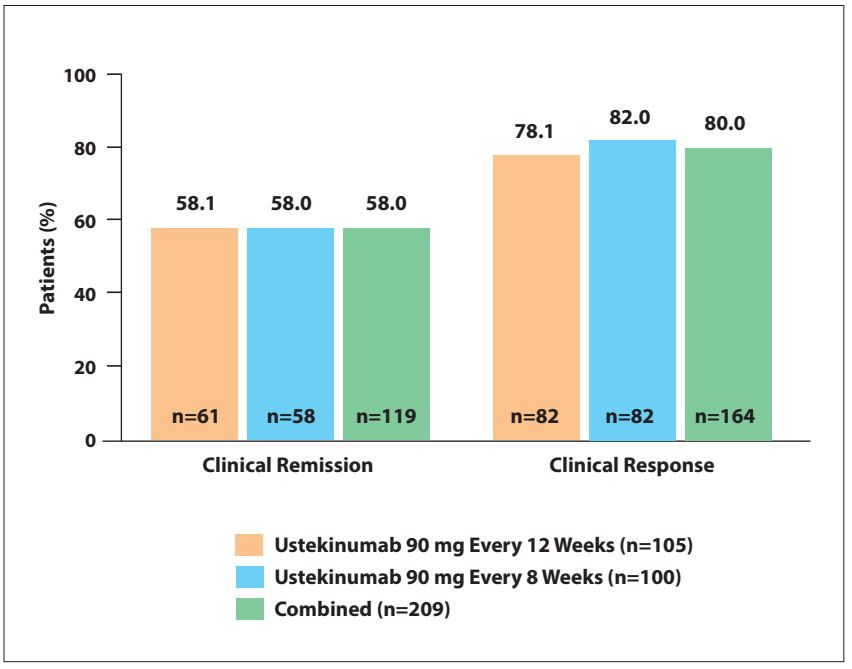

Figure 5. Clinical remission and response outcomes of patients with moderate to severe ulcerative colitis after 4 years of ustekinumab treatment. Adapted from Danese S, et al. Abstract OP15. Presented at: 18th Congress of European Crohn's and Colitis Organisation (ECCO); March 1-4, 2023; Copenhagen, Denmark.[5]

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The Effects of Upadacitinib on UC Symptom Resolution and Fatigue Normalization in Patients With Moderately to Severely Acute Ulcerative Colitis: Phase 3 U-ACHIEVE and U-ACCOMPLISH Results

A long-term treatment goal for patients with IBD is achieving a normal quality of life by reducing the debilitating symptoms that characterize the disease.[1] Upadacitinib is a reversible inhibitor of JAK1, a proinflammatory molecule that has been implicated in the pathology of UC. In the phase 3 U-ACHIEVE and U-ACCOMPLISH studies, upadacitinib demonstrated efficacy and tolerable safety in the treatment of patients with moderately to severely active UC, with efficacy observed as early as day 1 of therapy.[2,3] In the pooled population of the 2 studies, 660 patients were randomized to upadacitinib 45 mg daily and 328 patients to placebo. Patients who responded to upadacitinib were randomized to 52 weeks of maintenance therapy with daily upadacitinib (15 mg or 30 mg) or placebo.

A post hoc analysis evaluated the ability of upadacitinib therapy to achieve complete resolution of symptoms and normalization of fatigue in patients from the U-ACHIEVE and U-ACCOMPLISH studies.[4] Complete symptom resolution was defined by no bowel urgency, no abdominal pain, no rectal bleeding, and a stool frequency score of 1 or lower. Normalization of fatigue was according to a Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) score of at least 40.1. The analysis included 328 patients treated with placebo and 660 patients treated with upadacitinib. The mean disease duration in both arms was approximately 8 years. At baseline, the majority of patients (89%-90%) had abdominal pain, a stool frequency score of greater than 1 (94%-95%), and a rectal bleeding score of greater than 0 (92% in both arms). The mean FACIT-F score was 30.1 ± 11.7 in the upadacitinib group vs 31.5 ± 11.8 in the placebo group. At week 8 of induction, the proportion of patients with complete symptom resolution was 31.2% with upadacitinib vs 7.9% with placebo (Figure 6). At week 52 of maintenance, among patients who had exhibited a response during induction, the proportion of patients with complete symptom resolution was 46.1% with the higher dose of upadacitinib ($P<.001$) vs 37.2% with the lower dose ($P<.001$) vs 12.8% with placebo. The proportion of patients who achieved complete symptom resolution as well as normalization of fatigue according to FACIT-F scoring was superior with upadacitinib vs placebo, both at week 8 of induction (23.4% vs 6.7%; $P<.001$) and at week 52 of maintenance, with both the higher dose (36.4%; $P<.001$) and the lower dose of upadacitinib (24.3%; $P\leq.01$) vs placebo (12.1%).

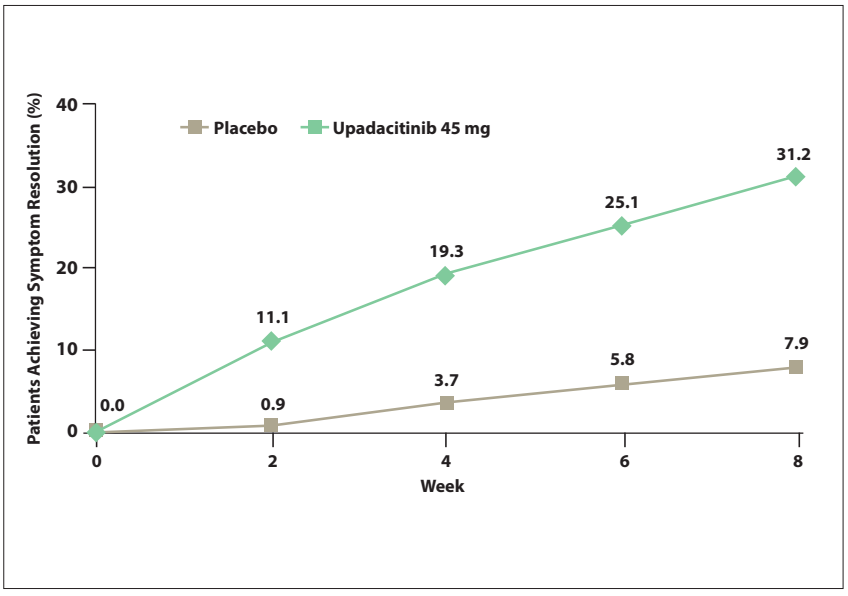

Figure 6. Percentage of patients with moderate to severe ulcerative colitis with symptom resolution during induction treatment. Adapted from D'Haens G, et al. Abstract OP20. Presented at: 18th Congress of European Crohn's and Colitis Organisation (ECCO); March 1-4, 2023; Copenhagen, Denmark.[4]

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Efficacy and Safety Outcomes Up to ~4 Years of Treatment With Filgotinib 200 mg Among Patients With Ulcerative Colitis: Results From the SELECTIONLTE Study

Filgotinib is a JAK1 inhibitor.[1] According to data from the phase 2b/3 SELECTION trial, filgotinib received approval by the European Medicines Agency for the treatment of patients with moderately to severely active UC who have failed prior therapy.[2,3] In the SELECTION study, patients with moderately to severely active UC were randomly assigned in a 2:2:1 fashion to receive daily filgotinib 200 mg, filgotinib 100 mg, or placebo as induction therapy for 11 weeks. Patients who demonstrated a response to therapy during the induction study and who completed the 47-week maintenance study continued their therapy during the LTE study. Patients without a response were assigned to receive open-label filgotinib.

The safety and efficacy of long-term use of filgotinib in patients with UC was investigated in the ongoing SELECTION LTE study.[4] Interim data at week 144 showed no new safety signals among 873 patients, representing 2055.5 patient-years of exposure. The most common treatment-emergent AEs of interest included all infections (EAIR100, 35.5%), herpes zoster (EAIR100, 0.5%), and malignancies excluding nonmelanoma skin cancer (EAIR100, 0.5%). The efficacy analysis included 148 patients who achieved a response with induction therapy and received filgotinib 200 mg during induction, maintenance, and the LTE study. Among these patients, long-term efficacy was evidenced by a decrease in mean partial Mayo score from approximately 6 at baseline to less than 2 by the start of the LTE study, with a low mean partial Mayo score maintained through week 144 (Figure 7). The rate of clinical remission was approximately 80% in this cohort. These patients also had a high rate of minimal clinically

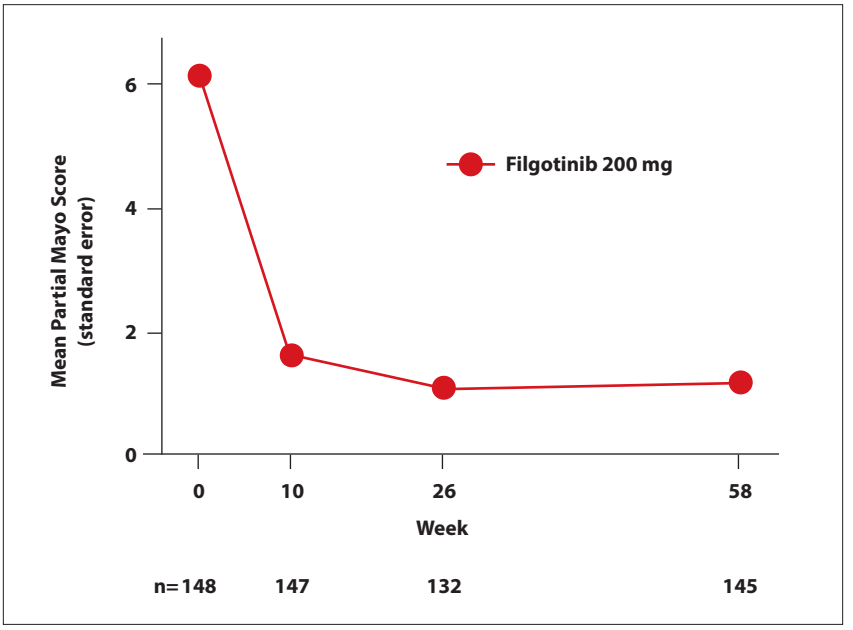

Figure 7. Mean partial Mayo score over time in SELECTION LTE among completers treated with filgotinib 200 mg. Adapted from Feagan BG, et al. Abstract OP35. Presented at: 18th Congress of European Crohn's and Colitis Organisation (ECCO); March 1-4, 2023; Copenhagen, Denmark.[4]

ABSTRACT SUMMARY Dual Therapy With Vedolizumab and Tofacitinib in Refractory Ulcerative Colitis Patients – Single Centre Experience

A case series investigated the combination of vedolizumab plus tofacitinib in patients with UC (Abstract P408). The study included 21 patients with complicated refractory or acute severe colitis who initiated combined therapy with vedolizumab plus tofacitinib, according to a shared clinical decision. All patients received tofacitinib 10 mg twice daily, and vedolizumab was administered with an intensified dosing regimen. Sixty-two percent of patients had extensive colitis and 38% had left-sided colitis. Eighty-six percent of patients had received prior therapy with at least 2 single-agent biologic regimens. The mean partial Mayo score improved from 5.6 ± 1.9 at baseline to 0.5 ± 0.9 at 6 months (P=.0020). The mean level of fecal calprotectin decreased from 1829 ± 2520 µg/g at baseline to 225 ± 257 µg/g at 6 months (P=.0068). The decrease in mean level of C-reactive protein (CRP) was not significant. Mean endoscopic Mayo score was 2.8 ± 0.5 at baseline, reflecting severe disease activity, and decreased to 1.4 ± 1.2 during follow-up endoscopy, which occurred at 2 to 6 months after initiating the combination therapy. Dual therapy was terminated in 7 patients.

important difference in Inflammatory Bowel Disease Questionnaire (IBDQ) score, ranging from 90.5% to 95.0% from week 10 through week 14 of the study. Rates of remission according to IBDQ peaked at 86.4% at week 144. Patients who did not show a response to filgotinib induction therapy showed lower rates of efficacy during the LTE study, according to partial Mayo scores and IBDQ scores.

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Mirikizumab in Moderately to Severely Active Colitis

Mirikizumab is a monoclonal antibody that binds to the p19 subunit of IL-23 and has demonstrated efficacy in phase 2 and phase 3 trials of patients with moderately to severely active UC.[1] Patients in the phase 2 AMAC and phase 3 LUCENT-1 trials received 12 weeks of induction therapy with mirikizumab every 4 weeks at doses ranging from 50 mg to 600 mg.[2] Patients with a response then received maintenance therapy with mirikizumab 200 mg administered every 4 weeks or every 12 weeks for up to 92 weeks. Pharmacokinetic analyses revealed that mirikizumab had a clearance rate of 0.022 L/hr (95% CI, 0.02-0.03). The volume of distribution was 3.11 L (95% CI, 3.07-3.15) for the central compartment and was 1.69 L (95% CI, 1.03-2.57) for the peripheral compartment and was best described by a 2-compartment model with first-order absorption. The rate of mirikizumab clearance increased with body weight as bioavailability decreased with body mass index. Clearance of mirikizumab decreased with albumin concentration. Modeling of the exposure-response relationship according to induction with mirikizumab in the AMAC study revealed a significant association between mirikizumab exposure and clinical response. The maximum effect exerted by mirikizumab was predicted at a dose of 300 mg, with no meaningful improvement observed at higher dose levels.

In the LUCENT-1 trial, 272 patients treated with mirikizumab 300 mg every 4 weeks failed to achieve a clinical response at week 12.[3] In the LUCENT-2 trial, these 272 patients received an additional 12 weeks of induction therapy with open-label mirikizumab 300 mg every 4 weeks for an additional 3 doses. One hundred forty-four of these patients exhibited a response at week 24 of continuous treatment and received open-label maintenance therapy with mirikizumab 200 mg every 4 weeks for 40 additional weeks of therapy. Among these 144 patients, 104 patients (72%) achieved a clinical response, 52 patients (36.1%) achieved clinical remission, 62 patients (43.1%) achieved endoscopic remission, and 60 patients (41.7%) achieved histologic improvement at week 52 (Table 2). A clinically meaningful reduction in bowel urgency was observed. Most treatment-emergent AEs were mild, and 5.4% were serious.

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Table 2. Clinical Outcomes for the Mirikizumab Induction Nonresponder Population at Week 52 of Extended Induction

Outcomes for miri IV extended induction	Week 52 (n=144)
Symptomatic remission	91 (63.2%)
Clinical remission	52 (36.1%)
Clinical response	104 (72.2%)
Symptomatic response	112 (77.8%)
HEMI	45 (31.3%)
Endoscopic remission	62 (43.1%)
Histologic improvement	60 (41.7%)
BU clinically meaningful improvement	80/136 (58.8%)

BU, bowel urgency; HEMI, histological-endoscopic mucosal improvement; IV, intravenous; miri, mirikizumab. Adapted from G D'Haens, et al. Abstract P554. Presented at: 18th Congress of European Crohn's and Colitis Organization (ECCO); March 1-4, 2023; Copenhagen, Denmark.[3]

Highlights in Ulcerative Colitis From the 18th Congress of ECCO: Commentary

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Presentations on ulcerative colitis (UC) at the 18th Congress of ECCO 2023 meeting provided important new insights regarding biology, prevention, and treatment of UC. The studies presented evaluated novel agents, including etrasimod, as well as currently approved treatments such as ozanimod and tofacitinib.

Ozanimod

Ozanimod is an oral sphingosine-1-phosphate (S1P) receptor modulator with a high affinity to S1P subtypes 1 (S1P1) and 5 (S1P5), leading to internalization of S1P1 receptors in lymphocytes and the prevention of lymphocyte egress from the lymph nodes, thus preventing lymphocytes from migrating to the inflamed tissue. Ozanimod is currently approved for the treatment of patients with moderate to severe UC in the United States and European Union.[1]

In the True North study, a joint US/European phase 3 randomized trial, ozanimod was evaluated for its efficacy in treating patients with moderate to severely active UC.[2] During a 10-week induction period, 2 cohorts of patients were evaluated. The patients in cohort 1 received oral ozanimod hydrochloride at a dose of 1 mg (equivalent to 0.92 mg of ozanimod) or placebo once daily in a double-blind manner, and patients in cohort 2 received open-label ozanimod at the same daily dose. After 10 weeks of therapy, patients who achieved a clinical response to ozanimod in cohort 1 or 2 were randomized again to receive double-blind ozanimod or placebo for the maintenance period (through week 52). In the induction portion of the trial, there were a total of 645 patients in cohort 1 and 367 patients in cohort 2, with a total of 457 patients included in the maintenance period.

A post hoc analysis by Sands and colleagues analyzed the efficacy of ozanimod among 185 patients in True North who were previously exposed to vedolizumab. The efficacy of ozanimod was evaluated at the end of induction (week 10) and maintenance (week 52). The study included 185 patients previously exposed to vedolizumab, an integrin receptor antagonist that interferes with lymphocyte trafficking ($\alpha_4\beta_7$ antagonist) to the gut. Patients were randomized into 2 cohorts to determine efficacy: oral once-daily ozanimod at 0.92 mg (n=63) or placebo (n=35) (cohort 1) or open-label ozanimod (n=87) (cohort 2).[3] Notably, in the subgroup of patients who had prior exposure to vedolizumab as first-line therapy, ozanimod showed an effective clinical response at week 10 of induction when compared with placebo. The findings were promising, with 50% (6/12) of patients in cohort 1 showing a clinical response, and 42% (5/12) of patients in cohort 2.

Although this is not a prospective randomized trial, the findings suggest that ozanimod could be effective in patients who have not responded to vedolizumab. A prospective randomized phase 3 trial would be necessary to confirm this hypothesis. However, such a trial is unlikely to occur, and post hoc analyses will likely continue to be used to explore potential signals in patient subgroups. Overall, these findings are promising for the clinical care of patients who require treatment but have not responded to vedolizumab.

Tofacitinib

The use of medications to treat patients with inflammatory bowel disease (IBD) has evolved. Tofacitinib is an oral Janus kinase (JAK) 1 and JAK3 inhibitor that has gained regulatory approval for the treatment of moderate to severe UC.[4] But can we better understand why patients do and do not respond to this medication?

To explore this, a study was presented by Dr Melon and colleagues to identify the relevant cellular subsets and genes involved in response and/or resistance to tofacitinib using temporal single-cell RNA sequencing.[5] Before

treatment, colon biopsies were obtained at baseline (n=11) from patients with moderate to severe UC and subsequently after starting tofacitinib 10 mg twice daily for 8 weeks and 5 or 10 mg twice daily thereafter (weeks 8, 16, 24, and/or 48; n=12 samples) and processed by single-cell RNA sequencing. After treatment, patients were classified as responders or nonresponders according to the decrease in the endoscopic Mayo score of at least 1 point from baseline during follow-up. There were a total of 31 patients, with 18 nonresponders and 13 responders. The study found an increase in inflammatory myeloid cells in nonresponders after treatment with tofacitinib, which is an exciting finding. Additionally, a specific profile developed in macrophages in individuals after receiving tofacitinib treatment. A lack of response is involved with the activation of various pathways, which helps to explain the basis for why patients do not respond.

This understanding can assist the development of future agents. If new drugs achieve these target endpoints directly and engage them, they are more likely to benefit the patient. In other words, if they do not have the desired target endpoints, they may not work for this patient population. This is an exciting preliminary finding that can aid clinical practice as well as the development of clinical trials. Phase 3 clinical trials can be very expensive, costing upward of $150 million each. If a subset of patients who are likely to respond to a specific treatment can be identified, time and money can potentially be saved in the development of new drugs. This study provides promising preliminary data and shows the potential for precision medicine to predict who will and will not respond to certain treatments.

Etrasimod

Etrasimod is an investigational, once-daily, oral, selective S1P1, S1P4, and S1P5 modulator in development for the treatment of patients with moderate to severely active UC.[6] Dr Chapparo and colleagues presented induction and maintenance results from the phase 3 ELEVATE UC 52 and ELEVATE UC 12 trials.[7] Symptomatic relief in both trials was measured by rectal bleeding (RB) and stool frequency (SF) subscores, and complete remission was SF of 0 and RB of 0. Approximately one-third of patients were exposed to prior biologics or JAK1 antagonists, and symptomatic remission was achieved early, at week 2 or week 4, depending on the trial. Symptomatic response was achieved at about week 2. Results suggest a greater benefit in patients who were naive to JAK1 antagonists. Etrasimod seems to have less benefit in patients with more refractory disease specifically those individuals who have previously used 1 or more biologic agents or JAK inhibitors.

In conclusion, relief was experienced by a greater proportion of patients with etrasimod vs placebo as early as week 2 and was sustained through week 52. At week 2, symptomatic response and improvement in the RB and the SF subscores were observed. The greatest benefit was observed in patients with no prior exposure to biologics or JAK1 antagonist agents, or patients who had received only 1 prior biologic or JAK1 antagonist. These are the populations that respond the best. This is in line with what we have seen with many other biologic agents. As a consequence of these results and data from other clinical trials, it is advocated to optimize the first biologic agent to the highest level that is being used. Treat the patient aggressively while optimizing that particular agent, and if they fail that agent, move on to the next. Keep in mind which agents do not work in patients who have failed prior biologics. The way in which therapy is positioned becomes an important component of the treatment of patients with IBD according to the evidence we have. This is, again, a post hoc analysis of these particular endpoints. The reviewed results do not

ABSTRACT SUMMARY Characteristics of Filgotinib-treated Patients With Ulcerative Colitis Who Achieve Sustained Corticosteroid-free Remission: Post Hoc Analysis of the Phase 2b/3 SELECTION Study

A post hoc analysis of the phase 2b/3 SELECTION study compared the proportion of patients with UC who achieved corticosteroid-free remission with daily filgotinib vs placebo (Abstract P319). Patients in the study received treatment with filgotinib 200 mg (n=92) or matched placebo (n=47) or filgotinib 100 mg (n=81) or matched placebo (n=37). The rate of corticosteroid-free remission was 13.6% with filgotinib 200 mg vs 5.4% with matched placebo. The rate of corticosteroid-free remission was 27.2% with the lower dose of filgotinib vs 6.4% with matched placebo. In the filgotinib 100 mg group, the only variable associated with corticosteroid-free remission was a baseline Mayo endoscopic score of 2 (P=.048). In the filgotinib 200 mg group of patients, mean baseline Robarts Histopathology Index was associated with 6-month corticosteroid-free remission (P=.023). In the same group, factors significantly associated with reduced odds of 6-month corticosteroid-free remission included male sex (P=.034), former smoker (P=.028), and prior exposure to a biologic agent (P=.004). A baseline Mayo endoscopic score of 2 was significantly associated with an increased likelihood of achieving 6-month corticosteroid-free remission (P=.001).

represent prospective randomized trial data, so it is important to recognize the context in which the data were obtained.

Ustekinumab

Ustekinumab is an interleukin-12/23p40 (IL-12/23p40) antagonist approved to treat patients with moderate to severe UC and Crohn's disease.[8] The initial treatment is intravenous, followed by subsequent subcutaneous injections for both acute treatment and maintenance of remission.

The long-term extension UNIFI study evaluated clinical and endoscopic outcomes according to the Mayo score of 205 patients with moderate to severe UC treated with 90 mg of subcutaneous ustekinumab for up to 4 years.[9] Discontinuation of ustekinumab for any reason was considered a treatment failure in the nonresponder imputation analysis.

Overall, 532 patients were randomized to subcutaneous maintenance therapy (ustekinumab 90 mg every 12 weeks or 90 mg every 8 weeks) or placebo. A total of 284 ustekinumab patients completed therapy up to week 44 and continued treatment in the long-term extension. The clinical remission, clinical response, and endoscopic improvement rates were similar for both groups at week 200. The clinical response rate was impressive overall at greater than 70% (78.1% in the 90 mg every 12 weeks group and 82% in the 90 mg every 8 weeks group in the modified observed case with treatment failure rules applied), indicating that a large number of patients achieved and maintained remission with ustekinumab. If remission is induced, remission is maintained in a large percentage of these patients. This is an attractive feature of the IL-12/23p40 antagonist, as an individual will typically stay in remission if it is initially achieved. Among 205 patients who were randomized to ustekinumab at maintenance baseline and continued treatment in the long-term extension, 58.0% were in clinical remission, 80% had a clinical response, 79.5% were in modified Mayo score response, and 67.3% showed endoscopic improvement, indicating a high level of maintenance of benefit. Ustekinumab has a very low level of immunogenicity and an excellent safety profile, making it a favorable treatment option for patients with UC.

This study's findings suggest the IL-12/23p40 antagonist ustekinumab is able to induce remission and retain a large percent of those remitters in a continued state of durable remission. The same phenomenon has been observed with the IL-23p19 antagonists including mirikizumab and guselkumab. This class effect provides a favorable benefit for patient care.

Upadacitinib

Upadacitinib is a JAK1-selective antagonist that is approved by the US Food and Drug Administration to treat patients with active UC and for maintenance of remission in UC after failing a tumor necrosis factor inhibitor.[10] Dr D'Haens and colleagues presented data on the effect of upadacitinib on symptom resolution and fatigue normalization in patients with moderate to severely active UC.[11]

A total of 988 patients were randomized in the U-ACHIEVE and U-ACCOMPLISH induction studies to receive upadacitinib 45 mg once daily (n=660) or placebo (n=328). The trial lasted for 8 weeks, and patients who were clinical responders at 8 weeks (n=451) were rerandomized 1:1:1 to upadacitinib 15 mg (n=148), upadacitinib 30 mg (n=154), or placebo (n=149) and followed for 52 weeks.

The study found that patients who were being treated with upadacitinib had moderate to severe disease activity, with a high percentage of patients experiencing abdominal pain and bowel urgency at the start of the trial. However, symptom resolution was rapid in this patient population,

ABSTRACT SUMMARY Effect of Upadacitinib on Inflammatory Markers and Clinical Outcomes in Patients With Crohn's Disease in the Phase 3 U-EXCEL, U-EXCEED, and U-ENDURE Studies

The double-blind, phase 3 U-EXCEL and U-EXCEED studies evaluated daily upadacitinib 45 mg vs placebo in patients with moderately to severely active Crohn's disease (Abstract P379). Patients with a response were randomized to receive daily upadacitinib 15 mg or 30 mg or placebo for 52 weeks of maintenance treatment. Among 1021 patients at baseline, 750 patients (73.5%) had elevated levels of fecal calprotectin and 645 (63.2%) had elevated levels of high-sensitivity C-reactive protein (hs-CRP). At week 12 of induction and at week 52, treatment with upadacitinib yielded a significantly greater proportion of patients with normalized levels of fecal calprotectin or hs-CRP ($P<.001$). Significant reductions in both of these markers of inflammation were observed as early as week 2 and maintained throughout the study period. Patients treated with upadacitinib demonstrated a significantly higher rate of clinical remission according to Crohn's Disease Activity Index plus normal hs-CRP and fecal calprotectin, clinical remission according to stool frequency and abdominal pain plus normal hs-CRP and fecal calprotectin, and a decrease of at least 100 points in Crohn's Disease Activity Index from baseline ($P<.001$ for all 3 endpoints at 12 weeks of induction and 52 weeks of maintenance).

and those receiving upadacitinib were more likely to achieve symptom resolution and normalization of fatigue during the induction treatment compared with placebo. Importantly, these results were sustained during maintenance therapy.

This study evaluated fatigue using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F), a 40-item measurement that assesses self-reported fatigue and its impact upon daily activities and function. Regarding symptom resolution of FACIT-F during induction and maintenance, the study found that at week 2, 11.1% of patients receiving upadacitinib 45 mg had resolved compared with 0.9% in the placebo group, and at week 8, 31.2% of patients in the upadacitinib arm had resolved vs 7.9% in the placebo group. In the maintenance arm at week 52, 46.1% of patients receiving upadacitinib 30 mg had resolved and 37.2% in the upadacitinib 15 mg group had resolved compared with 12.8% in the placebo group. These findings are important because symptoms like fatigue greatly impact patients' quality of life. Clinicians can now tell patients in induction that about one-quarter of them will have the resolution and normalization of fatigue, and about one-third will retain that up to week 52.

Although there are many reasons for fatigue, a subset of UC patients experience fatigue owing to disease activity, which can normalize with upadacitinib treatment. This study's findings are significant and demonstrate the potential for upadacitinib to help UC patients experiencing fatigue. It is important to note, however, that the effectiveness of upadacitinib compared with other medications for UC remains to be seen, as patient populations and inclusion criteria can differ across studies.

Disclosures

Dr Lichtenstein has consulted for AbbVie, American Regent, Eli Lilly, Fresenius Kabi, and MedEd Consultants; served on the Data Safety Monitoring Board for Eli Lilly; and received honoraria (CME program) from American Regent. He is a consultant and performed research for Bristol Myers Squibb, Janssen Ortho Biotech, Takeda and UCB, with funding directed to the University of Pennsylvania (IBD fellow education). He is a consultant for Pfizer Pharmaceuticals, with funding directed to the University of Pennsylvania (IBD fellow education). He has performed CME activities for the American Gastroenterological Association, Focus Medical Communication, IBD Horizon, Pennsylvania Society of Gastroenterology, and Physician Education Resource.

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