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A SPECIAL MEETING REVIEW EDITION

Highlights in the Management of Ulcerative Colitis and Crohn's Disease From the 2019 Digestive Disease Week Meeting

A Review of Selected Presentations From the 2019 DDW Meeting • May 18-21, 2019 • San Diego, California

Special Reporting on:

- Vedolizumab Shows Superior Efficacy Versus Adalimumab: Results of VARSITY—The First Head-To-Head Study of Biologic Therapy for Moderate-to-Severe Ulcerative Colitis
- Real-World Effectiveness and Safety of Vedolizumab and Anti-TNF in Biologic-Naive Ulcerative Colitis Patients: Results From the EVOLVE Study
- Subgroup Analyses of Upadacitinib as Induction Therapy From the U-ACHIEVE Trial
- Analyses of Vedolizumab From the VISIBLE 1 and 2 Trials
- Ustekinumab in Ulcerative Colitis: Results From the UNIFI Trial
- The Impact of Vedolizumab on Rates of Surgery in the GEMINI Trials
- Long-Term Analyses of Vedolizumab From the GEMINI Trials
- Efficacy and Safety of Mirikizumab (LY3074828) in a Phase 2 Study of Patients With Crohn's Disease

PLUS Meeting Abstract Summaries

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It Began

In **UC** & **Crohn's**

FOR ADULTS WITH MODERATELY TO SEVERELY ACTIVE UC OR CD FOR WHOM OTHER THERAPIES HAVE NOT WORKED WELL ENOUGH

Your decision to prescribe Entyvio for your appropriate patients may change the next chapter of their treatment journey

Only Entyvio combines:

LONG-TERM AND REMISSION

UC and CD patients achieved remission at 52 weeks vs placebo in study populations that included bio-naïve and anti-TNFα–experienced patients[1,2]

Individual results may vary.

INDICATIONS

Adult Ulcerative Colitis (UC)
ENTYVIO (vedolizumab) is indicated in adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids for inducing and maintaining clinical response, inducing and maintaining clinical remission, improving endoscopic appearance of the mucosa, and achieving corticosteroid-free remission.

Adult Crohn's Disease (CD)
ENTYVIO (vedolizumab) is indicated in adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids for achieving clinical response, achieving clinical remission, and achieving corticosteroid-free remission.

IMPORTANT SAFETY INFORMATION

- ENTYVIO (vedolizumab) for injection is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients.
- Infusion-related reactions and hypersensitivity reactions including anaphylaxis have occurred. Allergic reactions including dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have also been observed. If anaphylaxis or other serious allergic reactions occur, discontinue administration of ENTYVIO immediately and initiate appropriate treatment.
- Patients treated with ENTYVIO are at increased risk for developing infections. Serious infections have been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, and cytomegaloviral colitis. ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding ENTYVIO in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice.

With... Entyvio® vedolizumab

GUT SELECTIVITY[3-8]

Entyvio helps address inflammation where it occurs—in the gut

Entyvio specifically binds to the α4β7 integrin and blocks the interaction between the α4β7 integrin and MAdCAM-1, which is mainly expressed on GI tract endothelial cells[1]

AND

SAFETY FOR THE LONG TERM

Clinical trials evaluated in more than 3300 patients; the 5-year analysis that included an open-label continuation study demonstrated consistent results across safety parameters[1,9]

IMPORTANT SAFETY INFORMATION *(continued)*

- Although no cases of PML have been observed in ENTYVIO clinical trials, JC virus infection resulting in progressive multifocal leukoencephalopathy (PML) and death has occurred in patients treated with another integrin receptor antagonist. A risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist; if confirmed, discontinue ENTYVIO dosing permanently.
- There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury.
- Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines and may receive live vaccines if the benefits outweigh the risks.
- Most common adverse reactions (incidence ≥3% and ≥1% higher than placebo): nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities.

Please see brief summary of Prescribing Information on adjacent pages.

MAdCAM-1 = mucosal addressin cell adhesion molecule-1.

References: 1. Entyvio [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc. **2.** Data on file. Takeda Pharmaceuticals America, Inc. Deerfield, IL. **3.** Briskin M, Winsor-Hines D, Shyjan A, et al. *Am J Pathol*. 1997;151(1):97-110. **4.** Fedyk E, Wyant T, Yang LL, et al. *Inflamm Bowel Dis*. 2012;18(11):2107-2119. **5.** Soler D, Chapman T, Yang LL, et al. *J Pharmacol Exp Ther*. 2009;330(3):864-875. **6.** Wyant T, Fedyk E, Abhyankar B. *J Crohns Colitis*. 2016;10(12):1437-1444. **7.** Wyant T, Leach T, Sankoh S, et al. *Gut*. 2015;64(1):77-83. **8.** Milch C, Wyant T, Xu J, et al. *J Neuroimmunol*. 2013;264:123-126. **9.** Colombel JF, Sands BE, Rutgeerts P, et al. *Gut*. 2017;66(5):839-851.

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Learn how you can help your patients reach remission—visit EntyvioHCP.com

Takeda

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

ENTYVIO (vedolizumab) for injection, for intravenous use

INDICATIONS AND USAGE

Adult Ulcerative Colitis

ENTYVIO (vedolizumab) is indicated for:

- inducing and maintaining clinical response,
- inducing and maintaining clinical remission,
- improving the endoscopic appearance of the mucosa, and
- achieving corticosteroid-free remission

in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

Adult Crohn's Disease

ENTYVIO (vedolizumab) is indicated for:

- achieving clinical response,
- achieving clinical remission, and
- achieving corticosteroid-free remission

in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

CONTRAINDICATIONS

ENTYVIO is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients (such as dyspnea, bronchospasm, urticaria, flushing, rash and increased heart rate) *[see Warnings and Precautions and Adverse Reactions]*.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions and Hypersensitivity Reactions

In UC Trials I and II and CD Trials I and III, hypersensitivity reactions occurred including a case of anaphylaxis (one out of 1434 patients [0.07%]) *[see Adverse Reactions]*. Allergic reactions including dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have also been observed. The majority were mild to moderate in severity as assessed by the investigator. Experience with other biologic medications suggests that hypersensitivity reactions and anaphylaxis to ENTYVIO may vary in their time of onset from during infusion or immediately post-infusion to occurring up to several hours post-infusion.

If anaphylaxis or other serious allergic reactions occur, discontinue administration of ENTYVIO immediately and initiate appropriate treatment (e.g., epinephrine and antihistamines).

Infections

Patients treated with ENTYVIO are at increased risk for developing infections *[see Adverse Reactions]*. The most commonly reported infections in clinical trials occurring at a rate greater on ENTYVIO than placebo involved the upper respiratory and nasal mucosa (e.g., nasopharyngitis, upper respiratory tract infection). Serious infections have also been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis.

ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding treatment in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution when considering the use of ENTYVIO in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice. For progressive multifocal leukoencephalopathy (PML), see *Warnings and Precautions*.

Progressive Multifocal Leukoencephalopathy

Another integrin receptor antagonist has been associated with progressive multifocal leukoencephalopathy (PML), a rare and often fatal opportunistic infection of the central nervous system (CNS). PML is caused by the John Cunningham (JC) virus and typically only occurs in patients who are immunocompromised.

In ENTYVIO clinical trials, patients were actively monitored for PML with frequent and regular screenings, and evaluations of any new, unexplained neurological symptoms, as necessary. While zero cases of PML were identified among patients with at least 24 months of exposure, a risk of PML cannot be ruled out. No claims of comparative safety to other integrin receptor antagonists can be made based on this data.

Monitor patients on ENTYVIO for any new onset, or worsening, of neurological signs and symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist; if confirmed, discontinue dosing permanently.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. In general, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury *[see Adverse Reactions]*.

Live and Oral Vaccines

Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines (e.g., influenza vaccine injection) and may receive live vaccines if the benefits outweigh the risks. There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVIO *[see Adverse Reactions]*.

ADVERSE REACTIONS

The following topics are also discussed in detail in the Warnings and Precautions section:

- Infusion-Related Reactions and Hypersensitivity Reactions *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Progressive Multifocal Leukoencephalopathy *[see Warnings and Precautions]*
- Liver Injury *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to ENTYVIO in 3,326 patients and healthy volunteers in clinical trials, including 1,396 exposed for greater than one year, and 835 exposed for greater than two years.

The safety data described in *Table 2* are derived from four controlled Phase 3 trials (UC Trials I and II, and CD Trials I and III); data from patients receiving open-label ENTYVIO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included.

In these trials, 1,434 patients received ENTYVIO 300 mg for up to 52 weeks, and 297 patients received placebo for up to 52 weeks. Of these, 769 patients had ulcerative colitis and 962 patients had Crohn's disease. Patients were exposed for a mean duration of 259 days (UC Trials I and II) and 247 days (CD Trials I and III).

Adverse reactions were reported in 52% of patients treated with ENTYVIO and 45% of patients treated with placebo (UC Trials I and II: 49% with ENTYVIO and 37% with placebo; CD Trials I and III: 55% with ENTYVIO and 47% with placebo). Serious adverse reactions were reported in 7% of patients treated with ENTYVIO compared to 4% of patients treated with placebo (UC Trials I and II: 8% with ENTYVIO and 7% with placebo; CD Trials I and III: 12% with ENTYVIO and 9%, with placebo).

The most common adverse reactions (reported by ≥3% of patients treated with ENTYVIO in the UC Trials I and II and CD Trials I and III combined group and ≥1% higher than in combined placebo group) were nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain and pain in extremities (*Table 2*).

Table 2. Adverse Reactions in ≥3% of ENTYVIO-treated Patients and ≥1% Higher than in Placebo (UC Trials I and II* and CD Trials I and III*)

Adverse Reaction	ENTYVIO† (N=1434)	Placebo‡ (N=297)
Nasopharyngitis	13%	7%
Headache	12%	11%
Arthralgia	12%	10%
Nausea	9%	8%
Pyrexia	9%	7%
Upper respiratory tract infection	7%	6%
Fatigue	6%	3%
Cough	5%	3%
Bronchitis	4%	3%
Influenza	4%	2%
Back pain	4%	3%
Rash	3%	2%
Pruritus	3%	1%
Sinusitis	3%	1%
Oropharyngeal pain	3%	1%
Pain in extremities	3%	1%

*Data from patients receiving open-label ENTYVIO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included.

†Patients who received ENTYVIO for up to 52 weeks.

‡Patients who received placebo for up to 52 weeks.

Safety data for patients (n=279) in UC Trials I and II and CD Trials I and III who received ENTYVIO at Weeks 0 and 2 and were then randomized to placebo at Week 6 for up to 52 weeks, and for patients (n=416) in CD Trial II, a 10 week Crohn's disease trial, are similar to those listed in *Table 2*.

Infusion-Related Reactions and Hypersensitivity Reactions

Serious infusion-related reactions and hypersensitivity reactions including anaphylaxis have been reported following ENTYVIO administration in clinical trials *[see Warnings and Precautions]*. In UC Trials I and II and Crohn's Trials I and III, one case of anaphylaxis [one out of 1434 patients treated with ENTYVIO (0.07%)] was reported by a Crohn's disease patient during the second infusion (symptoms reported were dyspnea, bronchospasm, urticaria, flushing, rash and increased blood pressure and heart rate) and was managed with discontinuation of infusion and treatment with antihistamine and intravenous hydrocortisone.

In UC Trials I and II and CD Trials I and III, 4% of patients treated with ENTYVIO and 3% of patients treated with placebo experienced an infusion-related reaction (IRR). The most frequently observed IRR in the patients treated with ENTYVIO (reported more than twice) were nausea, headache, pruritus, dizziness, fatigue, infusion-related reaction, pyrexia, urticaria and vomiting (each of these adverse reactions occurred in <1% in all patients treated with ENTYVIO) and no individual adverse reaction reported occurred at a rate above 1%. These reactions generally occurred within the first two hours after the infusion and resolved with no treatment or following antihistamine and/or IV hydrocortisone treatment. Less than 1% of patients treated with ENTYVIO had IRRs assessed by the investigator as severe, and IRRs requiring discontinuation of study treatment occurred in <1%.

In clinical trials, for patients with mild IRRs or hypersensitivity reactions, physicians were allowed to pretreat with standard medical treatment (e.g., antihistamine, hydrocortisone and/or acetaminophen) prior to next infusion.

Infections

In UC Trials I and II and CD Trials I and III, the rate of infections was 0.85 per patient-year in the patients treated with ENTYVIO and 0.7 per patient-year in the patients treated with placebo *[see Warnings and Precautions]*. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infection. Two percent of patients discontinued ENTYVIO due to infections.

In UC Trials I and II and CD Trials I and III, the rate of serious infections was 0.07 per patient-year in patients treated with ENTYVIO and 0.06 per patient-year in patients treated with placebo. Serious infections were more common in Crohn's disease patients than ulcerative colitis patients, and anal abscesses were the most frequently reported serious adverse reaction in Crohn's disease patients. Over 48 months, there was no increase in the rate of serious infections.

In controlled- and open-label long-term extension trials in adults treated with ENTYVIO, serious infections have been reported, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis.

In UC Trials I and II and CD Trials I and III, sepsis, including bacterial sepsis and septic shock, was reported in four of 1434 (0.3%) patients treated with ENTYVIO and in two of 297 patients treated with placebo (0.7%). During these trials, two Crohn's disease patients treated with ENTYVIO died due to reported sepsis or septic shock; both of these patients had significant comorbidities and a complicated hospital course that contributed to the deaths. In an open label long-term extension trial, additional cases of sepsis (some fatal), including bacterial sepsis and septic shock, were reported. The rate of sepsis in patients with ulcerative colitis or Crohn's disease receiving ENTYVIO was two per 1000 patient-years.

In clinical trials, all patients were screened for tuberculosis. One case of latent, pulmonary tuberculosis was diagnosed during the controlled trials with ENTYVIO. Additional cases of pulmonary tuberculosis were diagnosed during the open-label trial. All of these observed cases occurred outside the United States, and none of the patients had extrapulmonary manifestations.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO *[see Warnings and Precautions]*. In UC Trials I and II and CD Trials I and III, three patients reported serious adverse reactions of hepatitis, manifested as elevated transaminases with or without elevated bilirubin and symptoms consistent with hepatitis (e.g., malaise, nausea, vomiting, abdominal pain, anorexia). These adverse reactions occurred following two to five ENTYVIO doses; however, based on case report information it is unclear if the reactions indicated drug-induced or autoimmune etiology. All patients recovered following discontinuation of therapy with some requiring corticosteroid treatment. In controlled trials, the incidence of ALT and AST elevations ≥3 x ULN was <2% in patients treated with ENTYVIO and in patients treated with placebo. In the open-label trial, one additional case of serious hepatitis was observed.

Malignancies

In UC Trials I and II and CD Trials I and III, malignancies (excluding dysplasia and basal cell carcinoma) were reported in six of 1434 (0.4%) patients treated with ENTYVIO, including colon cancer (n=2), transitional cell carcinoma (n=1), breast cancer (n=1), carcinoid tumor of the appendix (n=1) and squamous cell carcinoma (n=1). Malignancy was reported in one of 297 (0.3%) patients treated with placebo (squamous cell carcinoma).

Malignancies (excluding dysplasia and basal cell carcinoma) observed during the ongoing open-label long-term extension trial included B-cell lymphoma, breast cancer, colon cancer, malignant hepatic neoplasm, malignant lung neoplasm, malignant melanoma, lung cancer of primary neuroendocrine carcinoma, renal cancer and squamous cell carcinoma. Overall, the number of malignancies in the clinical trials was small; however, long-term exposure was limited.

Live and Oral Vaccines

There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVIO.

In a placebo-controlled study of healthy volunteers, 61 subjects were given a single ENTYVIO 750 mg dose (2.5 times the recommended dose), and 62 subjects received placebo followed by intramuscular vaccination with Hepatitis B surface antigen and oral cholera vaccine. After intramuscular vaccination with three doses of recombinant Hepatitis B surface antigen, those treated with ENTYVIO did not have lower rates of protective immunity to Hepatitis B virus. However, those exposed to ENTYVIO did have lower seroconversion rates and anti-cholera titers relative to placebo after receiving the two doses of a killed, oral cholera vaccine. The impact on other oral vaccines and on nasal vaccines in patients is unknown.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to vedolizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In UC Trials I and II and CD Trials I and III, in patients who received ENTYVIO, the frequency of antibodies detected in patients was 13% at 24 weeks after the last dose of study drug (greater than five half-lives after last dose). During treatment, 56 of 1434 (4%) of patients treated with ENTYVIO had detectable anti-vedolizumab antibody at any time during the 52 weeks of continuous treatment. Nine of 56 patients were persistently positive (at two or more study visits) for anti-vedolizumab antibody and 33 of 56 patients developed neutralizing antibodies to vedolizumab. Among eight of these nine subjects

with persistently positive anti-vedolizumab antibody and available vedolizumab concentration data, six had undetectable and two had reduced vedolizumab concentrations. None of the nine subjects with persistently positive anti-vedolizumab antibody achieved clinical remission at Weeks 6 or 52 in the controlled trials.

DRUG INTERACTIONS

Natalizumab

Because of the potential for increased risk of PML and other infections, avoid the concomitant use of ENTYVIO with natalizumab.

TNF Blockers

Because of the potential for increased risk of infections, avoid the concomitant use of ENTYVIO with TNF blockers.

Live Vaccines

Live vaccines may be administered concurrently with ENTYVIO only if the benefits outweigh the risks *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ENTYVIO during pregnancy. Information about the registry can be obtained by calling 1-877-TAKEDA7 (1-877-825-3327).

Pregnancy Category B:

Risk Summary

There are no studies with ENTYVIO in pregnant women. No fetal harm was observed in animal reproduction studies with intravenous administration of vedolizumab to rabbits and monkeys at dose levels 20 times the recommended human dosage. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the benefits to the mother outweigh the risk to the unborn child.

Clinical Considerations

Any adverse pregnancy effect from ENTYVIO would likely be greater during the second and third trimesters of pregnancy. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Animal Data

A reproduction study has been performed in pregnant rabbits at single intravenous doses up to 100 mg/kg administered on gestation Day 7 (about 20 times the recommended human dosage) and has revealed no evidence of impaired fertility or harm to the fetus due to vedolizumab. A pre- and post-natal development study in monkeys showed no evidence of any adverse effect on pre- and post-natal development at intravenous doses up to 100 mg/kg (about 20 times the recommended human dosage).

Nursing Mothers

It is unknown whether vedolizumab is present in human milk. Vedolizumab was detected in the milk of lactating monkeys. Exercise caution when administering vedolizumab to a nursing woman.

Pediatric Use

Safety and effectiveness of ENTYVIO in pediatric patients have not been established.

Geriatric Use

Clinical trials of ENTYVIO did not include sufficient numbers of subjects aged 65 and over (46 Crohn's and ulcerative colitis patients aged 65 and over were treated with ENTYVIO during controlled Phase 3 trials) to determine whether they respond differently from younger subjects. However, no overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Manufactured by:
Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

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For more information, go to www.ENTYVIO.com or call 1-877-825-3327

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VMB245 R2_Brf. L-BZV-0218-4

Vedolizumab Shows Superior Efficacy Versus Adalimumab: Results of VARSITY—The First Head-To-Head Study of Biologic Therapy for Moderate-to-Severe Ulcerative Colitis

The VARSITY trial (A Double-Blind, Double-Dummy, Randomised, Controlled Trial of Vedolizumab Versus Adalimumab in Patients With Active Ulcerative Colitis) was the first head-to-head clinical trial to directly compare 2 biologic therapies for the treatment of ulcerative colitis.[1] VARSITY evaluated the intravenous (IV) agent vedolizumab, a gut-selective humanized immunoglobulin (Ig) G1 monoclonal antibody that targets the α4β7 integrin, and adalimumab, a subcutaneously (SC) administered recombinant human IgG1 monoclonal antibody that binds to tumor necrosis factor alpha (TNFα).[2,3] Initially reported at the 14th Congress of the European Crohn's and Colitis Organisation (ECCO), the primary results of the VARSITY trial showed that vedolizumab was associated with superior clinical and endoscopic efficacy outcomes compared with adalimumab.[4] At the 2019 Digestive Disease Week (DDW) meeting, Dr Bruce E. Sands and colleagues presented further results, which more fully characterized the treatment effects of vedolizumab vs adalimumab across clinical, endoscopic, and histologic outcomes.[1]

VARSITY was a phase 3b double-blind, double-dummy, multicenter, active-controlled trial in patients with moderately to severely active ulcerative colitis. Patients were randomly assigned to treatment with vedolizumab at 300 mg IV at weeks 0, 2, and 6, and every 8 weeks thereafter until week 46 (n=385) or adalimumab at 160 mg SC at week 0, 80 mg SC at week 2, and 40 mg SC every 2 weeks thereafter until week 50 (n=386). To control for the different routes of administration, patients in the vedolizumab arm also received an SC placebo every 2 weeks until week 50, and patients in the adalimumab arm also received IV placebo on the same schedule as vedolizumab until week 46.

The study enrolled adult patients (ages 18 to 85 years) diagnosed more than 3 months prior with moderately to severely active ulcerative colitis (defined as a Mayo score of 6-12 and an endoscopic subscore of ≥2). Patients had at least 15 cm of involved colonic tissue. Previous use of adalimumab or vedolizumab was not permitted. Previous exposure to a TNFα inhibitor other than adalimumab was allowed, but limited to a maximum of 25% of the total enrolled study population.

The mean patient age in each arm was similar (40.8 years in the vedolizumab arm vs 40.5 years in the adalimumab arm), as was the proportion of patients who were male (60.8% vs 56.0%, respectively). The proportion of patients with moderate ulcerative colitis (defined as a Mayo score of 6-8) was 40.0% in the vedolizumab arm and 43.8% in the adalimumab arm. The proportion of patients with severe ulcerative colitis (defined as a Mayo score of 9-12) was 56.4% vs 54.4%, respectively. At baseline, use of a concomitant corticosteroid was reported in 36.1% of the vedolizumab arm and 36.3% of the adalimumab arm. Use of immunomodulators was reported in 26.2% vs 25.9%, respectively. Prior use of a TNFα inhibitor was reported in 20.8% vs 21.0%.

The primary endpoint of the VARSITY trial was clinical remission at week 52, which was defined as a complete Mayo score of 2 points or less, coupled with no individual subscore greater than 1 point. This endpoint was achieved by 31.3% of the vedolizumab arm vs 22.5% of the adalimumab arm (95% CI, 2.5%-15.0%; *P*=.0061; Figure 1). A prespecified subgroup analysis of the primary endpoint evaluated the rate of clinical remission at week 52 according to prior use of TNFα inhibitors. Among patients who had not received a TNFα inhibitor, the rates of remission were 34.2% with vedolizumab vs 24.3% with adalimumab (95% CI, 2.8%-17.1%; *P*=.0070). Among patients who had received a TNFα inhibitor, these rates were 20.3% with vedolizumab vs 16.0% with adalimumab, a difference that did not reach

ABSTRACT SUMMARY Real-World Analyses of Tofacitinib

Two abstracts examined the oral small-molecule JAK inhibitor tofacitinib in a real-world setting. In a multicenter, retrospective cohort study, 57.6% of 184 patients with ulcerative colitis achieved the primary outcome of clinical response at 8 weeks (Abstract 796). Several secondary outcomes were measured, and in general showed improved clinical response and remission by week 16 in patients who had achieved a response at week 8. Efficacy outcomes were highest among those patients with no prior exposure to a biologic agent. The second abstract focused on the safety of tofacitinib among 246 patients (150.2 patient-years) with ulcerative colitis in a real-world setting (Abstract 797). The data from this retrospective cohort study showed a safety profile for tofacitinib that was similar to what had been observed in the pivotal OCTAVE studies (Sandborn WJ et al. *N Engl J Med*. 2017;376[18]:1723-1736).

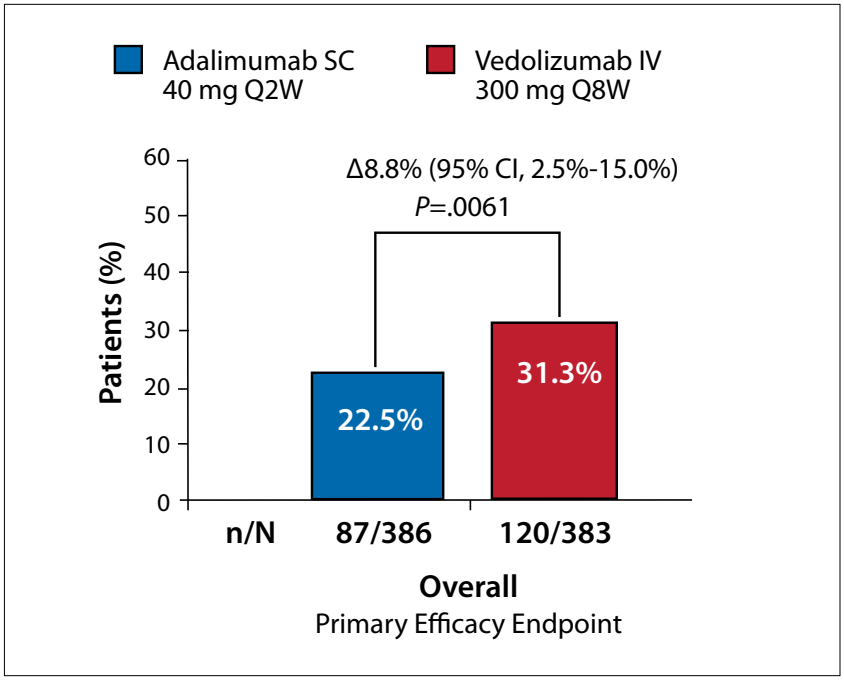

Figure 1. Overall clinical remission at week 52 for patients with ulcerative colitis treated with vedolizumab or adalimumab in the VARSITY trial. IV, intravenous; SC, subcutaneous; Q2W, every 2 weeks; Q8W, every 8 weeks; VARSITY, A Double-Blind, Double-Dummy, Randomised, Controlled Trial of Vedolizumab Versus Adalimumab in Patients With Active Ulcerative Colitis. Adapted from Sands BE et al. DDW abstract 416a. *Gastroenterology*. 2019;156(suppl 1).[1]

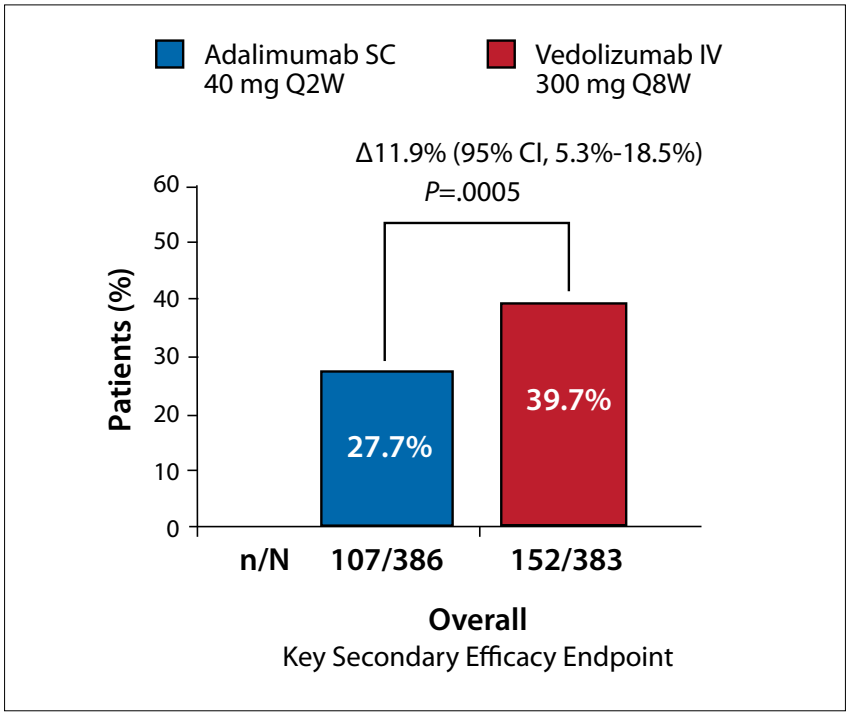

Figure 2. Mucosal healing at week 52 for patients with ulcerative colitis treated with vedolizumab or adalimumab in the VARSITY trial. IV, intravenous; SC, subcutaneous; Q2W, every 2 weeks; Q8W, every 8 weeks; VARSITY, A Double-Blind, Double-Dummy, Randomised, Controlled Trial of Vedolizumab Versus Adalimumab in Patients With Active Ulcerative Colitis. Adapted from Sands BE et al. DDW abstract 416a. *Gastroenterology*. 2019;156(suppl 1).[1]

statistical significance (95% CI, –7.8% to 16.2%; *P*=.4948).[1]

Endoscopic improvement at week 52, a secondary endpoint, was defined as mucosal healing with a Mayo endoscopic subscore of 1 point or less. The rate of endoscopic improvement was 39.7% with vedolizumab vs 27.7% with adalimumab (95% CI, 5.3%-18.5%; *P*=.0005; Figure 2). Among patients who had not received a TNFα inhibitor, endoscopic improvement was seen in 43.1% of the vedolizumab arm vs 29.5% of the adalimumab arm (95% CI, 6.0-21.2; *P*=.0005). The difference in endoscopic improvement was not statistically significant among patients who had been exposed to TNFα inhibitors, at 26.6% with vedolizumab vs 21.0% with adalimumab (95% CI, –7.7 to 18.8; *P*=.4136).

The study's secondary endpoint of corticosteroid-free clinical remission at week 52 was assessed among those patients who were receiving corticosteroids at baseline. The study design

Subgroup	Adalimumab SC n/N (%)	Vedolizumab IV n/N (%)	Δ	95% CI
Without baseline[a] corticosteroid use[b]				
Clinical remission[c]	50/246 (20.3)	83/245 (33.9)	13.6	5.8-21.3
Endoscopic improvement[d]	62/246 (25.2)	104/245 (42.4)	17.2	9.0-25.5
Without baseline[a] immunomodulator use[b]				
Clinical remission[c]	61/286 (21.3)	96/282 (34.0)	12.7	5.4-20.0
Endoscopic improvement[d]	75/286 (26.2)	119/282 (42.2)	16.0	8.3-23.7
With baseline[a] corticosteroid use				
Clinical remission[c]	37/140 (26.4)	37/138 (26.8)	0.4	–10.0 to 10.8
Endoscopic improvement[d]	45/140 (32.1)	48/138 (34.8)	2.6	–8.5 to 13.7
With baseline[a] immunomodulator use				
Clinical remission[c]	26/100 (26.0)	24/101 (23.8)	–2.2	–14.2 to 9.7
Endoscopic improvement[d]	32/100 (32.0)	33/101 (32.7)	0.7	–12.3 to 13.6

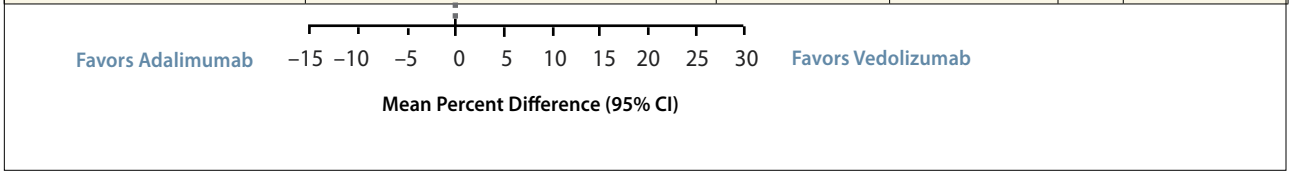

Figure 3. Efficacy outcomes at week 52 in the VARSITY trial of vedolizumab vs adalimumab according to baseline use of corticosteroids or immunomodulators. [a]Baseline use of corticosteroids was recorded by an interactive web response system. Baseline use of immunomodulators was recorded by electronic case report forms. [b]Post hoc analyses. [c]Complete Mayo score ≤2 points and no individual subscore >1 point. [d]Mayo score endoscopic subscore of ≤1 point. IV, intravenous; SC, subcutaneous; VARSITY, A Double-Blind, Double-Dummy, Randomised, Controlled Trial of Vedolizumab Versus Adalimumab in Patients With Active Ulcerative Colitis. Adapted from Sands BE et al. DDW abstract 416a. *Gastroenterology*. 2019;156(suppl 1).[1]

advised that corticosteroid tapering should be initiated starting at week 6 if the patient achieved a response. However, this decision was left to the treating physician, and there was no forced taper. There was no statistically significant difference between the treatments for this key secondary endpoint. The rates were 12.6% with vedolizumab vs 21.8% with adalimumab (95% CI, –18.9 to 0.4; *P*=.0641). Similar trends were observed in the prespecified analysis according to prior TNFα inhibitor use. The rates of corticosteroid-free clinical remission in the TNFα inhibitor–naive group were 14.9% with vedolizumab and 21.7% with adalimumab (95% CI, –18.1 to 4.5; *P*=.2412). Among patients treated with a TNFα inhibitor, these rates were 4.2% with vedolizumab and 22.2% with adalimumab (95% CI, –44.2 to 10.0; *P*=.1034).[1]

Predefined and post hoc analyses of efficacy outcomes at week 52 showed that in the patients with no concomitant use of corticosteroids or immunomodulators at baseline, vedolizumab was superior to adalimumab (Figure 3).[1] However, among patients using concomitant corticosteroids or immunomodulators at baseline, the 2 biologic therapies were essentially equivalent in terms of efficacy.

Rates of histologic remission at week 52 were 10.4% with vedolizumab vs 3.1% with adalimumab (95% CI, 3.8-10.8; *P*<.0001) using a Geboes score of less than 2. When using a Robarts Index of less than 3, these rates were 37.6% with vedolizumab vs 19.9% with adalimumab (95% CI, 11.3-23.8; *P*<.0001). Using slightly less stringent criteria for each—a Geboes score of less than 3.2 and a Robarts Index of less than 5—there was again a statistically significant difference in favor of vedolizumab, with an effect size of 19.6% (*P*<.0001) with the Geboes criteria and 16.6% (*P*<.0001) with the Robarts criteria. Clinical response according to patient visits throughout the study is shown in Figure 4.

Both of the biologic agents exhibited expected safety profiles. Adverse events required drug discontinuations in 4.4% of the vedolizumab arm and 6.5% of the adalimumab arm. The 1 death that occurred in the study was not considered related to the treatment (vedolizumab). The rate of infections and infestations was 23.4% in the vedolizumab arm and 34.6% in the adalimumab arm. There was no difference between the 2 treatment groups in the incidence of arthralgia (4.1% vs 4.5%, respectively). The rate of psoriasis was 1.7% with adalimumab vs 0.2% with vedolizumab.

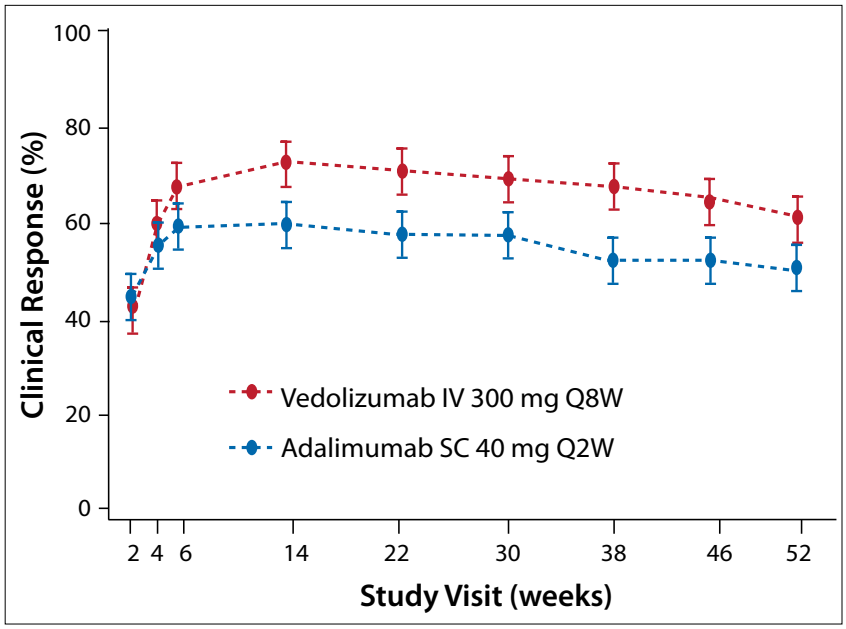

Figure 4. Clinical response by visit based on changes in the partial Mayo score from baseline in the VARSITY trial of patients with ulcerative colitis treated with vedolizumab vs adalimumab. The 95% CI of the percentage, also shown, is based on the Clopper-Pearson method. Clinical response based on the partial Mayo score was defined as a reduction in partial Mayo score of ≥2 points and ≥25% from baseline, with an accompanying decrease in the rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point. Patients with missing clinical response status were considered nonresponders. The full analysis set included all randomized patients who received ≥1 dose of the study drug. IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous; VARSITY, A Double-Blind, Double-Dummy, Randomised, Controlled Trial of Vedolizumab Versus Adalimumab in Patients With Active Ulcerative Colitis. Adapted from Sands BE et al. DDW abstract 416a. *Gastroenterology*. 2019;156(suppl 1).[1]

Dr Sands therefore concluded that vedolizumab showed superior clinical and endoscopic efficacy compared with adalimumab in the treatment of moderately to severely active ulcerative colitis. These treatment effects seemed most pronounced among patients who were naive to TNFα inhibitors. Both drugs were generally safe and well tolerated. According to Dr Sands, these results provide the most direct evidence to date on the comparative efficacy of biologics to support clinical decision-making in the management of moderately to severely active ulcerative colitis.

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Real-World Effectiveness and Safety of Vedolizumab and Anti-TNF in Biologic-Naive Ulcerative Colitis Patients: Results From the EVOLVE Study

In a poster presentation, Dr Andres Yarur and coworkers presented findings from the EVOLVE study (Vedolizumab Outcomes in Real-World Bio-Naive Ulcerative Colitis and Crohn's Disease Patients), a multicountry, multicenter, retrospective chart review that compared the efficacy and safety of treatment with vedolizumab or TNFα inhibitors in patients with ulcerative colitis.[1] The analysis included adult patients from Canada, Greece, and the United States who had not received prior treatment with a biologic agent. Outcomes were assessed using data from the patients' medical records.

Among the 527 patients included in the analysis, 325 had received vedolizumab and 202 had received infliximab, adalimumab, or golimumab. The disease duration was 5.0 years among patients treated with vedolizumab vs 2.0 years among those treated with a TNFα inhibitor. However, differences in baseline characteristics led the authors to believe that patients treated with a TNFα inhibitor may have had more severe disease at initiation compared with patients treated with vedolizumab. Patients treated with a TNFα inhibitor had higher rates of extensive colitis, elevated C-reactive protein, and ulcerative colitis–related hospitalizations, and a lower rate of left-sided disease.

The analysis found no significant differences in the rates of clinical remission or mucosal healing between the treatment groups. At 24 months, clinical remission was reported in 79.0% of the vedolizumab group vs 66.2% of the TNFα inhibitor group (P=.37). Mucosal healing at 24 months was seen in 92.0% vs 84.4%, respectively (P=.67).[1]

At the time points of 12, 18, and 24 months, the cumulative probability of treatment persistence was significantly higher with vedolizumab than with a TNFα inhibitor (Figure 5).

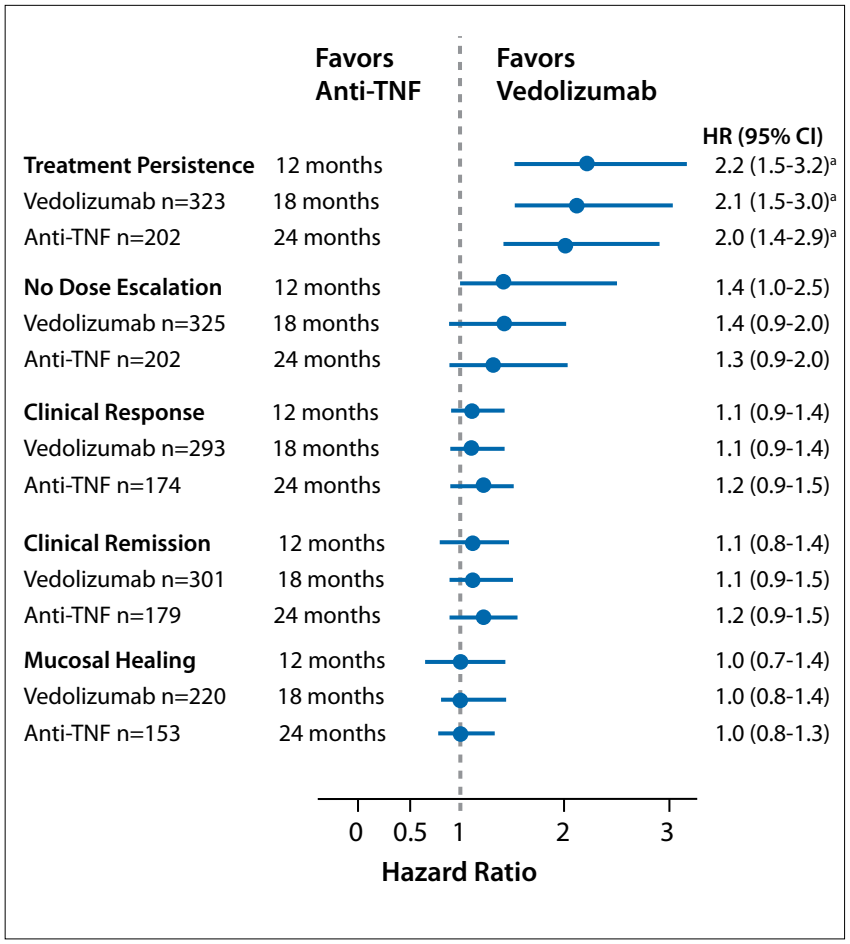

Figure 5. Adjusted hazard ratios for treatment patterns, dose escalation, and clinical effectiveness among patients with biologic-naive ulcerative colitis treated with vedolizumab or anti-TNF agents in the EVOLVE study. [a]Denotes a significant difference between vedolizumab and anti-TNF therapy based on an adjusted Cox proportional hazards model. EVOLVE, Vedolizumab Outcomes in Real-World Bio-Naive Ulcerative Colitis and Crohn's Disease Patients; TNF, tumor necrosis factor. Adapted from Yarur AJ et al. DDW abstract 1858. *Gastroenterology*. 2019;156(suppl 1).[1]

The unadjusted rates of treatment persistence were 82.5% with vedolizumab vs 65.0% with a TNFα inhibitor at 12 months, 79.1% vs 60.3% at 18 months, and 75.1% vs 53.8% at 24 months (P<.01 at each time point). After adjusting for baseline characteristics, patients treated with vedolizumab were twice as likely to persist on-treatment compared with patients treated with a TNFα inhibitor.

After adjusting for the baseline characteristics, patients treated with vedolizumab were significantly less likely to develop an exacerbation of ulcerative colitis (hazard ratio [HR], 0.7; 95% CI, 0.5-0.9). However, rates of colectomy were similar between the 2 treatment groups (HR, 0.9; 95% CI, 0.3-2.9). The rates of serious adverse events were 4.9% with vedolizumab vs 10.4% with TNFα inhibitors. The most frequently documented serious adverse events were anemia for vedolizumab and pain for the TNFα inhibitors.

The authors of the EVOLVE study concluded that these results support the long-term effectiveness and safety of first-line vedolizumab for the treatment of biologic-naive patients.

Reference

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Subgroup Analyses of Upadacitinib as Induction Therapy From the U-ACHIEVE Trial

The U-ACHIEVE study evaluated the efficacy and safety of upadacitinib, an oral selective Janus kinase (JAK) 1 inhibitor, as an 8-week induction therapy in patients with moderately to severely active ulcerative colitis who developed an inadequate response, loss of response, or intolerance to corticosteroids, immunosuppressants, or biologic therapies. U-ACHIEVE was a double-blind, placebo-controlled, dose-ranging phase 2b study that included 250 patients with moderately to severely active ulcerative colitis who were treated with either placebo or upadacitinib (at daily doses of 7.5 mg, 15 mg, 30 mg, or 45 mg). The results of the U-ACHIEVE study demonstrated that upadacitinib was associated with significantly greater efficacy in the overall population compared with placebo.[1] Two abstracts presented at the 2019 DDW Meeting discussed subgroup analyses from the study.

A subgroup analysis presented by Dr Remo Panaccione and coworkers examined differences in efficacy outcomes between patients with an inadequate response, loss of response, or intolerance to biologic therapies (referred to as Bio-IR) and patients in whom treatment was successful

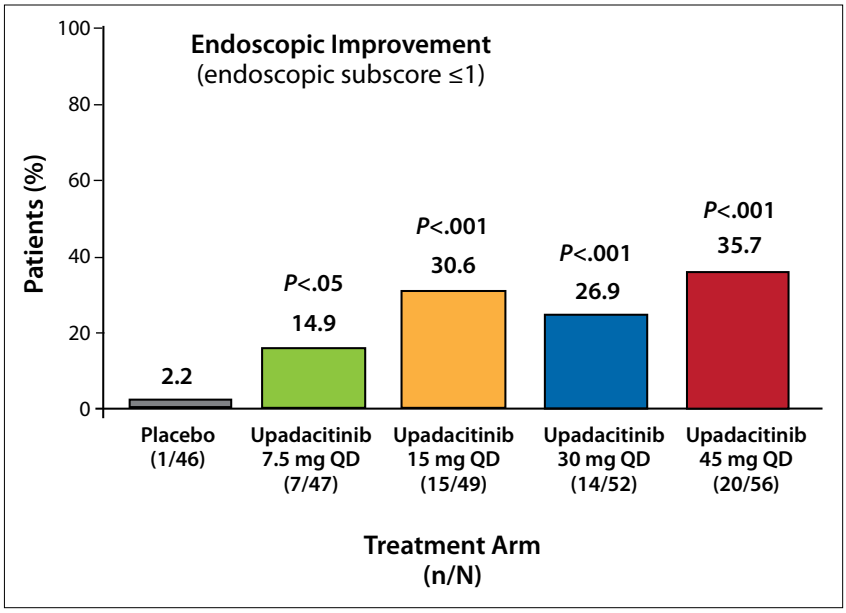

Figure 6. Rates of endoscopic improvement in patients with ulcerative colitis who received upadacitinib in the U-ACHIEVE study. QD, once daily. Adapted from Sandborn WJ et al. DDW abstract 800. *Gastroenterology*. 2019;156(suppl 1).[3]

ABSTRACT SUMMARY Effects of Intravenous Vedolizumab on Health-Related Quality of Life and Work Productivity in Patients With Crohn's Disease: Results From the Phase 3b VERSIFY Trial

The open-label, single-arm phase 3b VERSIFY trial demonstrated that IV vedolizumab was associated with endoscopic healing in patients with moderately to severely active Crohn's disease (ECCO 2018 Abstract OP023). An analysis reported at the 2019 DDW Meeting evaluated quality of life and work productivity among patients in the trial (Abstract 1881). The analysis was an exploratory evaluation of these measures performed in a substudy population of 56 patients; VERSIFY was not statistically powered to detect changes in quality of life. The study authors found that IV vedolizumab was associated with early and substantial improvements in both quality of life and work productivity. These improvements were apparent at week 14, and were maintained through week 52. The mean IBDQ total scores were 127.2 at week 0, 167.5 at week 14, and 169.2 at week 52. The authors noted that the improvements in quality of life and work productivity at week 52 were higher among patients who had achieved endoscopic remission with vedolizumab vs those who did not (mean IBDQ total scores of 178 vs 157, respectively).

(referred to a non–Bio-IR).[2] In general, efficacy outcomes in the non–Bio-IR group were numerically greater than in the Bio-IR group. In the overall study population, the primary endpoint of clinical remission per adapted Mayo score at week 8 was 19.6% with 45 mg, 13.5% with 30 mg, 14.3% with 15 mg, and 8.5% with 7.5 mg, vs 0% with placebo.[1] Statistical significance vs placebo was seen with the doses of 45 mg (P<.01), 30 mg (P<.05), and 15 mg (P<.05). In the Bio-IR group, the rates of clinical remission at week 8 were 11.9% with 45 mg, 10.0% with 30 mg, 8.3% with 15 mg, and 5.9% with 7.5 mg, vs 0% with placebo.[2] For this group, none of the improvements seen with upadacitinib were statistically significant vs placebo. In the non–Bio-IR group, the rates of clinical remission at week 8 were 42.9%, 25.0%, 30.8%, and 15.4%, respectively, vs 0% with placebo. Of these, only the difference for the 45 mg group was significantly improved vs placebo (P<.05).

A similar trend was observed in the Bio-IR and non–Bio-IR groups with regard to multiple secondary endpoints, including clinical response per adapted Mayo score at week 8, clinical response per partial Mayo score at week 2, endoscopic improvement and remission at week 8, and histologic improvement at week 8. In each of these efficacy outcomes, in general, the non–Bio-IR group achieved greater benefit with upadacitinib than the Bio-IR group. Both groups showed a dose response in benefit compared with placebo. The study authors noted that the patient numbers in both groups were small, and that these findings must be confirmed in larger phase 3 studies.

Dr William J. Sandborn and colleagues presented an analysis of the U-ACHIEVE study that evaluated endoscopic outcomes and mucosal healing.[3] At week 8, patients were assessed for endoscopic improvement and remission, histologic improvement and remission, and mucosal healing. Each of these outcomes showed an overall dose-response relationship with upadacitinib. The rates of endoscopic improvement (defined as an endoscopic subscore of ≤1) were 35.7% with 45 mg, 26.9% with 30 mg, 30.6% with 15 mg, and 14.9% with 7.5 mg, vs 2.2% with placebo (Figure 6). Similar trends were also observed with rates of endoscopic remission, histologic improvement, and histologic remission. The rates of mucosal healing defined by an endoscopic subscore of 0 and a Geboes score of less than 2 were 14.3% with upadacitinib at 45 mg vs 0% with placebo (P=.01).

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Analyses of Vedolizumab From the VISIBLE 1 and 2 Trials

An SC formulation of vedolizumab was investigated in the double-blind, randomized, placebo-controlled VISIBLE 1 (Efficacy and Safety of Vedolizumab Subcutaneously [SC] as Maintenance Therapy in Ulcerative Colitis) and VISIBLE 2 (Efficacy and Safety of Vedolizumab Subcutaneous [SC] as Maintenance Therapy in Crohn's Disease) trials. The recently completed VISIBLE 1 trial found that SC vedolizumab was efficacious and generally well tolerated as maintenance therapy in patients with ulcerative colitis.[1] VISIBLE 2 is an ongoing trial in patients with Crohn's disease.[2] These trials followed a similar design. They enrolled patients with moderately to severely active ulcerative colitis (VISIBLE 1) or Crohn's disease (VISIBLE 2) who demonstrated an inadequate response, loss of response, or intolerance to 1 or more therapies (including corticosteroids, immunosuppressive agents, and/or TNFα inhibitors). For both trials, patients were enrolled into an open-label induction phase, in which they received IV vedolizumab at 300 mg at weeks 0 and 2. After evaluation of clinical response at week 6, responders were randomly assigned into the double-blind maintenance phase, where they received either SC vedolizumab (108 mg every 2 weeks), IV vedolizumab (300 mg every 8 weeks), or placebo up to week 50. Additionally, patients who were not responding at week 6 received an additional dose of open-label IV vedolizumab at week 6, and were then evaluated for clinical response at week 14.[1,2] At the 2019 DDW meeting, 2 studies with data from these trials were presented.

Dr Edward V. Loftus Jr and colleagues examined the efficacy and safety of either 2 or 3 doses of IV vedolizumab when administered as open-label induction therapy in VISIBLE 1 and VISIBLE 2.[3] The authors noted that only preliminary efficacy results were available for VISIBLE 2. In the 383 patients with ulcerative colitis from VISIBLE 1, 56.1% achieved a clinical response at week 6 after receiving 2 IV infusions. Among the remaining patients who were not responding at week 6 and who went on to receive a third dose of IV vedolizumab, the rate of clinical response at week 14 was 79.1%. Together, 84.9% of patients with ulcerative colitis achieved a clinical response after 2 or 3 IV infusions of vedolizumab.

Among the 644 patients with Crohn's disease from VISIBLE 2, 60.6% achieved a clinical response at week 6 after 2 IV infusions. Among the remaining patients who were not responding at week 6 and received a third dose of IV vedolizumab, the rate

ABSTRACT SUMMARY Analysis of Hematological Changes in Tofacitinib-Treated Patients With Ulcerative Colitis Across Phase 3 Induction and Maintenance Studies

A study evaluated the impact of tofacitinib on hematologic parameters among patients in the OCTAVE Induction 1 and 2 trials and the OCTAVE Sustain trial (Abstract 1752). In the OCTAVE Induction 1 and 2 trials, after 8 weeks of treatment with placebo or tofacitinib at 10 mg twice daily, hemoglobin levels, absolute lymphocyte counts, and absolute neutrophil counts were stable, whereas platelet counts declined from baseline. The OCTAVE Sustain trial compared placebo with tofacitinib at 2 doses: 5 mg twice daily and 10 mg twice daily. Up to week 52, there was an increase in hemoglobin levels and a decrease in absolute lymphocyte count, absolute neutrophil count, and platelet count. In the induction studies, anemia occurred in 2.6% of patients treated with tofacitinib vs 3.5% of those treated with placebo. In the OCTAVE Sustain trial, anemia occurred at an incidence rate (defined as unique patients with events per 100 patient-years) of 0 with placebo, 0 with tofacitinib at 5 mg twice daily, and 2.55 with tofacitinib at 10 mg twice daily. In the induction studies, lymphopenia occurred in 0.3% of patients treated with tofacitinib vs 0.4% of patients treated with placebo. There were no reports of lymphopenia in OCTAVE Sustain. No cases of neutropenia were reported during the OCTAVE Induction 1 and 2 trials or the OCTAVE Sustain trial.

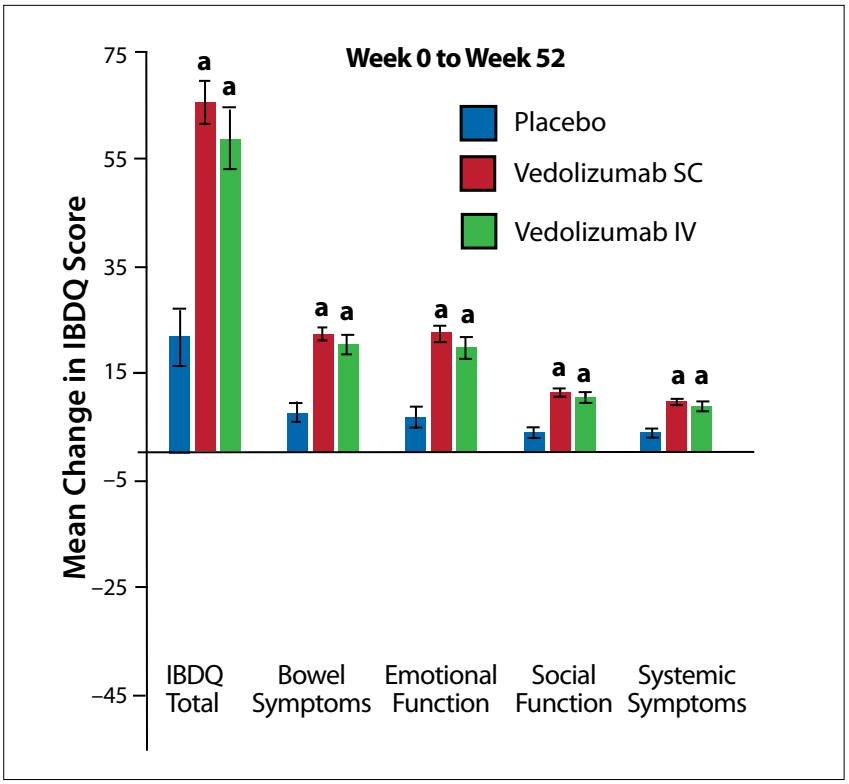

Figure 7. Mean changes in the IBDQ overall score and subscale scores among patients with ulcerative colitis treated with vedolizumab maintenance therapy in the VISIBLE 1 trial. [a]Nominal *P*<.05 for the difference between the placebo and maintenance treatment arm. IBDQ, Inflammatory Bowel Disease Questionnaire; IV, intravenous; SC, subcutaneous; VISIBLE 1, Efficacy and Safety of Vedolizumab Subcutaneously (SC) as Maintenance Therapy in Ulcerative Colitis. Adapted from Vermeire S et al. DDW abstract 1878. *Gastroenterology*. 2019;156(suppl 1).[4]

of clinical response at week 14 was 63.0%. Overall, 79.3% of patients with Crohn's disease achieved a clinical response after either 2 or 3 IV infusions of vedolizumab.

Safety data reported in this study were limited to results from VISIBLE 1. A treatment-related adverse event occurred in 17% of patients. Severe adverse events were reported in 6.5%, and 5.5% experienced an adverse event leading to treatment discontinuation.[3]

A report from Dr Séverine Vermeire and coworkers focused on patients with ulcerative colitis from VISIBLE 1.[4] The study analyzed the effects of vedolizumab maintenance treatment on patient-reported quality of life (assessed by the Inflammatory Bowel Disease Questionnaire [IBDQ] and EQ-5D Visual Analogue Scale instruments) and work productivity (assessed by the Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis instrument). The mean total IBDQ improved substantially throughout the study in both the SC and IV vedolizumab groups compared with the placebo group (week 52 mean IBDQ total scores of 180.7, 170.7, and 135.2, respectively). Each individual component of the IBDQ score also showed substantial clinical improvement with both SC and IV vedolizumab compared with placebo (Figure 7). The changes in total IBDQ scores from baseline to week 52 were significantly greater with both the SC (+65.3) and IV (+58.6) formulations of vedolizumab compared with placebo (*P*<.001 for both comparisons).

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Ustekinumab in Ulcerative Colitis: Results From the UNIFI Trial

Two abstracts presented at the 2019 DDW Meeting by Dr Bruce E. Sands and colleagues provided results from the phase 3 UNIFI study (A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Participants With Moderately to Severely Active Ulcerative Colitis). In the UNIFI study, a single IV induction dose of ustekinumab was associated with a benefit in multiple efficacy endpoints in patients with moderately to severely active ulcerative colitis.[1] Among patients in the induction portion of UNIFI, 50.5% had previously received at least 1 TNFα inhibitor and/or vedolizumab, but they did not

initially respond, responded initially but then lost response, or were intolerant to treatment (classified as biologic failures); and 49.5% were biologic-naive or had prior biologic exposure but did not show inadequate response or intolerance to treatment (classified as non–biologic failures).[2] Patients with a clinical response at week 8 after the single induction dose entered into a maintenance portion of the study. Patients were randomly assigned to treatment with either SC ustekinumab at 90 mg every 12 weeks or every 8 weeks, or placebo.

At week 8, the rates of clinical remission were 15.5% with IV ustekinumab at 6 mg/kg and 15.6% with IV ustekinumab at 130 mg, compared with 5.3% with placebo (*P*<.001 for both comparisons with placebo).[2] Among patients with an unsuccessful response to biologic therapy, rates of clinical remission were 12.7%, 11.6%, and 1.2%, respectively (*P*<.001 for both comparisons with placebo). Among patients who were biologic-naive or who responded adequately to biologic therapy, these rates were 18.6%, 19.9%, and 9.5%, respectively (*P*<.05 for both comparisons with placebo). Similar trends were observed at week 8 in endoscopic improvement, clinical response, and mucosal healing outcomes.

In the maintenance phase of the study, 523 patients were randomly assigned to treatment with a SC 90 mg dose of ustekinumab administered every 8 weeks or every 12 weeks, or placebo.[3] The patients' baseline characteristics were consistent with moderately to severely active disease activity, and included a median Mayo score of 9.0. A score of more than 10 was seen in 13.1% of patients, 47.1% had evidence of extensive disease, and the median duration of disease was 6.1 years. Nearly half of the patients (47.6%) had a history of biologic therapy failure, and 49.3% were considered biologic-naive.

The primary endpoint of the maintenance portion was clinical remission, defined as a Mayo score of 2 points or less, with no individual subscore higher than 1.[3] At week 44, this rate was 43.8% with SC ustekinumab given every 8 weeks (*P*<.001 compared with placebo), 38.4% with SC ustekinumab given every 12 weeks (*P*=.002 compared with placebo), and 24.0% with placebo (Figure 8). A similar trend was observed with the rates of corticosteroid-free remission, a major secondary endpoint. These rates were 42.0% with SC ustekinumab given every 8 weeks (*P*<.001 compared with placebo), 37.8% with SC ustekinumab given every 12 weeks (*P*=.002 compared with placebo), and 23.4% with placebo. Rates of clinical remission were slightly lower in patients classified as biologic failures, at 39.6% (*P*<.001), 22.9% (*P*<.05), and 17.0%, respectively, and slightly higher in patients classified as non–biologic failures, at 48.2%, 49.0%, and 31.0%, respectively (*P*<.05 for both comparisons with placebo).

Maintenance of clinical response was seen in 71.0%, 68.0%, and 44.6%, respectively (*P*<.001 for both comparisons with placebo). The rates of key safety events, including infections, were similar between the ustekinumab and placebo arms.

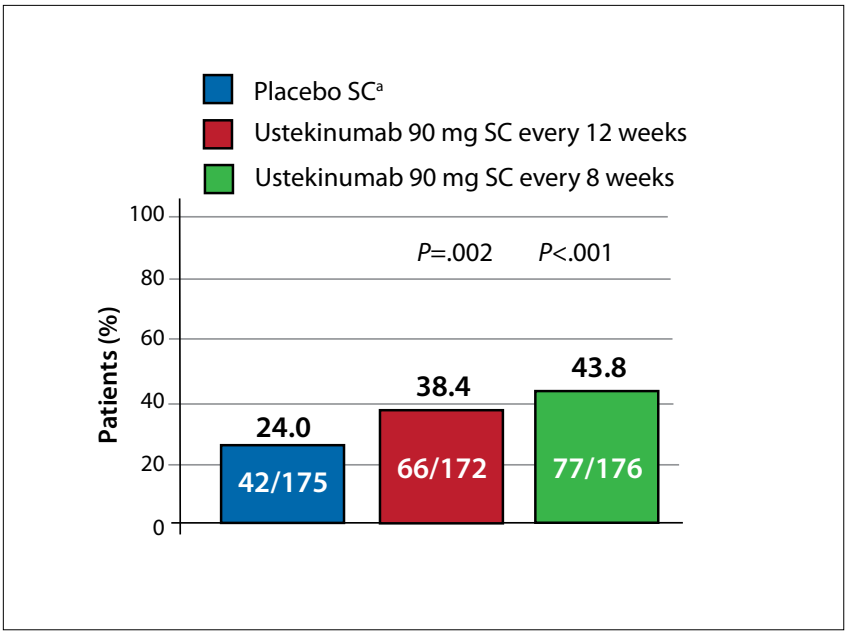

Figure 8. Rates of clinical remission among patients with ulcerative colitis treated with a 90 mg SC dose of ustekinumab administered every 8 weeks or every 12 weeks in the maintenance phase of the UNIFI trial. [a]Patients who were in a clinical response to intravenous ustekinumab induction dosing and were randomly assigned to SC placebo on entry into the maintenance study. SC, subcutaneous; UNIFI, A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Participants With Moderately to Severely Active Ulcerative Colitis. Adapted from Sands BE et al. DDW abstract 833a. *Gastroenterology*. 2019;156(suppl 1).[2]

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The Impact of Vedolizumab on Rates of Surgery in the GEMINI Trials

Studies presented at the 2019 DDW Meeting examined the impact of vedolizumab on surgical rates in patients enrolled in the pivotal phase 3 GEMINI trials, which evaluated the efficacy and safety of vedolizumab as induction and maintenance therapy for the treatment of either ulcerative colitis (GEMINI 1) or Crohn's disease (GEMINI 2).[1,2] A post hoc analysis of patient data from GEMINI 2 and the GEMINI long-term safety (LTS) study investigated whether rates of Crohn's disease–related surgery (defined as any resective bowel surgery) were affected if vedolizumab was administered earlier vs later in the disease course.[3] A total of 1253 patients with Crohn's disease were included. Across the study population, 55.1% were female, and the mean patient age was 36.4 years. Most patients (83.5%) had colonic or ileocolonic disease involvement; 16.5% had ileum disease only. Approximately one-third of patients (36.3%) had a history of fistulizing Crohn's disease. A total of 43.8% of patients had undergone a prior bowel surgery (before study enrollment), and 65.6% of patients had an inadequate response to previous treatment with a TNFα inhibitor. At baseline, use of concomitant corticosteroids was reported in 51.6% and use of immunomodulators was noted in 30.9%. The study investigators utilized a previously validated clinical decision support tool to stratify each patient's baseline probability of clinical response to vedolizumab.

Throughout the 7-year follow-up period, 113 patients (9.0%) underwent at least 1 bowel surgery related to Crohn's disease.[3] These surgeries included bowel resection in 58.4% and colectomy in 41.6%. The patients were stratified according to their probability of clinical response. Surgical rates were 12.9% for the low-probability group, 8.1% for the intermediate-probability group, and 6.0% for the high-probability group. Patients with a low probability of response to vedolizumab were more than twice as likely to undergo Crohn's disease–related bowel surgery compared with patients with a high probability of response (HR, 2.32; 95% CI, 1.29-4.30). Patients with an intermediate probability of response also had a heightened risk of surgery compared with patients in the high-probability group (HR, 1.37; 95% CI, 0.77-2.52).

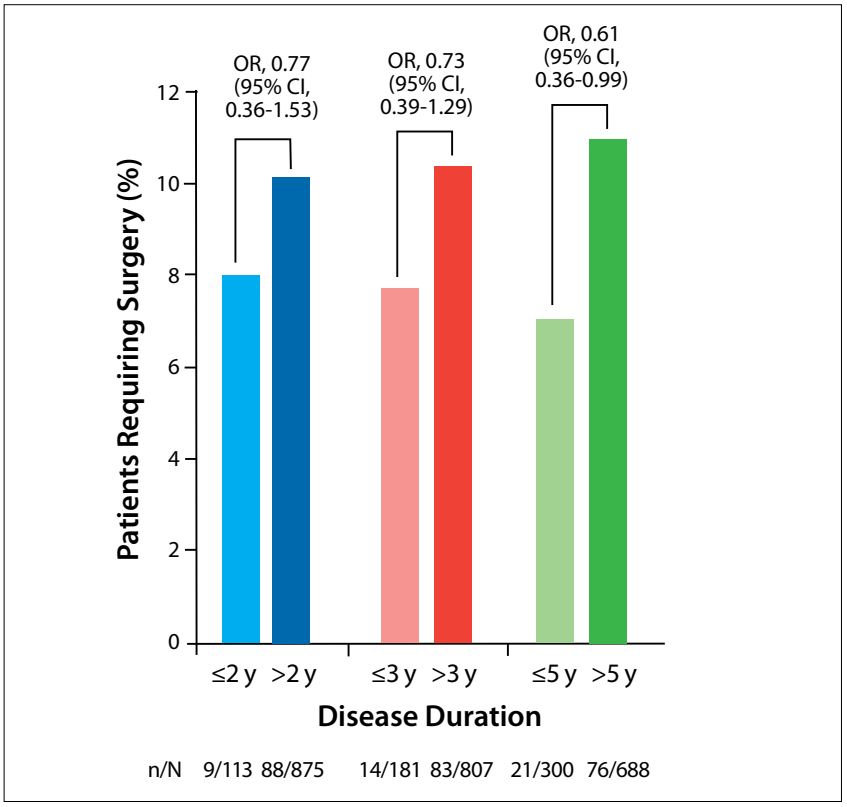

Figure 9. Risk of Crohn's disease–related surgery among patients with a low/intermediate probability of response to vedolizumab according to disease duration. Data are drawn from a post hoc analysis of the GEMINI trials. OR, odds ratio; y, years. Adapted from Dulai PS et al. DDW abstract 1726. *Gastroenterology*. 2019;156(suppl 1).[3]

Additionally, this study identified a trend toward lower rates of Crohn's disease–related bowel surgery among patients treated with vedolizumab earlier in their disease course.[3] For example, among patients with a low or intermediate probability of response to vedolizumab, those with a disease duration of 5 years or less had 39% lower odds of requiring Crohn's disease–related bowel surgery compared with patients who had a low or intermediate probability of response and a disease duration of more than 5 years (odds ratio, 0.61; 95% CI, 0.36-0.99; Figure 9). For patients with a high probability of response, those with a disease duration of 5 years or less had 29% lower odds of requiring Crohn's disease–related bowel surgery vs patients with a high probability of response and more than 5 years of disease duration (odds ratio, 0.71; 95% CI, 0.25-2.03).

Another post hoc analysis compared the surgical incidence rates between the vedolizumab and placebo arms of the GEMINI 1 and 2 studies.[4] In addition, this study was designed to describe the surgical incidence rates reported with vedolizumab in the GEMINI LTS trial. During the first

year of observation, surgery rates were lower among patients treated with vedolizumab compared with patients who received placebo in these trials. It also appeared that this benefit was durable. Patients with either ulcerative colitis or Crohn's disease who received vedolizumab had lower rates of surgery for up to 5 years. Detailed results from this post hoc analysis are expected to be published in the near future.

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Long-Term Analyses of Vedolizumab From the GEMINI Trials

Two studies presented at the 2019 DDW meeting discussed safety and immunogenicity findings from the GEMINI program, which evaluated the efficacy and safety of vedolizumab in ulcerative colitis and Crohn's disease.[1,2] A study provided the final results from the GEMINI LTS study in patients with ulcerative colitis and Crohn's disease.[3] GEMINI LTS was a multinational, multicenter, open-label phase 3 study in which patients received vedolizumab at 300 mg IV every 4 weeks. Among the 894 patients with ulcerative colitis, the median duration of exposure to vedolizumab was 43.0 months (range, 1 day to 113.7 months). Among the 1349 patients with Crohn's disease, the median vedolizumab exposure was 31.9 months (range, 1 day to 101.7 months).

Serious adverse events according to the patient cohort are shown in the Table. Among patients with ulcerative colitis, adverse events were mild in 18%, moderate in 50%, and severe in 24%.[3] Common adverse events, as calculated by incident rate per 1000 patient-years, included disease exacerbation (105.2), nasopharyngitis (93.9), arthralgia (51.6), abdominal pain (34.4), headache (55.5), and upper respiratory tract infection (55.7). Additionally, several adverse events of special interest were noted, including infections (388.9), neoplasms (17.2), and hepatic events (8.4). A total of 4 deaths occurred among patients with ulcerative colitis, although only 1 was considered treatment-related.

Among the patients with Crohn's disease, adverse events were mild in 17%, moderate in 49%, and severe

Table. Serious Adverse Events Among Patients With Ulcerative Colitis or Crohn's Disease Treated With Vedolizumab in the GEMINI LTS Study

	Ulcerative Colitis (n=894)		Crohn's Disease (n=1349)	
	n[a] (%)	Incident Rate per 1000 Patient-Years[b]	n[a] (%)	Incident Rate per 1000 Patient-Years[b]
Serious adverse events	277 (31)	90.9	548 (41)	146.5
Disease exacerbation	119 (13)	34.8	224 (17)	50.3
Abdominal pain	9 (1)	2.6	41 (3)	9.0
Anal abscess	0	0	33 (2)	7.3
Small intestinal obstruction	4 (<1)	1.1	25 (2)	5.5
Treatment-related serious adverse events	37 (4)	NA	79 (6)	NA
Deaths	4 (0.4)[c]	NA	6 (0.4)[d]	NA
Treatment-related deaths	1 (0.1)[e]	NA	1 (0.1)[f]	NA

GEMINI LTS, An Open-Label Study of Vedolizumab (MLN0002) in Participants With Ulcerative Colitis and Crohn's Disease Long-Term Safety; NA, not available.

[a]n values are the number of patients with an event.

[b]Time-adjusted incidence rate per 1000 patient-years = (Number of patients experiencing an adverse event of interest/total person-time in years) × 1000.

[c]Respiratory failure, acute stroke, West Nile virus encephalitis, pulmonary embolism.

[d]Traumatic intracranial hemorrhage, hepatocellular carcinoma, suicide, pneumonia, septicemia, leiomyosarcoma.

[e]West Nile virus encephalitis.

[f]Hepatocellular carcinoma.

Adapted from Loftus EV et al. DDW abstract 835. *Gastroenterology*. 2019;156(suppl 1).[3]

in 31%.[3] Common adverse events, as calculated by the incident rate per 1000 patient-years, included disease exacerbation (121.4), nasopharyngitis (94.1), arthralgia (90.3), abdominal pain (80.0), headache (76.4), and infection of the upper respiratory tract (53.2). Adverse events of special interest included infections (492.1), neoplasms (20.8), and hepatic events (14.1). Among the 6 deaths in patients with Crohn's disease, 1 was attributed to treatment.

Another analysis presented data on the long-term immunogenicity of vedolizumab among patients with ulcerative colitis and Crohn's disease enrolled in GEMINI LTS.[4] Two cohorts of patients from GEMINI LTS were included in this analysis. A continuous vedolizumab group included 1966 patients who received vedolizumab as induction and maintenance therapy in either GEMINI 1 or 2, and then received vedolizumab in GEMINI LTS. A vedolizumab rechallenge group consisted of 240 patients who received vedolizumab during induction followed by placebo during maintenance in either GEMINI 1 or 2, and then received vedolizumab in GEMINI LTS.

In the continuous vedolizumab group, a total of 4% of patients were positive for anti–vedolizumab antibodies.[4] Of these patients, 11 were persistently positive (during ≥2 consecutive tests), and 42 developed neutralizing antibodies. In the vedolizumab rechallenge group, a total of 18% were positive for anti–vedolizumab antibodies. Among these patients, 27 were persistently positive and 23 developed neutralizing antibodies. Immunogenicity rates were higher during the GEMINI 1 and 2 trials (ie, during the first 52 weeks of treatment), compared with the GEMINI LTS trial.

An infusion reaction was reported in 5% of patients overall. None of the patients in the continuous vedolizumab group who had an infusion reaction were persistently positive for anti–vedolizumab antibodies. In contrast, 15% of patients in the vedolizumab rechallenge group who had an infusion reaction were persistently positive for the antibodies.

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Efficacy and Safety of Mirikizumab (LY3074828) in a Phase 2 Study of Patients With Crohn's Disease

Dr Bruce E. Sands and colleagues presented data from the AMAG study (A Study of Mirikizumab [LY3074828] in Participants With Active Crohn's Disease), which evaluated mirikizumab, a humanized monoclonal antibody that binds to the p19 subunit of interleukin (IL) 23.[1] This multicenter, parallel-arm, double-blind, placebo-controlled, randomized trial enrolled patients with moderate to severe Crohn's disease. A total of 191 patients were randomly assigned in a 2:1:1:2 fashion to the following treatment arms: mirikizumab at 1000 mg every 4 weeks, mirikizumab at 600 mg every 4 weeks, mirikizumab at 200 mg every 4 weeks, or placebo.

The primary endpoint of the study was endoscopic response, defined as a 50% reduction from baseline in the Simple Endoscopic Score for Crohn's Disease (SES-CD). An endoscopic response was reported in 43.8% of the 1000 mg group (*P*<.001), 37.5%

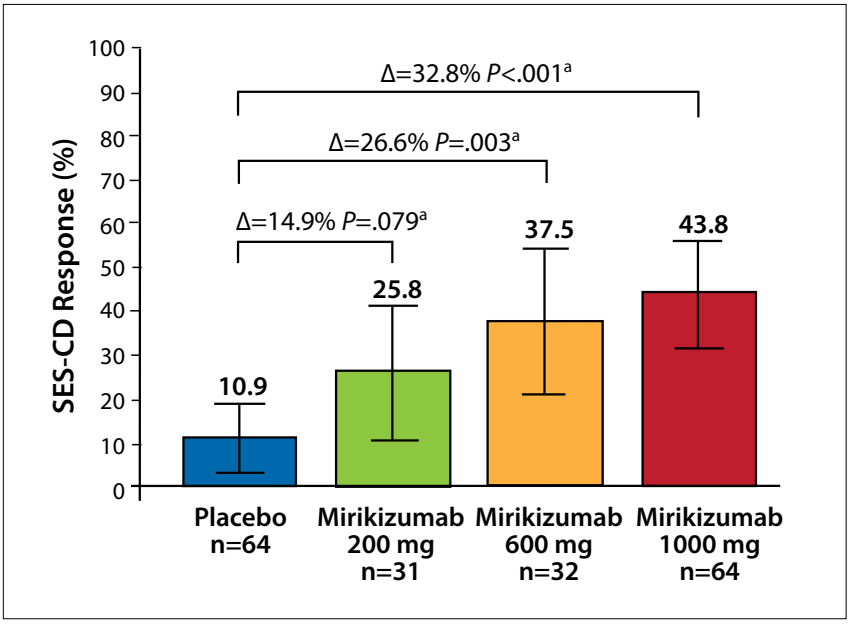

Figure 10. Endoscopic response among patients with Crohn's disease treated with mirikizumab in the AMAG trial. [a]Statistically significant by a prespecified 2-sided alpha level of 0.1. AMAG, A Study of Mirikizumab (LY3074828) in Participants With Active Crohn's Disease; SES-CD, Simple Endoscopic Score for Crohn's Disease. Adapted from Sands BE et al. DDW abstract 1003. *Gastroenterology*. 2019;156(suppl 1).[1]

of the 600 mg group (*P*=.003), and 25.8% of the 200 mg group (*P*=.079), compared with 10.9% of the placebo group (Figure 10).

A secondary endpoint of the study was endoscopic remission, defined as an SES-CD score of less than 4 for ileal-colonic disease or less than 2 for isolated ileal disease, and no subscore higher than 1. The proportion of patients who achieved an endoscopic remission was 20.3% for 1000 mg (*P*=.009), 15.6% for 600 mg (*P*=.032), and 6.5% for 200 mg (*P*=.241), compared with 1.6% for placebo.

Treatment with mirikizumab significantly improved patient-reported response and remission outcomes, as well as response and remission outcomes according to the Crohn's Disease Activity Index. Treatment was discontinued by 1 patient in the 200 mg group, 3 patients in the 600 mg, and no patients in the 1000 mg group. The most common treatment-emergent adverse events differed among the mirikizumab doses. In the 1000 mg group, the most common ones were headache (10.9%) and nasopharyngitis (6.3%).

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Highlights in the Management of Ulcerative Colitis and Crohn's Disease From the 2019 Digestive Disease Week Meeting: Commentary

Gary R. Lichtenstein, MD

Several presentations at the 2019 Digestive Disease Week (DDW) meeting provided important data that could impact the management of patients with inflammatory bowel disease (IBD). The VARSITY trial of vedolizumab vs adalimumab provided the first comparative effectiveness data of biologic therapies for IBD. Data were also presented for other biologic agents, including ustekinumab, mirikizumab, and upadacitinib. Studies offered insights into other aspects of management, including costs of hospitalization, the need for surgical intervention, and postoperative infections during treatment with anti–tumor necrosis (TNF) factor agents.

Clinical Trials of Treatments for IBD

Vedolizumab

When treating patients with IBD, one of the most important aspects of patient care is selection of the most appropriate drug for the particular clinical scenario encountered. This goal can be facilitated through acquiring data from comparative effectiveness trials. The VARSITY trial is the first comparative effectiveness trial performed in patients with IBD. Results were initially presented at the 14th Congress of the European Crohn's and Colitis Foundation in Copenhagen, Denmark and subsequently reported at the DDW meeting.[1,2] VARSITY was a multicenter, double-blind, double-dummy, randomized, controlled phase 3b trial of vedolizumab vs adalimumab in patients with active ulcerative colitis. Vedolizumab is a gut-selective humanized immunoglobulin (Ig) G1 monoclonal antibody that binds to the integrin $\alpha4\beta7$. Adalimumab is a human IgG1 monoclonal antibody that binds and neutralizes TNF, exerting systemic anti-inflammatory effects. The objective of the VARSITY trial was to compare the efficacy and safety of intravenous vedolizumab vs subcutaneous adalimumab at week 52 in patients with moderately to severely active ulcerative colitis. Intravenous vedolizumab was administered at a standard loading dose of 300 mg at weeks 0, 2, and 6, and then given every 8 weeks thereafter until week 46. Placebo was given at week 0 and every 2 weeks until week 50. Subcutaneous adalimumab was given at a standard loading dose of 160 mg initially at week 0, then 80 mg at week 2, and 40 mg every 2 weeks until week 50. Placebo was given at 0, 2, and 6 weeks, and then every 8 weeks thereafter until week 46.

The trial initially assessed 1285 patients; 514 were excluded. The trial randomly assigned 771 patients to vedolizumab or adalimumab. Treatment was completed by 74.5% of the vedolizumab arm and 61.9% of the adalimumab arm. The demographics of both treatment arms were relatively similar. In both groups, approximately 21% of patients had received a prior anti-TNF agent. Approximately 36% had received concomitant corticosteroids, and approximately 26% had received concomitant immunomodulators. The proportion of patients with a Mayo score of 9 to 12 was a little higher than 50%. Therefore, the patients in this study were relatively ill and had refractory disease.

The primary endpoint was clinical remission at week 52, as defined by a complete Mayo score of 2 points or less, with no individual subscore of more than 1 point. The proportion of patients who achieved clinical remission at week 52 was 31.3% with vedolizumab vs 22.5% with adalimumab (*P*=.0061). Among patients who were anti-TNF–naive, the rates of clinical remission were 34.2% with vedolizumab vs 24.3% with adalimumab (*P*=.0070). In patients with prior exposure to anti-TNF therapy, these rates were 20.3% vs 16.0% (*P*=.4948),

respectively. Mucosal healing at week 52 was achieved in 39.7% of the vedolizumab arm vs 27.7% of the adalimumab arm (*P*=.0005). Among patients who were anti-TNF–naive, mucosal healing occurred in 43.1% of the vedolizumab arm vs 29.5% of the adalimumab arm (*P*=.0005). At week 52, the mean daily dose of oral corticosteroids was 7.4 mg in the vedolizumab arm vs 8.6 mg in the adalimumab arm. The change from baseline was 11.6 mg with vedolizumab vs 8.6 with adalimumab. The improvement in partial Mayo score from baseline was greater with vedolizumab vs adalimumab.

Adverse events, including serious adverse events, were similar in both treatment groups. Infections and infestations were numerically higher with adalimumab.

In conclusion, the VARSITY trial showed superior clinical remission and mucosal healing with vedolizumab compared with adalimumab among patients with moderately to severely active ulcerative colitis. The improvement was most pronounced among patients who were anti-TNF–naive. The differences in clinical response tended to emerge around weeks 6 and 14. Rates of corticosteroid-free remission numerically favored adalimumab, but the absolute reduction in the use of corticosteroids was higher with vedolizumab. (For both of these endpoints, the differences were not statistically significant.)

These results were exciting. A critique of the study design might be that there was no forced tapering of corticosteroids; tapering was at the discretion of the individual provider. Additionally, dose escalation of either adalimumab or vedolizumab was not permitted. In clinical practice, we often adjust the doses of these drugs among patients who do not respond to initial dosing. Nonetheless, the VARSITY trial represents an excellent start in the comparative evaluation of IBD drugs. More of these types of studies are needed to help us better understand which, if any, patient populations fare better in certain clinical scenarios.

Several other studies examined various aspects of the use of vedolizumab. The EVOLVE trial was a real-world analysis comparing outcomes and safety among biologic-naive patients with ulcerative colitis treated with vedolizumab or an anti-TNF agent.[3] During the 24-month study period, patients who received vedolizumab were twice as likely to remain on treatment. These patients were less likely to develop exacerbation of their disease. The rates of clinical effectiveness were similar regardless of the treatment.

Dr Edward V. Loftus Jr and colleagues presented a long-term safety analysis of vedolizumab from the GEMINI Long-Term Safety Study.[4] This analysis confirmed earlier reports.[5] Long-term treatment with vedolizumab was safe and well tolerated. There was no increased risk in clinically important safety concerns, such as progressive multifocal leukoencephalopathy, serious infections, or infusion reactions. Patients who continued to receive treatment in the study had favorable clinical outcomes.

Among patients with IBD, the use of immunomodulators, including thiopurines and biologics, has been associated with an increased risk of malignancy.[6] Dr Timothy Card and colleagues analyzed data from the GEMINI Long-Term Safety Study, as well as postmarketing data, to determine whether the use of vedolizumab increases the risk of malignancy.[7] The study included 1034 patients with Crohn's disease and 751 patients with ulcerative colitis who had received vedolizumab for at least a year. The use of vedolizumab did not appear to increase the incidence of malignancy among these patients with IBD.

A retrospective, multicenter observational study conducted in Europe examined whether treatment with vedolizumab impacted pregnancy.[8] The study compared data for 3 groups of women with IBD: those treated with vedolizumab, those treated with an anti-TNF agent, and those who had not received immunomodulatory or biologic therapies. Rates of miscarriage were 16%, 13%, and 8%, respectively. However, after excluding patients with active disease during pregnancy, these rates were adjusted to 14%, 14%, and 12%. There was no significant difference in the number of infants born prematurely or with a congenital anomaly among the 3 cohorts.

The impact of vedolizumab on quality of life and work productivity was evaluated in 2 studies. An analysis of data from the phase 3b VERSIFY trial examined these measures among 56 patients with Crohn's disease treated with intravenous vedolizumab.[9] The analysis found early, substantial improvements in quality of life and work productivity that began at week 14 and persisted through week 52. Improvements for both of these measures were greater among patients with endoscopic remission. An analysis of data for patients with Crohn's disease enrolled in the phase 3 VISIBLE 1 trial found similar results.[10] Early improvements in quality of life and work productivity were seen at week 6 after intravenous vedolizumab induction therapy and were maintained through week 52 among patients who received vedolizumab intravenously or subcutaneously. This analysis included a control arm, and subcutaneous vedolizumab showed statistically significant and clinically meaningful improvements vs placebo in quality of life and work productivity.

Ustekinumab

Dr Bruce E. Sands and coworkers presented data for ustekinumab as maintenance therapy in the double-blind, randomized phase 3 UNIFI trial for patients with active ulcerative colitis.[11] Ustekinumab is already in use and approved for patients with moderate to severe Crohn's disease. The induction portion of this study showed that ustekinumab improved clinical remission, clinical response, and other endpoints.[12] The maintenance phase randomly assigned treatment to 523 patients with moderate to severe ulcerative colitis who required further treatment after receiving therapies such as vedolizumab and anti-TNF agents.[11] The patients had achieved

a state of clinical response at 8 weeks after a single intravenous induction dose of ustekinumab. The patients were then randomly assigned to treatment with ustekinumab at 90 mg given every 8 weeks or every 12 weeks, or placebo. The primary endpoint of clinical remission at week 44 was 43.8% with ustekinumab given every 8 weeks, 38.4% with ustekinumab given every 12 weeks, and 24% with placebo. Endoscopic healing at week 44 occurred in 51.1%, 43.6%, and 28.6%, respectively. The safety profile was consistent with other studies. Ustekinumab was already known to be effective for active Crohn's disease.[13] I anticipate that ustekinumab will be the next agent to gain regulatory approval from the US Food and Drug Administration (FDA) for the treatment of ulcerative colitis.

A study by Dr Katherine Li and colleagues examined the impact of ustekinumab induction therapy on endoscopic and histologic healing in the phase 3 UNIFI study of patients with moderate to severe ulcerative colitis.[14] In this study, patients underwent biopsies from the distal colon at screening and again at week 8 of induction treatment. At week 8, patients in the placebo group who were not responding received ustekinumab at 6 mg/kg intravenously. Patients not responding to intravenous ustekinumab received a subcutaneous dose of 90 mg.

At week 8, endoscopic healing was seen in 26.3% of patients receiving ustekinumab at 130 mg, 27.0% of patients receiving ustekinumab at 6 mg/kg, and 13.8% of the placebo group. Compared with placebo, intravenous ustekinumab was associated with higher rates of endoscopic and histologic healing as separate endpoints, as well as for the histologic/endoscopic healing combination. About 10% of patients who did not achieve clinical response at week 8 after intravenous ustekinumab achieved histologic endoscopic healing following a second subcutaneous dose. Histologic healing was associated with reduction in clinical and endoscopic disease activity, as well as an improvement in patient-reported symptoms. Although it is now possible to achieve histologic healing, I would suggest that it should not be the ultimate endpoint. A response should still be defined as endoscopic healing in a patient who is doing well, regardless of histologic healing. Previous studies have shown that histologic healing predicts fewer future disease flares over 6 to 12 months.[15]

Mirikizumab

Dr Sands and colleagues presented a multicenter, randomized, parallel-armed, double-blind, placebo-controlled phase 2 study of mirikizumab in patients with active Crohn's disease.[16] Mirikizumab is an IgG4 monoclonal antibody that targets the p19 subunit of the interleukin (IL) 23 cytokine. It is more selective than ustekinumab, which inhibits the p40 components of IL-12 and IL-23. Several different agents that inhibit IL-23 are currently in development, such as the anti-p19 agents brazikumab, risankizumab, guselkumab, mirikizumab, and tildrakizumab. Previous studies have shown that mirikizumab is an effective treatment for psoriasis and ulcerative colitis.[17,18] The study presented by Dr Sands evaluated whether mirikizumab was superior to placebo in inducing endoscopic response. At week 12, endoscopic findings, patient-reported outcomes, and Crohn's Disease Activity Index score improvements were statistically greater for the mirikizumab groups vs the placebo group. Mirikizumab was associated with a relatively low rate of adverse events that was similar to placebo and consistent with the prior overall patient safety profile. This proof-of-concept study affirms that mirikizumab can induce meaningful improvements in clinical and endoscopic outcomes. The sustained efficacy and safety are currently being evaluated in a maintenance trial.[19] These findings suggest that the IL-23 component of IL-12/23 lessens inflammation. I anticipate that many such compounds will move forward in development in the future.

Upadacitinib

Dr Remo Panaccione and colleagues presented results from the dose-ranging phase 2b U-ACHIEVE study, which evaluated the efficacy of upadacitinib as an induction therapy for the treatment of patients with moderately to severely active ulcerative colitis.[20] Enrolled patients had already received a prior biologic therapy, and they required further treatment. Upadacitinib is an investigational Janus kinase (JAK) 1 inhibitor that shows potential for the treatment of patients with active ulcerative colitis. Initial data from an 8-week, double-blind, placebo-controlled phase 2b study showed that upadacitinib was well tolerated and had significantly greater efficacy than placebo in patients with moderately to severely active ulcerative colitis.[21] This subgroup analysis focused on patients with an inadequate response, who lost response, or who were intolerant to the agent. The analysis identified a dose response in patients who were intolerant to biologic therapies compared with patients who were not intolerant to biologic therapies. Efficacy was numerically greater in the patients who were not intolerant to biologic therapy. These data are different from those in other studies. It had been presumed that the second course of biologic therapy is less effective than the first. Historically, with use of a small molecule, such as the oral JAK inhibitor tofacitinib, outcomes were similar regardless of the patient's prior exposure to biologic therapy.

The Impact of Hospital Teaching Status on IBD Hospitalization Outcomes

A large amount of the expenditure for IBD is related to hospitalization. It is important to attempt to reduce the cost of care without compromising quality of care for IBD patients. Patient outcomes are a top priority. In general, teaching hospitals are thought to have higher costs of care and more trainees than community hospitals. It is not known how hospital teaching status influences the outcomes for patients with IBD. My colleagues and I investigated the impact of hospital teaching status on IBD hospitalization outcomes.[22] Our study identified 29,863 patients with ulcerative colitis discharged from 291

hospitals, and 62,698 patients with Crohn's disease discharged from 314 hospitals. The unadjusted mean length of stay, discharge, and 30-day readmission rates were higher among teaching hospitals for both Crohn's disease and ulcerative colitis. The mortality rate was higher among major teaching hospitals for patients with ulcerative colitis, but not Crohn's disease. After a multivariable analysis, however, only the 30-day readmission rate for ulcerative colitis was increased in major teaching hospitals compared with nonteaching hospitals (hazard ratio, 1.98%; 95% CI, 0.33-3.61). We concluded that the differences in outcomes when looking at cost-effective hospital care for patients with IBD seem to be driven primarily by the disease severity, rather than by hospital teaching status. Future research should be done to better characterize the factors driving resource utilization in IBD hospitalizations. Teaching hospitals were perceived to be more costly, which is likely a byproduct of the "funnel" effect, as these hospitals often treat sicker patients who were referred by other hospitals. Patients who are sicker and use more resources receive care in places with greater expertise and capability.

Surveillance With Chromocolonoscopy

My colleague Dr Anna Buchner presented our study examining surveillance with chromocolonoscopy with endoscopic mucosal resection of colitis-associated "defiant" lesions in patients with long-term IBD.[23] We defined a defiant lesion as one identified during colonoscopy that defied resection by standard snare polypectomy techniques. The SCENIC Consensus Statement suggested that well-circumscribed, defined lesions that are dysplastic are potentially removable if they do not have a malignant appearance and are not malignant on biopsy.[24] Since the publication of this consensus statement, there has been an increase in the number of patients with long-term IBD who have new index lesions or dysplasia and are referred to pan-chromocolonoscopy before consideration of colectomy. During pan-chromocolonoscopy, the clinician can attempt a curative colonoscopic resection of defiant lesions.

The study evaluated the characteristics of defiant lesions, as well as outcome in these patients. Among the 51 patients enrolled in the study, 7 had been referred for a known lesion that was deemed defiant. The remainder had been referred for pan-chromocolonoscopy examination after identification of dysplasia during a colonoscopy performed within the prior 12 months. The study identified 66 lesions, of which 32 were defiant. They ranged in size from 1.6 cm to 4 cm. The Paris classification of the lesions was Is in 24 and IIa in 8. Two-thirds of the lesions were located in the right side of the colon. En bloc resection was performed in 24 of the defiant lesions (75%), and piecemeal resection was done in 8 lesions (25%). The findings were low-grade dysplasia in 50%, serrated adenoma in 38%, and hyperplastic in 13%. Among 4 of 27 patients (14.8%), the procedure identified evidence of recurrent residual tissue at the site of colonoscopy, which was eradicated with endoscopic resection or ablation. It is important to perform another procedure, after 3 to 6 months, to identify any material that persists or recurs and can be eradicated. In the past, the standard approach had been to refer patients with defiant lesions to surgery to undergo complete or subtotal colectomy. In our study, most of the defiant lesions were successfully eradicated with dedicated therapeutic chromocolonoscopy using adjunctive resection and ablation techniques directly. This important finding can decrease the need for surgical intervention.

No Rise in Postoperative Infections During Anti-TNF Therapy

An abstract presented at the plenary session evaluated whether anti-TNF therapy is a risk factor for postoperative infection in a prospective cohort of patients with ulcerative colitis or Crohn's disease.[25] There has been concern that anti-TNF therapy might increase the risk of postoperative infectious complications in patients with IBD, and this treatment is sometimes discontinued in preparation for surgical procedures. This multicenter, prospective study enrolled 955 patients undergoing intra-abdominal surgery. Preoperative exposure to anti-TNF therapy was reported in 40% of patients. Anti-TNF trough drug levels were assessed in 322 patients. Detectable anti-TNF inhibitor trough levels were found in 23.7% of the entire cohort. The rates of infection were 19.4% for patients exposed to anti-TNF therapy vs 20.2% for those not exposed, a difference that was not statistically significant (P=.8). In a multivariate analysis, neither current anti-TNF therapy nor detectable anti-TNF levels were associated with infection. These data are practice-changing. They suggest that it is not necessary for patients to discontinue treatment with anti-TNF therapy when undergoing operative intervention.

Rates of Lymphopenia With Tofacitinib

Tofacitinib is approved by the FDA for the treatment of patients with ulcerative colitis. Tofacitinib is primarily an inhibitor of JAK1 and JAK3. Other JAK inhibitors in development include peficitinib, a JAK1 and JAK3 inhibitor; upadacitinib, a JAK1 inhibitor; delgocitinib, a JAK1 inhibitor; and TD-1473, a pan-JAK inhibitor. The JAK inhibitors are small molecules, not biologics. They act as immune suppressants. Studies have evaluated JAK inhibitors in ulcerative colitis and Crohn's disease.[26,27] Tofacitinib was not effective in the treatment of patients with Crohn's disease.[28] (Some might argue that this outcome was related to clinical trial design.)

I presented results of a study that evaluated the rates of lymphopenia in studies of tofacitinib.[29] Tofacitinib is known to lower lymphocytes.[30] The study found that patients treated with tofacitinib as induction or mainte-

nance therapy exhibited small changes in hemoglobin, absolute lymphocyte count, absolute neutrophil count, and platelet count. There was no decrease in serum hemoglobin; JAK inhibition has been known to inhibit erythropoietin, which is involved in the escalation of hemoglobin.[31] In a phase 3 trial of tofacitinib, discontinuations due to laboratory abnormalities were low.[32] Only 6 patients required early termination of tofacitinib based on prespecified discontinuation criteria related to decreased hemoglobin, and 2 patients discontinued owing to absolute lymphocyte count decline. There was no dose dependency in anemia, lymphopenia, or neutropenia. There were no infectious complications related to these events. These data are reassuring. However, during treatment with tofacitinib, the patient's absolute lymphocyte count, absolute neutrophil count, and hemoglobin should be monitored.

Disclosure

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