GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

August 2018 Volume 14, Issue 8, Supplement 4

A SPECIAL MEETING REVIEW EDITION

Highlights in Ulcerative Colitis and Crohn's Disease From the 2018 DDW Meeting

A Review of Selected Presentations From the 2018 Digestive Disease Week Meeting • June 2-5, 2018 • Washington, DC

Special Reporting on:

- Comparative Effectiveness of Vedolizumab and Tumor Necrosis Factor–Antagonist Therapy in Ulcerative Colitis: A Multicenter Consortium Propensity Score–Matched Analysis
- Comparative Safety Profile of Vedolizumab and Tumor Necrosis Factor–Antagonist Therapy for Inflammatory Bowel Disease: A Multicenter Consortium Propensity Score–Matched Analysis
- Comparative Effectiveness of Vedolizumab and Tumor Necrosis Factor–Antagonist Therapy in Crohn's Disease: A Multicenter Consortium Propensity Score–Matched Analysis
- Adherence and Persistence With Vedolizumab Among Patients With Inflammatory Bowel Disease in an Academic Medical Center
- Efficacy and Safety of Anti–Interleukin-23 Therapy With Mirikizumab (Ly3074828) in Patients With Moderate-to-Severe Ulcerative Colitis in a Phase 2 Study
- Efficacy and Safety of Tofacitinib Retreatment for Ulcerative Colitis After Treatment Interruption: Results From the OCTAVE Clinical Trials
- Efficacy and Safety of Upadacitinib Maintenance Treatment for Moderate-to-Severe Crohn's Disease: Results From the CELEST Study
- Ustekinumab Responders Versus Nonresponders in Refractory Pediatric Inflammatory Bowel Disease

PLUS Meeting Abstract Summaries

With Expert Commentary by:

Edward V. Loftus Jr, MD
Professor of Medicine
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester, Minnesota

ON THE WEB:
gastroenterologyandhepatology.net

Indexed through the National Library of Medicine
(PubMed/Medline), PubMed Central (PMC), and EMBASE

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.

In UC & CD

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

With...

Entyvio®
vedolizumab

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

Long-term focus—from the start:

GI-FOCUSED ACTION

Entyvio specifically binds to α4β7 integrin, blocking its interaction with MAdCAM-1, which is mainly expressed on gut endothelial cells[1]

WITH

REMISSION ACHIEVED

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

AND

5-YEAR INTEGRATED SAFETY

A 5-year analysis, including an open-label continuation study, demonstrated consistent results with clinical trials across safety parameters[1,3]

Individual results may vary.

Begin the Change

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.

References: 1. Entyvio [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc. **2.** Data on file. Takeda Pharmaceuticals America, Inc. Deerfield, IL. **3.** Colombel JF, et al. *Gut*. 2017;66:839-851.

Printed in U.S.A./April 2018 USD/VED/17/0097(2)

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

U.S. License No. 1898

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

Revised: February 2018

VMB245 R2_Brf. L-BZV-0218-4

Comparative Effectiveness of Vedolizumab and Tumor Necrosis Factor–Antagonist Therapy in Ulcerative Colitis: A Multicenter Consortium Propensity Score–Matched Analysis

Ulcerative colitis (UC) is one of the main types of inflammatory bowel disease (IBD) and is characterized by pathologies associated with a dysregulated immune response.[1] Current treatments include glucocorticoids, immunomodulators, and inhibitors of tumor necrosis factor (TNF); however, not all patients respond to these treatments, many patients lose their response after some time, and toxicities often limit the use of these treatments. In addition, although anti-TNF agents have revolutionized IBD therapy, treatment with a second TNF inhibitor generally elicits reduced efficacy. Vedolizumab is a humanized monoclonal antibody that selectively targets the α4β7 integrin, which is expressed by T lymphocytes that migrate to the gastrointestinal tract. The antibody interferes with migration and adhesion of these T cells, providing a gut-selective reduction in inflammation and a completely different mechanism of action from that of TNF inhibitors.[2,3] In clinical practice, prior exposure to anti-TNF therapy is a predictor of reduced vedolizumab effectiveness, but trials that directly compare the 2 agents have been lacking. Indirect comparisons have suggested that anti-TNF therapy and vedolizumab may be equally effective in the treatment of UC.

Dr David Faleck presented results from a retrospective study that evaluated outcomes in UC patients who completed induction therapy with vedolizumab or a TNF inhibitor between 2014, the year of vedolizumab's approval, and 2017, using data from the Victory Consortium.[4] The Victory Consortium consists of US practice sites that specialize in the care of patients with IBD.[5] Data were collected at these sites using standardized extraction forms, followed by central pooling, collation, and analysis. Propensity score matching was used to account for age, sex, UC-related hospitalization within the prior year, disease extent and severity, corticosteroid refractoriness or dependence, and prior failure to anti-TNF therapy. The purpose of propensity score matching is to reduce confounding bias within the study population and to mimic the randomized clinical trial design by eliminating systemic differences in patients at baseline.[6] The strategy is best applied to large observational cohorts by eliminating duplicate patients and those without a close match of characteristics. The propensity score matching method results in a histogram for each subpopulation, allowing visual evaluation of how well the subpopulations are matched.[5]

In this study, Cox proportional hazard models were used to compare cumulative rates of response. Clinical remission was defined as complete resolution of UC-related symptoms. Corticosteroid-free remission was defined as tapering off of corticosteroid use, with no repeat corticosteroid prescription for 4 weeks. Endoscopic healing was defined as a Mayo endoscopic score of 0 or 1.[7]

The analysis initially identified 646 UC patients who began treatment with vedolizumab or an anti-TNF agent between 2014 and 2017. Propensity score matching yielded a cohort of 334 patients (Figure 1). The propensity score model predicted treatment status with an area under the curve of 0.73. Among the patients included in the treatment comparison, 167 (50%) were treated with vedolizumab, 49% were male, and the median age was 36 years. Baseline demographics were

ABSTRACT SUMMARY Reduced Rates of Crohn's-Related Surgeries, Hospitalizations, and Alternate Biologic Initiation With Ustekinumab in the IM-UNITI Study Through 2 Years

Rates of CD-related surgeries, hospitalizations, and the need to initiate treatment with a new biologic agent were retrospectively evaluated in patients from the phase 3 IM-UNITI (A Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Patients With Moderately to Severely Active Crohn's Disease) study of ustekinumab maintenance therapy (Abstract Sa1743). Patients in IM-UNITI were evenly randomized to receive placebo, ustekinumab 90 mg every 12 weeks, or ustekinumab 90 mg every 8 weeks. Patients who completed week 44 were eligible to enter the long-term extension study while continuing their current regimen. With 2-year data from the extension study, the combined incidence of CD-related hospitalization, surgery, or the need to switch to an alternate biologic therapy at week 96 was reduced relative to placebo in patients treated with ustekinumab every 8 weeks (HR, 0.679; 95% CI, 0.486-0.950; *P*=.020) and every 12 weeks (HR, 0.508; 95% CI, 0.264-0.977; *P*=.039). The improvement with ustekinumab vs placebo was also observed for the combination of hospitalization and surgery (ustekinumab every 8 weeks: HR, 0.601; 95% CI, 0.411-0.879; *P*=.006; ustekinumab every 12 weeks: HR, 0.477; 95% CI, 0.238-0.957; *P*=.033). The incidence of switching to an alternate biologic therapy was significantly reduced in patients receiving ustekinumab every 8 weeks vs placebo (*P*=.042) but not with the 12-week dosing schedule (*P*=.467).

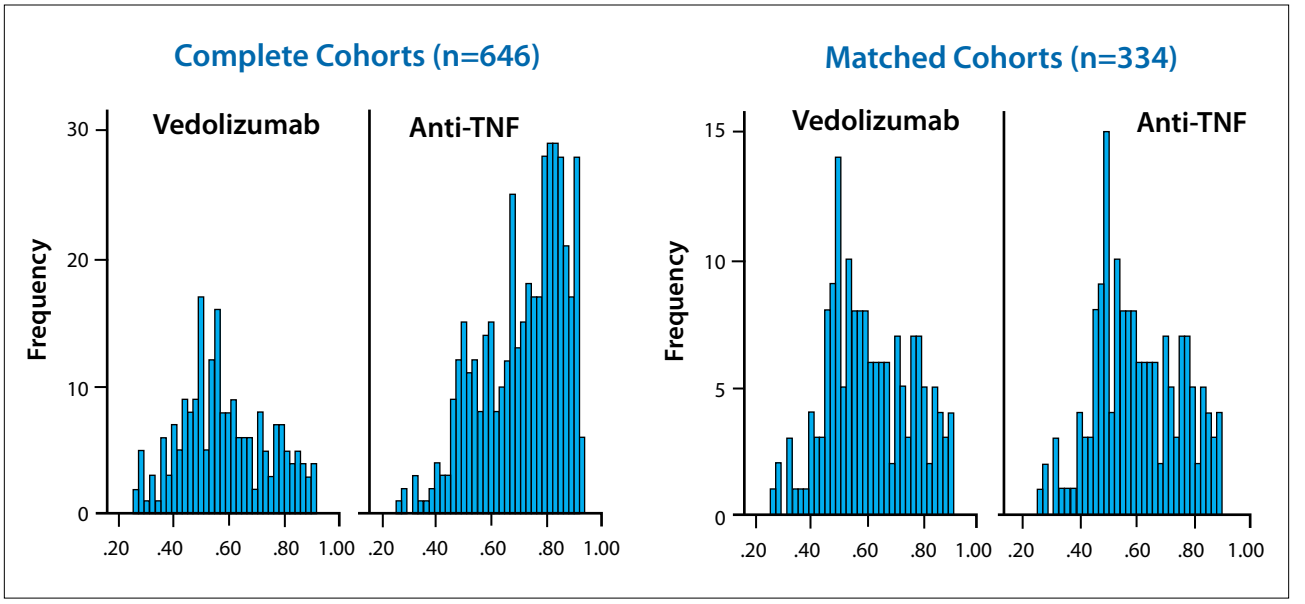

Figure 1. Histograms of complete cohorts and matched cohorts. The propensity score accurately predicted vedolizumab vs anti-TNF therapy with an area under the curve of 0.73. TNF, tumor necrosis factor.

Adapted from Faleck D et al. DDW abstract 328. *Gastroenterology*. 2018;154(suppl 1):S82.[4]

Table 1. Primary Outcomes of Vedolizumab and Anti-TNF Therapy in Patients With Ulcerative Colitis

	Vedolizumab (n=167)	Anti-TNF Agent (n=167)	aHR[a] 95% CI
Clinical Remission	54%	37%	1.54 1.08-2.18
Corticosteroid-Free Remission	49%	38%	1.43 0.79-2.60
Endoscopic Healing	50%	42%	1.73 1.10-2.73

[a]Adjusted for the number of prior anti-TNF agents and for concomitant corticosteroid or immunomodulator use. aHR, adjusted hazard ratio; TNF, tumor necrosis factor.

Adapted from Faleck D et al. DDW abstract 328. *Gastroenterology*. 2018;154(suppl 1):S82.[4]

comparable between the 2 treatment groups. Patients in the anti-TNF arm showed a greater extent of disease that was not significant. However, both groups had a 31% rate of failure to anti-TNF therapy. In the anti-TNF cohort, 64% had not received prior treatment with a TNF antagonist vs 52% in the vedolizumab cohort. In the vedolizumab cohort, 19% of patients had been exposed to at least 2 prior anti-TNF agents vs 5% in the anti-TNF cohort. Use of concomitant medications at baseline, including corticosteroids and immunomodulators, was higher in the anti-TNF cohort (corticosteroids, 54% vs 50%; immunomodulators, 37% vs 32%). The propensity model does not take into consideration concomitant medication use because that is not a variable related to prescribing anti-TNF agents or vedolizumab, hence the imbalance between the 2 cohorts. However, this imbalance was addressed in the final Cox modeling.

Rates of clinical remission and endoscopic healing were higher with vedolizumab (Table 1). After adjusting for concomitant corticosteroid use, concomitant immunomodulator use, and the number of prior anti-TNF therapies, the 12-month cumulative rate of clinical remission was 54% with vedolizumab vs 37% with anti-TNF therapy (adjusted hazard ratio [HR], 1.54; 95% CI, 1.08-2.18). The 12-month cumulative rate of endoscopic healing was 50% with vedolizumab vs 42% with anti-TNF therapy (adjusted HR, 1.73; 95% CI, 1.10-2.73). Cumulative 12-month rates of corticosteroid-free remission showed a similar trend but did not reach statistical significance (49% vs 38%; adjusted HR, 1.43; 95% CI, 0.79-2.60). The power to detect the latter outcome was reduced because only half of the cohort was on corticosteroids at baseline. The findings were consistent when stratified by disease extent and prior exposure to anti-TNF agents.

References

1. Rawla P, Sunkara T, Raj JP. Role of biologics and biosimilars in inflammatory bowel disease: current trends and future perspectives. *J Inflamm Res*. 2018;11:215-226.
2. Feagan BG, Greenberg GR, Wild G, et al. Treatment of active Crohn's disease with MLN0002, a humanized

antibody to the alpha4beta7 integrin. *Clin Gastroenterol Hepatol*. 2008;6(12):1370-1377.
3. Scribano ML. Vedolizumab for inflammatory bowel disease: from randomized controlled trials to real-life evidence. *World J Gastroenterol*. 2018;24(23):2457-2467.
4. Faleck D, Shashi P, Meserve J, et al. Comparative effectiveness of vedolizumab and tumor necrosis factor–antagonist therapy in ulcerative colitis: a multicenter consortium propensity score–matched analysis [DDW abstract 328]. *Gastroenterology*. 2018;154(suppl 1):S82.
5. Lukin DJ, Weiss A, Aniwan S, et al. Comparative safety profile of vedolizumab and tumor necrosis factor–antagonist therapy for inflammatory bowel disease: a multicenter consortium propensity score–matched analysis [DDW abstract 277]. *Gastroenterology*. 2018;154(suppl 1):S68.
6. Austin PC, Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. *Stat Med*. 2006;25(12):2084-2106.
7. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*. 1987;317(26):1625-1629.

Comparative Safety Profile of Vedolizumab and Tumor Necrosis Factor–Antagonist Therapy for Inflammatory Bowel Disease: A Multicenter Consortium Propensity Score–Matched Analysis

Vedolizumab provides gut-selective activity by targeting the α4β7 integrin and disrupting its interaction with mucosal vascular addressin cell adhesion molecule 1.[1,2] Targeting the gut may offer a superior safety profile compared with immunosuppressive agents—including thiopurines and methotrexate—and inhibitors of TNF. Outside of a controlled clinical trial setting, multiple factors contribute to the development of adverse events (AEs), and the real-world safety of vedolizumab compared with anti-TNF therapy has not been quantified. The GEMINI trials evaluated the safety and efficacy of vedolizumab in patients with UC or Crohn's disease (CD).[3,4] GEMINI 1 (Study of Vedolizumab [MLN0002] in Patients With Moderate to Severe Ulcerative Colitis) showed no significant differences in the occurrence of serious infection or serious AEs in UC patients treated with vedolizumab vs placebo. In GEMINI 2 (Study of Vedolizumab [MLN0002] in Patients With Moderate to Severe Crohn's Disease), CD patients treated with vedolizumab or placebo had similar rates of AEs, with the exceptions of an increased rate of nasopharyngitis (12.3% vs 8.0%) and any serious AE (24.4% vs 15.3%).

A retrospective study evaluated the real-world safety of vedolizumab vs anti-TNF therapy in IBD patients using data from the Victory Consortium.[5] Data were collected at the practice sites at 3- to 6-month intervals and, after removing identifying information, were sent to the central collection site. Propensity score matching in a 1:1 ratio was used to match patients according to baseline characteristics. Other matching characteristics related to serious infection and serious AEs. Serious infection was defined as any infection that required the use of antibiotics or that resulted in hospitalization, discontinuation of vedolizumab or anti-TNF therapy, or death. Serious AEs included serious infections and any AE that required discontinuation of therapy or resulted in death.

From an initial group of 1768 patients, 538 with CD and 334 with UC were included after matching. In the CD population, those in the vedolizumab cohort were more likely to have received 2 or more prior anti-TNF agents (58% vs 15%), were more likely to be using concomitant corticosteroids (43% vs 32%), and were less likely to be using concomitant immunomodulators (42% vs 54%). In the UC population, patients in the vedolizumab cohort were also more likely to have received treatment with at least 2 anti-TNF agents (19% vs 5%), but other characteristics were well matched between the 2 cohorts. For the entire IBD population, the rate of serious AEs was significantly reduced in patients treated with vedolizumab (7.1% vs 13.1%; odds ratio [OR], 0.51; 95% CI, 0.32-0.82), and the rate of serious infections was numerically lower (6.9% vs 10.1%; OR, 0.67; 95% CI, 0.41-1.07; Table 2).

Table 2. Serious Infections and Serious Adverse Events for the Entire Cohort and Subsets of Patients on Biologic Monotherapy or Combination Therapy

	Vedolizumab	Anti-TNF Agent	Odds Ratio	95% CI
Entire Cohort				
Serious Infections	6.9%	10.1%	0.67	0.41-1.07
Serious Adverse Events	7.1%	13.1%	0.51	0.32-0.82
Biologic Monotherapy				
Serious Infections	4.1%	10.1%	0.37	0.13-1.02
Serious Adverse Events	4.7%	14.5%	0.29	0.12-0.73
Biologic Agent + Corticosteroids + Immunomodulator				
Serious Infections	11.5%	13.9%	0.81	0.31-2.07
Serious Adverse Events	14.0%	14.0%	0.66	0.27-1.65

TNF, tumor necrosis factor.

Adapted from Lukin DJ et al. DDW abstract 277. *Gastroenterology*. 2018;154(suppl 1):S68.[5]

Table 3. Serious Infections and Serious Adverse Events for Patients With Crohn's Disease and Patients With Ulcerative Colitis

	Vedolizumab	Anti-TNF Agent	Adjusted Odds Ratio[a]	95% CI
Crohn's Disease				
Serious Infections	8.2%	8.9%	0.91	0.50-1.67
Serious Adverse Events	8.2%	11.2%	0.71	0.40-1.27
Ulcerative Colitis				
Serious Infections	4.8%	12.0%	0.38	0.16-0.89
Serious Adverse Events	5.4%	16.2%	0.29	0.13-0.65

[a]Adjusted for concomitant corticosteroid and/or immunomodulator use. TNF, tumor necrosis factor.

Adapted from Lukin DJ et al. DDW abstract 277. *Gastroenterology*. 2018;154(suppl 1):S68.[5]

Among patients who received biologic monotherapy with vedolizumab or an anti-TNF agent, the rate of serious AEs was again reduced in the vedolizumab cohort (4.7% vs 14.5%; OR, 0.29; 95% CI, 0.12-0.73), and the rate of serious infections was lower with vedolizumab but did not reach significance (4.1% vs 10.1%; OR, 0.37; 95% CI, 0.13-1.02). However, in the subset of patients who received a biologic agent plus corticosteroids plus an immunomodulator, the safety signal was eliminated for both serious AEs (OR, 0.66; 95% CI, 0.27-1.65) and serious infections (OR, 0.81; 95% CI, 0.31-2.07). Looking only at the subset of patients with CD and using an OR that was adjusted for concomitant corticosteroid and/or immunomodulator use, both the vedolizumab and anti-TNF arms showed similar rates of serious AEs (adjusted OR, 0.71; 95% CI, 0.40-1.27) and serious infections (adjusted OR, 0.91; 95% CI, 0.50-1.67; Table 3). A similar result was obtained for UC patients, showing comparable rates of serious AEs (adjusted OR, 0.29; 95% CI, 0.13-0.65) and serious infections (adjusted OR, 0.38; 95% CI, 0.16-0.89).

References

1. Feagan BG, Greenberg GR, Wild G, et al. Treatment of active Crohn's disease with MLN0002, a humanized antibody to the alpha4beta7 integrin. *Clin Gastroenterol Hepatol*. 2008;6(12):1370-1377.
2. Scribano ML. Vedolizumab for inflammatory bowel disease: from randomized controlled trials to real-life evidence. *World J Gastroenterol*. 2018;24(23):2457-2467.
3. Feagan BG, Rutgeerts P, Sands BE, et al; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013;369(8):699-710.
4. Sandborn WJ, Feagan BG, Rutgeerts P, et al; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013;369(8):711-721.
5. Lukin DJ, Weiss A, Aniwan S, et al. Comparative safety profile of vedolizumab and tumor necrosis factor–antagonist therapy for inflammatory bowel disease: a multicenter consortium propensity score–matched analysis [DDW abstract 277]. *Gastroenterology*. 2018;154(suppl 1):S68.

Comparative Effectiveness of Vedolizumab and Tumor Necrosis Factor–Antagonist Therapy in Crohn's Disease: A Multicenter Consortium Propensity Score–Matched Analysis

Vedolizumab has demonstrated efficacy in treatment-naive CD patients, as well as those with prior exposure to anti-TNF agents. However, the latter is a predictor of reduced vedolizumab efficacy in clinical practice.[1] Although the efficacy of vedolizumab compared with anti-TNF agents has been estimated by indirect comparisons, real-world data comparing outcomes with the 2 strategies have been lacking. The US-based Victory Consortium identified 1122 CD patients who underwent treatment with vedolizumab or an anti-TNF agent. Propensity score matching was used to identify a cohort of matched patients by accounting for age; sex; history of stricturing or penetrating disease complication; disease severity; corticosteroid refractoriness or dependence; and prior bowel surgery, hospitalization, or TNF-antagonist failure.

After propensity score matching, 538 patients were included in the CD cohort.[2] The Physician Global Assessment was used to categorize treatment response. Cox proportional hazard models were used to compare efficacy outcomes and were adjusted for concomitant corticosteroid or immunomodulator use, disease location, and the number of prior TNF inhibitors used. Clinical remission was defined as complete resolution of CD-related symptoms, and corticosteroid-free remission was defined as being on corticosteroids at baseline, and tapering off during treatment with no repeat corticosteroid prescription for 4 weeks. Endoscopic healing was defined as the absence of ulcers or erosions.

The propensity model accurately predicted vedolizumab vs anti-TNF therapy with an area under the curve of 0.80. Fifty-eight percent of patients in the vedolizumab cohort and 15% in the anti-TNF cohort had

Table 4. Cumulative Rates of Outcomes of Vedolizumab and Anti-TNF Therapy in Patients With Crohn's Disease

	Vedolizumab	Anti-TNF Agent	aHR 95% CI
Clinical Remission	38%	34%	1.27 0.91-1.78
Corticosteroid-Free Remission	26%	18%	1.75 0.90-3.43
Endoscopic Healing	50%	41%	1.67 1.13-2.47

aHR, adjusted hazard ratio; TNF, tumor necrosis factor.

Adapted from Bohm M et al. DDW abstract Sa1723. *Gastroenterology*. 2018;154(suppl 1):S369-S370.[2]

Table 5. Vedolizumab Vs Anti-TNF Therapy in Crohn's Disease Stratified by Location

	Clinical Remission aHR, 95% CI	Corticosteroid-Free Remission aHR, 95% CI	Endoscopic Healing aHR, 95% CI
Isolated Small Bowel Disease	0.70 0.32-1.51	0.60 0.17-2.05	1.45 0.52-4.10
Colonic or Ileocolonic Disease	1.51 1.04-2.20	4.90 2.44-9.83	1.70 1.10-2.61

aHR, adjusted hazard ratio; TNF, tumor necrosis factor.

Adapted from Bohm M et al. DDW abstract Sa1723. *Gastroenterology*. 2018;154(suppl 1):S369-S370.[2]

ABSTRACT SUMMARY Long-Term Effectiveness and Safety of Adalimumab Based on Crohn's Disease Duration: Results From the PYRAMID Registry

The relationship between CD duration at baseline and patient outcomes after treatment with adalimumab was evaluated in patients from the PYRAMID (A Long-Term Registry of Humira [Adalimumab] in Subjects With Moderately to Severely Active Crohn's Disease) registry (Abstract Sa1808). Adults with moderate-to-severe CD who initiated or were already receiving treatment with adalimumab were followed for 6 or more years. Outcomes were analyzed by subgroups based on CD duration at baseline. Among 2057 patients who were adalimumab-naive at baseline, CD duration was less than 2 years in 18.8%, 2 to less than 5 years in 16.9%, 5 to less than 10 years in 25.9%, and 10 years or longer in 38.4% of patients. Mean total scores from the Harvey-Bradshaw Index and the Short Inflammatory Bowel Disease Questionnaire decreased from baseline in all subgroups at 1 year. The degree of improvement was numerically similar across subgroups, and improvements were maintained through 6 years. Work Productivity and Activity Impairment scores improved in all subgroups at 1 year compared with baseline. These scores generally remained stable through 6 years. The improvement was greater in patients with CD duration of less than 5 years at baseline compared with CD duration of 5 or more years at baseline. Rates of AEs were generally similar across subgroups.

prior exposure to at least 2 anti-TNF agents. In the vedolizumab vs anti-TNF cohort, 43% vs 32% were using concomitant corticosteroids and 42% vs 54% were using concomitant immunomodulators, respectively. Based on the adjusted Cox proportional hazard model, vedolizumab showed numerically higher 12-month cumulative rates of clinical remission (38% vs 34%; adjusted HR, 1.27; 95% CI, 0.91-1.78) and corticosteroid-free remission (26% vs 18%; adjusted HR, 1.75; 95% CI, 0.90-3.43) compared with anti-TNF therapy (Table 4). The 12-month cumulative rate of endoscopic healing was significantly improved in patients treated with vedolizumab (50% vs 41%; adjusted HR, 1.67; 95% CI, 1.13-2.47). For the subset of patients with isolated small bowel disease, rates of clinical remission, corticosteroid-free remission, and endoscopic healing were not significantly different in the vedolizumab vs anti-TNF cohort. However, among patients with colonic or ileocolonic disease, vedolizumab yielded superior outcomes in terms of clinical remission (adjusted HR, 1.51; 95% CI, 1.04-2.20), corticosteroid-free remission (adjusted HR, 4.90; 95% CI, 2.44-9.83), and endoscopic healing (adjusted HR, 1.70; 95% CI, 1.10-2.61; Table 5). A prospective, randomized, controlled trial is needed to adequately evaluate these findings and to determine the optimal use of vedolizumab in treatment algorithms for CD patients.

References

1. Dulai PS, Singh S, Jiang X, et al. The real-world effectiveness and safety of vedolizumab for moderate-severe Crohn's disease: results from the US VICTORY Consortium. *Am J Gastroenterol*. 2016;111(8):1147-1155.

2. Bohm M, Sagi S, Fischer M, et al. Comparative effectiveness of vedolizumab and tumor necrosis factor–antagonist therapy in Crohn's disease: a multicenter consortium propensity score–matched analysis [DDW abstract Sa1723]. *Gastroenterology*. 2018;154(suppl 1):S369-S370.

Adherence and Persistence With Vedolizumab Among Patients With Inflammatory Bowel Disease in an Academic Medical Center

Low adherence to treatment increases the risk of treatment failure and disease recurrence.[1,2] Moreover, failure to adhere to treatment leads to higher medical costs than consistent treatment. However, as many as 45% of IBD patients with prescriptions for anti-TNF treatment are nonadherent. A retrospective analysis investigated rates of induction completion, persistence, and adherence to vedolizumab in adults with IBD.[3] The patients were treated at a single medical center from June 1, 2013 to March 31, 2017. Data were collected from electronic health records, and patients were required to have follow-up data for at least 12 months after initiation of vedolizumab. Among the 197 included patients, 58.4% had been prescribed treatment with vedolizumab within 2 years of the first IBD diagnosis. The mean age at vedolizumab initiation was 37.6 years, 54.8% of patients had CD, and 44.7% had UC. Six percent of patients had had prior IBD-related surgeries. IBD-related medications included corticosteroids (56.3%), biologic agents (34.0%), immunomodulators (29.4%), and 5-aminosalicylic acid (25.4%).

In the CD cohort, 87.0% (95% CI, 80.7%-93.4%) of patients completed vedolizumab induction treatment through dose 3 by day 98, and 75.9% (95% CI, 67.9%-84.0%) completed induction through dose 4 by day 120 (Figure 2). Treatment persistence was observed in 48.1% (95% CI, 38.7%-57.6%), and a proportion of days covered (PDC) of at least 80% was observed in 61.1% (95% CI, 51.9%-70.3%) of patients. In the UC cohort, completion of the third induction dose by day 98 was noted in 92.1% (95% CI, 86.5%-97.7%), and completion of the fourth induction dose by day 120 was noted in 82.0% (95% CI, 74.0%-90.0%).

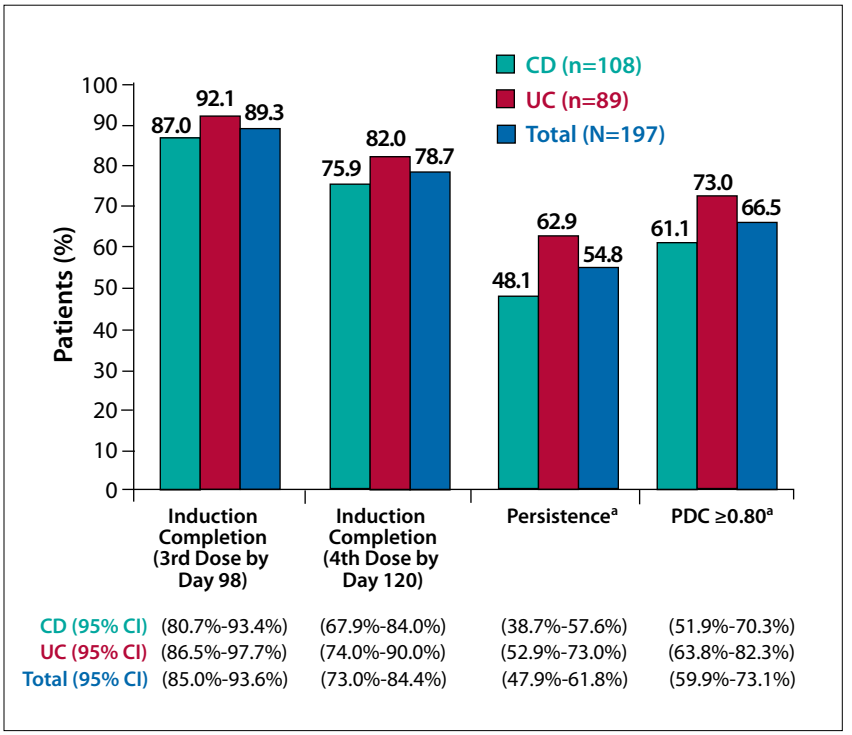

Figure 2. Induction completion, persistence, and adherence in patients taking vedolizumab. CD, Crohn's disease; PDC, proportion of days covered; UC, ulcerative colitis. [a]Over 12 months.

Adapted from Null KD et al. DDW abstract Su1019. *Gastroenterology*. 2018;154(suppl 1):S456-S457.[3]

ABSTRACT SUMMARY Anti-TNF Inhibitors Are Not Associated With Increased Risk of Infection After Joint Replacement Surgery

A retrospective case-control study investigated the impact of treatment with anti-TNF inhibitors on rates of infection in IBD patients undergoing hip, knee, or shoulder replacement (Abstract 160). The primary outcome was serious infection within 90 days after surgery. Among 1455 IBD patients who underwent joint replacement, 631 patients (43%) had a diagnosis of CD, 727 (50%) had a diagnosis of UC, and 97 (7%) had a diagnosis of indeterminate colitis. More IBD patients developed a serious infection after surgery compared with the control population (3.9% vs 2.4%; $P<.05$). Specifically, the rate of infection with *Clostridium difficile* was significantly increased in IBD patients compared with controls ($P<.05$). Based on Cox proportional hazard modeling, IBD was associated with an increased risk of serious infection, as was opioid use. Use of an immunomodulator or anti-TNF inhibitor was not associated with an increased risk of infection. However, use of a corticosteroid without concomitant use of a corticosteroid-sparing agent was associated with a nearly 3-fold increase in the risk of developing a serious infection following joint replacement.

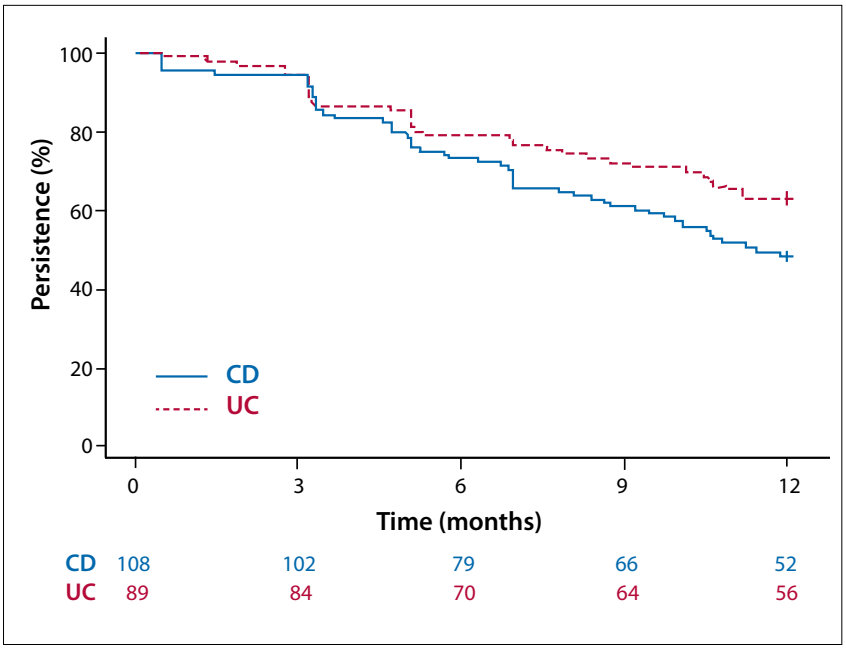

Figure 3. Kaplan-Meier curve for vedolizumab persistence. CD, Crohn's disease; UC, ulcerative colitis.

Adapted from Null KD et al. DDW abstract Su1019. *Gastroenterology*. 2018;154(suppl 1):S456-S457.[3]

Treatment persistence was observed in 62.9% (95% CI, 52.9%-73.0%), and a PDC of at least 80% was observed in 73.0% (95% CI, 63.8%-82.3%) of patients. In the total study population, induction completion was reported in 89.3% (95% CI, 85.0%-93.6%) of patients for the third dose and in 78.7% (95% CI, 73.0%-84.4%) for the fourth dose. Persistence was reported in 54.8% (95% CI, 47.9%-61.8%; Figure 3) of patients, and a PDC of at least 80% was reported in 66.5% (95% CI, 59.9%-73.1%). The results suggest that, in an academic setting, which is likely to include more complex IBD patients, nearly 90% of patients assigned to treatment with vedolizumab completed induction therapy, and over half were persistent with treatment for more than 1 year.

References

1. Fidder HH, Singendonk MM, van der Have M, Oldenburg B, van Oijen MG. Low rates of adherence for tumor necrosis factor-α inhibitors in Crohn's disease and rheumatoid arthritis: results of a systematic review. *World J Gastroenterol*. 2013;19(27):4344-4350.
2. Lopez A, Billioud V, Peyrin-Biroulet C, Peyrin-Biroulet L. Adherence to anti-TNF therapy in inflammatory bowel diseases: a systematic review. *Inflamm Bowel Dis*. 2013;19(7):1528-1533.
3. Null KD, Chang HL, Lissoos T, et al. Adherence and persistence with vedolizumab among patients with inflammatory bowel disease in an academic medical center [DDW abstract Su1019]. *Gastroenterology*. 2018;154(suppl 1):S456-S457.

Efficacy and Safety of Anti–Interleukin-23 Therapy With Mirikizumab (Ly3074828) in Patients With Moderate-to-Severe Ulcerative Colitis in a Phase 2 Study

Interleukin (IL)-23 is a proinflammatory molecule that is critically associated with the pathogenesis of IBD.[1] Blockade of the IL-23 pathway has been shown to induce a higher rate of remission compared with placebo in patients with active CD.[2] A multicenter, double-blind, placebo-controlled, phase 2 study (A Study of Mirikizumab [Ly3074828] in Participants With Moderate to Severe Ulcerative Colitis) investigated the safety and efficacy of mirikizumab, an anti–IL-23 antibody that binds to p19, in patients with moderate-to-severe UC.[3] The study's primary objective was clinical remission at week 12, defined by the 9-point Mayo disease activity index score that assesses stool frequency, rectal bleeding, and endoscopic appearance. Eligible patients had moderate-to-severe UC and were required to have failed at least 1 conventional therapy for UC. Patients were allowed to continue treatment with 5-aminosalicylic acid, corticosteroids, and/or thiopurines. After stratification based on prior biologic therapy, patients were evenly randomized into 3 mirikizumab arms and 1 placebo arm. Mirikizumab was administered every 4 weeks for a total of 3 doses. The mirikizumab dose was initiated at 50 mg (arm 1), 200 mg (arm 2), or 600 mg (arm 3). In the 50-mg and 200-mg arms, the mirikizumab dose was increased at weeks 4 and 8 if serum trough concentrations fell below 0.5 µg/mL or 2.0 µg/mL, respectively. Patients who discontinued from the trial at any time prior to week 12 were considered nonresponders, and patients who demonstrated a response at week 12 entered into a trial of maintenance treatment.

Across the 4 arms, baseline characteristics were well balanced. Patients had a mean age of 41.8 to 43.4 years, and mean disease duration ranged from 6.0 to 9.5 years. Over half of the patients had severe UC based on

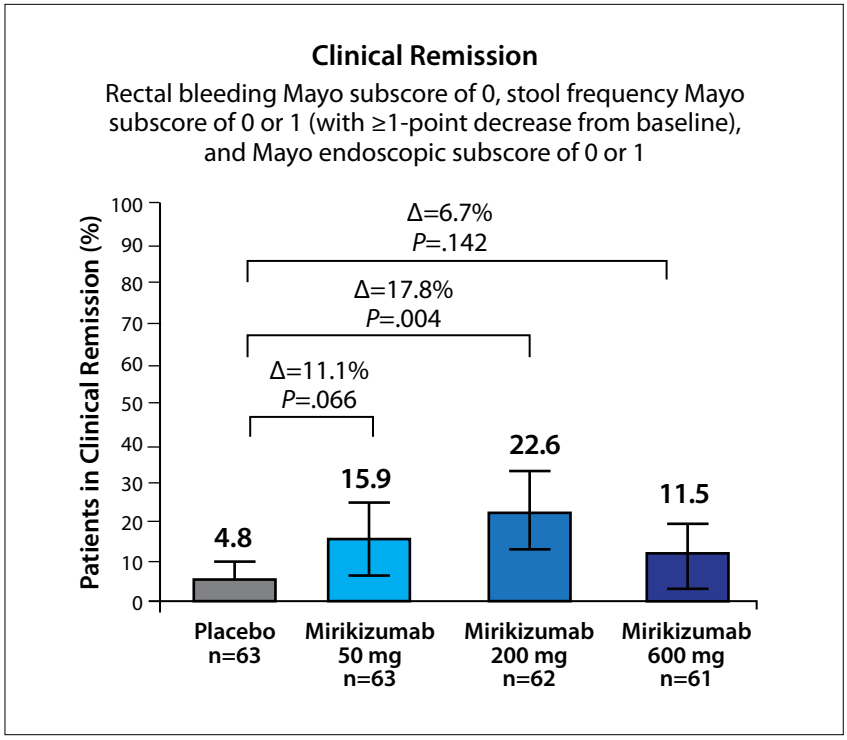

Figure 4. Clinical remission at week 12 (nonresponder imputation). All patients who discontinued from the study at any time prior to week 12 for any reason or failed to have an adequate week 12 efficacy assessment were considered nonresponders at week 12.

Adapted from Sandborn WJ et al. DDW abstract 882. *Gastroenterology*. 2018;154(suppl 1): S1360-S1361.[3]

ABSTRACT SUMMARY Lower Incidence of Herpes Zoster in Vedolizumab-Treated Vs Tofacitinib-Treated Patients With Ulcerative Colitis

The risk of herpes zoster infection in UC patients treated with vedolizumab vs tofacitinib was investigated in a retrospective, post hoc analysis (Abstract Tu1704). The analysis included 620 patients treated with vedolizumab and 394 treated with tofacitinib in randomized clinical trials. Included patients were adults with active UC who had failed or were intolerant to standard treatment. The primary outcome was the number needed to harm (NNH), which describes the number of patients that need to be treated for 1 additional patient to be harmed (ie, to experience an AE). The mean disease duration was 7 years for patients in both treatment cohorts. Mayo Clinic scores were 8.6 for the vedolizumab cohort and 8.9 to 9.1 for the tofacitinib cohort. Vedolizumab was associated with a favorable NNH (-2436 for the combined safety population and -257 for the combined intent-to-treat groups), suggesting that the drug may not be associated with an increased risk of herpes zoster infection compared with placebo. However, vedolizumab every 4 weeks was associated with a NNH of -126, while vedolizumab every 8 weeks was associated with a NNH of 3843 vs placebo. Tofacitinib treatment yielded a NNH of 36, consistent with an increased risk of herpes zoster infection compared with placebo.

modified Mayo disease activity index scores, and between 41.0% and 54.2% of patients in each arm had levels of C-reactive protein above 6 mg/L. Approximately one-half of patients were using concomitant corticosteroids at baseline, and thiopurine use ranged from 18.0% to 39.7%. Between 35.5% and 42.9% of patients in each arm had not received prior biologic therapy. Due to dose adjustments, the average induction dose was 100 mg in arm 1 and 250 mg in arm 2, and 73% and 44% of patients received dose adjustments, respectively. Compared with placebo, treatment with mirikizumab induced a greater rate of clinical remission in arm 2 (17.8% difference; *P*=.004), but did not reach significance in arm 1 (11.1% difference; *P*=.066) or arm 3 (6.7% difference; *P*=.142; Figure 4). The clinical response rate was superior with mirikizumab for all 3 antibody treatment arms (*P*<.05), and the difference in clinical response rates compared with placebo ranged from 20.6% to 28.5%. The rate of endoscopic healing was significantly improved with mirikizumab vs placebo in arm 1 (17.5% difference; *P*=.012) and arm 2 (24.3% difference; *P*<.001), but did not reach significance at the highest dose (6.8% difference; *P*=.215). Subgroup analysis based on prior biologic therapy generally showed a superior result with mirikizumab vs placebo. Symptomatic remission, assessed by a stool frequency score of 0 or 1 and a rectal bleeding score of 0, was numerically improved by 15.9% in arm 1 (*P*=.054) and was significantly improved in arm 2 (37.4% difference; *P*<.001) and in arm 3 (25.3% difference; *P*=.003) vs placebo.

Treatment-emergent AEs were observed in half of the patients in the placebo arm and in 51.6% to 57.1% of patients in the mirikizumab treatment arms. Serious AEs were observed in 3.2% of patients in the placebo arm, 0% of patients in arm 1, 3.2% of patients in arm 2, and 5.0% of patients in arm 3. Discontinuations due to an AE were rare. The most common

treatment-emergent AEs of any grade in the 3 mirikizumab arms were nasopharyngitis, anemia, and headache.

References

1. Argollo M, Fiorino G, Hindryckx P, Peyrin-Biroulet L, Danese S. Novel therapeutic targets for inflammatory bowel disease. *J Autoimmun*. 2017;85:103-116.
2. Feagan BG, Sandborn WJ, D'Haens G, et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet*. 2017;389(10080):1699-1709.
3. Sandborn WJ, Ferrante M, Bhandari BR, et al. Efficacy and safety of anti–interleukin-23 therapy with mirikizumab (Ly3074828) in patients with moderate-to-severe ulcerative colitis in a phase 2 study [DDW abstract 882]. *Gastroenterology*. 2018;154(suppl 1):S1360-S1361.

Efficacy and Safety of Tofacitinib Retreatment for Ulcerative Colitis After Treatment Interruption: Results From the OCTAVE Clinical Trials

Tofacitinib is an orally available Janus kinase inhibitor that blocks inflammatory signaling mediated by several ILs. Due to its size and structure, tofacitinib is not expected to result in the production of neutralizing antidrug antibodies that could limit treatment. A series of global, double-blind, phase 3 trials—OCTAVE (Oral Clinical Trials for Tofacitinib in Ulcerative Colitis) Induction 1, OCTAVE Induction 2, and OCTAVE Sustain—evaluated the efficacy and safety of tofacitinib in UC patients.[1] OCTAVE Open (Long-Term Study of CP-690,550 in Subjects With Ulcerative Colitis) is an ongoing study that enrolled nonresponders from OCTAVE Induction 1 and 2, as well as patients who completed or failed treatment in OCTAVE Sustain.[2,3] The objective of OCTAVE Open is to evaluate the safety and efficacy of tofacitinib (10 mg twice daily) in patients who responded to tofacitinib induction therapy and reinitiated treatment with tofacitinib after treatment interruption of 52 weeks or less. Included patients had received 8 weeks of treatment with tofacitinib (10 mg twice daily) as induction, demonstrated a response, were then randomized to placebo as part of the OCTAVE study, experienced treatment failure between week 8 and week 52, and were then retreated with tofacitinib at the same dose. Clinical response, mucosal healing, and remission endpoints were assessed at months 2 and 12, with endoscopic subscores read locally. Mucosal healing was defined as a Mayo endoscopic score of 0 or 1. Remission was defined as a total Mayo disease activity index score of 2 or less, with no individual subscore greater than 1, and a rectal bleeding score of 0.

The 101 patients had a mean age of 44.3 years, with a mean total Mayo score of 9.1 ± 1.6. Nearly three-fourths had experienced prior corticosteroid failure and/or immunosuppressant failure, and 45.5% had experienced prior failure with a TNF inhibitor. At month 2 and month 12, using nonresponder imputation, rates of remission were 40.4% and 43.4%, rates of clinical response were 75.8% and 67.5%, and rates of mucosal healing were 55.4% and 53.6%, respectively (Figure 5). Safety outcomes with tofacitinib retreatment were generally consistent with those observed in the overall study population. AEs of interest included 2 deaths and 2 malignancies: 1 case of acute myeloid leukemia and 1 case of hepatic angiosarcoma. The findings suggest that tofacitinib treatment in UC patients can be interrupted and then continued with a likelihood of efficacy and good tolerability.

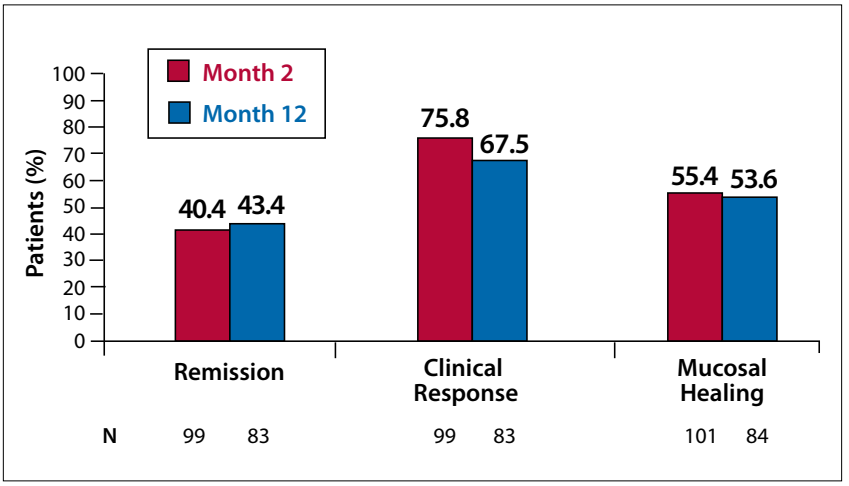

Figure 5. Efficacy of tofacitinib at months 2 and 12 after treatment interruption (nonresponder imputation). Data were based on local read of endoscopy and the July 2016 data cut. Patients were treated as nonresponders after the time of discontinuation up to the visit they would have reached if they had stayed in the study. No imputation for missing data was applied for ongoing patients. N, number of evaluable patients.

Adapted from Panes J et al. DDW abstract 905. *Gastroenterology*. 2018;154(suppl 1):S178.[3]

References

1. Sandborn WJ, Su C, Sands BE, et al; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2017;376(18):1723-1736.
2. Lichtenstein GR, Loftus EV, Bloom S, et al. Tofacitinib, an oral Janus kinase inhibitor, in the treatment of ulcerative colitis: open-label, long-term extension study [ACG abstract 714]. *Am J Gastroenterol*. 2017;112(S1):S395.
3. Panes J, Bressler B, Colombel JF, et al. Efficacy and safety of tofacitinib retreatment for ulcerative colitis after treatment interruption: results from the OCTAVE clinical trials [DDW abstract 905]. *Gastroenterology*. 2018;154(suppl 1):S178.

Efficacy and Safety of Upadacitinib Maintenance Treatment for Moderate-to-Severe Crohn's Disease: Results From the CELEST Study

Upadacitinib is an orally available inhibitor of Janus kinase 1 that was investigated in CD patients in the CELEST (A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of ABT-494 for the Induction of Symptomatic and Endoscopic Remission in Subjects With Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or Are Intolerant to Immunomodulators or Anti-TNF Therapy) study. The phase 2 study included patients with moderate-to-severe CD who had an inadequate response or were intolerant to an immunomodulator or TNF antagonist.[1] Patients 18 to 75 years of age were randomized to placebo or upadacitinib at doses ranging from 3 mg to 6 mg twice daily or 24 mg once daily for 16 weeks, followed by optional participation in an extension for 36 weeks. All patients who completed induction therapy were allowed to enter the extension portion of the study. CELEST demonstrated endoscopic and clinical improvements with upadacitinib vs placebo at week 16 and an acceptable safety profile.

In the double-blind extension study, patients were evenly randomized to receive upadacitinib at 3 mg (twice daily), 12 mg (twice daily), or 24 mg (once daily).[2] Based on new results, the latter arm was stopped and another arm was initiated, with dosing of upadacitinib 6 mg (twice daily). Two intent-to-treat populations were evaluated. The Clinical Responders cohort included patients who achieved a clinical response, but not an endoscopic response, at week 16. The Responders cohort included patients who achieved both a clinical and an endoscopic response at week 16. Among the 180 patients who were randomized for the extension study, 153 had received active treatment during induction. Ninety-four of these patients achieved a clinical response and 54 achieved a clinical and endoscopic response. In the Responders cohort, a dose-dependent response was observed at week 16, with rates of modified clinical remission of 41.2%, 62.5%, and 73.3% for upadacitinib doses of 3, 6, or 12 mg twice daily, and rates of endoscopic response were 50.0%, 50.0%, and 68.8%, respectively (Figure 6). In the Clinical Responders cohort, rates of modified clinical remission were 28.6%, 42.9%, and 51.9% for upadacitinib doses of 3, 6, or 12 mg twice daily, and rates of endoscopic response were 34.4%, 35.7%, and 44.8%, respectively. Treatment-emergent AEs were observed in 60.9% to 75.0% of patients in the 4 upadacitinib arms. Serious infection was common in the

ABSTRACT SUMMARY A Comparison of Medication Adherence and Persistence Between Intravenous Biologics and Oral Small-Molecule Therapies

A retrospective cohort study investigated patient adherence and persistence in using vedolizumab, an intravenous drug, vs tofacitinib, an oral drug, in patients with IBD or rheumatoid arthritis (Abstract Su1008). Adherence over 12 months was determined by the PDC and cumulative days with a gap of at least 20% beyond the expected interval (CG20). Persistence was determined by the time to treatment discontinuation over 12 months of follow-up. The study included 457 IBD patients treated with vedolizumab and 898 rheumatoid arthritis patients treated with tofacitinib. Mean PDC was significantly increased in IBD patients treated with vedolizumab compared with rheumatoid arthritis patients treated with tofacitinib (77.7% vs 68.2%; *P*<.001). Mean CG20 was 67.4 days in the IBD/vedolizumab cohort and 98.6 days in the rheumatoid arthritis/tofacitinib cohort (*P*<.001). Multivariate modeling that adjusted for differences in IBD vs rheumatoid arthritis patients also showed a significant difference in mean PDC for vedolizumab vs tofacitinib. The proportion of persistent patients was significantly higher in IBD patients treated with vedolizumab compared with rheumatoid arthritis patients treated with tofacitinib (65.6% vs 54.9%; *P*=.0001). IBD patients treated with vedolizumab had a 24% reduction in the risk of discontinuation vs rheumatoid arthritis patients treated with tofacitinib.

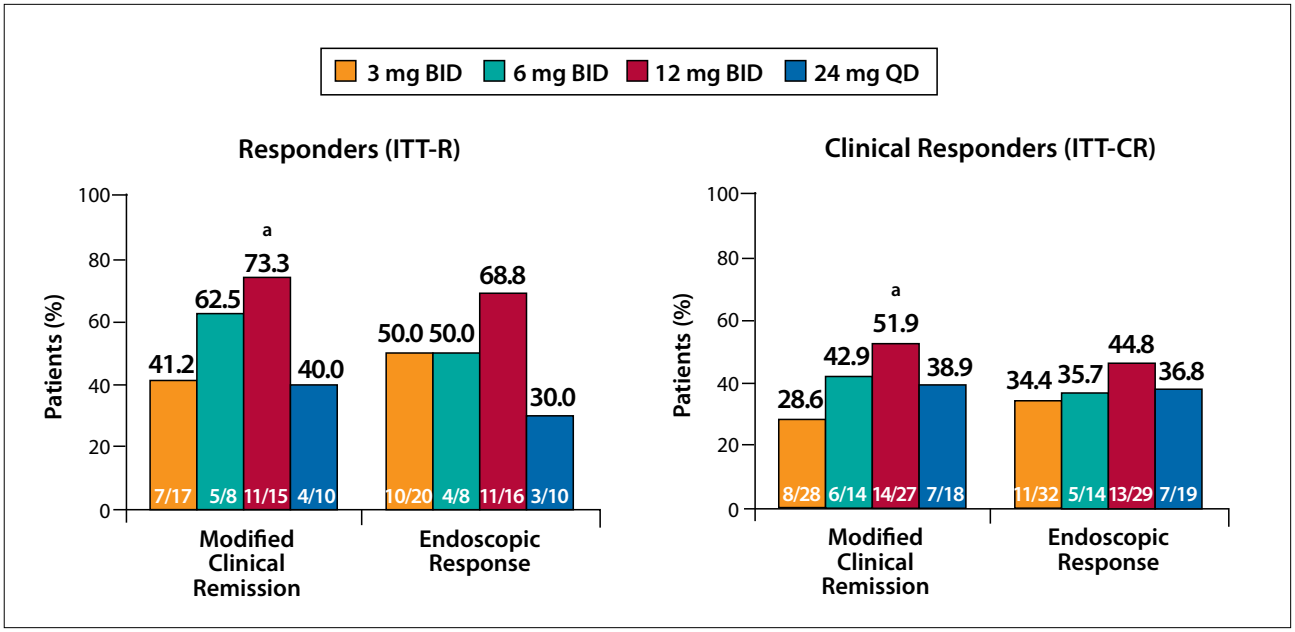

Figure 6. Modified clinical remission and endoscopic response 50% at week 52 in patients who were responders or clinical responders at week 16. BID, twice daily; ITT-CR, intent-to-treat clinical responders; ITT-R, intent-to-treat responders; QD, once daily.

[a]Statistically significant at ≤0.1 level.

Adapted from Panes J et al. DDW abstract 906. *Gastroenterology*. 2018;154(suppl 1):S178-S179.[2]

lowest dose cohort. Two malignancies, Hodgkin lymphoma and malignant neoplasm of the thymus, were reported in the cohort of patients receiving upadacitinib 12 mg twice daily.

References

1. Sandborn WJ, Feagan BG, Panes J, et al. Safety and efficacy of ABT-494 (upadacitinib), an oral JAK1 inhibitor, as induction therapy in patients with Crohn's disease: results from CELEST [DDW abstract 874h]. *Gastroenterology*. 2017;152(suppl 1):S1308-S1309.

2. Panes J, Sandborn WJ, Loftus EV, et al. Efficacy and safety of upadacitinib maintenance treatment for moderate-to-severe Crohn's disease: results from the CELEST study [DDW abstract 906]. *Gastroenterology*. 2018;154(suppl 1):S178-S179.

Ustekinumab Responders Versus Nonresponders in Refractory Pediatric Inflammatory Bowel Disease

In pediatric patients with IBD, disease is often more extensive than in adult patients. In addition, pharmacokinetics and response to therapy may differ in young patients compared with adults. The risk of surgery is greater, and few therapeutic options exist outside of TNF inhibitors. Ustekinumab is a humanized monoclonal antibody that inhibits the activity of IL-12 and IL-23 by binding to the p40 subunit.[1] In adult CD patients, ustekinumab has demonstrated efficacy vs placebo as induction or maintenance therapy.[2]

A prospective, single-center, observational cohort study investigated ustekinumab in young CD patients.[3] The study enrolled patients under 21 years of age with a diagnosis of CD or indeterminate colitis and clinically active disease. All patients had failed prior TNF inhibitor therapy. The primary outcome was clinical response at week 6 and at last follow-up. The 25 included patients had a median age at diagnosis of 11 years (range, 2-17 years). Median disease duration was 5 years (range, 1-14 years), and 80% had a diagnosis of CD. Concomitant medications when upadacitinib therapy was initiated included systemic corticosteroids (32%) and immunomodulators (52%). The median stool calprotectin level was 1020 µg/g (interquartile range, 310-2500 µg/g), and 70% of patients had ileocolonic involvement. The clinical response rate to ustekinumab was 52% at week 6 and 45% at the last follow-up (Figure 7). Rates of corticosteroid-free clinical remission were 24% at week 6 and 40% at the last follow-up. Pediatric CD Activity Index scores decreased over time. No significant differences were observed in levels of C-reactive protein, albumin, or hematocrit; however, the median C-reactive protein level decreased and there was a trend toward improvement of hematocrit over the study period.

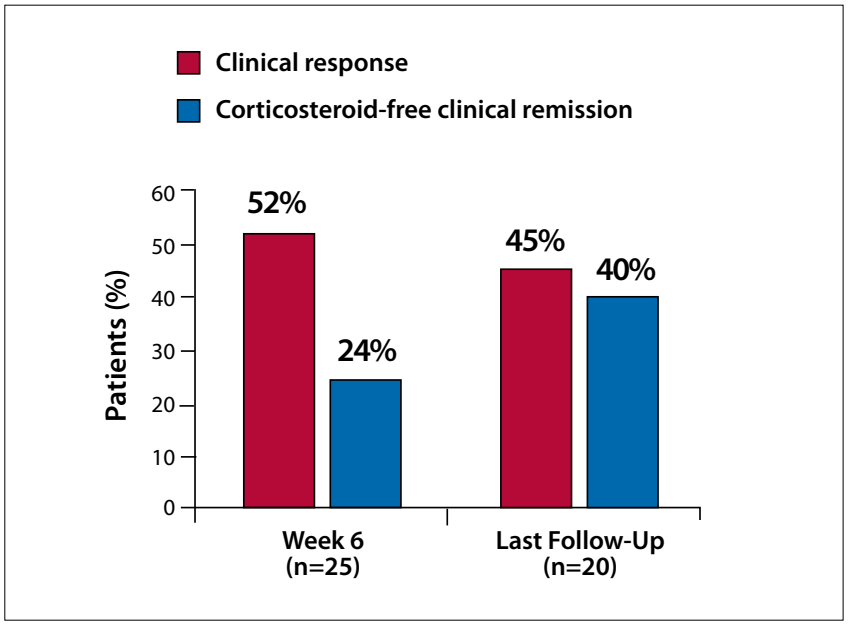

Figure 7. Clinical response to ustekinumab and corticosteroid-free clinical remission. Adapted from Fusillo SJ et al. DDW abstract 329. *Gastroenterology*. 2018;154(suppl 1):S82.[3]

ABSTRACT SUMMARY Vedolizumab Treatment Persistence Up to 3 Years: Post Hoc Analysis in Vedolizumab-Naive Patients From the GEMINI Long-Term Safety Study

A post hoc analysis evaluated vedolizumab treatment persistence in 421 IBD patients from the GEMINI long-term safety study (An Open-Label Study of Vedolizumab [MLN0002] in Participants With Ulcerative Colitis and Crohn's Disease; Abstract Sa1766). One hundred ninety UC patients and 231 CD patients were included. Prior failure with anti-TNF therapy was noted in 61% of UC patients and 74% of CD patients. Median disease duration was 5.8 years (range, 0.4-50.2 years) for UC patients and 8.3 years (range, 0.3-50.0 years) for CD patients. Among 218 patients who discontinued vedolizumab therapy during follow-up, 46% discontinued due to lack of efficacy and 27% due to AEs. The probability of continuing vedolizumab treatment at 3 years was 64% in UC patients vs 55% in CD patients. Vedolizumab treatment persistence at 3 years was higher among patients without prior failure to a TNF antagonist compared with patients who previously failed anti-TNF treatment, both in UC patients (69% vs 61%) and in CD patients (68% vs 51%). Patients were more likely to discontinue due to a lack of efficacy than due to AEs. Vedolizumab treatment persistence was numerically lower in patients with fistulizing CD vs those without fistulizing CD (48% vs 59%).

Eight patients experienced treatment failure, defined as discontinuation of therapy or having major gastrointestinal surgery. Four patients underwent colectomy, 3 underwent diverting ileostomy, and 1 patient discontinued ustekinumab therapy. Three AEs were noted. One patient who had a diverting ileostomy in place developed a peristomal abscess and fistula. This patient ultimately healed and continued ustekinumab therapy. Another patient with a history of hidradenitis developed an axillary abscess that resolved with treatment, and the patient was able to continue with ustekinumab therapy. The third patient reported severe fatigue after receiving a maintenance dose of ustekinumab. His dose was reduced from 90 mg to 45 mg. However, no improvement was observed, and the patient discontinued ustekinumab treatment. Predictors of response to ustekinumab have been identified in adults.[4] In the current (pediatric) population, predictors of long-term response to ustekinumab included having an initial response to the drug (P=.015) and having failed at least 2 classes of biologic drugs (P=.037). The long-term response rate was 64% in patients who showed a response at week 6 but was only 11% in patients who did not have an early response (P=.028).

References

1. Koutruba N, Emer J, Lebwohl M. Review of ustekinumab, an interleukin-12 and interleukin-23 inhibitor used for the treatment of plaque psoriasis. *Ther Clin Risk Manag*. 2010;6:123-141.
2. Feagan BG, Sandborn WJ, Gasink C, et al; UNITI–IM-UNITI Study Group. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2016;375(20):1946-1960.
3. Fusillo SJ, Chang V, Stein RE, et al. Ustekinumab responders versus nonresponders in refractory pediatric inflammatory bowel disease [DDW abstract 329]. *Gastroenterology*. 2018;154(suppl 1):S82.
4. Barré A, Colombel JF, Ungaro R. Review article: predictors of response to vedolizumab and ustekinumab in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018;47(7):896-905.

Highlights in Ulcerative Colitis and Crohn's Disease From the 2018 DDW Meeting: Commentary

Edward V. Loftus Jr, MD
Professor of Medicine
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester, Minnesota

Oral and poster presentations at the 2018 Digestive Disease Week (DDW) meeting highlighted a number of interesting issues in ulcerative colitis and Crohn's disease management. A late-breaking abstract focused on the novel agent mirikizumab. Several other studies provided insight on the efficacy, safety, adherence, and/or persistence of vedolizumab, tofacitinib, upadacitinib, ustekinumab, and adalimumab.

Late-Breaking Data on Mirikizumab

In the late-breaking abstract session, Dr William J. Sandborn presented results of a phase 2 study on mirikizumab.[1] This novel biologic agent is a monoclonal antibody directed against the p19 subunit of interleukin (IL)-23. There are a number of novel molecules currently being developed for inflammatory bowel disease (IBD) treatment, but this presentation offers the first data that we have seen for an anti–IL-23 agent for the treatment of ulcerative colitis.

The other interesting aspect of this study is its design. Three different doses of mirikizumab were examined, but for 2 of the doses, there was an adaptive dose design based on drug trough levels. Thus, at the time point when the patient was due for the second or third intravenous loading dose, if the patient's drug trough level was low, an increased dose was given. This design was a novel way to address the wide variability in the pharmacokinetics of biologic agents. The primary endpoint of clinical remission at week 12 was met for the middle dose of 200 mg (overall average induction dose, 250 mg). This same dose met most of the secondary endpoints, such as clinical response and endoscopic healing (Mayo endoscopic subscore 0 or 1), while the highest dose of 600 mg (fixed) achieved only 2 of the secondary endpoints.

These results serve as proof of concept that anti–IL-23 agents may be effective in the treatment of ulcerative colitis and will help inform phase 3 trials for these agents going forward. Moreover, given the sometimes refractory nature of IBD and its subtypes, it is always good to have new treatment options with novel mechanisms of action.

Mirikizumab is similar to ustekinumab in that the latter blocks IL-12 and IL-23 while the former blocks just IL-23; therefore, we expect that mirikizumab will be relatively safe. We know from psoriasis studies[2-4] that anti–IL-23 agents seem to be quite safe, so mirikizumab will likely have a clean safety profile and no black box warnings.

Vedolizumab

Data From the Victory Consortium

Several presentations focused on retrospective, observational, nonrandomized, comparative effectiveness or safety studies from the Victory Consortium, a multicenter US-based consortium of academic centers.[5-7] It is a useful construct to examine not only randomized, controlled trial data but also observational data, which show real-world experiences. Although observational studies may have confounders in the types of patients who are put on certain therapies (eg, sicker patients may be more likely to go on a particular therapy), real-world studies include the types of patients who are often excluded from clinical trials (such as patients who are older and those with multiple comorbidities). Dr David Faleck presented results from a comparative effectiveness study of vedolizumab vs anti–tumor necrosis factor (TNF) therapies for ulcerative colitis.[5] The authors used propensity score matching to try to remove observational biases from the comparison by examining all of the potential factors that might influence the decision to prescribe one biologic agent over another and then matching scores to include patients who were similarly matched. However, by only including patients with similar propensity scores, the sample size was reduced; for example, only 334 of the total 646 patients were included (167 patients on vedolizumab and 167 patients on anti-TNF agents). The authors tried to adjust for concomitant corticosteroid or immunomodulator use as well as prior anti-TNF agent use. The 1-year remission rate was 54% with vedolizumab vs 37% with anti-TNF agents. Corticosteroid-free remission was also higher with vedolizumab than with anti-TNF agents (49% vs 38%, respectively), although

this difference was not statistically significant.

These results highlight that vedolizumab is an effective first-line biologic agent for the treatment of ulcerative colitis and, thus, should definitely be in the therapeutic armamentarium. Stated another way, the take-home message for doctors in the community is that vedolizumab should not be considered only if a patient has failed an anti-TNF agent; vedolizumab is a legitimate first-line biologic option for ulcerative colitis.

Dr Dana Lukin presented the results of a comparative safety study examining vedolizumab and anti-TNF agents.[6] This study, also from the Victory Consortium, included patients with Crohn's disease as well as patients with ulcerative colitis. Again, propensity score matching was performed, so of 1768 patients, 872 were studied (436 patients treated with vedolizumab and 436 patients treated with anti-TNF agents). Approximately two-thirds of the patients had Crohn's disease, and approximately one-third had ulcerative colitis.

The authors found that serious infections were numerically less frequent with vedolizumab and serious adverse events were significantly less frequent with vedolizumab, compared to anti-TNF agents. When some of the safety issues were stratified by monotherapy vs combination therapy (defined as being on either an immunomodulator or corticosteroid), the safety benefit was primarily seen in patients on vedolizumab monotherapy, compared to patients on anti-TNF agents. When adding an immunomodulator or corticosteroid, the rates of adverse events were roughly similar between patients on vedolizumab and patients on anti-TNF agents. These results suggest that patients need not be too concerned about the safety of vedolizumab. By highlighting these data, it may be easier for doctors to have a conversation with patients to initiate them on vedolizumab, in addition to highlighting the drug's gut specificity and the fact that it does not have any black box warnings for safety.

In a poster presentation, Dr Matthew Bohm and colleagues used data from the Victory Consortium to examine the comparative effectiveness of vedolizumab and anti-TNF agents in Crohn's disease.[7] The study design was similar to that of the study presented by Dr Faleck[5]—propensity score matching identified 538 Crohn's disease patients treated with either vedolizumab or an anti-TNF agent, and then the authors adjusted for corticosteroids, immunomodulators, and the number of previous biologic agents. There were numerically but not statistically significant higher rates of clinical remission or corticosteroid-free remission with vedolizumab; however, the 12-month rate of endoscopic healing was significantly higher for vedolizumab. When the endpoints were stratified by disease location, it was the patients with colonic Crohn's disease who consistently had better results with vedolizumab than their respective anti-TNF controls. Those with small bowel Crohn's disease only did not see the same advantage with vedolizumab.

Herpes Zoster

A poster by Dr Freddy Caldera and colleagues compared the risk of herpes zoster between vedolizumab in the GEMINI trials with that of tofacitinib in the OCTAVE trials.[8] The researchers found that there was a higher risk of developing herpes zoster while on tofacitinib vs vedolizumab. This is not surprising because vedolizumab is gut-specific, and we know from the OCTAVE maintenance trial that approximately 5% of patients on the higher tofacitinib dose (10 mg twice daily) developed herpes zoster.[9] This poster reminds us that although tofacitinib is highly potent, it significantly increases the risk of herpes zoster; thus, doctors should strongly consider using the new recombinant zoster vaccine to vaccinate patients starting on this drug.

Adherence and Persistence

In a poster presentation, Dr Kyle Null and colleagues examined adherence and persistence in IBD patients at Mount Sinai Medical Center who were taking vedolizumab.[10] The researchers found that by day 98, 89.3% of patients had received their 3 induction doses, which is a high adherence rate. Over 12 months, 54.8% of patients stayed on therapy. Treatment persistence was higher in ulcerative colitis (62.9%) than in Crohn's disease (48.1%). This difference may be a reflection that the drug seems more effective in ulcerative colitis; if a drug is not working, patients often go off therapy. The poster highlights that patients have good adherence and persistence to vedolizumab treatment. This may be because intake of vedolizumab is directly observed (because it is an intravenous therapy), as opposed to oral therapy, which can be taken without direct observation.

Adherence and persistence were also examined in a poster by Dr Sunanda Kane and colleagues.[11] The researchers studied both IBD and rheumatoid arthritis patients in the MarketScan database who were taking either vedolizumab or tofacitinib. The percent of days that patients were considered to be on therapy was significantly higher in vedolizumab-treated patients (77.7%) than in tofacitinib-treated patients (68.2%). However, it should be noted that the patient populations were not identical; the vedolizumab-treated patients had IBD, whereas the tofacitinib-treated patients had rheumatoid arthritis. Another measure that was examined was the number of days that the patient was 20% beyond the expected gap in therapy, and the cumulative days gap was higher in tofacitinib-treated patients than in vedolizumab-treated patients. Overall, the proportion of persistence was 65.6% with vedolizumab and 54.9% with tofacitinib. As with the previous poster, these results likely demonstrate that patients on a medication schedule who have to come in to get treatment are more likely to

actually take it, as opposed to patients who are taking pills, who may or may not be taking the medications and may not even refill their prescriptions.

My colleagues and I also examined treatment persistence with vedolizumab.[12] We looked at long-term extension data from the GEMINI trial, which consisted of a mixture of ulcerative colitis patients and Crohn's disease patients, to examine patients who discontinued vedolizumab therapy due to adverse events or loss of effectiveness. (Patients who stopped the drug for other reasons were not included.) The probabilities of ulcerative colitis patients continuing vedolizumab therapy was 77% at 1 year and 64% at 3 years; for Crohn's disease, these numbers were a little lower but still fairly good (67% vs 55%, respectively). As previously mentioned, treatment persistence is likely a proxy for drug efficacy. Not counting patients who discontinued the drug for other reasons might be inflating the persistence data slightly, but these figures still demonstrate that there is a good chance that patients who are initial responders to vedolizumab are likely to continue to respond.

Novel Therapies

Tofacitinib

Tofacitinib, a molecule that blocks Janus kinase (JAK) 1, JAK 3, and, to a lesser extent, JAK 2, was approved by the US Food and Drug Administration for the treatment of moderate-to-severe ulcerative colitis just before the 2018 DDW meeting. Dr Jean-Frederic Colombel presented results from a retreatment trial of tofacitinib,[13] which was a secondary analysis of the phase 3 tofacitinib trial.[9] Patients in this analysis received drug induction, were rerandomized to placebo in the maintenance portion of the trial, and then in the open-label trial received the drug again. This group was studied to see whether the drug would work if the patients were retreated after a prolonged drug holiday. The results served as proof of concept that retreatment did, in fact, work with tofacitinib in this study.

Retreatment and treatment interruption have always been a concern with biologic agents. Because they are large proteins and potentially immunogenic, there is often concern that if a patient has a prolonged drug holiday and then is retreated, the patient might be more likely to develop antibodies for the drug. The study results presented by Colombel[13] show that with a small molecule such as tofacitinib, drug treatment can likely be held without worry of immunogenicity, as the drug seemed to work after retreatment. Although retreatment was not 100% effective, it did work in many of the patients.

Upadacitinib

Dr Julian Panes presented follow-up data on another new molecule, the JAK 1 inhibitor upadacitinib (formerly known as ABT-494); I was a coauthor of this study.[14] Unlike tofacitinib, which blocks JAK 1, 2, and 3 (to different extents), upadacitinib selectively blocks JAK 1, so this agent theoretically might have a better safety profile. We know from the phase 2 induction data presented at last year's DDW meeting that upadacitinib seems to be effective in Crohn's disease patients.[15] The study results presented by Dr Panes[14] were from the follow-up maintenance study. Patients who completed the initial 16-week induction were randomized to 1 of 3 doses of upadacitinib. Halfway through the study, the dose of the 24-mg once-daily treatment arm was changed to 6 mg twice daily because the researchers realized that 24 mg once daily was not going to work. There was no placebo comparison for maintenance. The study results showed that upadacitinib seemed to be effective for some of the endpoints; in general, it was numerically more effective at the higher twice-daily doses.

Importantly, this was one of the first trials that used recent guidance to move away from using the Crohn's Disease Activity Index as an endpoint.[16,17] Therefore, the trial had 2 coprimary endpoints: a clinical endpoint based on stool frequency and abdominal pain scores, as well as an endoscopic endpoint. The study looked at 2 different groups of patients: those who had a clinical response at week 16 and those who seemed to have both a clinical and endoscopic response at week 16. As expected, the patients who had both clinical and endoscopic response had higher rates of meeting the various endpoints than the patients who had just a clinical response. However, it should be noted that the new conceptualization of endpoints is still a work in progress.

In terms of safety, some serious adverse events were reported. Numerically, they seemed to be higher at lower upadacitinib doses than at higher doses. This might mean that some of those adverse events were related to flares of Crohn's disease. This issue will need to undergo further investigation.

Other New Data

Ustekinumab

A poster by Dr Sandborn and colleagues examined the rates of surgery, hospitalization, and the need for another biologic agent through 2 years of Crohn's disease treatment with ustekinumab in the phase 3 IM-UNITI maintenance trial.[18] The researchers found that both of the ustekinumab dosing regimens studied (90 mg every 8 weeks and 90 mg every 12 weeks) significantly reduced the composite endpoint of either surgery, hospitalization, or transition to another biologic agent, compared to placebo. Thus, there was a risk reduction of approximately 30% for ustekinumab dosing every 8 weeks and approximately 50% for dosing every 12 weeks. If the composite endpoint was just surgery or hospitalization, there was a risk reduction of approximately 40% for ustekinumab dosing every 8 weeks and approximately 50% for dosing every 12 weeks, compared

to placebo. These results show that patients responding to ustekinumab not only experience improvement in disease activity and symptoms, but also experience a change in the natural history of the disease.

Dr Steven J. Fusillo presented the results of a single-center experience of ustekinumab in pediatric patients (under 21 years of age).[19] Patients had to have received at least 2 doses of ustekinumab (at least 1 intravenous dose and then a subcutaneous dose). Fifty-two percent of patients experienced clinical response at week 6, but by the last follow-up, that had decreased to 45%. Nonresponders were more likely to have had disease limited to the colon and also were more likely to have had previous biologic failure. Some of those patients with colonic disease were probably acutely ill children in whom the entire colon was inflamed, which may have meant that they were losing the biologic agent (a protein) in their feces. With bad colitis, patients often have a protein-losing colopathy, so they frequently lose the drug through their stool, which may explain the low rates of response. Some of these data came from before ustekinumab was approved, so the results might underestimate the true effectiveness of the drug since it was only studied in fairly ill children. Further research is needed in pediatric patients.

Adalimumab

My colleagues and I looked at effectiveness data collected in the PYRAMID registry (the safety registry for adalimumab) that were then stratified by the duration of Crohn's disease.[20] We know from secondary analysis of clinical trials[21] that patients with shorter durations of Crohn's disease tend to have higher response and remission rates than patients with longer durations of disease. This poster looked at a subset of patients who were adalimumab-naive when they entered the safety registry and then followed them up to 6 years in the safety registry. Each of the effectiveness measures, the Harvey-Bradshaw Index, the Short Inflammatory Bowel Disease Questionnaire, and the Work Productivity and Activity Impairment score, had improved by year 1 on therapy, and the improvements persisted.

Upon stratification, it appeared that patients with a disease duration of less than 5 years had numerically higher improvements in work productivity impairment than patients who had longer durations of disease. Perhaps patients with longer disease durations, a group that may include patients who are on disability, find it harder to get back into the workforce. However, these effectiveness data may be a little biased in favor of the drug because if the drug was not working, patients would stop treatment and then would often drop out of the registry. Because patients who dropped out are not being accounted for, it is not altogether surprising that the effectiveness measures look better over time.

Risk of Complications After Joint Replacement Surgery

Dr Martin H. Gregory presented results from a retrospective cohort study examining the effect of various IBD medications on the risk of complications after patients have joint replacement surgery.[22] This study, of which I was a coauthor, used a large insurance claims database to review diagnostic and procedure codes to identify types of patients and various types of outcomes. The researchers identified patients who had Crohn's disease or ulcerative colitis and, of those, patients who had either a hip, shoulder, or knee replacement. Serious infections were defined as a composite of joint infections, surgical site infections (also known as wound infections), pneumonia, sepsis, and *Clostridium difficile* infection. Risk was stratified by the medications that the patients were on at the time of the surgery. Similar to what has been reported in studies of safety registries, such as the TREAT registry,[23] the highest risk of complications was seen with patients who were on corticosteroids; these patients had more than double the risk of complications. However, for anti-TNF agents and immunomodulators, there was not a significantly elevated risk of complications. Ironically, there is still concern from some patients and providers regarding the safety of anti-TNF agents, but that concern should, instead, be directed toward corticosteroids. Thus, it is probably beneficial to get patients on anti-TNF agents if only so that they can taper off corticosteroids. Not only would this move likely reduce their infection risk, but they would also be on a more effective therapy.

However, the limitations of database studies should be taken into account when reviewing study findings. The case-finding algorithms in these studies, which often use a combination of diagnostic and procedure codes, are not always validated by medical record reviews. On the other hand, database studies enable researchers to obtain larger numbers of cases in order to examine lower-frequency events.

Disclosure

Dr Loftus has consulted for Eli Lilly, Janssen, Takeda, Pfizer, AbbVie, and UCB. He has also received research support from Janssen, Takeda, Pfizer, AbbVie, and UCB.

References

1. Sandborn WJ, Ferrante M, Bhandari BR, et al. Efficacy and safety of anti–interleukin-23 therapy with mirikizumab (Ly3074828) in patients with moderate-to-severe ulcerative colitis in a phase 2 study [DDW abstract 882]. *Gastroenterology*. 2018;154(suppl 1): S1360-S1361.

2. Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti–interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol.* 2017;76(3):405-417.

3. Papp K, Thaçi D, Reich K, et al. Tildrakizumab (MK-3222), an anti–interleukin-23 p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. *Br J Dermatol.* 2015;173(4):930-939.

4. Papp KA, Blauvelt A, Bukhalo M, et al. Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis. *N Engl J Med.* 2017;376(16):1551-1560.

5. Faleck D, Shashi P, Meserve J, et al. Comparative effectiveness of vedolizumab and tumor necrosis factor–antagonist therapy in ulcerative colitis: a multicenter consortium propensity score–matched analysis [DDW abstract 328]. *Gastroenterology*. 2018;154(suppl 1): S82.
6. Lukin DJ, Weiss A, Aniwan S, et al. Comparative safety profile of vedolizumab and tumor necrosis factor–antagonist therapy for inflammatory bowel disease: a multicenter consortium propensity score–matched analysis [DDW abstract 277]. *Gastroenterology*. 2018; 154(suppl 1):S68.
7. Bohm M, Sagi S, Fischer M, et al. Comparative effectiveness of vedolizumab and tumor necrosis factor–antagonist therapy in Crohn's disease: a multicenter consortium propensity score–matched analysis [DDW abstract Sa1723]. *Gastroenterology*. 2018;154(suppl 1): S369-S370.
8. Caldera F, Lasch K, Cao C, Bhayat F. Lower incidence of herpes zoster in vedolizumab-treated vs tofacitinib-treated patients with ulcerative colitis [DDW abstract Tu1704]. *Gastroenterology*. 2018;154(suppl 1):S994.
9. Sandborn WJ, Su C, Sands BE, et al; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2017;376(18):1723-1736.
10. Null KD, Chang HL, Lissoos T, et al. Adherence and persistence with vedolizumab among patients with inflammatory bowel disease in an academic medical center [DDW abstract Su1019]. *Gastroenterology*. 2018;154(suppl 1):S456-S457.
11. Kane SV, Moran K, Null KD, Huang Z, Lissoos T. A comparison of medication adherence and persistence between intravenous biologics and oral small-molecule therapies [DDW abstract Su1008]. *Gastroenterology*. 2018;154(suppl 1):S452-S453.
12. Loftus EV, Vermeire S, Khalid JM, et al. Vedolizumab treatment persistence up to 3 years: post hoc analysis in vedolizumab-naive patients from the GEMINI long-term safety study [DDW abstract Sa1766]. *Gastroenterology*. 2018;154(suppl 1):S387.
13. Panes J, Bressler B, Colombel JF, et al. Efficacy and safety of tofacitinib retreatment for ulcerative colitis after treatment interruption: results from the OCTAVE clinical trials [DDW abstract 905]. *Gastroenterology*. 2018;154(suppl 1):S178.
14. Panes J, Sandborn WJ, Loftus EV, et al. Efficacy and safety of upadacitinib maintenance treatment for moderate-to-severe Crohn's disease: results from the CELEST study [DDW abstract 906]. *Gastroenterology*. 2018;154(suppl 1):S178-S179.
15. Sandborn WJ, Feagan BG, Panes J, et al. Safety and efficacy of ABT-494 (upadacitinib), an oral JAK1 inhibitor, as induction therapy in patients with Crohn's disease: results from CELEST [DDW abstract 874h]. *Gastroenterology*. 2017;152(suppl 1):S1308-S1309.
16. European Medicines Agency. Guideline on the development of new medicinal products for the treatment of Crohn's disease. Released July 21, 2016. Accessed January 22, 2018. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211430.pdf.
17. Williet N, Sandborn WJ, Peyrin-Biroulet L. Patient-reported outcomes as primary end points in clinical trials of inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2014;12(8):1246-1256.e6.
18. Sandborn WJ, Sands BE, Gasink C, et al. Reduced rates of Crohn's-related surgeries, hospitalizations, and alternate biologic initiation with ustekinumab in the IM-UNITI study through 2 years [DDW abstract Sa1743]. *Gastroenterology*. 2018;154(suppl 1): S377-S378.
19. Fusillo SJ, Chang V, Stein RE, et al. Ustekinumab responders versus nonresponders in refractory pediatric inflammatory bowel disease [DDW abstract 329]. *Gastroenterology*. 2018;154(suppl 1):S82.
20. Loftus EV, Reinisch W, Panaccione R, et al. Long-term effectiveness and safety of adalimumab based on Crohn's disease duration: results from the PYRAMID registry [DDW abstract Sa1808]. *Gastroenterology*. 2018;154(suppl 1):S403.
21. Schreiber S, Reinisch W, Colombel JF, et al. Subgroup analysis of the placebo-controlled CHARM trial: increased remission rates through 3 years for adalimumab-treated patients with early Crohn's disease. *J Crohns Colitis*. 2013;7(3):213-221.
22. Gregory MH, McKinnon A, Stwalley D, et al. Anti-TNF inhibitors are not associated with increased risk of infection after joint replacement surgery [DDW abstract 160]. *Gastroenterology*. 2018;154(suppl 1):S44-S45.
23. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol*. 2012;107(9):1409-1422.


G&H