A SPECIAL MEETING REVIEW EDITION

CCFA/Advances in Inflammatory Bowel Diseases 2015: Highlights in Ulcerative Colitis and Crohn's Disease

A Review of Selected Presentations From the CCFA/Advances in Inflammatory Bowel Diseases 2015 Clinical and Research Conference • December 10-12, 2015 • Orlando, Florida

Special Reporting on:

- New and Future Adhesion Molecule–Based Therapies in IBD
- Efficacy and Safety of Vedolizumab for Inflammatory Bowel Disease in Clinical Practice
- A Multicenter, Double-Blind, Placebo-Controlled Phase 3 Study of Ustekinumab, a Human IL-12/23p40 Monoclonal Antibody, in Moderate-Severe Crohn's Disease Refractory to Anti-TNFα: UNITI-1
- Intravenous Iron Sucrose for Treatment of Iron Deficiency Anemia in Pediatric Inflammatory Bowel Disease
- Does Vedolizumab Affect Postoperative Outcomes in Patients Undergoing Abdominal Operations for Inflammatory Bowel Disease?

PLUS Meeting Abstract Summaries

With Expert Commentary by:
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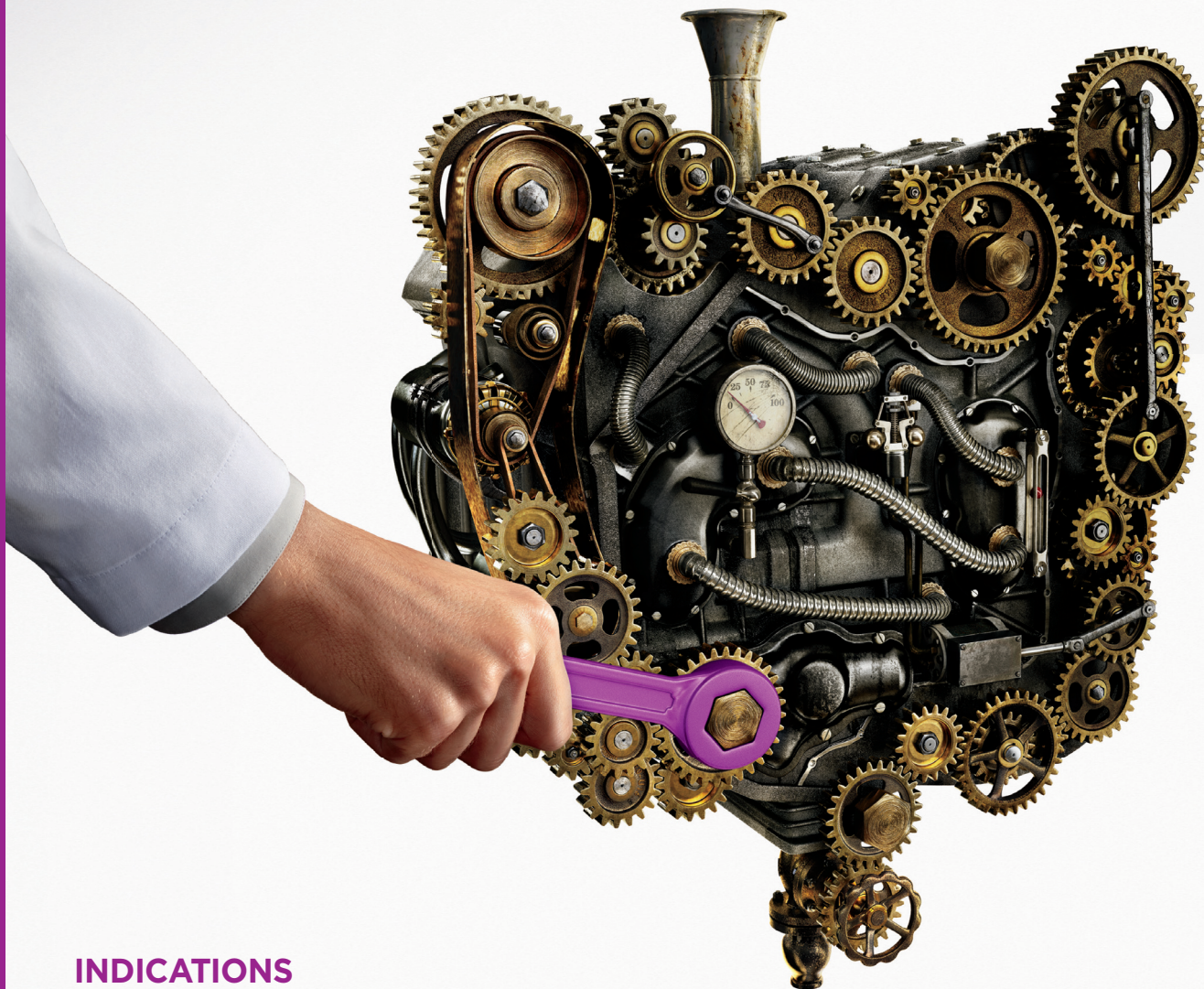University of Pennsylvania Health System
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INDICATIONS

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.

Entyvio: the first biologic with a specific binding action designed for a gut-homing inflammatory pathway[1]

ENGINEERED FOR UC AND CD

- **Provides remission for patients with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD)[1]**
  - Studied in patients who have failed conventional therapies or a biologic
  - Individual results may vary
- **Clinical trials evaluated safety in more than 3300 adults on Entyvio[1]**
  - Including more than 800 patients who received Entyvio for more than 2 years
- **A distinct mechanism of action that specifically blocks lymphocyte migration that is a key contributor to inflammation in the gut[1]**
- **Entyvio specifically binds to $\alpha 4\beta 7$ integrin, blocking its interaction with MAdCAM-1, which is mainly expressed on gut endothelial cells[1]**
- **300-mg dose for adult patients[1]**

EFFECTIVE JANUARY 1, 2016, ENTYVIO HAS A CMS-ASSIGNED PRODUCT-SPECIFIC J-CODE OF J3380[2]*

*Medicare and payer policies regarding the use of product codes vary. Healthcare provider should consult the payer or Medicare contractor to determine which product code is most appropriate for use of Entyvio.

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.** Centers for Medicare and Medicaid Services. CMS-1633-FC; CMS-1607-F2. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/Hospital OutpatientPPS/Hospital-Outpatient-Regulations-and-Notices-Items/CMS-1633-FC.html. Accessed November 3, 2015.

Entyvio®
vedolizumab

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Takeda

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

ENTYVIO (vedolizumab) for injection, for intravenous use

INDICATIONS AND USAGE

Adult Ulcerative Colitis (UC)

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 (CD)

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 1* 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 1*).

Table 1. 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 1*.

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. 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.

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 sample handling, timing of sample collection, concomitant medications, presence of vedolizumab, and underlying disease. For these reasons, comparison of the incidence of antibodies to ENTYVIO with the incidence of antibodies to other products may be misleading.

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.

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New and Future Adhesion Molecule–Based Therapies in IBD

Dr Brian Feagan presented an overview of recent advances in adhesion molecule–based therapies for treating patients with inflammatory bowel disease (IBD).[1] Although use of antibodies that inhibit the activity of tumor necrosis factor alpha (TNFα) represent an important advance in the management of IBD, alternative options are required for patients who do not respond to conventional treatment, lose response to treatment, or develop unacceptable adverse events (AEs), including serious infections. To address the need for improved treatments, new drugs are being developed to target molecules that mediate leukocyte traffic in the gut.[2] Natalizumab, etrolizumab, and vedolizumab attack integrin molecules that facilitate leukocyte adhesion to the vascular endothelium.

Natalizumab is an antagonist of α4-integrin that inhibits leukocyte adhesion and migration into inflamed tissue in multiple organs, including the gut and brain. It exhibited efficacy compared with placebo in patients with relapsing multiple sclerosis, resulting in a significant reduction in the number of gadolinium-positive, inflammatory brain lesions ($P<.001$) and fewer relapses ($P=.02$).[3] Natalizumab also proved more efficacious than placebo in patients with Crohn's disease (CD), yielding more sustained responses (61% vs 28%; $P<.001$) and remissions (44% vs 26%; $P=.003$) and enabling more patients to stop treatment with corticosteroids ($P=.01$).[4] However, natalizumab is associated with a risk of progressive multifocal leukoencephalopathy, a brain infection that is caused by reactivation of the latent JC polyomavirus and is usually fatal.

Vedolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody approved for moderate-to-severe, active CD and ulcerative colitis (UC).[5,6] It binds to the integrin α4β7, inhibiting its interaction with mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1). The antibody selec-tively blocks gut lymphocyte trafficking without affecting trafficking to the central nervous system. After demonstrating preliminary efficacy and safety in several phase 1 and 2 trials of IBD patients, vedolizumab was evaluated in a series of phase 3 trials.[2] The phase 3 GEMINI I (Study of Vedolizumab [MLN0002] in Patients With Moderate to Severe Ulcerative Colitis [GEMINI I]) trial evaluated vedolizumab as induction and maintenance therapy in patients with moderate-to-severe UC.[7] In the induction portion of the trial, 374 patients were randomized to receive vedolizumab (300 mg) or placebo at weeks 0 and 2, and 521 patients received open-label vedolizumab at weeks 0 and 2. Patients were evaluated at week 6. In the maintenance portion of the trial, patients who had achieved a response to vedolizumab induction therapy at week 6 were randomized to continue receiving vedolizumab every 4 or 8 weeks or to switch to placebo, with treatment lasting up to 52 weeks.

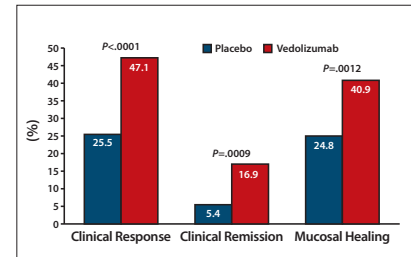Clinical response rates at week 6 were 47.1% for vedolizumab vs 25.5% for placebo ($P<.0001$; Figure 1). At 52

Figure 1. Response, remission, and mucosal healing at 6 weeks among the induction intent-to-treat population in the GEMINI 1 trial. Adapted from Feagan BG et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2013;369(8):699-710.[7]

weeks, the proportion of UC patients in clinical remission was 41.8% for the 8-week vedolizumab group vs 44.8% for the 4-week vedolizumab group, as compared with 15.9% for patients treated with placebo ($P<.001$ for vedolizumab every 4 weeks or every 8 weeks vs placebo). Patients without prior exposure to anti-TNFα agents showed superior response and remission rates vs those with prior exposure. The corticosteroid-free remission rates

ABSTRACT SUMMARY Evidence of Mucosal Healing in Patients With Crohn's Disease Treated With Open-Label Vedolizumab: A Case Series

Nine CD patients from GEMINI 2 and GEMINI 3 were enrolled in GEMINI LTS, which evaluated long-term use of vedolizumab. These patients received vedolizumab at 300 mg every 4 weeks. Among the 9 patients, 4 achieved mucosal healing (Shafran I, Burgunder P. *Inflamm Bowel Dis.* 2014;20:S26.) Extended follow-up was conducted on the 9 patients from GEMINI LTS plus 2 additional patients who received the approved vedolizumab induction and maintenance therapy (Abstract P-006). The mean duration of CD was 13 years. Patients had previously failed treatment with a TNFα antagonist. All patients had significant mucosal ulcerations during baseline colonoscopic evaluation. Complete reversal of mucosal ulcerations was observed in 11 patients within 1 to 5 years of vedolizumab therapy. Of the 4 patients from GEMINI LTS who previously demonstrated mucosal healing with vedolizumab maintenance therapy, all experienced continued healing. Mild recurrent CD was observed in 1 patient during a colonoscopy that occurred after more than 5 years of vedolizumab therapy.

were 31.4% for 4-week vedolizumab and 45.2% for 8-week vedolizumab (*P*<.05 for each) vs 13.9% with placebo. The vedolizumab and placebo groups had similar frequencies of AEs.

GEMINI II had a similar design and methodology to GEMINI I, but investigated vedolizumab as induction and maintenance therapy in CD patients.[8] The trial demonstrated a superior rate of clinical remission for vedolizumab vs placebo at week 6 (*P*<.0206). However, enhanced clinical response rates based on a reduction in the CD activity index (CDAI) of at least 100 points (CDAI-100) at week 6 were similar for the 2 arms. The GEMINI III trial tested vedolizumab solely as induction therapy in patients with CD. In this trial, vedolizumab did demonstrate increased rates of CDAI-100 vs placebo at week 6 (*P*=.0002) and week 10 (*P*<.0001) in both the overall population (N=416) and in the 315 patients who had not responded to previous anti-TNFα therapy (week 6, *P*=.0011; week 10, *P*<.0001).[9] Dr Feagan commented that the endpoint of week 6 used in GEMINI II might have been too early to detect differ-
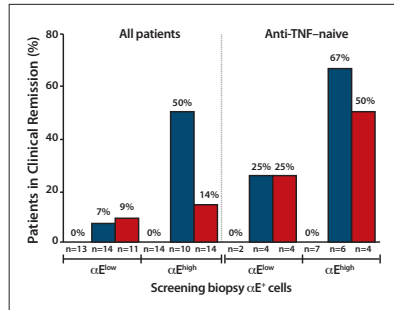

Figure 2. In a study of etrolizumab, expression of alphaE (αE) merged as a potential predictive biomarker for response. Results from an immunohistochemistry analysis are shown. Adapted from Vermeire S et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. *Lancet.* 2014;384(9940):309-318.[10]

ences in CDAI-100. In aggregate, the safety results from the GEMINI studies suggest that there is no increased risk of serious infection, in contrast to anti-TNFα agents.

Etrolizumab (rhuMAb β7) is a humanized IgG1 antibody that binds to the integrin subunit β7.[2] The antibody blocks interaction between α4β7 and MAdCAM-1 as well as that between

αEβ7 and E-cadherin, thus inhibiting leukocyte retention in the intraepithelial lining of the gut. A double-blind, randomized phase 2 study evaluated the safety and efficacy of 2 dose levels of etrolizumab in patients with moderate-to-severe UC who had not responded to conventional therapy.[10] Patients were randomized to treatment with etrolizumab (100 mg on weeks 0, 4, and 8, with placebo on week 2; n=39), etrolizumab (420 mg on week 0 followed by 300 mg on weeks 2, 4, and 8; n=39), or matching placebo (n=41). The trial achieved its primary endpoint, demonstrating clinical remission rates at week 10 of 21% for treatment with the lower dose of etrolizumab (*P*=.004), 10% for treatment with the higher doses of etrolizumab (*P*=.048), and 0% with placebo. Integrin blockade was again more effective in patients without prior exposure to anti-TNFα therapy. AEs occurred at a similar frequency in the 3 treatment groups. In the subset of patients with samples available for analysis, αE expression emerged as a potential predictive biomarker for response to etrolizumab (Figure 2).

PF-00547659 is an antibody that binds directly to MAdCAM-1 and has demonstrated preliminary safety and efficacy in UC patients. In the phase 2 TURANDOT (A Study of PF-00547659 in Patients With Moderate to Severe Ulcerative Colitis [TURANDOT]) study, 357 patients with active, refractory UC were randomized to receive placebo or PF-00547659, dosed at 7.5 mg, 22.5 mg, 75 mg, or 225 mg, administered every 4 weeks.[11,12] The most effective dose overall was 22.5 mg, which yielded week 12 efficacy outcomes of 16.7% for clinical remission, 54.2% for clinical response, and 27.8% for mucosal healing (vs 2.7%, 28.8%, and 8.2%, respectively, for placebo; *P*<.05 for each comparison). As with the integrin blockade, patients without prior exposure to anti-TNF therapy were more likely to achieve remission than those with prior exposure (*P*<.001). Rates of AEs, including serious AEs, were similar for active vs placebo treatment.

ABSTRACT SUMMARY The Relationship Between Early Mucosal Healing and Long-Term Outcomes in Patients With IBD

Two systematic reviews and meta-analyses were performed to determine the relationship between early mucosal healing and long-term outcomes in patients with CD (Abstract P-016) or UC (Abstract P-17). The literature search evaluated observational or interventional studies from PubMed, Embase, and the Cochrane library. The CD analysis identified 12 studies including 673 patients with active disease. For the CD patients who achieved early mucosal healing, the pooled odds ratios were 2.80 (95% CI, 1.91-4.10) for achieving long-term clinical remission, 2.22 (95% CI, 0.86-5.69) for remaining free of CD-related surgery, and 14.30 (95% CI, 5.57-36.74) for maintaining long-term mucosal healing. The UC analysis included 14 studies representing 2019 UC patients with active disease. For the UC patients who achieved early mucosal healing, the pooled odds ratios were 4.88 (95% CI, 2.54-9.37) for achieving long-term clinical remission, 5.34 (95% CI, 2.92-9.76) for remaining colectomy-free over the long-term, 8.40 (95% CI, 3.13-22.53) for sustaining long-term mucosal healing, and 9.70 (95% CI, 0.94-99.67) for remaining corticosteroid-free with a clinical remission over the long-term. No significant differences in outcomes were observed in those who achieved early mucosal healing with use of biologic vs nonbiologic therapy.

Ozanimod is a small, orally available drug that modulates the sphingosine-1-phosphate receptor. Blockade of sphingosine-1-phosphate receptor signaling is thought to prevent lymphocytes from exiting the lymph nodes. In the phase 2 TOUCHSTONE trial, daily ozanimod (0.5 mg or 1.0 mg) was evaluated in 197 patients with active moderate-to-severe UC.[13,14] The proportion of patients in remission at week 8 was 6.2% for placebo, 13.8% for the lower dose of ozanimod (P=.1422), and 16.4% for the higher dose of ozanimod (P=.0482). Both doses of ozanimod (0.5 mg vs 1.0 mg) yielded higher rates of mucosal improvement relative to placebo (P=.0348 and P=.0023, respectively), as well as higher rates of clinical response at week 8 (P=.0648 and P=.0140, respectively). Patients who showed a response at week 8 continued treatment through week 32, and continued activity has been observed with extended treatment. Ozanimod was generally well tolerated.

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ABSTRACT SUMMARY Hospitalizations and Characteristics of Patients With Ulcerative Colitis and Crohn's Disease Treated With Vedolizumab in the United States

A multicenter study examined rates of hospitalization before and after initiating vedolizumab treatment in IBD patients (Abstract P-025). The retrospective cohort study analyzed the electronic records of CD or UC patients with at least 1 year of medical history and at least 180 days of follow-up. Among the 237 enrolled patients, 62% were female, and 71% had CD. The mean age at the first vedolizumab infusion was 43 ± 15.7 years. The mean time since diagnosis was 5.2 ± 3.5 years. Forty patients (17%) had received no prior biologic therapy, and 19 (8%) had received at least 3 prior biologic therapies. Events of interest occurring within the 90 days prior to the first infusion of vedolizumab included prescription of corticosteroids (44.3%), surgery (38.0%), and fistulizing disease (32.5%). The proportion of patients with at least 1 hospitalization due to any cause was 20.7% in the 180 days before treatment with vedolizumab vs 14.3% in the 180 days after vedolizumab. The proportion of patients with at least 1 IBD-related hospitalization decreased from 16.0% to 11.4%.

Efficacy and Safety of Vedolizumab for Inflammatory Bowel Disease in Clinical Practice

Vedolizumab is approved by the US Food and Drug Administration (FDA) for use in adult patients with CD or UC that is moderately to severely active and who had an inadequate response, lost response, or were intolerant to an anti-TNFα agent or immunomodulator, or who had an inadequate response, were intolerant to, or demonstrated dependence on corticosteroids.[1] Approval followed the demonstration of efficacy and safety in phase 3 clinical trials.[2,3] However, it is not known how efficacy and safety data gathered from clinical trials compare with real-world experience.

To provide insight into this issue, a study was undertaken to quantify the treatment effect and safety of vedolizumab in clinical practice at a single institution.[4] All patients had moderately to severely active UC or CD confirmed by baseline endoscopy within 4 weeks of starting vedolizumab. Patients were required to have active symptoms prior to starting the antibody treatment, and they underwent clinical or endoscopic follow-up after induction. Outcomes included physician global assessment of disease activity, clinical response rates at induction and overall, corticosteroid-free response, and mucosal healing. The latter was defined as a Mayo endoscopic score
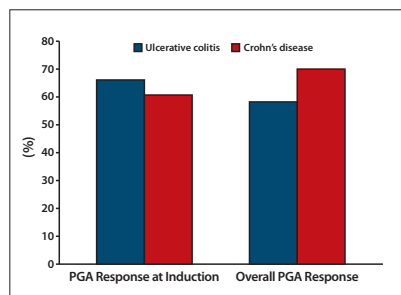
Figure 3. Response rates according to the Physician Global Assessment (PGA) in an analysis of vedolizumab in clinical practice at a single institution. Adapted from Chaudrey K et al. Efficacy and safety of vedolizumab for inflammatory bowel disease in clinical practice. Poster presented at: 2015 Advances in Inflammatory Bowel Disease; December 10-12, 2015; Orlando, Florida. Abstract P-033.[4]

Figure 4. Partial response rates in an analysis of vedolizumab in clinical practice at a single institution. Adapted from Chaudrey K et al. Efficacy and safety of vedolizumab for inflammatory bowel disease in clinical practice. Poster presented at: 2015 Advances in Inflammatory Bowel Disease; December 10-12, 2015; Orlando, Florida. Abstract P-033.[4]

of 0 or 1 for UC patients and healing of all ulcers and/or erosions for CD patients. A partial response was defined as a reduction in symptoms of 25% to 50%.

The study included 12 patients with UC and 51 with CD. Concomitant corticosteroid use was reported by 66% of UC patients and 53% of CD patients. In both groups, 17% of patients were receiving concomitant
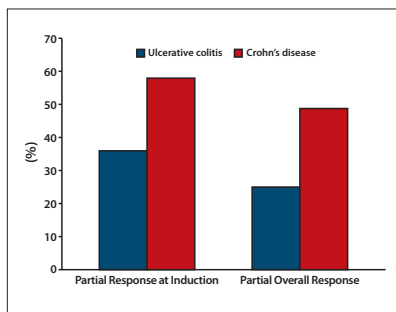
immunomodulator therapy. Nearly all patients had received prior treatment with an anti-TNFα agent, with the exception of 2 patients in the CD group. In the UC group, 66% achieved mucosal healing and 25% progressed to surgery, as compared with 20% and 16%, respectively, in the CD group. Response rates based on the physician global assessment of disease activity after

induction treatment were approximately 65% in the UC group and 60% in the CD group. Overall response rates were approximately 58% and 70%, respectively (Figure 3). In the UC arm, partial response rates were 36% after induction treatment and approximately 25% after treatment completion; these rates were 58% and 48% in the CD arm (Figure 4). Among the 33 patients assessed for mucosal healing, 24% achieved this endpoint. Five patients developed an infection, but most did not require antibiotic therapy or responded to outpatient antibiotic management. No new safety signals arose.

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A Multicenter, Double-Blind, Placebo-Controlled Phase 3 Study of Ustekinumab, a Human IL-12/23p40 Monoclonal Antibody, in Moderate-Severe Crohn's Disease Refractory to Anti-TNFα: UNITI-1

Interleukin (IL)-12 and IL-23 are key cytokines that mediate the immune cascade of Crohn's disease.[1] Both interleukins are heterodimeric proteins comprising a unique subunit covalently linked to a p40 subunit. Inhibition of the inflammatory pathways involving IL-12 and IL-23 presents an attractive therapeutic approach for CD. Ustekinumab is a humanized IgG1κ monoclonal antibody that binds with high affinity to the shared p40 subunit of IL-12 and IL-23, thus inhibiting downstream cytokine production and cellular activation. The antibody is approved for treatment of moderate-to-severe psoriasis and for psoriatic arthritis.[2]

Two phase 3 trials, UNITI-1 (A Study to Evaluate the Safety and Efficacy of Ustekinumab in Patients With Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to Tumor Necrosis Factor [TNF] Antagonist Therapy) and UNITI-2 (A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Patients With Moderately to Severely Active Crohn's Disease), were designed to evaluate ustekinumab in patients with CD. Although anti-TNFα agents have proven effective, nearly half of patients who initially respond to induction treatment eventually lose their response. UNITI-1

and UNITI-2 enrolled 2 different patient populations, based on their prior responses to anti-TNFα therapy. UNITI-1 enrolled patients with moderately to severely active CD (indicated by a CDAI score of 220 to 450) that was refractory to anti-TNFα therapy.[3] The trial randomized 245 patients to receive ustekinumab (130 mg), 249 to receive weight-based ustekinumab (approximately 6 mg/kg), and 225 to receive placebo. For the weight-based dosing, patients who weighed 55 kg or less received 260 mg of ustekinumab; patients who weighed between 56 kg and 85 kg received 390 mg of ustekinumab; and patients who
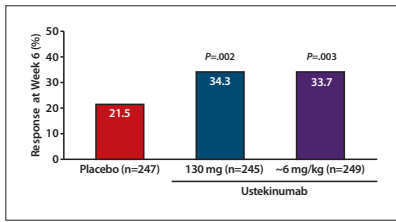
Figure 5. Clinical response at week 6 in the UNITI-1 trial, which evaluated ustekinumab in patients with moderately to severely active Crohn's disease that was refractory to anti-TNFα therapy. TNFα, tumor necrosis factor alpha. Adapted from Sandborn W et al. A multicenter, double-blind, placebo-controlled phase 3 study of ustekinumab, a human IL-12/23p40 mAB, in moderate-severe Crohn's disease refractory to anti-TFNα: UNITI-1. Paper presented at: 2015 Advances in Inflammatory Bowel Disease; December 10-12, 2015; Orlando, Florida. Abstract O-001.[3]

Figure 6. Clinical remission at week 8 in the UNITI-1 trial, which evaluated ustekinumab in patients with moderately to severely active Crohn's disease that was refractory to anti-TNFα therapy. TNFα, tumor necrosis factor alpha. Adapted from Sandborn W et al. A multicenter, double-blind, placebo-controlled phase 3 study of ustekinumab, a human IL-12/23p40 mAB, in moderate-severe Crohn's disease refractory to anti-TFNα: UNITI-1. Paper presented at: 2015 Advances in Inflammatory Bowel Disease; December 10-12, 2015; Orlando, Florida. Abstract O-001.[3]

weighed more than 85 kg received 520 mg. The primary endpoint was clinical response at week 6.

Patients had a median age of 36 years, and 42.8% were male. The median weight was 67.0 kg. Median CDAI score was 317.0, and the median duration of CD was 10.1 years. Median level of C-reactive protein (CRP) was 9.9 mg/L, with 78.3% of patients having an abnormal CRP level. The majority of patients were receiving concomitant medications. The trial reached its primary endpoint, yielding a clinical response rate at week 6 of 34.3% (P=.002) in the 130-mg arm, 33.7% (P=.003) in the weight-based arm, and 21.5% in the placebo arm (Figure 5). Assessment of health-related quality of life and measurement of fecal lactoferrin and calprotectin confirmed the clinical efficacy of treatment with ustekinumab at week 6. Clinical remission at week 8, defined by a CDAI of less than 150, was a secondary endpoint. This endpoint was also reached, with remission rates of 15.9% in the 130-mg arm (P=.003), 20.9% (P<.001) in the weight-based arm, and 7.3% in the placebo arm. For the 130-mg and weight-based dose arms, the clinical response rates at week 8 were 33.5% and 37.8%, respectively (P<.05 for both), vs 20.2% for placebo. Clinical remission rates were 15.9% and 20.9%, respectively (P<.05 for both), vs 7.3% for placebo (Figure 6). Also at week 8, CRP
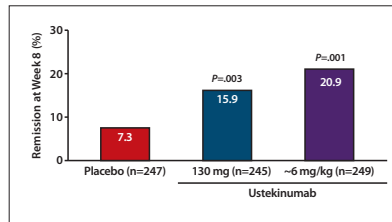
levels were significantly reduced with the 130-mg fixed-dose and the weight-based dose (P<.001 for both). Across the entire safety population of 495 patients, 65.3% experienced an AE of any grade, with a similar frequency in all 3 arms. Serious AEs were reported in 4.9% of patients who received 130 mg of ustekinumab, 7.2% of patients who received the weight-based dose of ustekinumab, and 6.1% of patients who received placebo. Serious infections were observed in less than 3% of patients in each arm. No anaphylaxis or serious infusion reactions were reported.

The results from UNITI-1 support the results obtained from UNITI-2, which enrolled patients who had either

achieved a prior response to anti-TNFα agents or had no prior exposure to them.[4] Patients had failed treatment with corticosteroids and/or immunosuppressive therapy. UNITI-2 randomly assigned patients to receive ustekinumab (at 130 mg or 6 mg/kg) or placebo. The primary endpoint, response rates at week 6, were 52% for the 130-mg arm, 56% for the weight-based arm, and 29% for the placebo arm (P<.001 for both doses). Both ustekinumab arms demonstrated a superior rate of clinical remission relative to placebo (P<.05 for both). Analyses of response, remission, and levels of CRP through week 8 showed continued responses to both doses of ustekinumab relative to placebo. The frequencies of AEs and serious AEs were similar in all 3 arms through week 8, with no deaths, opportunistic infections, or other relevant events occurring in patients treated with ustekinumab. Data from UNITI-1 and UNITI-2 demonstrate the induction efficacy and safety of ustekinumab in CD patients with moderately to severely active disease, including anti-TNFα naive patients as well as those who have failed treatment with anti-TNFα therapy.

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ABSTRACT SUMMARY The Effect of Vedolizumab on Extraintestinal Manifestations in Patients With Crohn's Disease in GEMINI 2

A post-hoc analysis of data from the GEMINI 2 study (Sandborn WJ, et al. *N Engl J Med*. 2013;369[8]:711-721) investigated the effect of vedolizumab on extraintestinal manifestations in the subset of CD patients who had extraintestinal manifestations at baseline (Abstract P-105). The extraintestinal manifestations were evaluated based on the CDAI complications reported. Extraintestinal manifestations were present in 494 patients in the vedolizumab arm and 107 patients in the placebo arm. Kaplan-Meier estimates for resolution of any extraintestinal manifestations were 13% for vedolizumab vs 4% for placebo at week 26 and 32% vs 23%, respectively, at week 52 (HR, 1.4; 95% CI, 0.7-2.79).

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Intravenous Iron Sucrose for Treatment of Iron Deficiency Anemia in Pediatric Inflammatory Bowel Disease

Iron-deficiency anemia (IDA) is a common complication of IBD. In a recent study of more than 1800 IBD patients from a prospective, longitudinal registry, more than 40% of patients were identified as anemic.[1] Oral iron treatment is limited by gastrointestinal side effects and problems with patient adherence. Oral iron acts slowly, which is especially problematic in patients with severe anemia. Moreover, an animal model of rats with induced colitis suggested that oral iron may exacerbate intestinal inflammation.[2] Parenteral iron treatment avoids many of the drawbacks associated with oral iron. The safety of parenteral iron has been an issue in the past, particularly with formulations that contain dextran.[3] To avoid AEs such as anaphylaxis, administration of a test dose is required for dextran-containing iron compounds. Iron sucrose can be given without an initial test dose and has emerged as a potential alternative for treating IDA. Its role in treating pediatric IBD patients remains largely unexplored.

A study was therefore undertaken to determine the clinical response to iron sucrose in pediatric patients with IDA and to identify AEs associated with iron sucrose therapy in this setting.[4] The primary endpoint of the single-center study was the change in hemoglobin level from baseline. Retrospective chart review was conducted for patients up to age 21 years who received iron sucrose for IDA between January 2011 and August 2015. The study excluded patients who had received a transfusion of blood or iron dextran and those who lacked laboratory evaluation within 4 months of receiving the iron sucrose infusion.

There were 73 IBD patients with IDA who had received iron sucrose. These patients received a total of 274 iron sucrose infusions. Forty-five patients met the full enrollment criteria, but 28 patients were excluded from the efficacy analysis. The 73 patients had a mean age of 14.6 ± 3.6 years, 56% were female, and 74% were white. The most common IBD subtype was CD (74%), followed by UC (15%) and IBD-unspecified (11%). The mean CRP level was 2.1 ± 2.9 mg/dL, and the mean hemoglobin level was 9.5 ± 1.4 g/dL. A meaningful increase in the mean hemoglobin level was observed at a mean of 39 days after iron sucrose treatment ($P<.0001$; Figure 7). The final hemoglobin measurement occurred at a mean of 105 days after treatment and showed an increase to a mean of 12.0 ± 1.2 g/dL after treatment with iron sucrose ($P<.0001$).

An analysis of the iron dose relative to the patient iron deficit (Figure 8) suggested that patients who received an iron dose that was greater than their calculated iron deficit were more likely to achieve a normal hemoglobin level with treatment. The majority of patients (71%) who received an iron dose that was below the calculated iron deficit had low hemoglobin levels after treatment. In contrast, of the patients who received an iron dose that was greater than or equal to the iron deficit, after-treatment hemoglobin levels were low in 48% and normal in 52%. The difference in outcomes did not reach significance ($P=.11$).

AEs were reported in 16 patients (21.9%). Among the 274 infusions, 24 (8.8%) were associated with AEs. The most common AEs of any grade were blood pressure fluctuations (n=8), pulse fluctuations (n=8), and pain at the injec-

ABSTRACT SUMMARY Comparing Fecal Microbial Transplant Outcomes in Patients With Recurrent *Clostridium Difficile* or Ulcerative Colitis

A prospective study was conducted in patients with recurrent *Clostridium difficile* infection or refractory UC to characterize the effect of colonoscopic fecal microbial transplant on the recipient's fecal microbiome (Abstract P-069). DNA was extracted from donor and recipient fecal samples at day 1 prior to, 1 week after, and 3 months after fecal microbiome transfer. The study included 9 patients with *C difficile* infection and 5 UC patients. Eight of the 9 *C difficile* patients experienced resolution of symptoms or tested negative for *C difficile* at 2 weeks after transplant.

In contrast, the UC patients did not exhibit any significant changes in the Mayo score for disease activity at 3-month follow-up. No serious AEs occurred. The fecal microbiome profiles of the donors vs the recipients differed significantly at baseline. In the *C difficile* patients, the fecal microbial population came to resemble that of the donor population, as evidenced by changes in the population of 16 microbial genera, including *Escherichia, Bacteroidetes,* and *Faecalibacterium*. A similar shift also occurred in the UC patients, but was less pronounced.
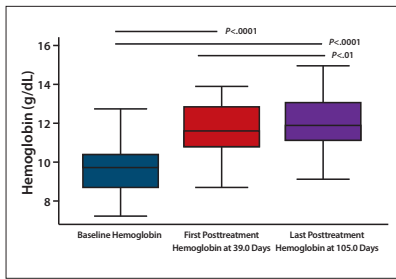
Figure 7. The effect of iron sucrose on hemoglobin in a study of pediatric IBD patients with iron-deficiency anemia. IBD, inflammatory bowel disease. Adapted from Plantz K et al. Intravenous iron sucrose for treatment of iron deficiency anemia in pediatric inflammatory bowel disease. Paper presented at: 2015 Advances in Inflammatory Bowel Disease; December 10-12, 2015; Orlando, Florida. Abstract O-022.[4]

Figure 8. The total iron deficit in a study of iron sucrose in pediatric IBD patients with iron-deficiency anemia. IBD, inflammatory bowel disease. Adapted from Plantz K et al. Intravenous iron sucrose for treatment of iron deficiency anemia in pediatric inflammatory bowel disease. Paper presented at: 2015 Advances in Inflammatory Bowel Disease; December 10-12, 2015; Orlando, Florida. Abstract O-022.[4]

iron sucrose is safe and may be efficacious for treating IDA in this setting. The study is limited by its retrospective nature, the lack of comparison with a control group, and the variation in iron sucrose dose levels and frequency.

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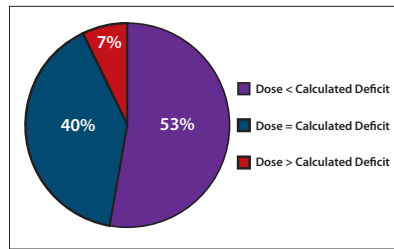tion site (n=6). There were no reports of anaphylaxis, life-threatening reactions, or hospitalizations. The study was one of the first to evaluate iron sucrose for the treatment of IDA in a pediatric IBD population. The findings suggest that

Does Vedolizumab Affect Postoperative Outcomes in Patients Undergoing Abdominal Operations for Inflammatory Bowel Disease?

Vedolizumab is increasingly being used to treat IBD patients who have had or will require surgical intervention.[1] However, the risk of infection in this setting has not been specifically explored. Clinical trials that assessed vedolizumab's efficacy and safety in IBD did not suggest an increased risk of any types of infection, including serious infections, compared with placebo.[2,3] However, no study to date has specifically investigated the risk of postoperative infectious complications among patients who received vedolizumab perioperatively.

A study was designed to determine the rate of 30-day postoperative infectious complications among patients who had received vedolizumab within 30 days of an abdominal operation.[4] The primary goal of the study was to evaluate whether vedolizumab was associated with any negative impact on

surgical outcomes. A retrospective chart review was conducted between January 2014 and August 2015. Enrolled patients were ages 18 to 70 years with

a diagnosis of UC or CD. Patients had received vedolizumab within 30 days of an abdominal operation performed at a single institution. Medical records

ABSTRACT SUMMARY Single-Center Experience: Vedolizumab in Patients With Crohn's Disease and Ulcerative Colitis at Georgetown University Hospital

A retrospective chart review was conducted at a single center to evaluate real-world clinical data relating to the use and efficacy of vedolizumab in IBD patients (Abstract P-073). The study included 11 CD and 7 UC patients, of whom 8 were female and 17 had failed prior anti-TNFα and/or immunomodulator therapy. Among the 11 CD patients, mean CRP levels increased from 6.87 mg/L before vedolizumab treatment to 17.18 mg/L after. Mean fecal calprotectin decreased from 438.7 µg/g before vedolizumab treatment to 237.4 µg/g after. In the 7 UC patients, mean CRP levels increased from 3.5 mg/L to 5.26 mg/L. Mean fecal calprotectin decreased from 591.6 µg/g before vedolizumab to 296.75 µg/g after. A clinical remission or response was observed in 5 of the 7 UC patients after 6 weeks of treatment and in 3 of the 11 CD patients after 8 to 12 weeks of treatment. Minimal to mild clinical improvement occurred in 3 of 4 CD patients whose vedolizumab treatment was increased to every 4 weeks.

were assessed for patient demographics, IBD subtype, and date of vedolizumab administration, as well as for the indication, date, and type of operation, and the occurrence of any postoperative infectious complications occurring within 30 days of the operation.

Among 164 patients who received vedolizumab, 15 patients had undergone an abdominal operation only, and 4 patients had had a combined abdominal and anorectal operation. Four patients had UC and 15 had CD. The most common types of procedures performed in the 19 patients were laparoscopic abdominal colectomy with end ileostomy and ileocolic resec-

tion, performed in 4 patients each. Of the 4 UC patients, 1 (25%) developed a superficial surgical site infection with no other infectious complications noted. Of the 15 CD patients, 5 (33%) experienced infectious complications within 30 days of the surgery. Four patients (27%) had surgical site infections and 1 (7%) developed infection in a peripherally inserted central catheter as well as a urinary tract infection. Of the 4 surgical site infections, 2 were superficial and were treated with incision and drainage with antibiotics. The other 2 were deep and were treated by percutaneous and operative drainage with antibiotics. Overall, 5 of the

19 IBD patients who had undergone abdominal surgery were treated for postoperative surgical site infections.

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Highlights From the CCFA/Advances in Inflammatory Bowel Diseases 2015 Conference: Commentary

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Presentations at the 2015 CCFA/Advances in Inflammatory Bowel Diseases (IBD) Clinical and Research Conference explored several aspects in the management of Crohn's disease and ulcerative colitis. New data were presented for therapies such as vedolizumab, ustekinumab, and the anti–tumor necrosis factor α (TNF) agents. Other studies focused on iron-deficiency anemia, mucosal healing, high-volume vitamin D_3 supplementation, and fecal microbial transplant.

Ustekinumab

Dr William Sandborn presented results for the UNITI-1 study, a multicenter, double-blind, placebo-controlled, phase 3 trial of ustekinumab.[1] Ustekinumab is a subcutaneous biologic that is currently approved for treatment of moderate-to-severe psoriasis and psoriatic arthritis. Preliminary data suggested that ustekinumab may have benefit for patients with IBD.[2] It has a unique mechanism of action: it inhibits the p40 component of interleukin 12– and interleukin 23–mediated signaling.

UNITI-1 enrolled patients with

moderate-to-severe Crohn's disease who had received 1 or more anti-TNF agents, but did not respond, did not maintain an initial response, or could not tolerate the treatment. The study evaluated 2 different dosing strategies: a standardized dose of 130 mg or a weight-based dose of approximately 6 mg/kg. The primary endpoint was clinical response at 6 weeks. Secondary endpoints included clinical remission and response at week 8. The study found that intravenous ustekinumab induced clinical response and remission. The magnitude of benefit was greater at the higher, weight-adjusted dose of 6 mg/kg than for the lower dose of 130 mg, particularly at induction week 8.

These study results were similar to those seen in the UNITI-2 trial, which evaluated ustekinumab in patients with inadequate responses to conventional therapy (corticosteroids or immunomodulators). Results from UNITI-2 were presented previously.[3] Ustekinumab was associated with significantly higher rates of remission compared with placebo. Data from both UNITI-1 and UNITI-2 suggest that induction with ustekinumab is effective in patients with moderately

to severely active Crohn's disease who did not respond to or could not tolerate previous therapy. These data are impressive. An ongoing maintenance study, IM-UNITI, has enrolled patients in UNITI-1 and UNITI-2 who responded to ustekinumab.[4] This study is comparing 90 mg of ustekinumab every 8 weeks or every 12 weeks vs placebo. Patients will be followed for up to 4 years.

Adhesion Molecule–Based Therapies

Dr Brian Feagan presented a review of adhesion molecule–based therapies in IBD.[5] The small-adhesion molecules currently approved for IBD are natalizumab and vedolizumab. Natalizumab is an α4 integrin in the immunoglobulin G subclass, and vedolizumab is an α4β7. Natalizumab was approved by the US Food and Drug Administration (FDA) in 2008 for the management of moderate-to-severe Crohn's disease in patients with inflammation who have not responded to previous treatment with conventional therapies or anti-TNFα agents. Vedolizumab was approved in 2014 for patients

with moderate to severe ulcerative colitis or Crohn's disease that has not responded to previous treatment. An important, albeit rare, complication associated with natalizumab is progressive, multifocal leukoencephalopathy.[6] Vedolizumab is more gut selective than natalizumab, and it therefore has not been associated with this complication. Natalizumab and vedolizumab have been associated with clear efficacy in IBD. Patients who have not received prior treatment with anti-TNF agents tend to do somewhat better than previously treated patients.

The positive results seen with natalizumab and vedolizumab have led to the development of other small-adhesion molecules. In a phase 2 trial of patients with ulcerative colitis, the β7 inhibitor etrolizumab was associated with clinical remission, regardless of prior use of anti-TNF therapy.[7] PF-547659 is a monoclonal antibody against MAdCAM-1, the ligand for the α4β7 integrin. In a study of patients with ulcerative colitis, this agent showed benefit in an intent-to-treat population, irrespective of previous treatment with anti-TNF agents.[8,9]

Ozanimod, a small-molecule sphingosine 1-phosphate 1 and 5 receptor modulator, has been effective in preliminary studies of ulcerative colitis.[10] It is an oral agent with a novel mechanism of action: it traps lymphocytes within lymph nodes, thereby decreasing the circulating lymphocyte count. When ozanimod is withdrawn, the normal expression of the receptor is restored, and lymphocytes exit the lymph nodes. Ozanimod is currently being evaluated in phase 3 studies in IBD.[11]

Fingolimod is a nonselective sphingosine phosphate inhibitor approved for the treatment of multiple sclerosis. Fingolimod has a similar mechanism of action to ozanimod, although it is less selective and has been associated with more reports of bradycardia. Fingolimod is an oral agent. In preliminary clinical trials of ulcerative colitis, fingolimod was effective in the induction and maintenance of remission.[12] Dr Feagan concluded that monoclonal antibodies and integrins are safe and effective for the induction and maintenance of remission in ulcerative colitis and Crohn's disease. Long-term data are needed for confirmation of this finding.

Vedolizumab

Dr Ira Shafran presented a subanalysis of patients from the GEMINI 2 and GEMINI 3 trials to evaluate the effect of vedolizumab on mucosal healing.[13] This analysis included 11 patients with moderately to severely active Crohn's disease who had significant mucosal ulcerations at baseline. After 1 to 5 years of vedolizumab, the ulcerations completely healed in all patients. One patient experienced mild recurrent disease. These promising data show that it is possible to achieve mucosal healing with an anti-integrin therapy.

A post-hoc analysis by Dr David Rubin evaluated the effect of vedolizumab on extraintestinal manifestations in Crohn's disease patients from the GEMINI 2 study.[14] Vedolizumab is thought to exert more action on the gut, as opposed to the periphery. This post-hoc analysis did not show a significant benefit for vedolizumab over placebo for the treatment of extraintestinal manifestations. However, a limitation to the analysis is that the GEMINI 2 trial was powered to evaluate efficacy, not extrain-testinal manifestations. Further study is needed. In clinical practice, vedolizumab does improve extraintestinal manifestations, although not every extraintestinal manifestation is disease-related. A previous analysis by Dr Bruce Sands showed that a minimum of 10 weeks is needed for vedolizumab to improve extraintestinal manifestations.[15]

A poster by Dr William Holderman and Betty White described the use of vedolizumab for the treatment of anti-TNF–induced psoriasis in a patient with Crohn's colitis.[16] This poster is important because psoriasis may occur as a distinct side effect of anti-TNF therapy. Psoriasis has been seen with the use of infliximab, as well as adalimumab and certolizumab. The severity of psoriasis can be assessed with the Psoriasis Area Severity Index (PASI), which indicates the percentage of area surface involvement. Mild psoriasis (PASI score of 5% or less) is treated initially with topical therapy. When an IBD patient develops significant psoriasis (PASI score greater than 5%), the traditional strategy has been to switch to another anti-TNF agent. This approach, however, is not always successful. It may be beneficial to switch to therapy with a different mechanism of action. This poster describes the case of a 17-year-old female patient with Crohn's colitis who developed psoriasis. The patient

ABSTRACT SUMMARY Harvey-Bradshaw Index Captures Clinical Efficacy of Vedolizumab Induction Therapy for Active Crohn's Disease

As an alternative to the Crohn's Disease Activity Index, a study evaluated the Harvey-Bradshaw Index (HBI) for monitoring improvement in CD patients after vedolizumab therapy (Abstract P-057). A retrospective cohort analysis was conducted in 30 patients with moderate-to-severe CD who received treatment with vedolizumab at a single center. Vedolizumab induction therapy was administered at 0, 2, and 6 weeks. The HBI score was recorded at week 0 and at the first follow-up visit after induction, which occurred at week 10 or 14. The average disease duration was 17.5 years. Eighty-three percent of patients had failed anti-TNFα treatment. At the first visit after induction treatment, 18 patients (60%) had achieved a clinical response, and 11 patients (37%) had achieved clinical remission. The mean decrease in HBI was 3.7 (P=.0002). No significant decrease occurred in the HBI subscore of extraintestinal complications (53% vs 43%; P=.2).

described in this report appears to have severe psoriasis, although the PASI score was not provided. In this patient, psoriasis was evident on the palms, hands, and soles of the feet. Topical corticosteroids were not effective. Vedolizumab resolved the psoriasis and also achieved sustained clinical and endoscopic remission. The authors suggested that vedolizumab should be considered in place of anti-TNF therapy when patients develop refractory psoriasis that does not respond to standard therapy.

A poster from Dr Matthew Reynolds examined hospitalizations and characteristics of patients with ulcerative colitis and Crohn's disease treated with vedolizumab in the United States.[17] The authors evaluated electronic health records from the US Explorys Universe Database to identify patients with a diagnosis of Crohn's disease or ulcerative colitis who had started treatment with vedolizumab between June 2014 and February 2015, had a documented medical history of more than a year, and had more than 180 days of follow-up. Among the 237 patients who met the criteria, 83% had previously received biologic therapy, mostly to treat refractory disease. There were fewer hospitalizations in the 180 days after initiation of vedolizumab than in the 180 days before, showing that vedolizumab is an effective therapy. Hospitalization and

surgery are among the most important metrics used to not only measure patient outcome but also to calculate costs.

Dr Khadija Chaudrey presented results of a study evaluating the efficacy and safety of vedolizumab in clinical practice.[18] The study included 91 patients who received vedolizumab from August 2013 to August 2015. Among the 91 patients, 63 were evaluable. Positive outcomes were seen in the cohort of patients with ulcerative colitis, who had relatively refractory disease, and in patients with Crohn's disease. There were no new toxicity signals, and the safety profile was relatively good. Among the 5 patients who developed an infection, most did not require antibiotics. Although this series of patients is small, the results appear promising and are consistent with the clinical trial data.

Dr Amy Lightner examined the impact of vedolizumab on postoperative outcomes in patients undergoing abdominal surgery for IBD.[19] Surgery is an option for patients with ulcerative colitis and Crohn's disease if systemic treatment is not effective and the disease flares. Complications of IBD may also require surgery. Vedolizumab inhibits the trafficking of leukocytes into the bowel. A question has been raised regarding whether use of vedolizumab might alter wound healing or lead to infectious complications. This retrospec-

tive study examined the 30-day postoperative infectious complication rate in patients who had received vedolizumab within 30 days of an abdominal operation to identify any negative impact on surgical outcomes. Among the 164 patients who had received vedolizumab, surgeries were performed in 4 patients with ulcerative colitis and 15 patients with Crohn's disease. The surgeries consisted of an abdominal operation alone in 15 patients, and abdominal and anal-rectal operations combined in 4 patients. The most common procedures were abdominal colectomy and end ileostomy. Among 4 patients with ulcerative colitis, 1 developed a superficial surgical site infection with no other complications. Among the 15 patients with Crohn's disease, 5 had postoperative infectious complications. Overall, 4 patients developed signs or symptoms of infection, and 1 patient had a peripherally inserted central catheter line infection and a urinary tract infection, for an infection rate of 26%.

There are several limitations to this study. The number of patients is small, and the study lacked a baseline control group of patients who did not receive vedolizumab. In addition, the study did not provide information regarding any concurrent medications. This omission is important because corticosteroids are the main drivers of postoperative infectious complications. As shown by Aberra and colleagues, there is a substantially escalated risk of postoperative infectious complications among patients with IBD who are receiving corticosteroids.[20] Further studies will be necessary to determine whether vedolizumab is a driver of infections or if other factors have an impact.

Anti-TNFα Therapies

Dr Júlio Pinheiro Baima presented results of a randomized trial evaluating infliximab vs adalimumab in Crohn's disease.[21] It was a comparative study, which is rare for these therapies. Overall, there was no difference in response between infliximab and adalimumab. An important limitation to this study,

ABSTRACT SUMMARY Impact of High Dose Vitamin D₃ Supplementation in Treatment of Crohn's Disease in Remission: A Randomized Double-Blind Controlled Study

Vitamin D deficiency has been implicated in the pathogenesis of CD (Ananthakrishnan AN. *Nat Rev Gastroenterol Hepatol.* 2015;12[4]:205-217). A double-blind, placebo-controlled trial assessed the tolerability and efficacy of high-dose vitamin D_3 in patients with CD (Abstract P-064). Patients in remission were randomized to receive vitamin D_3 daily at either a high dose (10,000 IU) or a low dose (1000 IU). There were 18 patients in the high-dose arm and 16 patients in the low-dose arm. Serum levels of 25-hydroxy vitamin D improved significantly in patients who received the high dose of vitamin D_3, with mean levels increasing from 73.5 ng/mL ± 11.7 to 160.8 ng/mL ± 43.2 (P=.02). There were no reports of relapse among the 12 patients who received the higher dose. Among the 8 patients who received the lower dose, 3 relapsed (P=.049). Both groups demonstrated improvements in depression. The safety profile was good.

however, was the small number of patients (N=16). Prospective, randomized, superiority trials with adequate power would be required to identify any differences in outcome.

Mucosal Healing

Dr Shailja Shah presented results from 2 systematic reviews evaluating the association between mucosal healing and long-term outcomes in IBD.[22,23] One review focused on Crohn's disease, and the other on ulcerative colitis. The authors identified interventional studies based on a literature search of PubMed, Embase, and the Cochrane Library. The primary outcome was long-term remission. The secondary outcomes were surgery-free rate and long-term mucosal healing.

The Crohn's disease studies included more than 670 patients.[22] The analysis showed that early mucosal healing with biologic or nonbiologic therapy was associated with an odds ratio of 2.80 for achieving long-term complete remission and 14.30 for maintaining long-term mucosal healing. The odds ratio for not needing surgery for Crohn's disease was 2.22, which is impressive, but did not reach statistical significance. The analysis therefore confirmed the widespread belief that patients who achieve mucosal healing have good short-term results and long-term outcomes. The analysis did not assess specific factors, such as fistulizing disease, early surgical intervention, early corticosteroid use, or early age of diagnosis.

The studies of ulcerative colitis included more than 2019 patients.[23] The primary outcome was long-term clinical remission. Secondary outcomes included long-term colectomy-free rate, mucosal healing, and corticosteroid-free clinical remission. As with the previous analysis in Crohn's disease, this review showed that mucosal healing with biologic or nonbiologic therapy improved long-term outcomes at a year and beyond. Early mucosal healing with biologic or nonbiologic therapy was associated with an odds ratio of 4.88 for achieving long-term complete remission, 5.34 for avoiding long-term colectomy, 8.40 for maintaining long-term mucosal healing, and 9.70 for maintaining long-term corticosteroid-free complete remission. Mucosal healing is an important treatment goal for patients with ulcerative colitis. Whether mucosal healing alters the natural history of ulcerative colitis or provides cost benefits must be evaluated in a well-designed clinical trial.

Fibrosis

Patients with chronic ulcerative colitis, with or without active disease, may experience symptoms of fecal urgency. If endoscopic evaluation reveals no inflammation, then the fecal urgency might be related to loss of muscle tone. The condition known as pipe stem colon, in which the colon appears tubular, was associated with fecal urgency and increased stool frequency in a study by Dr Neha Agrawal.[24] The study found that chronic, though not active, inflammation was associated with submucosal fibrosis and increased wall thickness in patients with ulcerative colitis. Pipe stem colon is therefore a clinically relevant finding. Patients who have long-standing ulcerative colitis with mucosal fibrosis may have a noncompliant colon, leading to a higher frequency of stool at baseline despite inactive disease. For years, research has suggested that fibrosis is more common with Crohn's disease than ulcerative colitis, but this study lends credence to these long-standing clinical observations.

Anemia

It is often underrecognized that iron-deficiency anemia may complicate the management of patients with IBD. Patients with active IBD often do not absorb iron well. Oral iron supplementation can have a slow onset and is associated with many side effects. Parenteral iron is used in patients with active disease who have low hemoglobin and significant anemia. Dr Ronen Stein presented results from a retrospective study evaluating the use of an intravenous formulation of iron sucrose in pediatric IBD patients with iron-deficiency anemia.[25] The study measured the clinical response (improvement in hemoglobin levels) and adverse events. The study included 75 patients: 57 with Crohn's disease, 10 with ulcerative colitis, and 8 with indeterminate colitis. The patients received 200-mg doses of iron infusions.

ABSTRACT SUMMARY Chronic But Not Active Inflammation Is Linked With Fibrosis in Ulcerative Colitis

Intestinal fibrosis is more prevalent in CD and has remained largely unexplored in UC patients. A study was conducted in UC patients to characterize the location and severity of fibrosis and to assess associated clinical parameters (Abstract P-030). Approximately 750 individual tissue cross sections from 95 patients were evaluated for presence and degree of inflammation, degree of fibrosis, and morphometric measurements of all layers of the intestinal wall. Submucosal fibrosis was observed in all colectomy specimens, and its presence was restricted to areas affected by inflammation. Submucosal fibrosis was associated with chronic, though not active, histopathologic changes. Inflammation was associated with thickening of the colonic wall, resulting from increased diameter of the lamina propria and muscularis mucosae ($P<.001$), but other layers did not contribute to colonic wall thickening. The degree of inflammation was associated with the degree of submucosal fibrosis ($P<.001$). Independent variables associated with increased fibrotic burden included male sex, refractory disease, and use of 5-aminosalicylic acid at the time of colectomy ($P<.05$ for all 3). Independent variables associated with increased thickness of the muscularis mucosa included use of 5-aminosalicylic acid and patient age ($P<.05$ for both).

The intravenous formulation showed clinical efficacy. Hemoglobin levels increased from 9.5+1.2 g/dL at baseline to 12.0+1.4 g/dL after treatment. The therapy was safe. There were 24 reported adverse events, consisting of blood pressure fluctuations (n=8), pulse fluctuations (n=8), pain at the intravenous site (n=6), chills (n=1), and intravenous infiltration (n=1). There were no reports of anaphylaxis. None of the adverse events were life-threatening or required treatment. In the patient with intravenous infiltration, the iron sucrose was discontinued. Although the number of patients in this study was small, the findings suggest that parenteral iron is safe and effective. It is comforting to know there was no anaphylaxis.

Probiotics

A Cochrane review presented by Dr Morris Gordon evaluated the efficacy of probiotics in the maintenance and remission of ulcerative colitis.[26] This analysis found that probiotics were more effective than placebo, but it included only 2 studies. There is no evidence suggesting that probiotics are superior to mesalazine for the maintenance of remission in ulcerative colitis, or that there are any differences in the adverse event profiles. Many IBD patients use probiotics because they are relatively easy to obtain, but there are few well-done studies with appropriate endpoints evaluating this approach. Further research is clearly needed to explore the potential for probiotics in this patient population.

Vitamin D₃

A randomized, double-blind, placebo-controlled trial evaluated the use of high-volume vitamin D_3 supplementation in Crohn's disease.[27] The T-cell proliferation and T-helper (TH) cells that produce IL-17 (TH 17 cells) and IFN-γ (TH 1 cells) are inhibited by 1,25(OH)2 vitamin D_3.[28] In IBD, an epidemiologic association has been established between active disease and low vitamin D levels. This study compared 2 doses of vitamin D_3 in patients with Crohn's disease. The high dose was 10,000 units daily and the low dose was 1000 units daily. The outcome was improvement in vitamin D levels. The study was small, with 18 patients in the high-dose arm and 16 patients in the low-dose arm.

The high dose of 10,000 units daily significantly improved vitamin D levels from a mean of 73.5 nmol/L to 160.8 nmol/L (P=.02). There was a lower rate of clinical relapse in patients receiving the high dose (0% vs 37.5%; P=.049). In both treatment groups, there were improvements in depression. Both dosages were well-tolerated.

The results of this small trial are exciting, but larger studies are needed. Vitamin D is relatively safe. If found to be effective, it could become part of the standard of care. Levels of vitamin D are measured in patients with active disease because they can be altered rapidly. Vitamin D appears to impact not only disease activity, but also bone mineral density. Low levels of vitamin D can be associated with osteomalacia in patients with Crohn's disease, and the tensile strength of bones may be altered as a consequence.

Fecal Microbial Transplant

An uncontrolled, prospective study presented by Michael Mintz compared fecal microbial transplant outcomes in patients with recurrent *Clostridium difficile* or ulcerative colitis.[29] This study evaluated the effect of colonoscopically induced fecal microbial transplant on the fecal microbiome. Fecal microbial transplant can be performed several ways, such as through an enema, a nasoenteric tube, and colonoscopic or sigmoidoscopic insertion of the stool. Also under evaluation is oral administration via an enteric-coated compound that releases fecal contents into the bowel. This particular study used colonoscopic insertion of the stool. It found that the fecal microbiomes of both ulcerative colitis and *C difficile* patients differed from healthy donors. At baseline, *C difficile* patients had more pronounced dysbiosis, but the fecal microbial transplant shifted the patient's microbiome toward the direction of the donor's microbiome. This effect was more pronounced in patients with *C difficile* infection, which might partly explain why fecal microbial transplants have been more successful in treating

ABSTRACT SUMMARY Vedolizumab Results in Resolution of Anti-Tumor Necrosis Factor Psoriasis and Sustained Clinical and Endoscopic Remission of Crohn's Colitis

Psoriasis has been associated with the use of anti-TNF agents in patients with IBD. Treatment strategies usually involve topical therapy or switching to another TNF agent. In clinical trials of vedolizumab, psoriasis has not been an AE. A case report described the use of vedolizumab in a Crohn's colitis patient who developed psoriasis in response to treatment with infliximab (Abstract P-230). The patient had psoriasis on the palms of her hands and the soles of her feet. Topical corticosteroids were not effective. The psoriasis persisted through a switch to certolizumab and worsened with adalimumab, leading to loss of hair and ulceration of the fingernail beds. After 4 months of treatment with vedolizumab, the psoriasis resolved completely, and the patient's hair and nails grew back. Treatment with vedolizumab also maintained clinical and endoscopic remission of the patient's IBD. The authors suggested that a switch to vedolizumab should be made early in the treatment course if an IBD patient receiving anti-TNF therapy develops psoriasis that does not resolve with topical treatment.

C difficile than ulcerative colitis. A recent meta-analysis showed efficacy of approximately 90% in treating patients with recurrent *C difficile*.[30] In ulcerative colitis, results have been more mixed; efficacy is thought to be approximately 50%. Investigational research studies performed in patients with IBD require an Investigational New Drug application number from the FDA. In contrast, this application is not required for patients with *C difficile*. The community has readily adopted the use of fecal microbiota transplant for recurrent *C difficile*. In this specific study, patients with ulcerative colitis did not experience a significant difference in their Mayo score at the 3-month follow-up flexible sigmoidoscopy. This finding reiterates that it is not yet known whether fecal microbial transplant affects the mucosa directly. Further evaluation is needed.

Disclosure

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