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A SPECIAL MEETING REVIEW EDITION

Highlights From the 2021 Advances in Inflammatory Bowel Diseases Conference

A Review of Selected Presentations From the 2021 AIBD Conference

• December 9-11, 2021 • Orlando, Florida

Special Reporting on:

- The Past, Present, and Future of Inflammatory Bowel Disease
- Personalized Medicine: Yesterday, Today, and Tomorrow
- Micronutrient Deficiencies in Inflammatory Bowel Disease
- Preparing for Inflammatory Bowel Disease Care in the Next Pandemic: Lessons Learned From COVID-19
- Positioning Medications: Yesterday, Today, and Tomorrow

PLUS Meeting Abstract Summaries

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TAKE CHARGE OF CD+UC

STELARA® FOR

*In both the CD and UC studies, many patients achieved

RAPID RESPONSE

Many patients achieved clinical response as early as Week 6 in CD and Week 8 in UC in clinical trials[1†]

LASTING REMISSION

Many patients achieved clinical remission at 1 year in the CD and UC clinical trials[1‡]

Clinical Response† at Week 6 (Predominantly TNF Blocker Naïve[II]) in CD (Primary Endpoint):
• STELARA®: 56% (n=116/209); Placebo: 29% (n=60/209); *P*<0.001

Clinical Response† at Week 6 (TNF Blocker Failure) in CD (Primary Endpoint):
• STELARA®: 34% (n=84/249); Placebo: 21% (n=53/247); *P*<0.01

Clinical Remission‡ at 1 Year (Overall Population) in CD (Primary Endpoint):
• STELARA®: 53% (n=68/128); Placebo: 36% (n=47/131); *P*<0.01

CD Study Designs: In CD-1 and CD-2 (Induction Studies, 8 Weeks), 741 and 627 patients, respectively, were randomized to either a single placebo IV (n=247, n=209) or STELARA® IV dose (based on the body weight of the patient at the time of dosing) of approximately 6 mg/kg administered over at least 1 hour at Week 0 (n=249, n=209). Eligible patients (≥18 years of age) had moderately to severely active CD (CDAI score of 220 to 250) and had failed or were intolerant to treatment with one or more TNF blockers (CD-1) or had failed or were intolerant to treatment with immunomodulators and/or corticosteroids, but never failed treatment with a TNF blocker (CD-2). In CD-3 (Maintenance Study, 44 Weeks), 388 patients who had achieved clinical response (≥100 point reduction in CDAI score) at Week 8 with the induction dose of STELARA® in CD-1 or CD-2 were randomized to receive a subQ maintenance regimen of either 90 mg of STELARA® q8w (n=128) or placebo (n=131) for 44 weeks. After completing the Maintenance Study at Week 44, patients were eligible to enter the open-label LTE study.

Clinical Response† at Week 8 in UC (Major Secondary Endpoint):
• STELARA®: 58% (n=186/322); Placebo: 31% (n=99/319); *P*<0.001

Clinical Remission‡ at Week 8 in UC (Primary Endpoint):
• STELARA®: 19% (n=62/322); Placebo: 7% (n=22/319); *P*<0.001

Clinical Remission‡ at 1 Year in UC (Primary Endpoint):
• STELARA®: 45% (n=79/176); Placebo: 26% (n=46/175); *P*≤0.001

HEMI§ at Week 8 (Overall Population) in UC (Other Secondary Endpoint):
• STELARA® : 17% (n=54/322); Placebo: 8% (n=26/319); P<0.001

HEMI§ at 1 Year (Overall Population) in UC (Prespecified Other Endpoint; not adjusted for multiplicity):
• STELARA®: 44% (n=75/172); Placebo: 23% (n=40/172)

The relationship of HEMI to long-term outcomes was not studied in the clinical trials.

UC Study Designs: In UC-1 (Induction Study, 8 Weeks), 961 patients were randomized to either a single placebo IV (n=319) or STELARA® IV dose (based on the body weight of the patient at the time of dosing) of approximately 6 mg/kg administered over at least 1 hour at Week 0 (n=322). Eligible patients (≥18 years of age) had moderately to severely active UC (ie, Mayo score of 6 to 12, including a Mayo endoscopy subscore ≥2) and had experienced an inadequate response to or failed to tolerate previous biologics (ie, TNF blocker and/or vedolizumab), corticosteroids, and/or 6-mercaptopurine or azathioprine therapy. In UC-2 (Maintenance Study, 44 Weeks), 523 patients who achieved clinical response 8 weeks following the IV administration of the induction dose of STELARA® in UC-1 were randomized to receive STELARA® 90 mg q8w (n=176) or placebo (n=175) for 44 weeks. After completing the Maintenance Study at Week 44, patients were eligible to enter the open-label LTE study.

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5-YEAR DATA IN CD
(1-year randomized clinical trials plus 4-year open-label LTE study)[2]

2-YEAR DATA IN UC
(1-year randomized clinical trials plus 1-year open-label LTE study)[2]

FOR YOUR BIO-NAÏVE PATIENTS

LASTING* REMISSION

clinical remission at 1 year with STELARA®. Please see supporting data below.

HISTO-ENDOSCOPIC MUCOSAL IMPROVEMENT (HEMI) IN UC

The *first* and *only* FDA-approved UC treatment to achieve HEMI. Some patients with UC achieved HEMI with STELARA® at the designated time points (Week 8 and 1 year) in clinical trials.[1§] **The relationship of HEMI to long-term outcomes was not studied in the clinical trials.**

SAFETY PROFILE

The overall safety profile in CD and UC studies through 1 year was consistent with that seen in other approved indications[1]

INDICATIONS

STELARA® (ustekinumab) is indicated for the treatment of adult patients with moderately to severely active Crohn's disease.

STELARA® (ustekinumab) is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis.

SELECTED IMPORTANT SAFETY INFORMATION

STELARA® is contraindicated in patients with clinically significant hypersensitivity to ustekinumab or excipients. Serious adverse reactions have been reported in STELARA®-treated patients, including bacterial, mycobacterial, fungal, and viral infections, malignancies, hypersensitivity reactions, Posterior Reversible Encephalopathy Syndrome (PRES), and noninfectious pneumonia. STELARA® should not be given to patients with any clinically important active infection. Patients should be evaluated for tuberculosis prior to initiating treatment with STELARA®. Live vaccines should not be given to patients receiving STELARA®. If PRES is suspected or if noninfectious pneumonia is confirmed, discontinue STELARA®.

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Please see related and other Important Safety Information on next page.

†In CD, clinical response was defined as reduction in CDAI score of ≥100 points or CDAI score of <150. In UC, clinical response was defined as a decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a decrease from baseline in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

‡In CD, clinical remission was defined as a CDAI score of <150. In UC, clinical remission was defined as Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0, and Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

§HEMI was defined as combined endoscopic improvement (Mayo endoscopy subscore of 0 or 1, modified so that 1 does not include friability) and histologic improvement of the colon tissue (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue).

‖69% of patients were TNF blocker naïve. Remaining population was patients previously exposed to, but who did not fail, treatment with TNF blockers. All patients in the study who failed or were intolerant of conventional treatment (eg, azathioprine, 6-mercaptopurine, methotrexate, or corticosteroids).

References: 1. STELARA® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Data on file. Janssen Biotech, Inc.

CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; HEMI=histo-endoscopic mucosal improvement; IV=intravenous; LTE=long-term extension; q8w=every 8 weeks; subQ=subcutaneous; TNF=tumor necrosis factor; UC=ulcerative colitis.

Stelara® (ustekinumab)

IMPORTANT SAFETY INFORMATION

STELARA® (ustekinumab) is contraindicated in patients with clinically significant hypersensitivity to ustekinumab or to any of the excipients.

Infections

STELARA® may increase the risk of infections and reactivation of latent infections. Serious bacterial, mycobacterial, fungal, and viral infections requiring hospitalization or otherwise clinically significant infections were reported. In patients with psoriasis, these included diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis, sepsis, osteomyelitis, viral infections, gastroenteritis, and urinary tract infections. In patients with psoriatic arthritis, this included cholecystitis. In patients with Crohn's disease, these included anal abscess, gastroenteritis, ophthalmic herpes zoster, pneumonia, and *Listeria* meningitis. In patients with ulcerative colitis, these included gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeriosis.

Treatment with STELARA® should not be initiated in patients with a clinically important active infection until the infection resolves or is adequately treated. Consider the risks and benefits of treatment prior to initiating use of STELARA® in patients with a chronic infection or a history of recurrent infection. Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur while on treatment with STELARA® and consider discontinuing STELARA® for serious or clinically significant infections until the infection resolves or is adequately treated.

Theoretical Risk for Vulnerability to Particular Infections

Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria, *Salmonella*, and *Bacillus Calmette-Guerin* (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients. It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA® may be susceptible to these types of infections. Appropriate diagnostic testing should be considered (eg, tissue culture, stool culture) as dictated by clinical circumstances.

Pre-Treatment Evaluation of Tuberculosis (TB)

Evaluate patients for TB prior to initiating treatment with STELARA®. Do not administer STELARA® to patients with active tuberculosis infection. Initiate treatment of latent TB before administering STELARA®. Closely monitor patients receiving STELARA® for signs and symptoms of active TB during and after treatment.

Malignancies

STELARA® is an immunosuppressant and may increase the risk of malignancy. Malignancies were reported among patients who received STELARA® in clinical studies. The safety of STELARA® has not been evaluated in patients who have a history of malignancy or who have a known malignancy. There have been reports of the rapid appearance of multiple cutaneous squamous cell carcinomas in patients receiving STELARA® who had risk factors for developing non-melanoma skin cancer (NMSC). All patients receiving STELARA®, especially those >60 years or those with a history of PUVA or prolonged immunosuppressant treatment, should be monitored for the appearance of NMSC.

Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with STELARA®. If an anaphylactic or other clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue STELARA®.

Posterior Reversible Encephalopathy Syndrome (PRES)

Two cases of posterior reversible encephalopathy syndrome (PRES), also known as Reversible Posterior Leukoencephalopathy Syndrome (RPLS), were reported in clinical trials. Cases have also been reported in postmarketing experience in patients with psoriasis, psoriatic arthritis and Crohn's disease. Clinical presentation included headaches, seizures, confusion, visual disturbances, and imaging changes consistent with PRES a few days to several months after ustekinumab initiation. A few cases reported latency of a year or longer. Patients recovered with supportive care following withdrawal of ustekinumab.

Monitor all patients treated with STELARA® for signs and symptoms of PRES. If PRES is suspected, promptly administer appropriate treatment and discontinue STELARA®.

Immunizations

Prior to initiating therapy with STELARA®, patients should receive all age-appropriate immunizations recommended by current guidelines. Patients being treated with STELARA® should not receive live vaccines. BCG vaccines should not be given during treatment or within one year of initiating or discontinuing STELARA®. Exercise caution when administering live vaccines to household contacts of STELARA® patients, as shedding and subsequent transmission to STELARA® patients may occur. Non-live vaccinations received during a course of STELARA® may not elicit an immune response sufficient to prevent disease.

Concomitant Therapies

The safety of STELARA® in combination with other biologic immunosuppressive agents or phototherapy was not evaluated in clinical studies of psoriasis. Ultraviolet-induced skin cancers developed earlier and more frequently in mice. In psoriasis studies, the relevance of findings in mouse models for malignancy risk in humans is unknown. In psoriatic arthritis studies, concomitant methotrexate use did not appear to influence the safety or efficacy of STELARA®. In Crohn's disease and ulcerative colitis induction studies, concomitant use of 6-mercaptopurine, azathioprine, methotrexate, and corticosteroids did not appear to influence the overall safety or efficacy of STELARA®.

Noninfectious Pneumonia

Cases of interstitial pneumonia, eosinophilic pneumonia, and cryptogenic organizing pneumonia have been reported during post-approval use of STELARA®. Clinical presentations included cough, dyspnea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalization. Patients improved with discontinuation of therapy and, in certain cases, administration of corticosteroids. If diagnosis is confirmed, discontinue STELARA® and institute appropriate treatment.

Allergen Immunotherapy

STELARA® may decrease the protective effect of allergen immunotherapy (decrease tolerance) which may increase the risk of an allergic reaction to a dose of allergen immunotherapy. Therefore, caution should be exercised in patients receiving or who have received allergen immunotherapy, particularly for anaphylaxis.

Most Common Adverse Reactions

The most common adverse reactions (≥3% and higher than that with placebo) in adults from psoriasis clinical studies for STELARA® 45 mg, STELARA® 90 mg, or placebo were: nasopharyngitis (8%, 7%, 8%), upper respiratory tract infection (5%, 4%, 5%), headache (5%, 5%, 3%), and fatigue (3%, 3%, 2%), respectively. The safety profile in pediatric patients with plaque psoriasis was similar to that of adults with plaque psoriasis. In psoriatic arthritis (PsA) studies, a higher incidence of arthralgia and nausea was observed in patients treated with STELARA® when compared with placebo (3% vs 1% for both). In Crohn's disease induction studies, common adverse reactions (3% or more of patients treated with STELARA® and higher than placebo) reported through Week 8 for STELARA® 6 mg/kg intravenous single infusion or placebo included: vomiting (4% vs 3%). In the Crohn's disease maintenance study, common adverse reactions (3% or more of patients treated with STELARA® and higher than placebo) reported through Week 44 for STELARA® 90 mg subcutaneous injection or placebo were: nasopharyngitis (11% vs 8%), injection site erythema (5% vs 0%), vulvovaginal candidiasis/mycotic infection (5% vs 1%), bronchitis (5% vs 3%), pruritus (4% vs 2%), urinary tract infection (4% vs 2%) and sinusitis (3% vs 2%). In the ulcerative colitis induction study, common adverse reactions (3% or more of patients treated with STELARA® and higher than placebo) reported through Week 8 for STELARA® 6 mg/kg intravenous single infusion or placebo included: nasopharyngitis (7% vs 4%). In the ulcerative colitis maintenance study, common adverse reactions (3% or more of patients treated with STELARA® and higher than placebo) reported through Week 44 for STELARA® 90 mg subcutaneous injection or placebo included: nasopharyngitis (24% vs 20%), headache (10% vs 4%), abdominal pain (7% vs 3%), influenza (6% vs 5%), fever (5% vs 4%), diarrhea (4% vs 1%), sinusitis (4% vs 1%), fatigue (4% vs 2%), and nausea (3% vs 2%).

Please see full Prescribing Information and Medication Guide for STELARA® at STELARAHCP.com. Provide the Medication Guide to your patients and encourage discussion.

cp-124933v3

Stelara® (ustekinumab)

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Brief Summary of Prescribing Information for STELARA® (ustekinumab)
STELARA® Injection, for subcutaneous use
See package insert for Full Prescribing Information

INDICATIONS AND USAGE: Psoriasis (Ps): STELARA® is indicated for the treatment of patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. **Psoriatic Arthritis (PsA):** STELARA® is indicated for the treatment of adult patients with active psoriatic arthritis. STELARA® can be used alone or in combination with methotrexate (MTX). **Crohn's Disease (CD):** STELARA® is indicated for the treatment of adult patients with moderately to severely active Crohn's disease. **Ulcerative Colitis:** STELARA® is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis. **CONTRAINDICATIONS:** STELARA® is contraindicated in patients with clinically significant hypersensitivity to ustekinumab or to any of the excipients *[see Warnings and Precautions]*. **WARNINGS AND PRECAUTIONS: Infections:** STELARA® may increase the risk of infections and reactivation of latent infections. Serious bacterial, mycobacterial, fungal, and viral infections were observed in patients receiving STELARA® *[see Adverse Reactions]*. Serious infections requiring hospitalization, or otherwise clinically significant infections, reported in clinical studies included the following: • *Psoriasis*: diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis, sepsis, osteomyelitis, viral infections, gastroenteritis and urinary tract infections. • *Psoriatic arthritis*: cholecystitis. • *Crohn's disease*: anal abscess, gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeria meningitis. • *Ulcerative colitis*: gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeriosis. Treatment with STELARA® should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. Consider the risks and benefits of treatment prior to initiating use of STELARA® in patients with a chronic infection or a history of recurrent infection. Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur while on treatment with STELARA® and consider discontinuing STELARA® for serious or clinically significant infections until the infection resolves or is adequately treated. **Theoretical Risk for Vulnerability to Particular Infections:** Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria (including nontuberculous, environmental mycobacteria), salmonella (including nontyphi strains), and Bacillus Calmette-Guerin (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients. It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA® may be susceptible to these types of infections. Appropriate diagnostic testing should be considered, e.g., tissue culture, stool culture, as dictated by clinical circumstances. **Pre-treatment Evaluation for Tuberculosis:** Evaluate patients for tuberculosis infection prior to initiating treatment with STELARA®. Do not administer STELARA® to patients with active tuberculosis infection. Initiate treatment of latent tuberculosis prior to administering STELARA®. Consider anti-tuberculosis therapy prior to initiation of STELARA® in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Closely monitor patients receiving STELARA® for signs and symptoms of active tuberculosis during and after treatment. **Malignancies:** STELARA® is an immunosuppressant and may increase the risk of malignancy. Malignancies were reported among subjects who received STELARA® in clinical studies *[see Adverse Reactions]*. In rodent models, inhibition of IL-12/IL-23p40 increased the risk of malignancy *[see Nonclinical Toxicology (13) in Full Prescribing Information]*. The safety of STELARA® has not been evaluated in patients who have a history of malignancy or who have a known malignancy. There have been post-marketing reports of the rapid appearance of multiple cutaneous squamous cell carcinomas in patients receiving STELARA® who had pre-existing risk factors for developing non-melanoma skin cancer. All patients receiving STELARA® should be monitored for the appearance of non-melanoma skin cancer. Patients greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy and those with a history of PUVA treatment should be followed closely *[see Adverse Reactions]*. **Hypersensitivity Reactions:** Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with STELARA® *[see Adverse Reactions]*. If an anaphylactic or other clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue STELARA®. **Posterior Reversible Encephalopathy Syndrome (PRES):** Two cases of posterior reversible encephalopathy syndrome (PRES), also known as Reversible Posterior Leukoencephalopathy Syndrome (RPLS), were reported in clinical trials. Cases have also been reported in postmarketing experience in patients with psoriasis, psoriatic arthritis and Crohn's disease. Clinical presentation included headaches, seizures, confusion, visual disturbances, and imaging changes consistent with PRES a few days to several months after ustekinumab initiation. A few cases reported latency of a year or longer. Patients recovered with supportive care following withdrawal of ustekinumab. Monitor all patients treated with STELARA® for signs and symptoms of PRES. If PRES is suspected, promptly administer appropriate treatment and discontinue STELARA®. **Immunizations:** Prior to initiating therapy with STELARA®, patients should receive all age-appropriate immunizations as recommended by current immunization guidelines. Patients being treated with STELARA® should not receive live vaccines. BCG vaccines should not be given during treatment with STELARA® or for one year prior to initiating treatment or one year following discontinuation of treatment. Caution is advised when administering live vaccines to household contacts of patients receiving STELARA® because of the potential risk for shedding from the household contact and transmission to patient. Non-live vaccinations received during a course of STELARA® may not elicit an immune response sufficient to prevent disease. **Concomitant Therapies:** In clinical studies of psoriasis the safety of STELARA® in combination with other biologic immunosuppressive agents or phototherapy was not evaluated. Ultraviolet-induced skin cancers developed earlier and more frequently in mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone *[see Concomitant Therapies, Nonclinical Toxicology (13.1) in Full Prescribing Information]*. **Noninfectious Pneumonia:** Cases of interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia have been reported during post-approval use of STELARA®. Clinical presentations included cough, dyspnea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalization. Patients improved with discontinuation of therapy and in certain cases administration of corticosteroids. If diagnosis is confirmed, discontinue STELARA® and institute appropriate treatment *[see Postmarketing Experience]*. **ADVERSE REACTIONS:** The following serious adverse reactions are discussed elsewhere in the label: • Infections *[see Warnings and Precautions]* • Malignancies *[see Warnings and Precautions]* • Hypersensitivity Reactions *[see Warnings and Precautions]* • Posterior Reversible Encephalopathy Syndrome (PRES) *[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. Adult Subjects with Plaque Psoriasis: The safety data reflect exposure to STELARA® in 3117 adult psoriasis subjects, including 2414 exposed for at least 6 months, 1855 exposed for at least one year, 1653 exposed for at least two years, 1569 exposed for at least three years, 1482 exposed for at least four years and 838 exposed for at least five years. Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the STELARA® groups than the placebo group during the placebo-controlled period of Ps STUDY 1 and Ps STUDY 2 *[see Clinical Studies (14) in Full Prescribing Information]*.

Table 1: Adverse Reactions Reported by ≥1% of Subjects through Week 12 in Ps STUDY 1 and Ps STUDY 2

		STELARA®	
	Placebo	**45 mg**	**90 mg**
Subjects treated	**665**	**664**	**666**
Nasopharyngitis	51 (8%)	56 (8%)	49 (7%)
Upper respiratory tract infection	30 (5%)	36 (5%)	28 (4%)
Headache	23 (3%)	33 (5%)	32 (5%)
Fatigue	14 (2%)	18 (3%)	17 (3%)
Diarrhea	12 (2%)	13 (2%)	13 (2%)
Back pain	8 (1%)	9 (1%)	14 (2%)
Dizziness	8 (1%)	8 (1%)	14 (2%)
Pharyngolaryngeal pain	7 (1%)	9 (1%)	12 (2%)
Pruritus	9 (1%)	10 (2%)	9 (1%)
Injection site erythema	3 (<1%)	6 (1%)	13 (2%)
Myalgia	4 (1%)	7 (1%)	8 (1%)
Depression	3 (<1%)	8 (1%)	4 (1%)

Adverse reactions that occurred at rates less than 1% in the controlled period of Ps STUDIES 1 and 2 through week 12 included: cellulitis, herpes zoster, diverticulitis and certain injection site reactions (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation). One case of PRES occurred during adult plaque psoriasis clinical studies *[see Warnings and Precautions]*. *Infections*: In the placebo-controlled period of clinical studies of psoriasis subjects (average follow-up of 12.6 weeks for placebo-treated subjects and 13.4 weeks for STELARA®-treated subjects), 27% of STELARA®-treated subjects reported infections (1.39 per subject-year of follow-up) compared with 24% of placebo-treated subjects (1.21 per subject-year of follow-up). Serious infections occurred in 0.3% of STELARA®-treated subjects (0.01 per subject-year of follow-up) and in 0.4% of placebo-treated subjects (0.02 per subject-year of follow-up) *[see Warnings and Precautions]*. In the controlled and non-controlled portions of psoriasis clinical studies (median follow-up of 3.2 years), representing 8998 subject-years of exposure, 72.3% of STELARA®-treated subjects reported infections (0.87 per subject-years of follow-up). Serious infections were reported in 2.8% of subjects

(0.01 per subject-years of follow-up). *Malignancies*: In the controlled and non-controlled portions of psoriasis clinical studies (median follow-up of 3.2 years, representing 8998 subject-years of exposure), 1.7% of STELARA®-treated subjects reported malignancies excluding non-melanoma skin cancers (0.60 per hundred subject-years of follow-up). Non-melanoma skin cancer was reported in 1.5% of STELARA®-treated subjects (0.52 per hundred subject-years of follow-up) *[see Warnings and Precautions].* The most frequently observed malignancies other than non-melanoma skin cancer during the clinical studies were: prostate, melanoma, colorectal and breast. Malignancies other than non-melanoma skin cancer in STELARA®-treated patients during the controlled and uncontrolled portions of studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender and race).[1] Pediatric Subjects with Plaque Psoriasis: The safety of STELARA® was assessed in two studies of pediatric subjects with moderate to severe plaque psoriasis. Ps STUDY 3 evaluated safety for up to 60 weeks in 110 adolescents (12 to 17 years old). Ps STUDY 4 evaluated safety for up to 56 weeks in 44 children (6 to 11 years old). The safety profile in pediatric subjects was similar to the safety profile from studies in adults with plaque psoriasis. Psoriatic Arthritis: The safety of STELARA® was assessed in 927 subjects in two randomized, double-blind, placebo-controlled studies in adults with active psoriatic arthritis (PsA). The overall safety profile of STELARA® in subjects with PsA was consistent with the safety profile seen in adult psoriasis clinical studies. A higher incidence of arthralgia, nausea, and dental infections was observed in STELARA®-treated subjects when compared with placebo-treated subjects (3% vs. 1% for arthralgia and 3% vs. 1% for nausea; 1% vs. 0.6% for dental infections) in the placebo-controlled portions of the PsA clinical studies. Crohn's Disease: The safety of STELARA® was assessed in 1407 subjects with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] greater than or equal to 220 and less than or equal to 450) in three randomized, double-blind, placebo-controlled, parallel-group, multicenter studies. These 1407 subjects included 40 subjects who received a prior investigational intravenous ustekinumab formulation but were not included in the efficacy analyses. In Studies CD-1 and CD-2 there were 470 subjects who received STELARA® 6 mg/kg as a weight-based single intravenous induction dose and 466 who received placebo *[see Dosage and Administration (2.3) in Full Prescribing Information].* Subjects who were responders in either Study CD-1 or CD-2 were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA® every 8 weeks, or placebo for 44 weeks in Study CD-3. Subjects in these 3 studies may have received other concomitant therapies including aminosalicylates, immunomodulatory agents [azathioprine (AZA), 6-mercaptopurine (6-MP), MTX], oral corticosteroids (prednisone or budesonide), and/or antibiotics for their Crohn's disease *[see Clinical Studies (14.4) in Full Prescribing Information].* The overall safety profile of STELARA® was consistent with the safety profile seen in the adult psoriasis and psoriatic arthritis clinical studies. Common adverse reactions in Studies CD-1 and CD-2 and in Study CD-3 are listed in Tables 2 and 3, respectively.

Table 2: Common adverse reactions through Week 8 in Studies CD-1 and CD-2 occurring in ≥3% of STELARA®-treated subjects and higher than placebo

	Placebo N=466	STELARA® 6 mg/kg single intravenous induction dose N=470
Vomiting	3%	4%

Other less common adverse reactions reported in subjects in Studies CD-1 and CD-2 included asthenia (1% vs 0.4%), acne (1% vs 0.4%), and pruritus (2% vs 0.4%).

Table 3: Common adverse reactions through Week 44 in Study CD-3 occurring in ≥3% of STELARA®-treated subjects and higher than placebo

	Placebo N=133	STELARA® 90 mg subcutaneous maintenance dose every 8 weeks N=131
Nasopharyngitis	8%	11%
Injection site erythema	0	5%
Vulvovaginal candidiasis/mycotic infection	1%	5%
Bronchitis	3%	5%
Pruritus	2%	4%
Urinary tract infection	2%	4%
Sinusitis	2%	3%

STELARA® (ustekinumab)

Infections: In patients with Crohn's disease, serious or other clinically significant infections included anal abscess, gastroenteritis, and pneumonia. In addition, listeria meningitis and ophthalmic herpes zoster were reported in one patient each *[see Warnings and Precautions]. Malignancies*: With up to one year of treatment in the Crohn's disease clinical studies, 0.2% of STELARA®-treated subjects (0.36 events per hundred patient-years) and 0.2% of placebo-treated subjects (0.58 events per hundred patient-years) developed non-melanoma skin cancer. Malignancies other than non-melanoma skin cancers occurred in 0.2% of STELARA®-treated subjects (0.27 events per hundred patient-years) and in none of the placebo-treated subjects. *Hypersensitivity Reactions Including Anaphylaxis*: In CD studies, two patients reported hypersensitivity reactions following STELARA® administration. One patient experienced signs and symptoms consistent with anaphylaxis (tightness of the throat, shortness of breath, and flushing) after a single subcutaneous administration (0.1% of patients receiving subcutaneous STELARA®). In addition, one patient experienced signs and symptoms consistent with or related to a hypersensitivity reaction (chest discomfort, flushing, urticaria, and increased body temperature) after the initial intravenous STELARA® dose (0.08% of patients receiving intravenous STELARA®). These patients were treated with oral antihistamines or corticosteroids and in both cases symptoms resolved within an hour. Ulcerative Colitis: The safety of STELARA® was evaluated in two randomized, double-blind, placebo-controlled clinical studies (UC-1 [IV induction] and UC-2 [SC maintenance]) in 960 adult subjects with moderately to severely active ulcerative colitis *[see Clinical Studies (14.5) in Full Prescribing Information].* The overall safety profile of STELARA® in patients with ulcerative colitis was consistent with the safety profile seen across all approved indications. Adverse reactions reported in at least 3% of STELARA®-treated subjects and at a higher rate than placebo were: • Induction (UC-1): nasopharyngitis (7% vs 4%). • Maintenance (UC-2): nasopharyngitis (24% vs 20%), headache (10% vs 4%), abdominal pain (7% vs 3%), influenza (6% vs 5%), fever (5% vs. 4%), diarrhea (4% vs 1%), sinusitis (4% vs 1%), fatigue (4% vs 2%), and nausea (3% vs 2%). *Infections*: In patients with ulcerative colitis, serious or other clinically significant infections included gastroenteritis and pneumonia. In addition, listeriosis and ophthalmic herpes zoster were reported in one patient each *[see Warnings and Precautions]. Malignancies*: With up to one year of treatment in the ulcerative colitis clinical studies, 0.4% of STELARA®-treated subjects (0.48 events per hundred patient-years) and 0.0% of placebo-treated subjects (0.00 events per hundred patient-years) developed non-melanoma skin cancer. Malignancies other than non-melanoma skin cancers occurred in 0.5% of STELARA®-treated subjects (0.64 events per hundred patient-years) and 0.2% of placebo-treated subjects (0.40 events per hundred patient-years). **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 ustekinumab in the studies described below with the incidence of antibodies to other products may be misleading.Approximately 6 to 12.4% of subjects treated with STELARA® in psoriasis and psoriatic arthritis clinical studies developed antibodies to ustekinumab, which were generally low-titer. In psoriasis clinical studies, antibodies to ustekinumab were associated with reduced or undetectable serum ustekinumab concentrations and reduced efficacy. In psoriasis studies, the majority of subjects who were positive for antibodies to ustekinumab had neutralizing antibodies. In Crohn's disease and ulcerative colitis clinical studies, 2.9% and 4.6% of subjects, respectively, developed antibodies to ustekinumab when treated with STELARA® for approximately one year. No apparent association between the development of antibodies to ustekinumab and the development of injection site reactions was seen. **Postmarketing Experience:** The following adverse reactions have been reported during post-approval of STELARA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to STELARA® exposure. *Immune system disorders:* Serious hypersensitivity reactions (including anaphylaxis and angioedema), other hypersensitivity reactions (including rash and urticaria) *[see Warnings and Precautions]. Infections and infestations:* Lower respiratory tract infection (including opportunistic fungal infections and tuberculosis) *[see Warnings and Precautions]. Neurological disorders:* Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions]. Respiratory, thoracic and mediastinal disorders:* Interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia *[see Warnings and Precautions]. Skin reactions:* Pustular psoriasis, erythrodermic psoriasis. **DRUG INTERACTIONS: Concomitant Therapies:** In

psoriasis studies the safety of STELARA® in combination with immunosuppressive agents or phototherapy has not been evaluated *[see Warnings and Precautions]*. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of STELARA®. In Crohn's disease and ulcerative colitis induction studies, immunomodulators (6-MP, AZA, MTX) were used concomitantly in approximately 30% of subjects and corticosteroids were used concomitantly in approximately 40% and 50% of Crohn's disease and ulcerative colitis subjects, respectively. Use of these concomitant therapies did not appear to influence the overall safety or efficacy of STELARA®. **CYP450 Substrates:** The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Thus, STELARA®, an antagonist of IL-12 and IL-23, could normalize the formation of CYP450 enzymes. Upon initiation of STELARA® in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitoring for therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) should be considered and the individual dose of the drug adjusted as needed *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. **Allergen Immunotherapy:** STELARA® has not been evaluated in patients who have undergone allergy immunotherapy. STELARA® may decrease the protective effect of allergen immunotherapy (decrease tolerance) which may increase the risk of an allergic reaction to a dose of allergen immunotherapy. Therefore, caution should be exercised in patients receiving or who have received allergen immunotherapy, particularly for anaphylaxis. **USE IN SPECIFIC POPULATIONS: Pregnancy:** Risk Summary: Limited data on the use of STELARA® in pregnant women are insufficient to inform a drug associated risk *[see Data]*. In animal reproductive and developmental toxicity studies, no adverse developmental effects were observed after administration of ustekinumab to pregnant monkeys at exposures greater than 100 times the human exposure at the maximum recommended human subcutaneous dose (MRHD). The background risk of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage of clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Data: *Human Data*: Limited data on use of STELARA® in pregnant women from observational studies, published case reports, and postmarketing surveillance are insufficient to inform a drug associated risk. *Animal Data*: Ustekinumab was tested in two embryo-fetal development toxicity studies in cynomolgus monkeys. No teratogenic or other adverse developmental effects were observed in fetuses from pregnant monkeys that were administered ustekinumab subcutaneously twice weekly or intravenously weekly during the period of organogenesis. Serum concentrations of ustekinumab in pregnant monkeys were greater than 100 times the serum concentration in patients treated subcutaneously with 90 mg of ustekinumab weekly for 4 weeks. In a combined embryo-fetal development and pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of ustekinumab twice weekly at exposures greater than 100 times the human subcutaneous exposure from the beginning of organogenesis to Day 33 after delivery. Neonatal deaths occurred in the offspring of one monkey administered ustekinumab at 22.5 mg/kg and one monkey dosed at 45 mg/kg. No ustekinumab-related effects on functional, morphological, or immunological development were observed in the neonates from birth through six months of age. **Lactation:** Risk Summary: There are no data on the presence of ustekinumab in human milk, the effects on the breastfed infant, or the effects on milk production. Ustekinumab was present in the milk of lactating monkeys administered ustekinumab. Due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. Maternal IgG is known to be present in human milk. Published data suggest that the systemic exposure to a breastfed infant is expected to be low because ustekinumab is a large molecule and is degraded in the gastrointestinal tract. However, if ustekinumab is transferred into human milk the effects of local exposure in the gastrointestinal tract are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for STELARA® and any potential adverse effects on the breastfed child from STELARA® or from the underlying maternal condition. **Pediatric Use:** The safety and effectiveness of STELARA® have been established in pediatric patients 6 to 17 years old with moderate to severe plaque psoriasis. Use of STELARA® in adolescents is supported by evidence from a multicenter, randomized, 60-week trial (Ps STUDY 3) that included a 12-week, double-blind, placebo-controlled, parallel-group portion, in 110 pediatric subjects 12 years and older *[see Adverse Reactions, Clinical Studies (14.2) in Full Prescribing Information]*. Use of STELARA® in children 6 to 11 years with moderate to severe plaque psoriasis is supported by evidence from an open-label, single-arm, efficacy, safety and

STELARA® (ustekinumab)

pharmacokinetics study (Ps STUDY 4) in 44 subjects *[see Adverse Reactions, Pharmacokinetics (12.3) in Full Prescribing Information]*. The safety and effectiveness of STELARA® for pediatric patients less than 6 years of age with psoriasis have not been established. The safety and effectiveness of STELARA® have not been established in pediatric patients with psoriatic arthritis, Crohn's disease or ulcerative colitis. **Geriatric Use:** Of the 6709 patients exposed to STELARA®, a total of 340 were 65 years or older (183 patients with psoriasis, 65 patients with psoriatic arthritis, 58 patients with Crohn's disease and 34 patients with ulcerative colitis), and 40 patients were 75 years or older. Although no overall differences in safety or efficacy were observed between older and younger patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients. **OVERDOSAGE:** Single doses up to 6 mg/kg intravenously have been administered in clinical studies without dose-limiting toxicity. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted immediately. **PATIENT COUNSELING INFORMATION:** Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use). *Infections*: Inform patients that STELARA® may lower the ability of their immune system to fight infections and to contact their healthcare provider immediately if they develop any signs or symptoms of infection *[see Warnings and Precautions]*. Malignancies: Inform patients of the risk of developing malignancies while receiving STELARA® *[see Warnings and Precautions]*. Hypersensitivity Reactions: • Advise patients to seek immediate medical attention if they experience any signs or symptoms of serious hypersensitivity reactions and discontinue STELARA® *[see Warnings and Precautions]*. • Inform patients the needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex *[see Dosage and Administration (2.4) in Full Prescribing Information]* Posterior Reversible Encephalopathy Syndrome (PRES): Inform patients to immediately contact their healthcare provider if they experience signs and symptoms of PRES (which may include headache, seizures, confusion, or visual disturbances) *[see Warnings and Precautions]* Immunizations: Inform patients that STELARA® can interfere with the usual response to immunizations and that they should avoid live vaccines *[see Warnings and Precautions]*. Administration: Instruct patients to follow sharps disposal recommendations, as described in the Instructions for Use.

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The Past, Present, and Future of Inflammatory Bowel Disease

At the 2021 Advances in Inflammatory Bowel Diseases conference, Dr Stephen B Hanauer provided a keynote presentation about the past, present, and future of inflammatory bowel disease (IBD). Early treatments of IBD included aminosalicylates, corticosteroids, and thiopurines.[1] The past 2 decades have seen the development of biologic therapies that specifically target key molecules involved in the pathology of IBD (Table 1). Infliximab, adalimumab, and golimumab are inhibitors of tumor necrosis factor (TNF) that have proven efficacy in treating both Crohn's disease and ulcerative colitis. Although the antibodies that are used to treat IBD are immunogenic, immunogenicity can be controlled by means of high-dose induction therapy followed by a reduced dose during maintenance therapy, combined with immunomodulators. Combination therapy may be more effective than anti-TNF monotherapy, but may reduce safety and tolerability. Anti-TNF therapy is typically associated with an eventual loss of response, which may be attributed to immunogenicity, pharmacology, or loss of the mechanism of action. The initial response to biologic therapy can be improved by treating the patient earlier in the course of the disease and by using a treat-to-target strategy that can improve the odds of a complete response. Insights may be gained from pharmacokinetic/pharmacodynamic analyses and through therapeutic drug monitoring.

IBD is marked by the presence of lymphocytes and myeloid cells in the intestine. Antibodies against the integrins can reduce leukocyte migration to the intestine. Vedolizumab inhibits integrin $\alpha_4\beta_7$ and was approved by the US Food and Drug Administration (FDA) for the treatment of patients with ulcerative colitis or Crohn's disease in 2014. Etrolizumab, a monoclonal antibody directed at the β_7 integrin, has shown mixed results in several IBD clinical trials.[2] Ustekinumab is a monoclonal antibody directed against the interleukins (IL) 12 and 23, key mediators of mucosal inflammation. Ustekinumab received FDA approval for treating Crohn's disease in 2016, followed by approval for ulcerative colitis in 2019. Monoclonal antibodies that target IL-12 and/or IL-23 that are in development include brazikumab, risankizumab, mirikizumab, and guselkumab. Small molecules directed to specific biologic targets are in development for IBD and may prove useful as monotherapy or in combination with antibody therapy.[3]

Small molecules may offer advantages over monoclonal antibodies in terms of ease of manufacture, shelf stability, and reduced immunogenicity. Tofacitinib, a small-molecule inhibitor of Janus kinase (JAK), received approval for the treatment of ulcerative colitis in 2018. The small-molecule JAK inhibitors in development for IBD include filgotinib and upadacitinib. JAK inhibitors are believed to reduce production of inflammatory cytokines associated with IBD. Although they have demonstrated efficacy, they are associated with an increased risk of thromboembolic events.[4] Another class of small-molecule therapy is directed against the sphingosine-1-phosphate (S1P) receptor. Ozanimod received approval for the treatment of ulcerative colitis in 2020. Etrasimod is in development.

Given the limitations of currently available IBD therapies, combination regimens are of interest.[5,6] To date, however, combinations have generally led to limited improvements in efficacy and increased safety concerns. In addition to the treat-to-target approach, another strategy to improve patient outcome is the use of new predictive tools, such as personalized medicine, proteomics, and serologic and fecal markers. These tools can also be applied to identify more narrow clinical phe-

Table 1. Small Molecules vs Biologics[7,8]

Small Molecules	Properties	Biologic Products (protein-based drugs)
Methotrexate **MW=454 Da** Simple and well-defined	**Example of Molecule Structure and Size**	**Monoclonal antibody** **MW≈150,000 Da** Complex, with many options for post-translational modification
Replicable in different laboratories	**Manufacturing**	Each manufactured in a unique living cell line
Relatively stable; usually degrade with first-order kinetics	**Stability**	Sensitive to storage and handling conditions
Reactions are intrinsic to the patient and not easily attributable to the product	**Immunogenicity**	Reactions may be attributable to both product- and host-related factors

MW, molecular weight. Adapted from Hanauer SB. Keynote: the past, present and future of IBD. Paper presented at: the 2021 Advances in Inflammatory Bowel Diseases Conference; Orlando, Florida; December 9-11, 2021.[1]

notypes or subclasses of IBD, such as Crohn's-like, colitis-like, early-onset, and postsurgical.

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Personalized Medicine: Yesterday, Today, and Tomorrow

Dr Marla Dubinsky discussed personalized medicine.[1] The current approach to selecting treatment for patients with IBD is imprecise. Relatively poor clinical outcomes are accompanied by patient dissatisfaction and concerns regarding expense. The available treatments are limited, and efficacy has plateaued. Personalized medicine identifies distinguishing disease characteristics for each patient, using analyses of genetics or other biomarkers, to tailor treatment based on the predicted response. Identification of disease characteristics that inform treatment offers the greatest chance of optimizing outcome.

Development of Models to Risk-Stratify Patients

Patients with IBD may initially be stratified according to risk based on characteristics such as age, extent and location of disease, biomarker levels, and other factors. In addition to disease characteristics, genetic and serologic markers can be examined. Rather than looking at a single gene, efforts are underway to develop genome-wide polygenic analyses that predict susceptibility to IBD. A genome-wide polygenic score was developed using 12,882 cases and 21,770 control subjects.[2] The strategy identified patients who were at least 3 times more likely than the general population to develop IBD. A prospective inception cohort study of pediatric patients with newly diagnosed Crohn's disease developed a model to predict the risk of stricturing.[3] The model incorporated age, race, disease location, and antimicrobial serology. The risk of penetrating complications was reduced in patients who received early anti-TNFα therapy (hazard ratio [HR], 0.30; 95% CI, 0.10-0.89; *P*=.0296). However, the risk of stricturing complication was not affected (HR, 1.13). When added to the risk model, a signature of ileal genes that control extracellular matrix

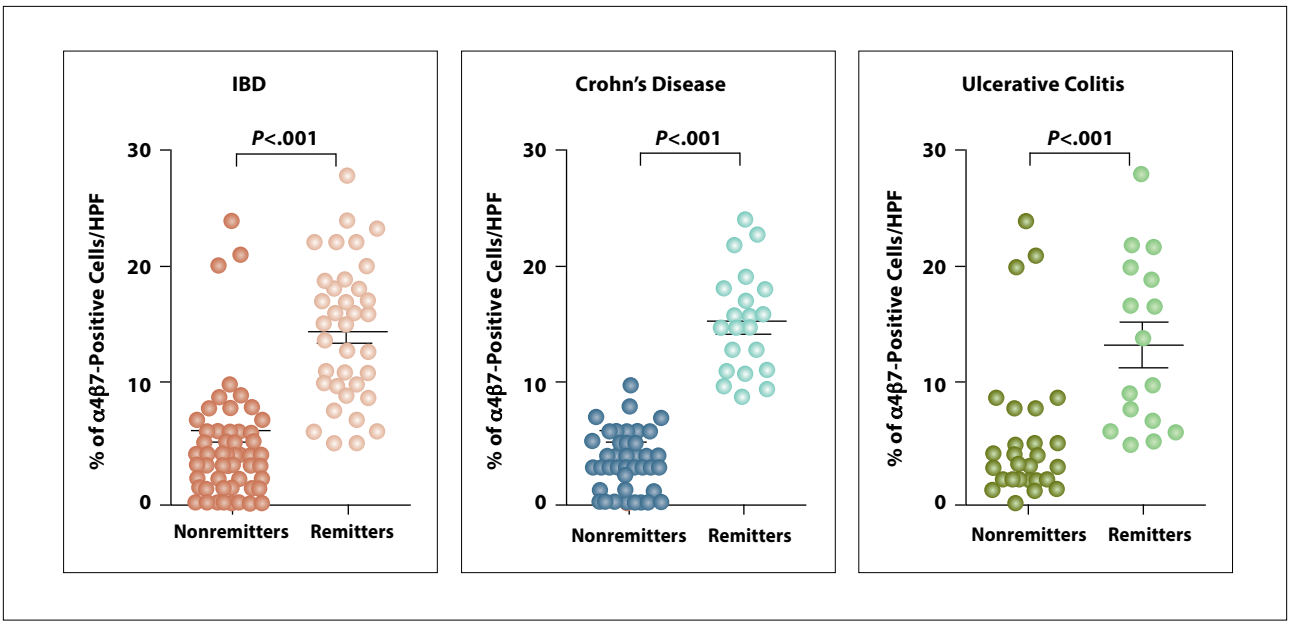

Figure 1. Expression of intestinal $\alpha_4\beta_7$ predicts response to vedolizumab. HPF, high-power field; IBD, inflammatory bowel disease. Adapted from Rath T et al. *Front Immunol*. 2018;9:1700.[7]

production was associated with an increased risk of stricturing (HR, 1.70; 95% CI, 1.12-2.57; *P*=.0120). In a study of 243 patients with Crohn's disease, significant variables in a multivariate Cox model included specific disease locations, as well as serologic markers, such as antibodies to *Saccharomyces cerevisiae* (HR, 1.35; 95% CI, 1.16-1.58) and antineutrophil cytoplasmic antibodies (HR, 0.77; 95% CI, 0.62-0.95).[4] Antibodies to CBir and OmpC have also been associated with a more aggressive course of Crohn's disease.[5]

Personalized Medicine

Personalized medicine offers the possibility of matching the best treatment to patients based on specific disease characteristics. Oncostatin M (OSM) is a proinflammatory cytokine in the IL-6 family whose expression is increased in IBD patients. In a study of 162 patients with Crohn's disease and 74 patients with ulcerative colitis, higher levels of OSM and the OSM receptor correlated with a reduced response to anti-TNF therapy.[6] In addition to OSM, mRNA levels of IL-6, IL-1A, and IL-1B were elevated in intestinal mucosal biopsy samples compared with controls. Moreover, higher levels of OSM and OSM receptor expression correlated to increased disease severity. Based on unsupervised hierarchical clustering, increased expression of a group of cytokines associated with OSM levels in pretreatment intestinal biopsies was strongly associated with a lack of response to anti-TNF therapy. Similarly, expression of intestinal $\alpha_4\beta_7$ predicted response to vedolizumab (Figure 1).[7] Other biomarkers, such as triggering receptor expressed on myeloid cells 1 (TREM1), may also predict response to anti-TNF therapy (Figure 2).[8]

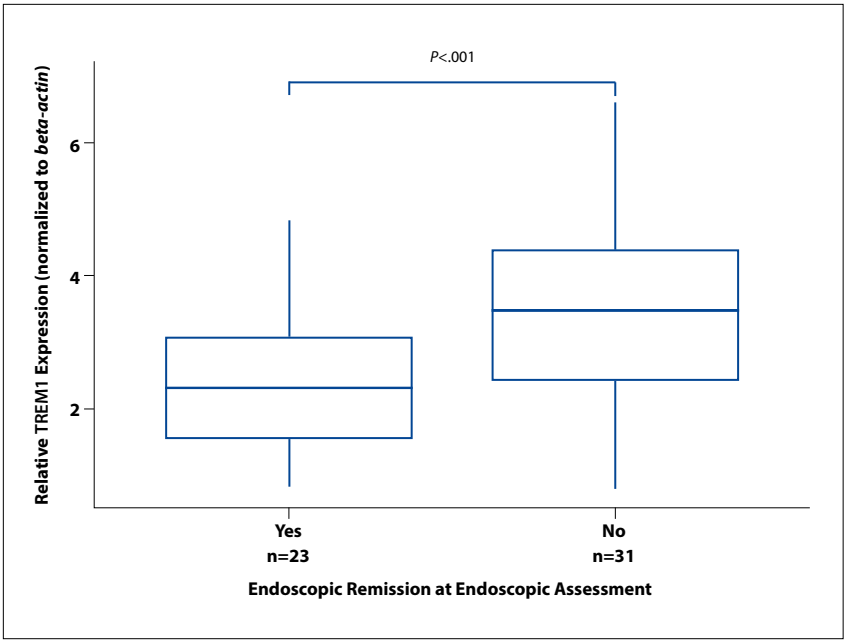

Figure 2. Baseline levels of TREM1 predicted response to anti-TNF therapy in a prospective trial. TNF, tumor necrosis factor; TREM1, triggering receptor expressed on myeloid cells 1. Adapted from Verstockt B et al. *EBioMedicine*. 2019;40:733-742.[8]

With many exciting developments providing new insights into this heterogeneous disease, it will be imperative to develop IBD disease assessment and treatment algorithms that improve the ability to match the right patient with the right treatment. These algorithms can incorporate genetic and serologic biomarkers, as well as patient and disease characteristics.

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Micronutrient Deficiencies in Inflammatory Bowel Disease

Dr Gary Lichtenstein discussed the micronutrient deficiencies that are seen in patients with IBD.[1] These patients may have deficiencies in selenium, folic acid, vitamin A, and vitamin K, as well as vitamin B_{12}, vitamin D, zinc, and iron.

Vitamin B_{12} Deficiency

In patients with Crohn's disease, vitamin B_{12} deficiency can arise due to malabsorption (enteritis), absence of a terminal ileum, and, rarely, pernicious anemia.[2] Risk factors in patients with Crohn's disease include ileal resection or disease in more than 30 cm of the ileum, fistula, bacterial overgrowth in the small bowel, inadequate intake of vitamin B_{12}, enteropathy resulting in protein loss, and hepatic dysfunction.

Findings were equivocal in patients with ileal resection from 20 cm to 30 cm. Patients with ulcerative colitis are not predisposed to vitamin B_{12} deficiency. The clinical manifestations of vitamin B_{12} deficiency include megaloblastic anemia and neurologic dysfunction.

In patients with Crohn's disease with ileal resection greater than 20 cm, vitamin B_{12} should be supplemented. Low-quality evidence suggests that oral and injected vitamin B_{12} may have similar efficacy.[3] The best formulation of B_{12} for a certain patient is the one that he or she will take and tolerate. However, patients with very low serum vitamin B_{12} and symptoms benefit from the use of a parenteral formulation.

Vitamin D Deficiency

Vitamin D deficiency is present in up to 95% of patients with IBD.[4] All patients should undergo evaluation for vitamin D deficiency.[4] The clinical manifestations include secondary hyperparathyroidism, osteopenia, and osteoporosis. Vitamin D deficiency is diagnosed by measurement of the serum level of 25-hydroxy-vitamin D (25-OHD). A level of 25-OHD between 20 ng/mL and 50 ng/mL (50 nmol/L-125 nmol/L) is considered adequate for healthy individuals and is crucial for maintaining bone health and overall health.

Zinc Deficiency

Zinc deficiency occurs in up to 40% of patients with IBD and is underrecognized in this population.[5,6] Among patients with Crohn's disease in remission, as many as two-thirds may have zinc levels that are below normal. Risk factors and causes of zinc deficiency include various "ostomies," fistulas, and profuse diarrhea. Clinical manifestations of zinc deficiency include dermatitis, diarrhea, dysgeusia, alopecia, and depressed immune function, which may result in frequent infections. Zinc levels can be measured in erythrocytes, neutrophils, lymphocytes, and hair. A zinc level below 60 µg/dL in plasma is considered deficient. Some patients, particularly those with severe diarrhea, should receive oral or parenteral zinc replacement with daily maintenance doses of 10 mg to 15 mg of elemental zinc. In an analysis of prospectively collected data from 773 patients with Crohn's disease and 223 patients with ulcerative colitis, zinc deficiency was associated with an increased risk of subsequent hospitalization, surgery, and disease-related complications.[7] Normalization of zinc levels was associated with improvement in the same outcomes in both Crohn's disease and ulcerative colitis. It should be mentioned, however, that these studies may be limited by confounding according to indication.

Iron Deficiency

Iron deficiency anemia is present in up to 76% of patients with IBD.[8] Iron deficiency correlates directly with disease activity and may arise owing to a lack of intake in the diet or malabsorption. Clinical manifestations include fatigue/weakness, microcytic anemia, and pica syndrome. Various iron formulations are available to tailor iron supplementation to the patient. High levels of hepcidin block the absorption of iron in the intestine as well as iron recycling, leading to anemia.[9] In order to provide the best care for IBD patients, screening and treatment for deficiencies in iron and other micronutrients is imperative.

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Preparing for Inflammatory Bowel Disease Care in the Next Pandemic: Lessons Learned From COVID-19

Dr David T. Rubin discussed COVID-19 and future pandemics.[1] The COVID-19 pandemic presented specific problems for the IBD population, such as lack of access to care and confusion regarding the risks. Several areas of success were reported. There was rapid coordination and collaboration among practitioners, regular updates and reassurances, effective use of social media, support from colleagues, and numerous recommendations from expert panels. IBD societies provided guidance based on input from national and international experts.

The inevitable advance of climate change, population growth, and the human push to inhabit environments that are occupied by animals are among the factors that set the stage for another pandemic.[2] Dr Rubin outlined steps to take to prepare for the next pandemic.

Eight Steps to Prepare for the Next Pandemic

Develop a National Network of IBD Providers and Patients for Crisis Management

The development of a network for rapid evaluation and assessment of emerging diseases would enable real-time guidance and recommendations for patients with IBD and their health care providers. The group could identify priorities for investment and strategic planning for future epidemics.

Prioritize Health Care Workers' Mental Health

The mental well-being of health care workers should be addressed according to specific occupations.[3] A national IBD network would provide early and organized communication regarding situation dynamics, such as who is affected, how dangerous the situation is, and the tools that are available to address the situation. Worker safety must be a priority.

Manage the Education and Improvement of Patients and Medical Professionals

COVID-19 outcomes are worse among patients who are taking corticosteroids, underscoring the need to achieve sustained, functional remission without corticosteroids wherever possible. Proactive disease monitoring should be emphasized.[4]

Develop a Pandemic Preparedness Plan

Offices should stockpile personal protective equipment. It is important to develop policies for every independent practice related to telehealth and working from home. Safety net plans need to be in place for employees, along with the means to rapidly communicate with patients en masse.

Identify and Fund Research Priorities for IBD

Research priorities for IBD should include uptake and response to COVID-19 vaccination, as well as long COVID-19. Clinicians need a detailed understanding of viral entry through the angiotensin-converting enzyme 2 (ACE2) receptor. Other areas of research should include infectious complications of therapies in patients with active IBD, the efficacy of antiviral therapies in patients receiving treatment for IBD, pandemic effects on the mental health of patients with IBD and their health care providers, and social determinants of health in IBD and the impact of social factors on access to care.

Address Access Issues for the Underserved

Patients with IBD who lack adequate access to health care clearly have worse outcomes. Similarly, access to vaccination is disproportionately lacking among economically disadvantaged patients. A higher level of disease activity and the use of corticosteroids were associated with worse outcomes from COVID-19.[5,6]

Build Trust: End Discrimination and Bias in Clinical Trial Recruitment

Enrollment of patients in clinical trials should reflect the true population of IBD patients. Trial investigators should follow good participatory practice, and thus include a spectrum of patients across racial and ethnic minorities.[7] By expanding the pool of patients who are recruited into clinical trials, the medical community can build trust with patients.

Promote Legislative Priorities for the IBD Population in the United States

Numerous legislative goals must be pursued at the federal, local, and institutional levels. Politicians must be held accountable to science and public health. There should be increased federal funding of pandemic preparedness for vulnerable populations, as well as for health care workers and patients. Benefits for the health care workforce at academic institutions and hospital-based practices should be protected.

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ABSTRACT SUMMARY Real-World Experience of Ustekinumab in Crohn's Disease Patients With Prior Anti-TNF Therapy at a Tertiary Care University Hospital

A retrospective study evaluated outcomes from ustekinumab in 34 patients with Crohn's disease who had received prior treatment with a TNF antagonist (Abstract P066). Clinical remission was documented in 70.5% of patients. Among patients who achieved clinical remission with ustekinumab, 29% were receiving concomitant corticosteroid therapy or immunomodulators. Among 17 patients with fistulizing disease, 70% achieved clinical remission with ustekinumab therapy. In 24 patients with available data, the mean level of C-reactive protein was 2.4 µg/mL before ustekinumab vs 1.98 µg/mL after treatment (*P*=.079).

Positioning Medications: Yesterday, Today, and Tomorrow

Dr Edward V. Loftus discussed how to position medications in IBD.[1] With several biologics and small molecules currently available and in the pipeline for the treatment of IBD, choosing the optimal first- and second-line therapies for each patient has become more complex.[1] The difficulty is compounded by disease heterogeneity, patient factors, and a lack of trials that directly compare outcomes from different drugs.

The multicenter, blinded, active-controlled, randomized phase 3b SEAVUE study compared ustekinumab vs adalimumab as induction and maintenance treatment in 386 patients with moderately to severely active Crohn's disease, without prior exposure to a biologic therapy.[2] The primary endpoint was clinical remission at 52 weeks, based on a Crohn's Disease Activity Index (CDAI) score of less than 150. At week 52, the rates of clinical remission were 61.0% with adalimumab vs 64.9% with ustekinumab, a difference that did not reach statistical significance (95% CI, –5.5% to 13.5%; *P*=.417). Rates of clinical remission through week 52 are shown in Figure 3. A major secondary endpoint was corticosteroid-free clinical remission at week 52. These rates were 60.7% for adalimumab vs 57.4% for ustekinumab (*P*=.485). An adverse event (AE) required discontinuation of treatment in 11.3% of the adalimumab arm vs 6.3% of the ustekinumab arm. Serious AEs were reported in 16.4% vs 13.1%, respectively.

A retrospective study evaluated safety outcomes in patients with IBD who had received treatment with vedolizumab or a TNF antagonist.[3] Rates of serious infection did not differ for the entire population of patients with IBD (HR, 0.92) or for the subset of patients with Crohn's disease (HR, 1.1). There was a reduced rate of serious infections in patients treated with vedolizumab vs a TNF antagonist (HR, 0.68; *P*<.05).

Treatment decisions can be guided by distinguishing patients with IBD who have severe disease that requires intervention from those with less severe disease or who are more risk-averse.[4] For patients with severe disease, infliximab and adalimumab are appropriate as first-line treatments. For the risk-averse patient or one with comorbidities, ustekinumab and vedolizumab are reasonable choices. Results from the phase 3b VARSITY trial showed that, in patients with ulcerative colitis, vedolizumab was superior to adalimumab in terms of clinical remission at week 52 (31.3% vs 22.5%; *P*=.0061).[5] Vedolizumab was superior to the TNF antagonist in the subpopulation of anti-TNF–naive patients (34.2% vs 24.3%; *P*=.0070), but not in patients with prior exposure to a TNF antagonist (20.3% vs 16.0%; *P*=.4948). Vedolizumab also was slightly better in terms of mucosal healing at week 52, specifically in patients without prior exposure to TNF-directed therapy (43.1% vs 29.5%; *P*=.0005). An analysis of histologic remission also supported the superiority of vedolizumab vs adalimumab in the VARSITY study.[6]

A meta-analysis in patients with moderately to severely active ulcerative colitis without prior exposure to biologic therapy found that infliximab led to the highest rates of endoscopic remission among patients receiving induction therapy.[7] The surface under the cumulative ranking (SUCRA) was 0.95 for infliximab, followed by 0.76 for vedolizumab.[7] In patients with prior anti-TNF exposure, tofacitinib was best (SUCRA, 0.91), followed by ustekinumab (SUCRA, 0.83).

Dr Loftus offered several recommendations. He noted that head-to-head data are limited. Infliximab is still a leading first-line treatment for many patients. For patients with ulcerative colitis, vedolizumab is a strong choice as first-line treatment and a reasonable option for the second line. Tofacitinib is an excellent biologic therapy for the second-line treatment of ulcerative colitis. Adalimumab is a reasonable choice for patients who do not respond to infliximab, especially in the setting of Crohn's disease. Ustekinumab is an excellent biologic therapy for the second-line treatment of Crohn's disease and possibly ulcerative colitis.

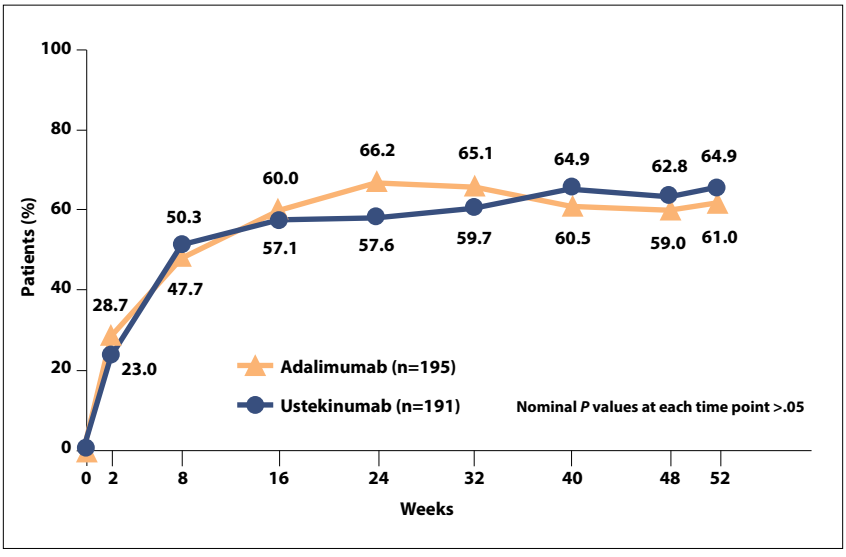

Figure 3. Clinical remission in the randomized, phase 3b SEAVUE trial, which compared adalimumab vs ustekinumab. Adapted from Sands BE et al. DDW abstract 775d. *Gastroenterology*. 2021;161(suppl 2).[2]

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Highlights From the 2021 Advances in Inflammatory Bowel Diseases Conference: Commentary

Gary R. Lichtenstein, MD

The 2021 AIBD conference featured exciting presentations pertaining to the many different agents and strategies available for the management of patients with IBD.

Dr Stephen Hanauer gave a keynote lecture focusing on the past, present, and future of IBD.[1] Dr Hanauer reviewed earlier treatments, such as the aminosalicylate sulfasalazine. Aminosalicylates are rapidly absorbed in the proximal GI tract, but they act primarily in a topical manner.[2] They are very well tolerated. In contrast, corticosteroids can be associated with notable adverse events.[3] Dr Hanauer also reviewed the role of delayed-release budesonide MMX in the treatment of patients with active ulcerative colitis. Corticosteroids are not suitable for maintenance therapy, but they are effective for inductive treatment in patients with moderate disease.[4] Thiopurines can be corticosteroid-sparing in ulcerative colitis and Crohn's disease. They can be used in combination with biologic agents to reduce immunogenicity. However, thiopurines are associated with neoplasia, including nonmelanoma skin cancer and lymphoma, as well as infectious complications (primarily viral pathogens).[5] In addition, genetic polymorphisms are associated with adverse events such as bone marrow suppression, transaminitis, and pancreatitis.

Biologic therapy is effective for Crohn's disease and ulcerative colitis.[6] All monoclonal antibodies are immunogenic, but the extent varies. In general, combination therapy is more effective than monotherapy. Combination therapy is especially beneficial for anti-TNF agents.[7] Data do not suggest that the use of antimetabolite therapy in combination with ustekinumab or vedolizumab is superior to biologic monotherapy.[8] However, these are no prospective, randomized, controlled trials evaluating monotherapy vs combination therapy with these agents. This statement is based upon retrospective post-hoc analyses of primary controlled trials. There are several ways to improve the initial response. Treatment early in the course of the disease is associated with an improved response to therapy with the treat-to-target approach. Clinicians can evaluate pharmacokinetics and pharmacodynamics, and perform prospective therapeutic drug monitoring. The role of prospective monitoring has not yet been well established by clinical trials. However, the practice is logical and therefore used by many clinicians.

There are many exciting new and novel molecules, with different mechanisms of action. Ozanimod, a sphingosine-1-phosphate (S1P) receptor 1 and 5 modulator, was recently added to the therapeutic armamentarium.[9] Other S1P agents are in development. The JAK inhibitor tofacitinib is currently approved for the treatment of moderate-to-severe ulcerative colitis. Two other JAK inhibitors are currently in development: filgotinib and upadacitinib. Filgotinib is approved in the European Union. Upadacitinib is undergoing clinical trials.[10] Other agents approved by the FDA include the anti-adhesion molecules natalizumab and vedolizumab, the anti–interleukin (IL) 12/23 antagonist agent ustekinumab, and the anti-TNF agents infliximab, adalimumab, golimumab, and certolizumab pegol. Other specific IL-23 antagonists are in development.

Dr Hanauer discussed the concept of combining biologics.[1] Although combination therapy has been widely used in other specialties, such as oncology, potential roadblocks to this approach include the possible safety issues associated with a high level of immune suppression and the cost of therapy. This strategy has become a standard approach for the treatment of various malignancies. Currently, there is limited experience with the use of biologic combinations in patients with IBD.[11] It appears that biologic combinations would be reasonable in certain patient populations.

Dr Hanauer noted that future advances in therapy will require new predictive tools, such as omics, serologic markers, and serum and fecal biomarkers to continue to define clinical phenotypes. An important treatment tenet will be to use pharmacology to optimize efficacy and safety. Clinicians use the treat-to-target strategy to maintain tight control. Definitions of pathogenesis and susceptibility will be important components of the therapeutic armamentarium.

Dr Marla Dubinsky discussed personalized medicine, which uses genetics or other biomarkers to guide treatment decisions for different groups of

patients.[12] Dr Dubinsky noted that personalized medicine shifts the emphasis from reaction to prevention, thus overcoming limitations of traditional medicine. With personalized medicine, clinicians can identify patients with high-risk disease, and initiate appropriately aggressive treatment while reducing the risk of adverse events.

Many arenas today follow an empirical strategy; treatment reflects a one-size-fits-all approach.[13] A treatment is administered, and the clinician evaluates efficacy. The biologic approach attempts to identify which patients will respond best to a particular agent and to predict the response. The trial-and-error approach has not demonstrated the best outcomes. It is more costly because many more patients receive treatment, and it is less efficient. Patients may be dissatisfied if they do not respond, and the probability of response is not high. This approach was driven by limited biologic options. There are now more available treatments. It is possible to begin to use the biologic approach in clinical practice. For example, no more than a third of patients will achieve remission. The response rate is approximately 50% to 60% in clinical trials of novel or existing biologics.[14,15] To increase this rate, it may be necessary to administer combination therapy and/or to select specific patient populations for treatment.

In the future, the biologic approach will likely become more common. A biologic approach to IBD would consider the patient's prognostic markers. Patients who have a poor prognosis might be candidates for a rapid step-up approach. Patients with a better prognosis might benefit from a slower approach, with less aggressive therapy associated with fewer potential adverse events. Clinicians should strive for the endpoint of disease modification. The AGA has provided guidance with suggestions to use specific parameters to stratify disease according to risk.[16] In ulcerative colitis, risk factors for colectomy include age younger than 40 years, extensive colitis, corticosteroid-requiring disease, deep ulcers, history of hospitalization, high levels of C-reactive protein or a high erythrocyte sedimentation rate, infection with *Clostridioides difficile*, and cytomegalovirus. In Crohn's disease, risk factors for rapid disease progression include age younger than 30 years at diagnosis, extensive anatomic involvement, perianal disease, severe rectal disease, deep ulcers, prior surgical resection, stricturing behavior, and penetrating behavior. This management protocol is one of the first attempts in the IBD arena to risk-stratify patients, thereby allowing treatment with appropriate interventions based upon the expected prognosis.

Dr Dubinsky also discussed genetic markers. The presence of the *NOD2* gene in patients with Crohn's disease is associated with complicated disease, which is defined as development of strictures and the need for surgery.[17] This discovery suggested that we could predict the phenotype, as well as the disease itself. More than 200 genes are associated with IBD; not all are as predictive as the *NOD2* gene. The need for aggressive intervention increases with the number of serologic markers, such as CBir, outer membrane protein C (OmpC), and anti-saccharomyces cerevisiae antibodies (ASCA).[18] Penetrating behavior, stricturing behavior, and surgical disease correspond to the number of positive markers. These characteristics indicate that the patient has a poor prognosis and will require aggressive treatment to minimize the risk of disease complications. Researchers have evaluated other extracellular and matrix gene expressions in a similar fashion.[19]

It will be key to make this information readily available for patients' care. In 2016, Dr Corey Siegel published a clinical decision support tool that used a patient's prognosis to guide selection of treatment and predict response.[20] Different disease states are associate with different signature cytokine profiles. Patients with ankylosing spondylitis, psoriatic arthritis, and rheumatoid arthritis respond differently to different therapeutic agents. There is a suggestion that the presence of specific gene signatures may be able to predict response,[21] but this concept is less advanced in IBD. A recent study suggested that oncostatin M might be able to help predict response to anti-TNF therapy in patients with IBD.[22] A prospective trial is currently underway evaluating the influence of this biomarker on response to therapy.[23] Data suggest that levels of TREM-1 may predict response to anti-TNF therapy.[24] Intestinal expression of the integrin alpha 4/beta 7 predicts response to vedolizumab.[25] Levels of IL-22 predict response to treatments that target the p19 subunits of IL-23.[26]

This area has evolved since thiopurine methyltransferase metabolism (TPMT) was evaluated to predict the metabolism of azathioprine in 1989.[27] Different milestones have improved our understanding of drug metabolism, and provided insight into how this information can be used in dosing based upon an agent's pharmacogenetics. Studies recently evaluated the association between thiopurine methyltransferase and NUDT15, a genetic marker that can predict response to azathioprine or 6-mercaptopurine and is commonly used in clinical practice.[28,29] Levels of thiopurine methyltransferase and NUDT15 are measured prior to initiation of therapy with azathioprine or 6-mercaptopurine. Use of thiopurines to treat IBD is associated with pancreatitis in up to 17% of patients.[30] This rate varies according to the presence of specific *HLA* genes. The risk of pancreatitis is 9% in heterozygotes and 17% in homozygotes of different *HLA* genes, such as HLA-DRB1*07:01 and HLA-DQA1*02:01.

The presence of the genetic marker HLA DQA105 is associated with a higher rate of immunogenicity against anti-TNF therapy.[31] Theoretically, it might be helpful to test patients for this maker. Patients who are positive should receive dual therapy (anti-TNF biologic therapy and immunomodulator therapy). This strategy has not been evaluated in a prospective randomized trial, but it is enticing. Anti-TNF therapy can be associated with paradoxical psoriasis, but only in patients with 2 certain SNPs, according to a small study.[32] Skin taping can be used

to evaluate for atopic dermatitis and psoriasis, in order to identify distinct profiles.[33] Skin taping is in the initial stages of assessment.

An algorithm is needed to help guide management to decrease the risks of nonresponse and immunogenicity, as well as to profile patients to determine when their disease course will require aggressive therapy, such as biologic agents. Many ongoing studies are addressing these questions. The era of precision medicine has arrived.

At the AIBD meeting, I discussed recognition and management of micronutrient deficiencies in patients with IBD.[34] Many micronutrient deficiencies arise in patients with IBD. My presentation focused on iron, vitamin B_{12}, zinc, and vitamin D. These nutrient deficiencies are often overlooked, and the downstream effects can be substantial. The many different etiologies for vitamin B_{12} deficiency include gastric issues such as autoimmune gastritis; pernicious anemia; post-gastrectomy surgery, such as a Billroth II surgery; and intestinal resection.[35] Typically, 20 cm to 30 cm of active ileal disease or the lack of 20 cm to 30 cm of the ileum in patients with Crohn's disease can prevent adequate absorption of vitamin B_{12}. Pancreatic disease can be associated with aberrant vitamin B_{12} absorption. Exocrine pancreatic insufficiency is a condition characterized by deficiency of the exocrine pancreatic enzymes, resulting in the inability to digest food properly, or maldigestion. The exocrine pancreas produces 3 specific types of enzymes: amylase, lipase, and protease. These pancreatic enzymes are normally present and function to cleave the R proteins (also known as haptocorrin and transcobalamin 1), which are produced in the salivary glands. When vitamin B_{12} couples with the R proteins, this serves to protect the vitamin B_{12} from degradation in the acidic environment of the stomach. The next step that occurs is that another binding protein for B_{12}—intrinsic factor (a protein synthesized by gastric parietal cells that is secreted in response to histamine, gastrin, and pentagastrin, as well as the presence of food)—comes into play. Several proteases are made in the pancreas and get secreted into the lumen of the duodenum. The 2 major pancreatic proteases are trypsin and chymotrypsin. In the duodenum, proteases digest the R-proteins and release their bound vitamin B_{12} to become unbound vitamin B_{12}. The unbound vitamin B_{12} then couples and binds with intrinsic factor to form an intrinsic factor/vitamin B_{12} complex that can be effectively absorbed in the terminal ileum. The intrinsic factor protects the vitamin B_{12} from catabolism by intestinal bacteria to facilitate its uptake.

It is important to recognize that R proteins have a higher affinity to vitamin B_{12}, so they compete with intrinsic factor to bind the vitamin B_{12}. When exocrine pancreatic insufficiency is present, the R proteins are not cleaved (since there is a lack of trypsin and chymotrypsin production) and the vitamin B_{12}-R protein complex is not taken up in the terminal ileum, leading to serum vitamin B_{12} deficiency. In addition, patients may be vegetarian or vegan, and lack B_{12} in their diet. Medications associated with B_{12} deficiency include proton pump inhibitors, metformin, colchicine, cholestyramine, and nitrous oxide.[36] Some rare congenital deficiencies of the intrinsic tract receptor or transcobalamin deficiency can also cause B_{12} deficiency. Thus, it is clear that IBD is not the only reason that patients may become deficient in vitamin B_{12}.

In Crohn's disease, malabsorption with inflammation in the ileum is the classic cause of vitamin B_{12} deficiency.[37] The deficiency can develop over time, as resection of the ileum may lead to inadequate surface area for absorption of nutrients. Pernicious anemia can create an antibody against intrinsic factor, which the ileum needs to absorb B_{12}. Patients with Crohn's disease may have undergone a resection that removed more than 30 cm of the ileum. Fistulas can bypass the ileum. Small intestinal bacterial overgrowth can occur, and the bacteria themselves metabolize vitamin B_{12} and decrease the amount of vitamin B_{12} available for absorption. There may be reduced intake or increased physiologic requirements, protein-losing enteropathy, or liver dysfunction. Clinically, this may manifest as megaloblastic anemia or neurologic dysfunction, such as neuropathy or dementia.

Vitamin B_{12} deficiency can be seen in up to 25% of patients with J pouches, which could be due to a decrease in absorption of vitamin B_{12} overall.[38] There may be fecal stasis, small intestinal bacterial overgrowth with bacterial utilization of vitamin B_{12}, and villous atrophy. Vitamin B_{12} deficiency is often overlooked in patients with J pouches. Based on clinical experience, I recommend that these patients undergo annual testing of their serum vitamin B_{12} levels.

A serum level of less than 200 pg/mL is considered abnormal.[39] Elevation of homocysteine and methylmalonic acid is a confirmatory biomarker. Data from 2 randomized controlled trials suggest that efficacy may be similar between oral and intramuscular injections of vitamin B_{12}.[40,41] These studies had small numbers of patients. However, it is comforting to realize that some patients may not need injections to treat their vitamin B_{12} deficiency. In addition, there are many ways to administer supplements of vitamin B_{12}: intramuscular, oral, sublingual, intranasal, and subcutaneous. The intramuscular formulation provides the best bioavailability for a patient who needs rapid vitamin B_{12} supplementation. The level of evidence is higher for the intramuscular route than for the other routes of administration. However, patients should receive the formulation that works best for them.

Heightened inflammatory states, such as active IBD, are associated with vitamin D deficiency. Approximately 16% to 95% of patients with IBD will have a vitamin D deficiency.[42] Causes include ileal disease or resection that impairs bile acid resorption, which leads to fat malabsorption.[43] Vitamin D is a fat soluble vitamin. Clinically, a vitamin D deficiency may result in osteopenia, osteoporosis, and secondary hyperparathyroidism. The diag-

nosis can be made by measuring the blood level of vitamin D. In the serum, vitamin D has a half-life of 15 days.

Vitamin D should be measured in patients with IBD. There is no evidence to support routine supplementation with fat-soluble vitamins in patients with IBD. Supplementation should be reserved for patients with risk factors for low levels or malabsorption. The National Institutes of Health recently published a consensus document categorizing levels of vitamin D.[44] A level of 12 ng/mL to less than 20 ng/mL is inadequate. A level of 20 ng/mL to 50 ng/mL is an appropriate goal to minimize the risk of osteopenia, osteoporosis, and other bone-related conditions. (This categorization reflects a recent update; the previous lower level was 30 ng/mL.) Levels above 50 ng/mL can be associated with toxicity. There is a perception that cardiovascular calcification of the coronaries can occur in patients with higher vitamin D levels and may be associated with the presence of a higher rate of coronary artery disease.

Supplementation with vitamin D may prevent disease relapse in patients with IBD. In a 2018 meta-analysis, the rate of IBD disease activity relapse was significantly lower among patients treated with vitamin D vs those in the control group.[45] There were no significant differences between the low dose and the high dose of vitamin D. Supplementation with vitamin D is therefore advantageous for abnormal bone mineral density, and may also decrease the chance of relapse in patients with IBD.

Maximum accumulation of calcium occurs in the mid-teenage years, and it may not be made up later in life. Decrease in bone mineral density can occur with poor calcium intake or vitamin D deficiency, as seen in approximately one-third of patients, as well as in individuals who have an increased level of systemic inflammation or decreased physical activity. Corticosteroids can also severely impact bone density.[46] A dose of 7.5 mg for 3 months is enough to lead a patient to develop an abnormal bone mineral density. Patients treated with this dose or higher should undergo bone density assessment with a DEXA scan. According to guidelines from the ACG, bone mineral density should be measured in patients treated with corticosteroids for longer than 3 months, malnourished or very thin patients with inactive disease, amenorrheic patients, and postmenopausal women regardless of disease status.[47] These guidelines are currently being updated.

In Crohn's disease, approximately two-thirds of patients have low levels of zinc.[48] A deficiency is defined as less than 60 μg/dL in the plasma. Levels can be measured in erythrocytes, neutrophils, lymphocytes, and hair.[49,50] Risk factors for low serum zinc levels include the presence of ostomies, fistulas, and profuse diarrhea.[51] Zinc deficiency can lead to depressed immunity, frequent infections, diarrhea, dysgeusia, and alopecia. Zinc is an essential mineral and coenzyme for cellular reactions. Serum zinc levels vary with serum albumin and fluctuate with intake, inflammation, pregnancy, and diurnal rhythm. Zinc deficiency is underrecognized. Low alkaline phosphatase can suggest a zinc deficiency because alkaline phosphatase is a zinc metalloenzyme. Oral and fractional zinc can be administered, with maintenance doses of 10 mg/day to 15 mg/day.

The presence of anemia is another common finding among patients with IBD.[52] Anemia is defined by hemoglobin levels at or below 12 g/dL for women, 13 g/dL for men, 12 g/dL for children ages 12 to 13 years, 11.5 g/dL for children ages 5 to 11 years, and 11 g/dL for children ages 6 months to 5 years. Iron deficiency has several causes, such as poor dietary intake, gastrointestinal bleeding, and malabsorption of inflamed mucosa in the duodenum.[53] Active inflammation traps the iron within enterocytes. Iron deficiency can manifest in many ways, such as fatigue, weakness, microcytic anemia, restless legs syndrome, dyspnea on exertion, and pica. Some patients eat ice. Serum hepcidin levels rise in the presence of active inflammation. The presence of elevated serum hepcidin levels block ferroportin (the iron transport protein located in the enterocyte in the duodenum and proximal jejunum) from absorbing iron.

For mild anemia, clinicians often initiate treatment with an oral formulation of iron. Parenteral iron is used in patients with severe anemia or in those patients with a history of blood transfusion. Hepcidin antagonists are under investigation for patients with chronic disease, such as rheumatoid arthritis, IBD, pneumonia, or other disorders of inflammation. Hepcidin blocks the uptake of iron. Iron deficiency is often present, but underrecognized and untreated in patients with IBD. Failure to test for iron deficiency is common.

Dr David Rubin discussed treatment of patients with IBD during the COVID-19 pandemic and preparations for future pandemics.[54] COVID-19 has accounted for substantial morbidity and mortality throughout the world. There were many problems with the approach to COVID-19, including inadequate national preparedness, lack of available testing, misinformation, and politicization of public health issues. In the field of IBD, there was success. There were regular updates and reassurances, and effective use of social media. The Surveillance Epidemiology of Coronavirus Under Research Exclusion registry was assimilated to help study the effect of COVID-19 on IBD and associated treatments.[55] The AGA, the ASGE, the ACG, the Crohn's & Colitis Foundation, and the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) were among many societies that came forth to help physicians, patients, and caregivers better understand what was transpiring. International meetings were held virtually to share knowledge and allow for collaboration.

In April 2021, the IOIBD published guidelines regarding vaccination in patients with IBD.[56] The guidelines recommended that all patients with IBD receive the COVID-19 vaccination, once they were eligible. Patients should receive whichever vaccine was available to them. The best time to administer the vaccine was the earliest opportunity to do so. There was

no need for a patient to discontinue IBD therapy for vaccination. The vaccination should not be deferred in a patient receiving immune-modifying therapy. Patients should try to decrease exposure to corticosteroids.

Dr Rubin and I published an ACG clinical practice update for patients with IBD who develop COVID-19.[57] The article reviews management strategies for various phases of the disease. A study that assessed patient portal messaging ("MyChart messages") demonstrated an increase of 100% from before the pandemic to September 2021.[54,58] Many patients did not want to visit their health care deliverer's office for medical care. This increase placed strains not only on the patients, but also on advanced practice practitioners and physicians.

The pandemic impacted the mental health of health care workers. Surveys noted difficulties in coping, stress, sleeping problems, worry, sadness, physical pain, and anger.[59] The disease and associated management strategies led to challenging levels of stress for many health care workers.

Discontinuation of IBD therapy was not recommended, as it could lead to relapses. Currently, most people who are hospitalized with or dying from COVID-19 are not vaccinated.[60,61] The United States was instrumental to the rapid development of vaccines and testing. The FDA approved the vaccines in world-record times. However, the United States ranks 38th in vaccination rates worldwide (as of September 2021).[62] We are not keeping up with the rates we hoped to achieve.

It is important to prepare for the next pandemic. Dr Rubin offered several recommendations based on lessons learned from the COVID-19 pandemic.[54] The recommendations focus on investments in public health, congressional and legal responses, and social networking. There are high stakes to not taking these steps. It would be advantageous to develop a national network of IBD providers and patients for crisis management. The network could also include societies such as the ACG, the AGA, the Crohn's and Colitis Foundation, and the Centers for Disease Control, as well as representatives from industry.

Occupational stress is another major area that has been influenced by COVID-19. The stress of treating patients has taken a high toll on health care workers.[63] Education of patients and colleagues is of paramount importance. Different organizations have provided several approaches. The key is education. It is necessary to stress that vaccination, mask-wearing, and social isolation when appropriate can decrease rates of infection. A pandemic preparedness plan is important. Practices should stockpile personal protective equipment, establish protocols related to telehealth and working from home, develop a safety net plan for coworkers and employees, and communicate the plan to patients en masse. The plan should be reviewed twice annually.

There are several research priorities for IBD. Access issues for the underserved is an important concern that is critical for the appropriate treatment of patients. COVID-19 outcomes were worse among patients with higher disease activity and who were receiving corticosteroids. Disadvantaged patients were more likely to have difficulties in accessing vaccines. Vaccination is one of the most important ways to decrease the risk and severity of COVID-19.

It is also necessary to build trust and end discrimination and bias in recruitment of clinical trials. Trials lack representation of many different individuals of different backgrounds, making it more difficult to generalize data to all patients.[64] There are also legislative steps for policy makers at the federal, local, and institutional levels.

As Dr Rubin summarized, the goals are to prioritize a national network of IBD providers and patients for crisis management, prioritize health care workers' mental health, improve management and education of patients and colleagues, develop a pandemic preparedness plan, identify and fund research priorities for IBD, address access issues to the underserved, build trust, end discrimination bias in clinical trial recruitment, and establish legislative priorities for the IBD population in the United States.[54] With these steps, we can be better prepared for future pandemics.

Disclosure

Dr Lichtenstein has consulted for AbbVie, American Regent, Bristol Myers Squibb, Celgene, Eli Lilly, Endo Pharmaceuticals, Ferring, Gilead, MedEd Consultants, Morphic Therapeutics, Prometheus Laboratories, Romark, Salix Pharmaceuticals/Valeant, Sandoz, Shire Pharmaceuticals, and UCB; conducted research for Bristol Myers Squibb, Celgene, and UCB; served on the Data Safety Monitoring Board for Eli Lilly; and received honoraria (CME program) from American Regent and Romark. He is a consultant and performed research for Janssen Ortho Biotech and Takeda, with funding directed to the University of Pennsylvania (IBD fellow education). He is a consultant for Pfizer Pharmaceuticals, with funding directed to the University of Pennsylvania (IBD fellow education). He has performed CME activities for Allergan, the American Gastroenterological Association, CHEMED, Imedex, Ironwood, the University of Kentucky, and Vindico. He is a consultant and received an honorarium (CME program) from Merck. He is a consultant (stock options) for Virgo.

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