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A SPECIAL MEETING REVIEW EDITION

Highlights From the 2020 Virtual Advances in Inflammatory Bowel Diseases Conference

A Review of Selected Presentations From the 2020 Virtual AIBD Conference • December 9-12, 2020

Special Reporting on:

- Positioning Biologics and Small Molecules in the Management of Moderate to Severe IBD
- Approach to Mild to Moderate IBD
- Disease Activity Assessment: What Should We Do in Clinical Practice?
- Precision Medicine in IBD
- Applying IBD Guidelines in the Real World

PLUS Meeting Abstract Summaries

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TAKE CHARGE OF UC+CD

STELARA® FOR

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

RAPID RESPONSE

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

LASTING REMISSION

Many patients achieved clinical remission at 1 year in the UC and CD clinical trials[1,2‡]

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

Histo-endoscopic Mucosal Improvement at Week 8 in UC (Other Secondary Endpoint):
• STELARA®: 17% (n=54/322); Placebo: 8% (n=26/319); *P*<0.001

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.

Clinical Response at Week 6 (Predominantly TNF Blocker Naïve) 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.

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LASTING* REMISSION

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[1§]

SAFETY PROFILE

The overall safety profile in UC and CD studies 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.

STELARA® DOSAGE FORMS AND STRENGTHS:

SubQ Injection: 45 mg/0.5 mL or 90 mg/mL
IV Infusion for CD and UC Initial Dose: 130 mg/26 mL (5 mg/mL)

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, one case of Reversible Posterior Leukoencephalopathy Syndrome (RPLS), 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 RPLS is suspected or if noninfectious pneumonia is confirmed, discontinue STELARA®.

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

[†] 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 response was defined as reduction in CDAI score of ≥100 points or 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). In CD, clinical remission was defined as a CDAI score of <150.

[§] 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).

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; 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®.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

One case of reversible posterior leukoencephalopathy syndrome (RPLS) was observed in clinical studies of psoriasis and psoriatic arthritis. No cases of RPLS were observed in clinical studies of Crohn's disease or ulcerative colitis. If RPLS is suspected, administer appropriate treatment and discontinue STELARA®. RPLS is a neurological disorder, which is not caused by an infection or demyelination. RPLS can present with headache, seizures, confusion, and visual disturbances. RPLS has been associated with fatal outcomes.

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 Brief Summary on adjacent pages. Please see full Prescribing Information and Medication Guide for STELARA® at STELARAhcp.com. Provide the Medication Guide to your patients and encourage discussion.

cp-124933v2

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®. **Reversible Posterior Leukoencephalopathy Syndrome:** One case of reversible posterior leukoencephalopathy syndrome (RPLS) was observed in clinical studies of psoriasis and psoriatic arthritis. The subject, who had received 12 doses of STELARA® over approximately two years, presented with headache, seizures and confusion. No additional STELARA® injections were administered and the subject fully recovered with appropriate treatment. No cases of RPLS were observed in clinical studies of Crohn's disease or ulcerative colitis. RPLS is a neurological disorder, which is not caused by demyelination or a known infectious agent. RPLS can present with headache, seizures, confusion and visual disturbances. Conditions with which it has been associated include preeclampsia, eclampsia, acute hypertension, cytotoxic agents and immunosuppressive therapy. Fatal outcomes have been reported. If RPLS is

suspected, 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]* • Reversible Posterior Leukoencephalopathy Syndrome *[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 RPLS occurred during 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]. 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 pharmacokinetics study (Ps STUDY 4) in 44 subjects *[see Adverse Reactions, Pharmacokinetics (12.3) in Full Prescribing Information]*. The

STELARA® (ustekinumab)

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]* 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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Positioning Biologics and Small Molecules in the Management of Moderate to Severe IBD

Dr William J. Sandborn discussed how the roles of biologics and small molecules are evolving in the management of moderate to severe inflammatory bowel disease (IBD).[1] First discussed was treatment sequencing. With regard to ulcerative colitis (UC), in a network meta-analysis, infliximab and vedolizumab achieved the highest rates of clinical remission and endoscopic improvement in patients receiving first-line therapy. For second-line therapy, the most effective agents were tofacitinib and ustekinumab. In this setting, tumor necrosis factor (TNF) blockers and vedolizumab have proved less effective at inducing clinical remission and endoscopic improvement.[2] As for head-to-head trials, in the VARSITY trial, vedolizumab proved superior to adalimumab for the treatment of active UC over the course of a year.[3]

With regard to safety, TNF blockers are associated with granulomatous infections, serious infections, non-Hodgkin lymphoma, and demyelination (Table 1). Tofacitinib is linked to serious infections, pulmonary embolism, deep vein thrombosis, and hyperlipidemia. Importantly, vedolizumab and ustekinumab do not cause these complications.

Dr Sandborn proposed an algorithm for treating moderate to severely active UC. For mild to moderate disease, treatment with mesalamine, rectal therapies, and perhaps corticosteroids is the approach of choice. For moderate to severe disease, the algorithm includes first- and second-line therapies. With first-line therapies, the clinician should consider whether extraintestinal manifestations are present, in which case an anti-TNF agent may be appropriate. If the disease is primarily in the gut, then vedolizumab may be best because of its safety profile.

In the treatment of Crohn's disease (CD), the absence of approved Janus kinase inhibitors means the choice is among infliximab, adalimumab (both anti-TNF agents), vedolizumab, and ustekinumab. In the first-line setting, outcomes have been strongest with the 2 TNF blockers. In the second-line setting, however, ustekinumab has demonstrated the greatest efficacy, with a narrow confidence interval. With regard to safety considerations, again vedolizumab and ustekinumab have proved safer than TNF blockers.

Table 1. Safety Considerations

	Infliximab	Adalimumab	Vedolizumab	Ustekinumab	Tofacitinib
Granulomatous infection	+	+	–	–	–
Serious infection	+	+	–	–	+
Herpes zoster	–	–	–	–	+
Non-Hodgkin lymphoma	+	+	–	–	?
Demyelination	+	+	–	–	–
DVT/PE	–	–	–	–	+
Hyperlipidemia	–	–	–	–	+

DVT, deep vein thrombosis; PE, pulmonary embolism. Adapted from Sandborn WJ. Positioning biologics and small molecules in the management of moderate to severe IBD. Presented at: 2020 Virtual Advances in Inflammatory Bowel Diseases Conference; December 9-12, 2020.[1]

In a study presented at United European Gastroenterology Week Virtual 2020, clinical remission (Crohn's Disease Activity Index score <150) was achieved with ustekinumab in patients who had not previously received a biologic drug and those who had previously failed biologic treatment. The anti-interleukin (IL) 23 drug guselkumab demonstrated a slight advantage over ustekinumab in attaining clinical remission.[4] This comparison will proceed to a phase 3 investigation.

As with UC, the positioning of therapies for CD begins with a determination of whether the disease is mild to moderate or moderate to severe. In the former case, the appropriate treatment may be budesonide or corticosteroids. In the latter, efficacy must be weighed against side effects. Patients who are particularly risk-averse may prefer vedolizumab or ustekinumab, even in the first-line setting (Figure 1).[5]

Dr Sandborn also highlighted decision support tools for UC and CD. In the case of UC, research has shown that patients who have a longer duration of disease (>2 years), have never received an anti-TNF agent, had moderate as opposed to severe baseline endoscopy findings, and have normal albumin levels are most likely to respond to anti-integrin therapy with vedolizumab.[6] In the case of CD, response and remission rates are better in patients without previous surgical resection, anti-TNF treatment, or fistulizing disease, with normal albumin levels, and with relatively low C-reactive protein levels.[7]

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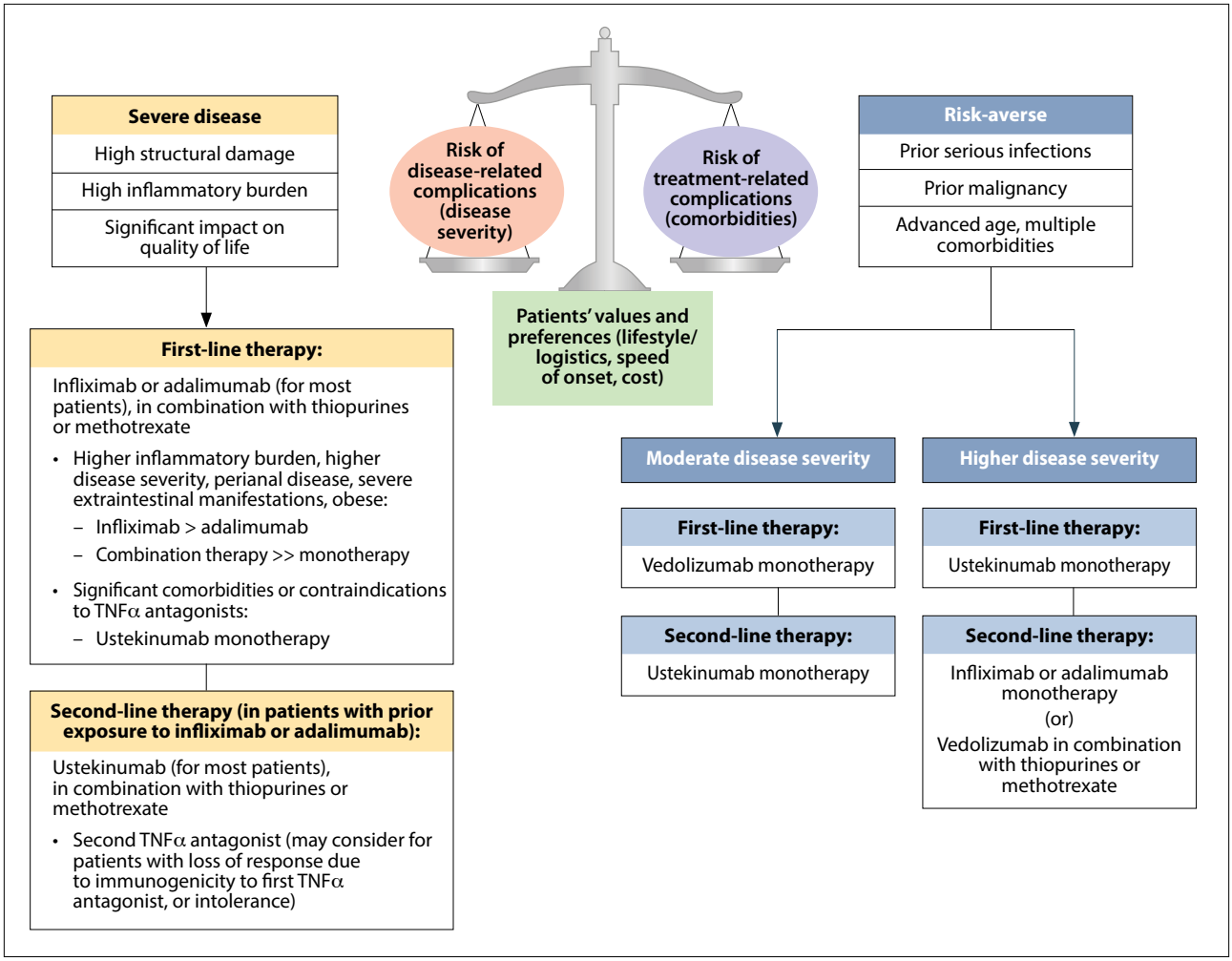

Figure 1. Proposed algorithm for positioning therapies for patients with high-risk Crohn's disease. TNF, tumor necrosis factor. Adapted from Nguyen NH et al. *Clin Gastroenterol Hepatol*. 2020;18(6):1268-1279[5] and Sandborn WJ. Positioning biologics and small molecules in the management of moderate to severe IBD. Presented at: 2020 Virtual Advances in Inflammatory Bowel Diseases Conference; December 9-12, 2020.[1]

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Approach to Mild to Moderate IBD

Dr Sunanda Kane reviewed the treatment of mild to moderate IBD.[1] In 2019, the American College of Gastroenterology issued new clinical guidelines for the treatment of adults with UC, in which urgency, measured as none, mild/occasional, or frequent, was added as a consideration.[2] The fecal calprotectin level was also added.

The diagnosis of UC should include both an assessment of the extent of disease and a biopsy, which will determine histologic severity; a current goal in IBD care is to distinguish between activity and severity. An additional goal is to induce a clinical response or remission. Mucosal healing is crucial because it is associated with sustained, corticosteroid-free remission and prevents the need for hospitalization as well as surgery. Maintenance therapy should be established for each patient according to the response to induction therapy and the prognosis. Screening and treatment for anxiety and depressive disorders should also be part of management. The prevention of complications, such as cancer and infections, is another important goal.

Table 2. Treatment for Mild to Moderate UC

Induction:
• Mild proctitis → rectal 5-ASA recommended (1 g/day)[1-5]
• Left-sided mild UC → rectal 5-ASA (≥1 g/day) in combination with oral 5-ASA (≥2.0 g/day)[1-6]
• Mild extensive UC → oral 5-ASA (≥2.0 g/day)[1,5]
• Mild UC (any extent) → use a low dose (2.0-2.4 g) of 5-ASA,[2] in comparison with a higher dose (4.8 g)[1]
• Mild to moderate UC not responding to oral 5-ASA → + budesonide MMX 9 mg/day[1-3,5]
Maintenance:
• Mildly active proctitis → rectal 5-ASA (1 g/day)[1,2,6]
• Mildly active left-sided or extensive UC → oral 5-ASA therapy (≥2 g/day)[1-4]
• Recommend against systemic corticosteroids[1,3,6]

UC, ulcerative colitis; 5-ASA, 5-aminosalicylic acid. [1]Rubin DT et al. *Am J Gastroenterol*. 2019;114(3):384-413. [2]Hardbord M et al. *J Crohns Colitis*. 2017;11(7):769-784. [3]Bressler B et al. *Gastroenterology*. 2015;148(5):1035-1058.e3. [4]Coi CH et al. *IntestRes*. 2017;15(1):7-37. [5]Ko CW et al. *Gastroenterology*. 2019;156(3):748-764. [6]Wei CS et al. *IntestRes*. 2017;15(3):266-284. Adapted from Kane S. Approach to mild to moderate IBD. Presented at: 2020 Virtual Advances in Inflammatory Bowel Diseases Conference; December 9-12, 2020.[1]

Dr Kane also reviewed induction and maintenance therapy for mild to moderate UC (Table 2). Rectal administration of a 5-aminosalicylic acid (5-ASA) drug at a dose of 1 g/day is recommended for patients with mild proctitis, although many patients may be fine with a dose taken every other day, or even every third day, once remission has been attained. During maintenance, topical therapy can be discontinued for patients with mildly active left-sided or extensive UC, and just oral 5-ASA therapy can be used (≥2 g/day). Systemic corticosteroids should be restricted to induction treatment.

Successful treatment is defined as overall improvement at week 6 according to a clinical assessment of rectal bleeding and stool frequency and the results of sigmoidoscopy. In the ASCEND III trial, additional treatment did not necessarily lead to better outcomes.[3] Clinicians must consider whether a patient's disease activity is mild or moderate when a 5-ASA drug is prescribed. For patients with distal UC, research has shown that a combination of oral and rectal mesalamine therapy is better than either agent alone, even if given for only 1 to 2 weeks.[4] If the combination can be continued for 6 weeks, then the chance of a successful outcome is even greater.

Budesonide MMX appears to be an effective agent for patients with UC who have failed 5-ASA treatment.[5,6] Dr Kane presented a treatment algorithm for maximizing remission and minimizing corticosteroid dependence in UC, noting that budesonide MMX may be the best option for patients with mild to moderate disease, rather than prednisone.

Budesonide MMX is also important in the treatment of CD, in which it has proved almost as effective as prednisolone and superior to placebo and mesalamine for patients with active ileal and right-sided colonic disease. In addition, it may be effective for maintaining remission in mild to moderate CD. Sulfasalazine may also be effective when disease is limited to the colon. Patients must be advised to stop smoking and should be screened for depression and anxiety, both of which will impede improvement.

5-ASA drugs, budesonide, azathioprine, 6-mercaptopurine, and methotrexate are all potential options for treating mild to moderate CD. Lack of efficacy may be due to inadequate dosing, lack of adherence, or preferential metabolism via the thiopurine methyltransferase pathway.

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Disease Activity Assessment: What Should We Do in Clinical Practice?

Dr Bruce E. Sands began his presentation by emphasizing how the goals of therapy have changed over time.[1] Clinical response was once the target outcome, and then it was remission; today, clinicians are aiming for deep remission.

Dr Sands noted the importance of distinguishing between disease activity and disease severity. Disease activity reflects cross-sectional evaluation of biologic inflammatory impact on symptoms, signs, endoscopy, histology, and biomarkers. It asks how the patient is today. In contrast, disease severity is a measure of longitudinal and historical factors. An assessment of disease severity provides a more complete

picture of a patient's prognosis and overall burden of disease. This assessment asks about the course of disease since the diagnosis.[2]

To assess disease severity, physicians must consider the effect of the disease on the patient, the course of the disease, the presence of any complications, and the inflammatory burden. Because CD and UC are progressive disorders, both disease severity and disease activity must be factored into clinical decisions.

An assessment of disease severity in CD considers whether mucosal lesions, fistulae, abscesses, and strictures are present. An assessment of disease severity in UC considers the presence of mucosal lesions; number of hospitalizations; levels of C-reactive protein, albumin, and hemoglobin; extent of disease; daily symptoms; nocturnal bowel movements; and effect of the disease on daily activities.

Treating to target is a useful new concept in IBD, Dr Sands noted. Borrowed from other medical conditions, treating to target in the context of IBD means adjusting therapy to achieve certain targets and then further considering how to improve outcomes while avoiding long-term bowel damage and other complications.

Dr Sands also discussed mucosal healing. Data suggest that partial healing may be sufficient.[3] The Ulcerative Colitis Endoscopic Index of Severity may seem complex, but it can be applied in practice fairly simply, Dr Sands noted. However, endoscopic scoring in UC does not necessarily reflect what is happening microscopically. Furthermore, histologic activity can persist even when mucosal healing suggests remission.[4]

The many evolving grading scales for histology are not all equivalent. Dr Sands suggested avoiding complications by applying the following criteria for histologic quiescence in UC: no more than 5% of crypts with neutrophils, no erosions, and no ulcers. If these are fulfilled, then the disease is histologically quiescent.

The corresponding situation in

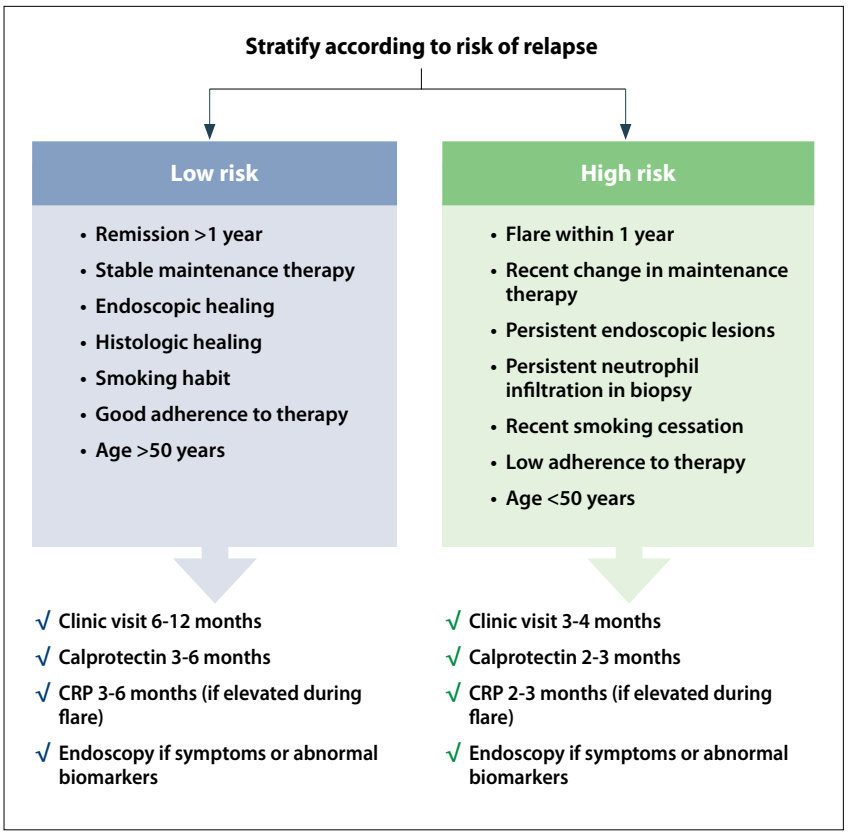

Figure 2. Monitoring in ulcerative colitis. CRP, C-reactive protein. Adapted from Panes J et al. *Gastroenterology*. 2017;152(2):362-373.e3[7] and Sands BE. Disease activity assessment: what should we do in clinical practice? Presented at: 2020 Virtual Advances in Inflammatory Bowel Diseases Conference; December 9-12, 2020.[1]

Ozanimod Efficacy, Safety, and Histology in Patients With Moderate to Severe Ulcerative Colitis During Induction and Maintenance in the Phase 3 True North Study

Dr Sandborn and colleagues reported results from the 10-week induction period of the phase 3 True North study, in which patients were randomized 2:1 to ozanimod or placebo (abstract P025). Of the 645 randomized patients (429 in the ozanimod arm and 216 in the placebo arm), clinical remission was achieved in more patients in the experimental arm (18.4% vs 6.0%; $P<.0001$). Those receiving ozanimod also experienced greater improvements across the secondary endpoints. After induction therapy, 457 patients were re-randomized to ozanimod (n=230) or placebo (n=227). Dr Silvio Danese and colleagues reported efficacy and safety at week 52 in the maintenance period of the study (abstract P030). A total of 124 patients (54.6%) in the placebo group and 184 patients (80.0%) in the ozanimod group completed week 52 of treatment. A total of 77 patients in the placebo group and 31 patients in the ozanimod group discontinued treatment because of disease relapse. Clinical remission, clinical response, endoscopic improvement, maintenance of remission, mucosal healing, durable remission, and corticosteroid-free remission were achieved in significantly more patients in the experimental arm. Safety was consistent with that seen in prior studies of ozanimod.

CD is more complicated. Dr Sands pointed out that endoscopic software enables clinicians to score various criteria automatically as part of the colonoscopy report. Cross-sectional imaging is also important for evaluating CD activity. Clinicians should look at thickening, hyperenhancement, and the severity of edema and ulcers. Patients with transmural healing on cross-sectional imaging are likely to have better outcomes and a reduced need for surgery and hospitalization.[5]

Finally, Dr Sands discussed the role of biomarkers in monitoring disease activity. The fecal calprotectin level is widely used in CD; the higher the score, the greater the endoscopic activity. In the CALM study, the outcomes of patients managed with the treat-to-target approach, which included biomarker monitoring, were greatly superior to the outcomes of those who received clinical management.[6]

Patients with UC can be categorized as low risk or high risk and monitored accordingly. Low-risk patients can be seen every 6 to 12 months, for example. High-risk patients should be seen every 3 to 4 months, with the calprotectin level checked every 2 to 3 months. An endoscopic examination should be performed if a patient is experiencing symptoms or has abnormal biomarker findings (Figure 2).[7]

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Precision Medicine in IBD

Dr Maria T. Abreu explored several reasons for pursuing precision medicine in IBD.[1] Because no single cause exists, no single cure exists. The range of treatments is expanding, with many different targets. The emergence of biomarkers is increasing the feasibility of tailoring treatment, and data are accruing on combination therapies. Each patient requires a unique approach that can be adapted as needed as care proceeds.

With regard to genetics, children who have mutations in IL-10 and the IL-10 receptor pathway overproduce IL-1 and can often be treated effectively with anti–IL-1 strategies, as well as hematopoietic bone marrow transplant. However, although more than 240 confirmed loci are associated with IBD, and more than 50 genes are associated with very early–onset IBD, genetic features have so far not been tightly tied to responses to specific treatment approaches in adults. Dr Abreu noted that in the management of IBD, clinicians often move from one treatment approach to another without allowing sufficient time for a response, and without stratifying patients according to phenotype, genotype, or meta-type.

Biomarkers are emerging as an important feature that can be applied in precision medicine in IBD. Data from a pediatric study showed that the biological signature correlating perforation and fibrotic complications is present in pediatric patients with IBD before treatment.[2] In addition, investigators have found distinct changes in DNA methylation and transcription patterns in the colon epithelium of patients with CD and patients with UC, compared with controls.[3]

The HLA-DQ polymorphism is likely to become important for patient stratification. Over 30% of patients with IBD have this polymorphism, and data show that anti-TNF agents are most effective in this population when combined with immunomodulators. Antidrug antibodies almost

Outcomes of Standard and Intensified Dosing of Ustekinumab for Chronic Pouch Disorders

Dr Rahul S. Dalal and colleagues used clinical data obtained from electronic health records to assess the outcomes of both standard and intensified dosing of ustekinumab (abstract P028). Of 13 patients, 4 discontinued antibiotics within a year after treatment initiation, and 10 of the 19 patients using corticosteroids at the start of treatment discontinued them within 16 weeks. A total of 18 of 42 patients required hospitalization within a year after starting treatment, and 23 of 46 patients received dose intensification. Of the 46 patients whose records were obtained, a clinical response was achieved in 37 within 16 weeks. The researchers concluded that dose intensification is effective for most patients. Patients who were female and those who had a pouch fistula were more likely to respond after treatment initiation, whereas those using cannabis were less likely to respond. The patients who required dose intensification the soonest tended to be younger at the time of IBD diagnosis.

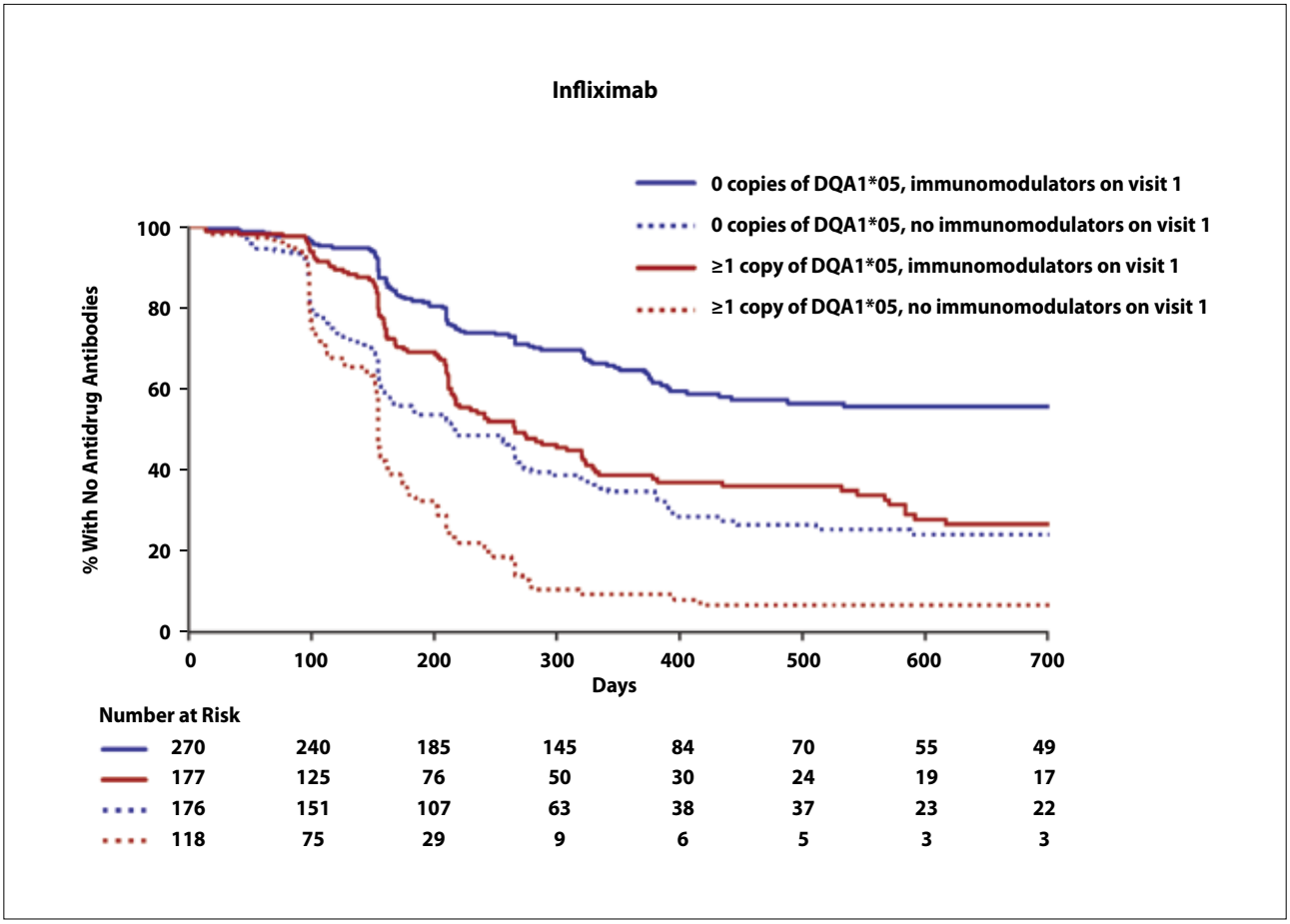

Figure 3. HLA-DQA1*05 is associated with the development of antibodies to anti–tumor necrosis factor therapy. Adapted from Sazonovs A et al. *Gastroenterology*. 2020;158(1):189-199[4] and Abreu MT. Precision medicine in inflammatory bowel diseases. Presented at: 2020 Virtual Advances in Inflammatory Bowel Diseases Conference; December 9-12, 2020.[1]

always develop in patients with the HLA-DQ polymorphism who are taking anti-TNF agents alone (Figure 3).[4]

In her presentation, Dr Abreu also discussed the microbiome, which is altered in patients with IBD, as a component of precision medicine. A study found higher rates of butyrate and short-chain fatty acid synthesis in the patients who were more likely to go into remission with anti-TNF therapy.[5] Adherent-invasive *Escherichia coli* bacteria are found in approximately 40% of patients with ileal CD.[6] In one ongoing study, a comparison of antibiotic treatment vs no treatment is being conducted in patients with these bacteria to see if outcomes differ. Several studies of fecal microbiota transplant are ongoing that may further inform the relevance of the microbiome in tailoring IBD care.

The microbiome may be significant in determining which patients can stop treatment once they are in deep remission. The STORI trial found that a decreased abundance of Firmicutes and Bacteroidetes bacteria and an increased abundance of Proteobacteria organisms were associated with earlier relapse after 6 months of corticosteroid-free remission following treatment with infliximab.[7] Protein, metabolomic, and fecal metagenomic biomarkers may also inform decisions about halting treatment.

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Applying IBD Guidelines in the Real World

Dr Corey A. Siegel began his presentation by noting that in most cases, the management of a patient with IBD does not fit perfectly into any specific set of guidelines.[1] Recent IBD guidelines consist of over 150 recommendations and include some conflicting information.[2-7] Insurance companies are not always willing to comply with the current standard of care, adding further complexity to the application of IBD guidelines in the real world (Figure 4).[8]

Dr Siegel focused on several guidelines. Patients with UC should be treated to achieve mucosal healing and the resolution of inflammatory changes, specified as a Mayo Endoscopic Score of 0 or 1. In this context, a score of 0 indicates normal colonoscopy findings; a score of 1 indicates mild erythema, blunting of the vascular pattern, and possibly some mild friability. Attempting to achieve a score of 0 or 1 is more practical than trying to achieve a score of 0 in all patients. Fixation on a score of 0 as the goal may lead clinicians to cycle through drugs too rapidly, and a score of 1 may be attained more easily.

Dr Siegel also discussed combination therapy with infliximab. When used as induction therapy for patients with moderate to severely active UC, infliximab should be combined with a thiopurine, according to data from the UC SUCCESS trial and other studies.[2,9]

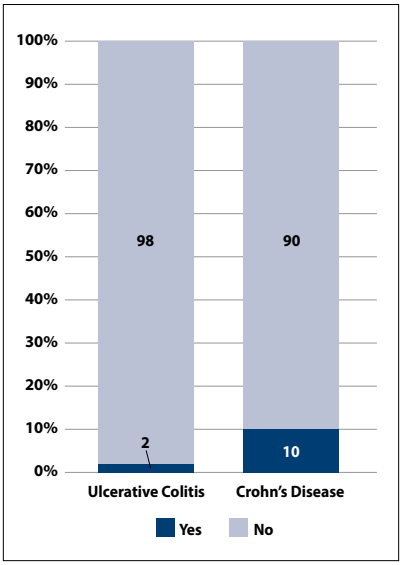

Figure 4. Compliance with American Gastroenterological Association clinical pathways. Adapted from Yadav A et al. *Inflamm Bowel Dis*. 2017;23(6):853-857[8] and Siegel CA. Applying IBD guidelines in the real world. Presented at: 2020 Virtual Advances in Inflammatory Bowel Diseases Conference; December 9-12, 2020.[1]

Many clinicians are being told by insurance companies that adalimumab should be used for first-line treatment of adult outpatients with moderate to severe UC. Data from the VARSITY trial, in which vedolizumab was more effective than adalimumab, invalidate that instruction.[10] Presenting these data to payors may lead to coverage changes on a patient-by-patient basis.

In addition, Dr Siegel noted that he disagreed with the suggestion by the American Gastroenterological Association to combine an anti-TNF agent, vedolizumab, or ustekinumab with a thiopurine or methotrexate rather than use biologic monotherapy.[4] The rates of biologic immunogenicity vary.[11] Combination therapy decreases biologic immunogenicity, but adding a second drug decreases the safety benefit of vedolizumab and ustekinumab.

Until about 2016, the vast majority of patients received either corticosteroids or 5-ASA drugs as first-line treatment; very few patients received immunomodulators or biologics at the start of care. A study found that more than 60% of patients were started on a corticosteroid and never received any other drug during the course of their treatment, an approach that is not in line with current guidelines or data.[12]

For patients with CD at low risk for progression, the use of symptomatic treatment alone is an effective approach. Patients with mild disease do not require 5-ASA drugs, for example. Budesonide may be useful as needed, but this group of patients can be treated for symptoms alone as long as the patients are monitored and tested.

In the postoperative setting, patients should undergo colonoscopy after 6 to 12 months. Anti-TNF agents are safe to begin within 4 weeks of surgery. Anti-TNF agents are the drug category of choice because the relative risks are much lower than those associated with other medications.

Long-Term Effectiveness and Safety of Ustekinumab for the Treatment of Crohn's Disease: A Brazilian Multicenter Real-World Study

Dr Rogerio S. Parra and colleagues conducted a retrospective study of 12 academic medical centers in Brazil to evaluate outcomes in patients with moderate to severe CD treated with ustekinumab in a real-world setting (abstract P008). All patients initially received a single, weight-based intravenous infusion of ustekinumab, followed by a 90-mg subcutaneous dose every 8 weeks. Clinical remission was achieved in 153 of the 245 patients (62.4%). Clinical response occurred in 189 patients at week 8. At 16 weeks into treatment, ileal location of disease, perianal disease, combination therapy, and younger age were associated with lower remission rates. At 6 months into treatment, significant inflammatory burden and combination therapy were associated with lower rates of remission. At 1 year, smoking and younger age were associated with lower remission rates. The findings confirmed that ustekinumab is effective and delivers long-term response in CD patients who previously received biologic therapy.

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Highlights From the 2020 Virtual Advances in Inflammatory Bowel Diseases Conference: Commentary

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The annual Advances in Inflammatory Bowel Diseases (AIBD) Conference reviews important issues and developments in the field of inflammatory bowel disease (IBD) management each year. In 2020, the conference was presented via a virtual format for the first time. Highlights of the 2020 Virtual AIBD Conference included oral presentations on the application of guidelines in the real world, the use of biologic agents and small molecules for moderate to severe IBD, and the role of precision medicine.

Real-World Application of Guidelines

Dr Corey A. Siegel discussed the application of IBD guidelines in the real world.[1] There have been numerous recent advances in IBD, many of which have been reflected in recent guidelines. Since 2017, there have been a total of 6 different IBD guidelines that have been published by the American College of Gastroenterology and the American Gastroenterological Association.[2-7] Within these guidelines, there are more than 150 recommendations, and many of them overlap and some even conflict. In addition, several of these guidelines are not presented in a user-friendly and easy-to-remember format, particularly for individuals who are not well versed in IBD. As a consequence, individual scenarios may have to be looked up, and clinicians may not always recall every nuance of a guideline, thus requiring that they go back to reread it. It would be a major advance if guidelines could be incorporated into electronic medical records. For example, if a practitioner prescribed corticosteroids, an alert or reminder could be made that referred to any related guidelines, such as whether tests are needed if the patient is on corticosteroids for a prespecified number of days.

It is difficult for practitioners to follow guidelines completely; in fact, many practitioners do not follow them very well. This was highlighted in a retrospective, observational study that Dr Siegel and colleagues recently published using administrative claims data from the Truven Health MarketScan Commercial and Medicare Database.[8] They found that 63% of Crohn's disease patients (n=16,260) who were started on a corticosteroid received only that treatment, and some patients received up to 10 cycles of corticosteroid therapy. Biologic agents were used in only 3% of patients initially and in combination with immunomodulators in 1% of patients overall. These numbers are substantially lower than expected and are concerning because they highlight that the majority of these patients were not treated according to the current standard of practice.

In his presentation, Dr Siegel highlighted that many insurance companies also do not follow guidelines when it comes to the current standard of care. A study from 2017 reviewed the top 125 insurance companies (according to market share in 2014) and examined the first 50 with online policies on vedolizumab and anti–tumor necrosis factor (TNF) use. This evaluation showed that early intensive intervention or top-down therapy was

allowed by only 2% of ulcerative colitis policies and 10% of Crohn's disease policies. In addition, at that time, 34% of policies required that patients had to fail to respond to 2 drugs before they could receive a biologic agent, and the vast majority of policies (90%) required stepwise drug therapy.[9] These findings go against current clinical practice as well as current guidelines.

In addition, Dr Siegel related that patients in clinical practice may not necessarily be representative of what is assessed directly in clinical trials. A study by Dr Christina Ha and colleagues found that only approximately 31% of patients seen in an office practice would be able to enroll in clinical trials.[10] If approximately two-thirds of patients in an office-based practice would not necessarily have met the eligibility criteria for enrolling in clinical trials and current clinical IBD guidelines are not adhered to, a large burden is being placed on the practitioner, and patient management becomes more challenging.

In particular, these impediments make management of patients with IBD more difficult for practitioners who treat not just IBD but a multitude of other gastrointestinal conditions, such as gastroesophageal reflux disease, liver disease, and colon cancer.

Biologics and Small Molecules for Moderate to Severe IBD

Dr William J. Sandborn discussed the use of biologic agents and small molecules in patients with moderate to severe IBD and highlighted treatment sequencing, new therapies, and individualizing treatment.[11] In addition, he reviewed first- and second-line treatment options, which have been evolving over time. Different biologic agents are now available, but there are very little comparative effectiveness data that have been derived from randomized, controlled, blinded research. Thus, if a patient has clinical, endoscopic, and laboratory features that suggest that the patient merits use of a biologic agent to treat his or her IBD, the question is which biologic agent should be initiated.

At present, the only prospective, randomized, controlled data published in full manuscript form focusing on comparative effectiveness in patients with IBD come from the VARSITY trial, which compared vedolizumab with adalimumab for the treatment of active ulcerative colitis (Table). This trial showed superiority for vedolizumab over adalimumab in endoscopic improvement and clinical remission. For corticosteroid-free clinical remission, there was no significant difference between the 2 treatment groups.[12]

Because such comparisons have been performed directly only for 2 other agents (although they have not yet been published as full manuscripts), assessment often relies upon the use of network meta-analyses. This research can help estimate the positioning of biologic agents but is not as reliable as head-to-head trials, which are the gold standard. Thus, there is a need for additional comparative effectiveness trials. Two were completed in 2020 and presented in abstract form only, and several other trials are currently ongoing.

When deciding among different biologic agents, practitioners should consider whether the agents have any associated risks (eg, serious infections, lymphoma risk, demyelination, deep vein thrombosis, pulmonary embolism). For example, we know that anti-TNF therapy is not appropriate in a patient who has had optic neuritis or multiple sclerosis because such treatment can worsen outcomes.[13] Vedolizumab and ustekinumab are often considered to be among the safest biologic agents currently in use.

Several agents have been approved for patients with moderate to severe ulcerative colitis, including tofacitinib, infliximab, adalimumab, golimumab, vedolizumab, and ustekinumab. When deciding which agent to use, it is important to assess whether patients have extraintestinal manifestations and whether they have comorbidities that would make it inadvisable to receive certain treatment. For example, if a patient has preexisting deep vein thrombosis, tofacitinib might not be

Table. Comparative Effectiveness Trials of Biologic Therapies for Inflammatory Bowel Disease

Trial Name	Agents Studied	Disease	Actual or Anticipated Trial Completion Date	ClinicalTrials.gov Identifier
VARSITY	Vedolizumab vs adalimumab	UC	2019	NCT02497469
GARDENIA	Etrolizumab vs infliximab	UC	2020	NCT02136069
HIBISCUS I	Etrolizumab vs adalimumab	UC	2020	NCT02163759
VEGA	Guselkumab + golimumab vs guselkumab vs golimumab	UC	2021	NCT03662542
EXPEDITION	Brazikumab vs vedolizumab vs placebo	UC	2022	NCT03616821
SEAVUE	Ustekinumab vs adalimumab	CD	2021	NCT03464136
INTREPID	Brazikumab vs adalimumab vs placebo	CD	2022	NCT03759288
VIVID-1	Mirikizumab vs ustekinumab vs placebo	CD	2023	NCT03926130
GALAXI	Guselkumab vs ustekinumab vs placebo	CD	2026	NCT03466411

CD, Crohn's disease; UC, ulcerative colitis. Adapted from Lichtenstein GR. *Gastroenterol Hepatol (N Y)*. 2019;15(12)(suppl 6):12-19.[31]

the first choice for treatment. On the other hand, if a patient has pyoderma gangrenosum, anti-TNF therapy might be considered for treatment. Practitioners should assess the patients' clinical scenario to determine which therapy is most appropriate as a first-line agent.

Appropriate medical therapy is also important for high-risk Crohn's disease. Dr Sandborn presented recommendations based upon data extracted from a recent network meta-analysis; however, this approach to determine which agent is most appropriate is not embraced by all clinical practitioners.

In his presentation, Dr Sandborn also reviewed new agents, including filgotinib, which is undergoing phase 3 clinical evaluation, and ozanimod, which prevents lymphocyte egress from lymph nodes and hence lessens bowel-related inflammation. Ozanimod, an oral sphingosine-1-phosphate receptor modulator, has been shown to selectively inhibit sphingosine-1-phosphate subtypes 1 and 5, whereas filgotinib has been shown to selectively inhibit subtype 1. Dr Sandborn discussed induction data[14] from a 10-week trial on ozanimod in patients with moderate to severe ulcerative colitis that were presented at United European Gastroenterology (UEG) Week Virtual 2020. Ozanimod demonstrated superiority over placebo in terms of clinical remission and response, endoscopic improvement, and mucosal healing. Also at UEG Week Virtual 2020, maintenance data on ozanimod were highlighted that demonstrated persistence of clinical remission and response, endoscopic improvement, maintenance of remission, corticosteroid-free remission, mucosal healing, and durable remission. All of the prespecified trial endpoints were met.[15] At the same meeting, filgotinib showed superiority over placebo for induction of patients with moderate to severe ulcerative colitis,[16] and it was able to maintain remission at week 58 more than placebo.[17] Given the initial success of ozanimod, there are likely to be other similar compounds within the class of sphingosine-1-phosphate receptor modulators investigated for use in patients with IBD in the future.

Finally, Dr Sandborn reviewed data on clinical decision support tools and companion diagnostic testing for the future. He and his colleagues recently created a prognostic decision tool that stratified treatment outcomes for patients with ulcerative colitis in the VICTORY consortium. The researchers investigated different factors, such as disease duration greater than or equal to 2 years, no prior anti-TNF use, moderate disease at baseline endoscopy, and baseline serum albumin concentration, and assigned a certain number of points for each factor to determine the probability of response to vedolizumab. Fewer than 13 points indicated a low probability of response, 13 to 19 points an intermediate probability, and more than 19 points a high probability.[18] Other similar tools are also in development.

Precision Medicine

Dr Maria T. Abreu discussed precision medicine and addressed several areas of interest, including whether we can predict if individual patients will develop more severe disease, and additionally who should receive early aggressive treatment; whether we can better match treatment to patients; and whether we can predict who is able to stop medical therapy and maintain remission.[19] She also discussed how to incorporate biomarkers into clinical trials, and specifically what they do and how they help us.

One of the questions that is commonly discussed is which patients are likely to develop more severe disease and who needs earlier treatment. In 2017, data on ileal gene stratification were published showing that ileal gene signatures were able to help clinicians risk-stratify patients.[20] In addition, epigenetic research of colonic epithelium of patients with Crohn's disease and patients with ulcerative colitis has shown that distinct DNA methylation and transcription patterns might be present that differ from controls.[21]

In an effort to see if we can better match patient responses to specific therapies and predict patient prognosis, genes have been evaluated. There are more than 200 genes associated with IBD at the present time, as well as 30 Crohn's disease–specific loci and 23 ulcerative colitis–specific loci. There are also 110 IBD loci that are common to both pathways and that can be seen in *Mycobacterium*, leprosy, and other immune disorders.[22-24] More than 50 genes have been associated with very early–onset IBD.[25]

In her discussion, Dr Abreu highlighted that the classic step-up treatment approach initiates therapy with 5-aminosalicylic acid, corticosteroids, azathioprine, and subsequently a biologic agent. In contrast, top-down treatment starts with a biologic agent such as an anti-TNF agent plus an immunomodulator, and then the immunomodulator is classically stopped after a period of time while maintaining the anti-TNF agent or biologic agent. She mentioned that it may eventually be possible to stratify patients to treatment based on phenotype, genotype, and metatype.

She also noted that, interestingly, HLA-DQA1*05 has been associated with the development of antibodies to anti-TNF therapy.[26] There is clearly a difference between patients with and without HLA-DQA1*05, but whether it becomes a useful tool for the clinician in clinical practice is an important issue.

In addition, Dr Abreu noted that the microbiome may be an important tool that enables the clinician to take advantage of precision medicine. The metabolome state might predict response to biologic agents, especially anti-TNF therapy.[27] A prospective study of stool metagenomes of IBD patients who were initiating biologic treatment found that butyrate-producing bacteria was more abundant at baseline in Crohn's disease patients who responded to treatment. Baseline enrichment occurred in 13 microbial pathways in Crohn's disease patients who responded to therapy. In responders, microbial changes noted at week 14 remained up to a year.[28]

This is exciting work because it allows for better prediction. There are also many other ongoing studies trying to improve prediction of patient outcomes.

Fecal microbiota transplantation (FMT) was discussed as well. FMT was initially pioneered in patients with *Clostridioides difficile* infection, and then its utility was assessed in the treatment of patients with ulcerative colitis. However, there have been only a few small randomized, controlled clinical trials assessing the efficacy of FMT in the treatment of patients with IBD.[29] Interestingly, SER-287, a live biotherapeutic formulated for oral dosing, is composed of Firmicute spores. These bacterial spores are resistant to gastric acid, allowing formulation into capsules for effective colonic delivery. This product, which has been nicknamed "FMT in a pill," has undergone phase 1b research[30] and is now entering larger trials. This compound appears reasonably effective, but phase 3 research is needed to determine whether it truly is effective at treating patients. There are several selective microbiome modulators in various phases of development for the treatment of different diseases.

Finally, Dr Abreu discussed which patients can stop medications and whether there is a microbiome signature that predicts response or relapse in patients. These particular hypotheses have not been adequately evaluated and represent areas of current research.

Disclosures

Dr Lichtenstein has consulted for AbbVie, American Regent, Celgene, Eli Lilly, Endo Pharmaceuticals, Ferring, Gilead, Janssen Orthobiotech, Merck, Morphic Therapeutics, Pfizer Pharmaceuticals, Prometheus Laboratories, Romark, Salix Pharmaceuticals/Valeant, Shire Pharmaceuticals, Takeda, and UCB; conducted research for Celgene, Janssen Orthobiotech, and UCB; served on the DSMB for Eli Lilly; received honoraria (CME program) from American Regent, Merck, and Romark; and received funding to the University of Pennsylvania (IBD fellow education) from Janssen Orthobiotech, Pfizer Pharmaceuticals, and Takeda.

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1. Gut 2015 Jan;64(1):20-5. doi: 10.1136/gutjnl-2013-305506. Epub 2014 Apr 3.
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