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GI & LIVER UPDATE

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Updates on Positioning IBD Therapies and Comparative Efficacy

Disclosures

Research grant:

ABBVIE, JANSSEN, BMS, Protagonist, Pfizer, AMT

Consulting:

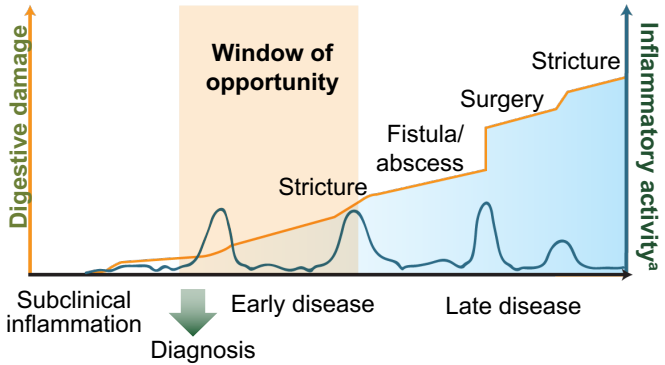
ABBVIE, JANSSEN, TAKEDA, PFIZER, BMS, Protagonist, AMT

Positioning Factors to Consider

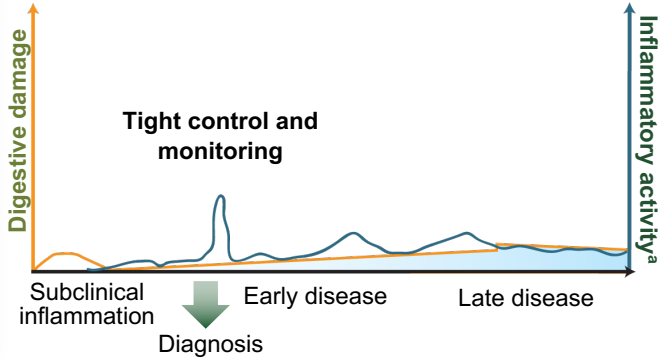
- Individual's risk of IBD based on current and historical disease
- Safety of Treatment
  - Relative to disease
  - Relative to other available treatments
- Efficacy of treatment
- Comparative efficacy to available therapies
- Patient specific considerations
  - Current disease burden
  - Previous medication failures
  - Co-morbid illness
  - Other ongoing medical therapy
  - Contraindications to medications

Treating IBD: Why the Urgency?
Individual's Risk of IBD

Natural course of Crohn's disease (and UC?)



Theoretical impact of early effective treatment on disease progression



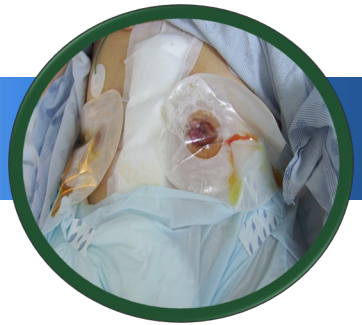
[a]Assessed by CDAI, CDEIS, and/or CRP.
CDAI, Crohn's Disease Activity Index; CDES, Crohn's Disease Endoscopic Index Severity; CRP, C-reactive protein.
Colombel JF et al. *Gastroenterology*. 2017;152:351-361.

Treatment Strategies for UC Are Driven By Patient Risk of Complicated Disease

Individual's Risk of IBD

Low risk
for colectomy

Limited anatomic extent
Mild endoscopic disease



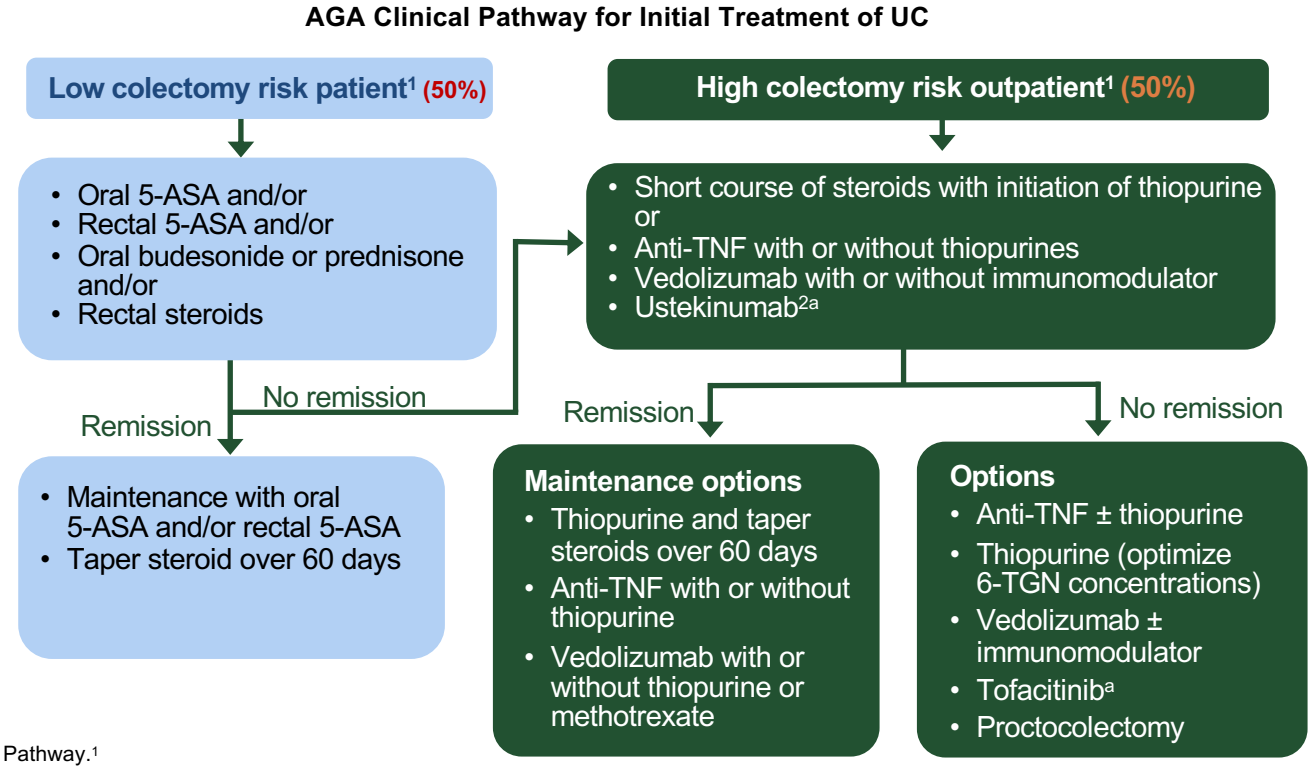
High risk
for colectomy

Age <40 years
Extensive colitis
Deep ulcers
Corticosteroid dependent
History of hospitalization
High CRP and ESR
C difficile infection
CMV infection

Dassopoulos T, Scherl, E, Schwartz R, Kosinski L, Cohen C, and Regueiro M. *Gastroenterology*. 2015;149:238-245.

Risk of Colectomy in UC Dictates (First Line) Therapy

Individual's Risk of IBD



[a]Adapted from AGA Clinical Pathway.[1]

5-ASA, 5-aminosalicylate; TGN, thioguanine nucleotide.

1. Dassopoulos T, Scherl, E, Schwartz R, Kosinski L, Cohen C, and Regueiro M. *Gastroenterology*. 2015;149:238-245; 2. Sands BE et al. *N Engl J Med*. 2019;381(13):1201-1214.

Relative Risk Assessment
Individual's Risk of IBD

- Endoscopic severity/ulcer severity
- Biochemical – High CRP, Low HCT/HGB, low albumin
- Disease burden – Extensive bowel involvement
- Perianal disease

The above are easy clinical parameters to determine need for advanced therapy

Relative Safety of IBD Therapies
Safety of Treatment

Vedolizumab, Ustekinumab, Risankizumab

- **Black box warning – NONE**
- Contraindications – allergic history to medication
- Clear associated side effects – **none with statistical sig**
- Low infusion and injection reactions

Relative Safety of IBD Therapies
Safety of Treatment

S1P

Ozanimod

- Black box warning – NONE
- Contraindications – In the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure. Presence of Mobitz type II second-degree or third degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker. Severe untreated sleep apnea. Concomitant use of a monoamine oxidase inhibitor. Allergic history to medication
- Common associated side effects – liver test increased, upper respiratory infection, and headache

Relative Safety of IBD Therapies
Safety of Treatment

TNF inhibition

- **Black box warning** –SERIOUS INFECTIONS, Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens. Discontinue therapy if a patient develops a serious infection or sepsis during treatment.Perform test for latent TB; if positive, start treatment for TB prior to starting INSERT TNF NAME. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. MALIGNANCY Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including therapy .
- **Contraindications** –Serious infections: Do not start during an active infection. If an infection develops, monitor carefully, and stop If infection becomes serious. Invasive fungal infections: For patients who develop a systemic illness. consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic. Malignancies: Incidence of malignancies was greater than in controls Anaphylaxis or serious hypersensitivity reactions may occur Hepatitis B virus reactivation: Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop and begin anti-viral therapy Demyelinating disease: Exacerbation or new onset, may occur. Cytopenias, pancytopenia: Advise patients to seek immediate medical attention if symptoms develop, and consider stopping. Heart failure: Worsening or new onset, may occur. Lupus-like syndrome: Stop therapy if syndrome develops. allergic history to medication
- Clear associated side effects – Psoriasis like rash

Relative Safety of IBD Therapies
Safety of Treatment

Jak inhibitors – Tofacitinib and Upadacitinib

Black box warning –
Increased risk of death in people 50 years of age and older who have at least 1 heart disease (cardiovascular) risk factor and are taking Tofa 5 mg twice daily or Tofa 10 mg twice daily.
Cancer.

Tofacitinib may increase your risk of certain cancers by changing the way your immune system works. Lymphoma and other cancers, including skin cancers, can happen. People taking Tofa 5 mg twice daily or Tofa 10 mg twice daily have a higher risk of certain cancers including lymphoma and lung cancer, ***especially if you are a current or past smoker***. Tell your healthcare provider if you have ever had any type of cancer.

Higher dose. People with ulcerative colitis taking the higher dose of Tofa (10 mg twice daily) or Tofa XR (22 mg one time each day) have a higher risk of serious infections, shingles, or skin cancers.

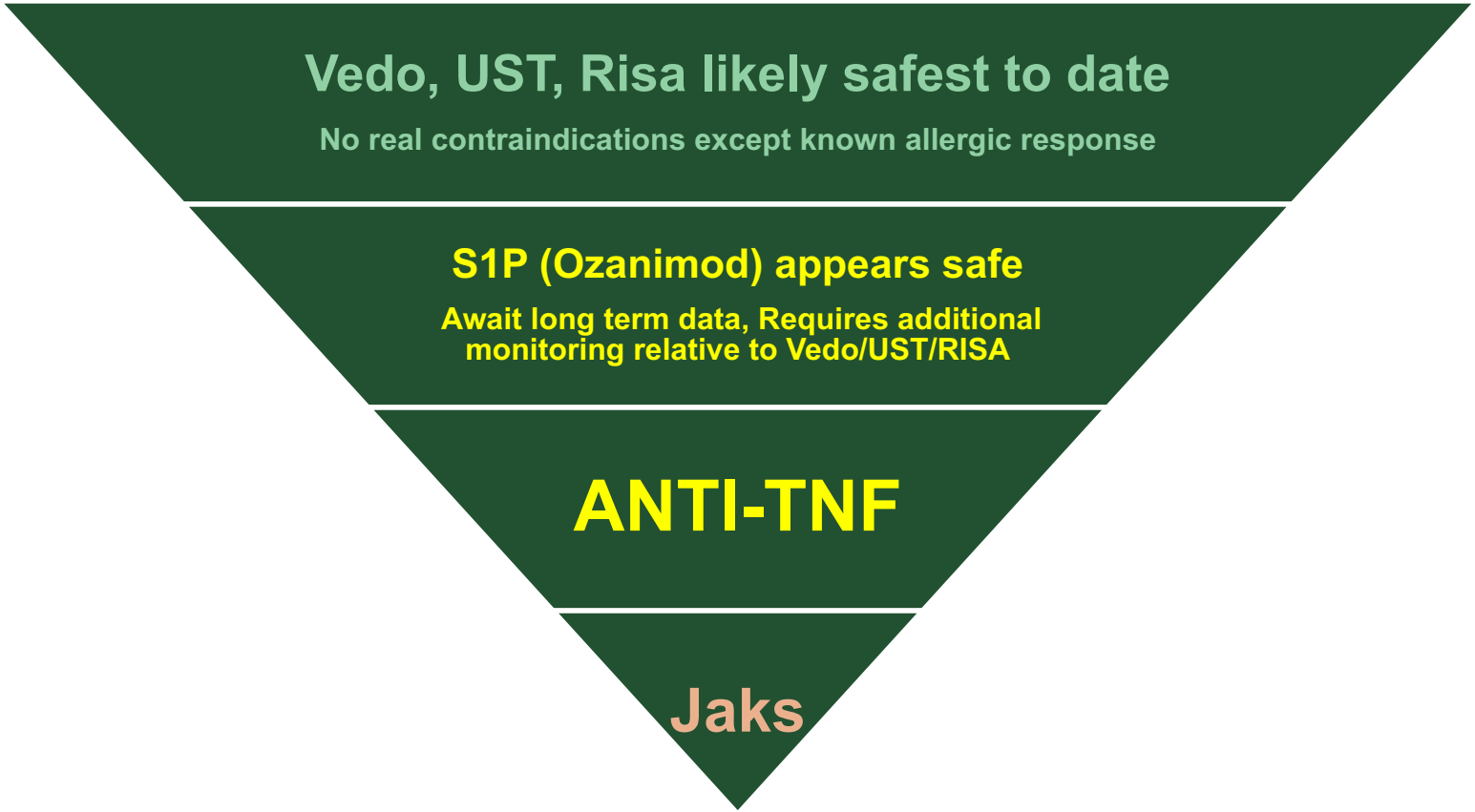
Immune system problem. Some people who have taken Tofa with certain other medicines to prevent kidney transplant rejection have had a problem with certain white blood cells growing out of control (Epstein Barr Virus–associated post-transplant lymphoproliferative disorder).

Get emergency help right away if you have any symptoms of a heart attack or stroke while taking Tofacitinib, including:

- **Contraindications – See black box warning**
- **Common associated side effects – alteration of lipids, risk of shingles**

Relative Safety of IBD Therapies

Safety of Treatment



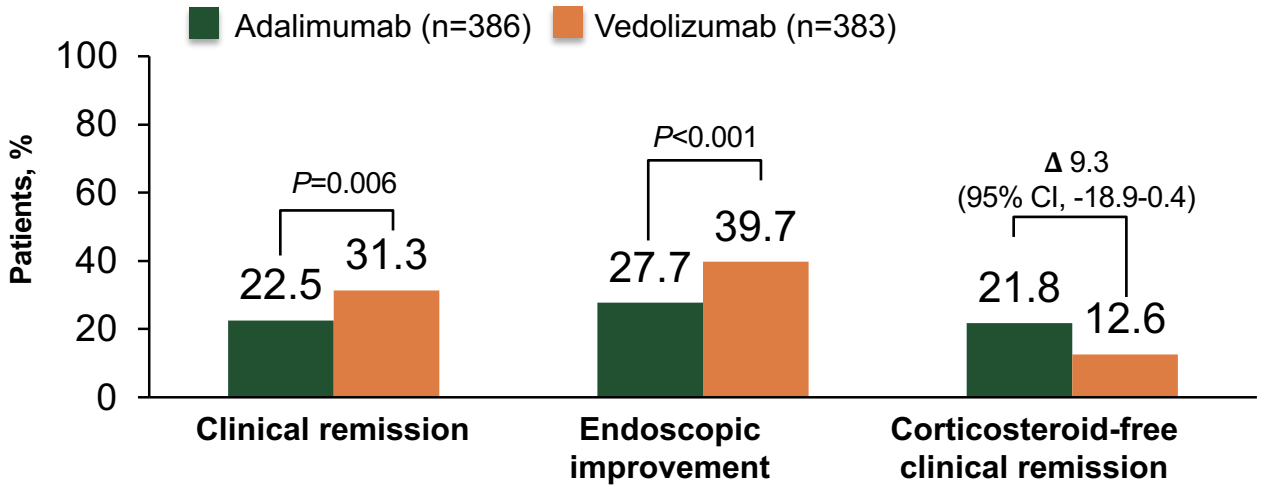
Relative Efficacy

Only 2 completed head to head trials

More head to head trials are coming

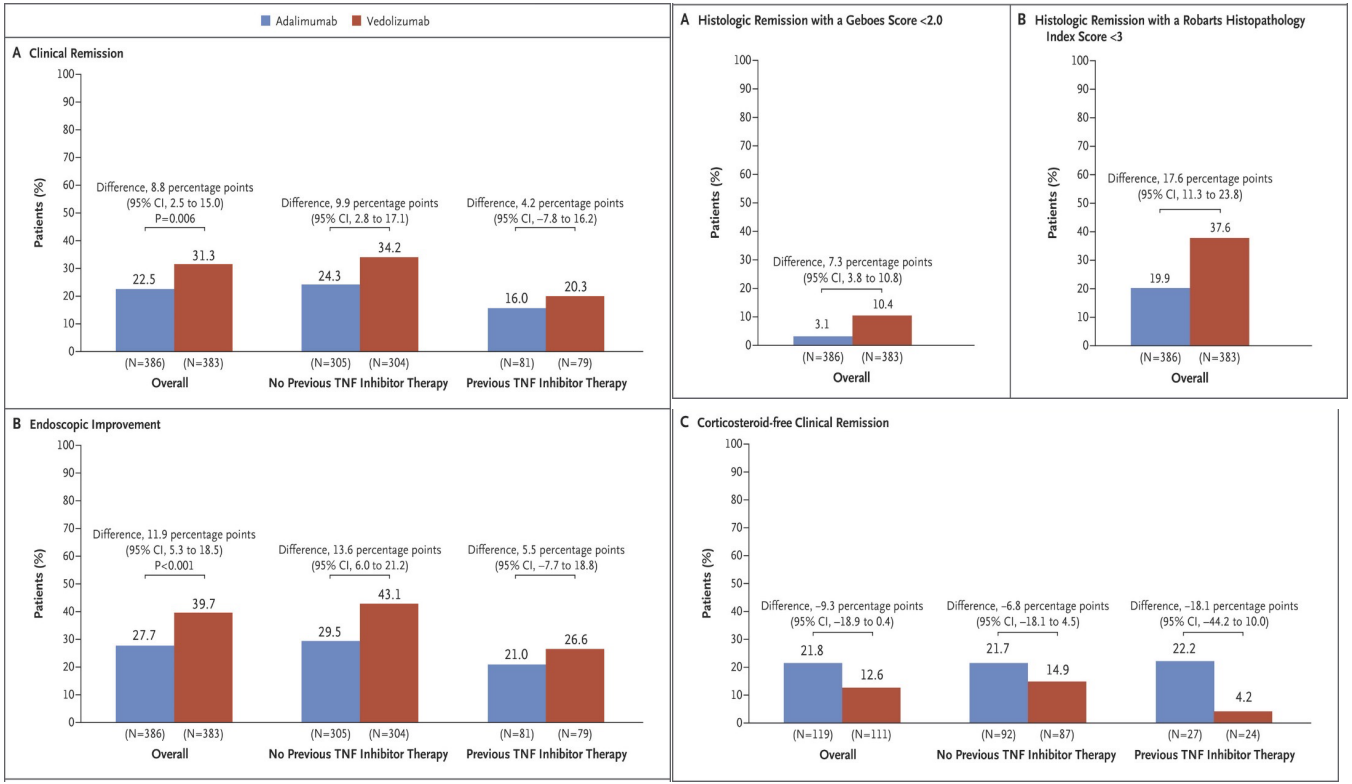
Adalimumab vs Vedolizumab in Moderate to Severe UC: The VARSITY Trial

Comparative Efficacy



Sands BE et al. *N Engl J Med*. 2019;381:121501226.

VARSITY
Comparative Efficacy



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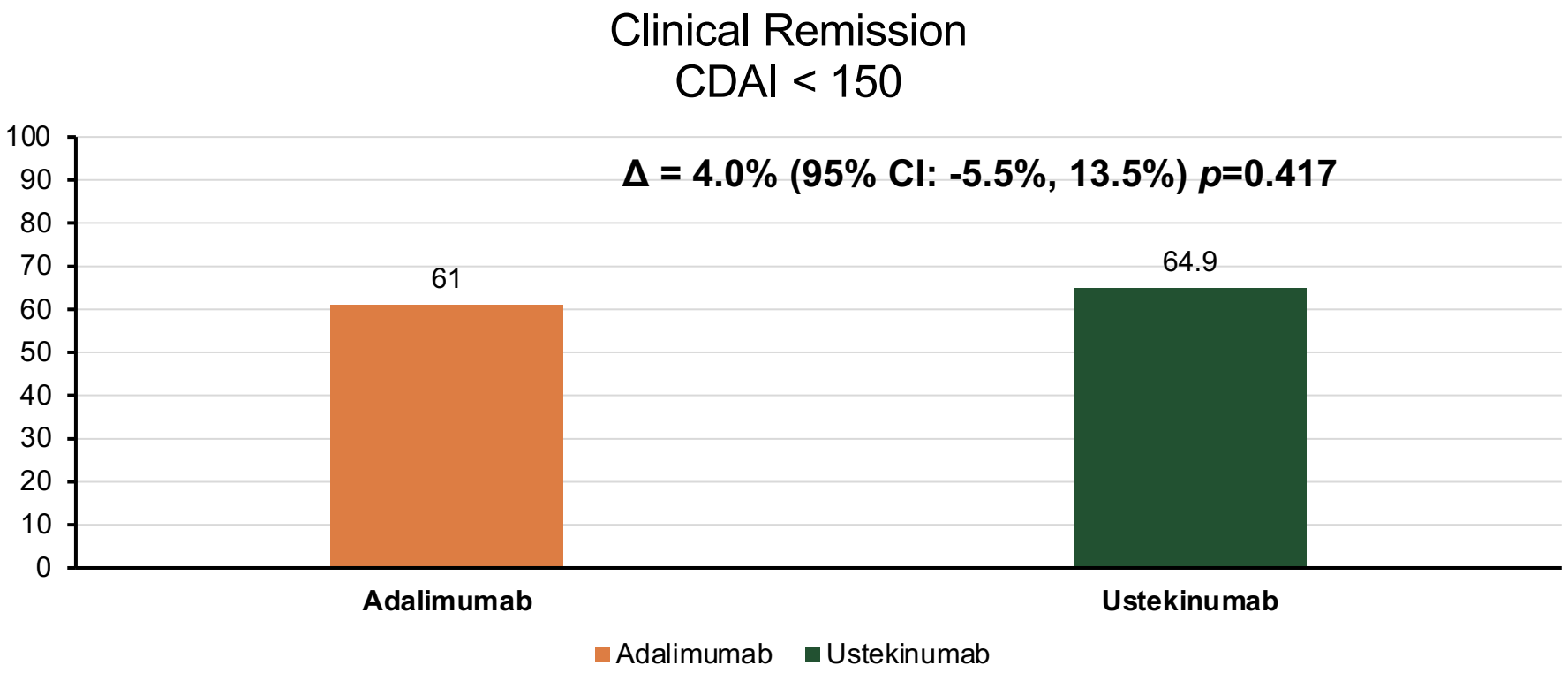
Ustekinumab Versus Adalimumab for Induction and Maintenance Therapy in Moderate-to-Severe CD
The SEAVUE Study
Comparative Efficacy



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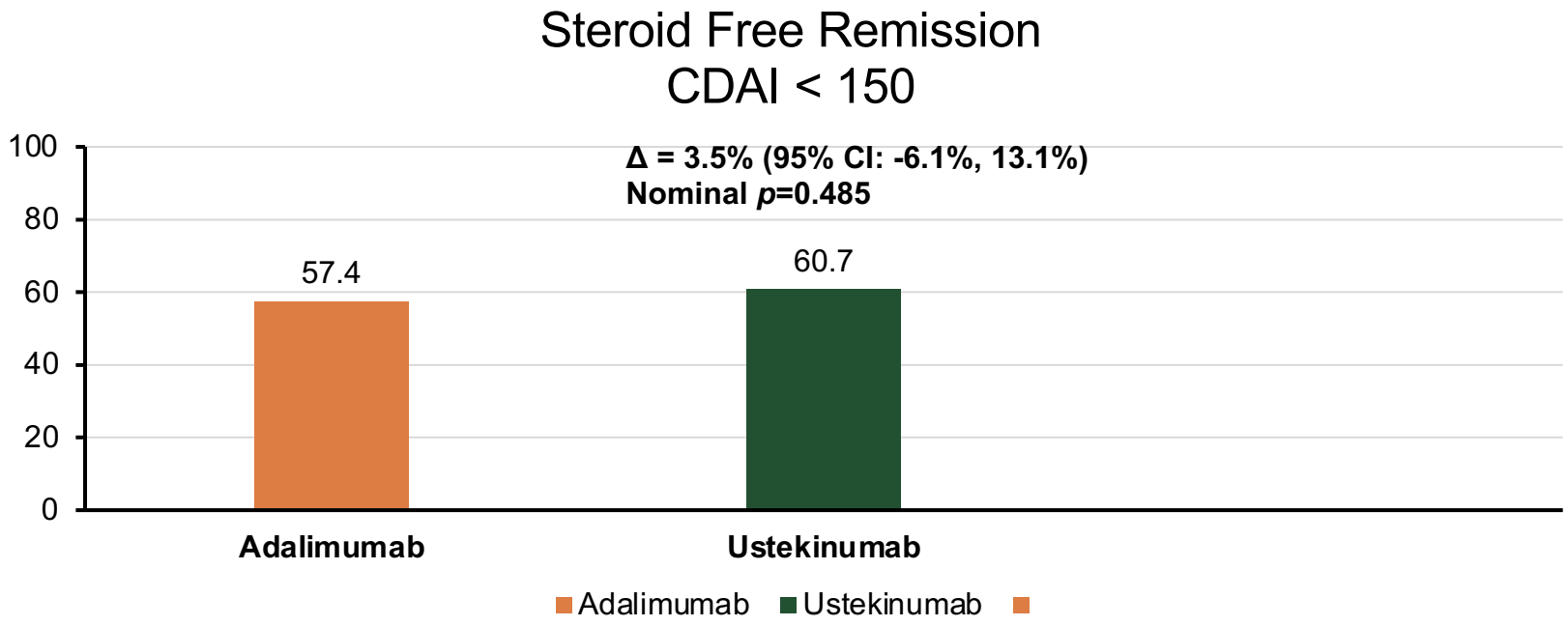

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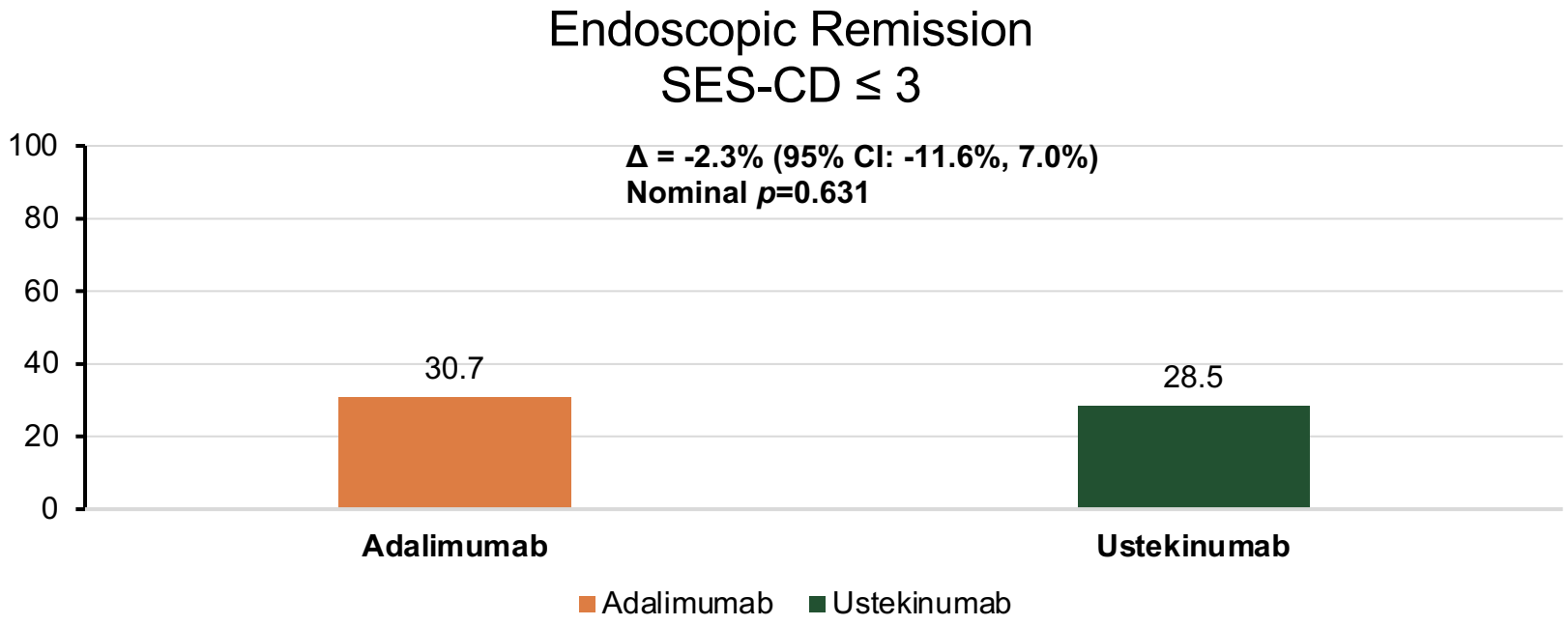


Relative Efficacy

Even with superior efficacy in head to head other factors or lack there of –safety and other patient factors may be more important (including insurance coverage)

Patient Specific Considerations

Heavy disease burden – fixed dose SQ biologic may not be ideal

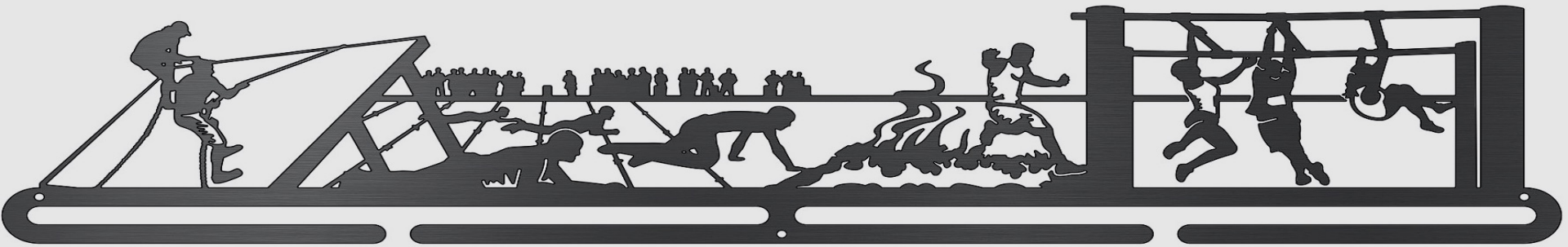
Previous medication failures – TNF failure predicts poor response to all future therapies regardless of MOA

Comorbid illness –

- If RA – TNF or Jak to potentially treat 2 disease with 1 MOA
- Psoriasis – consider UST, Risa or TNF
- MS or CHF – avoid TNF
- MS – consider S1P
- Sig Cardiac disease – might avoid JAK and possibly S1P
- Significant smoking – avoid JAK

Medical interactions – Possible with small molecules, but few concerns with biologics

How Do I Position Biologics? The Obstacles of Starting Biologic Therapy for IBD



Diagnosing full disease extent and prognosis

Discussion of risks and benefits

Prior authorization and coverage

Managing expectations, logistics and adherence

Adapted from Corey Siegel, MD

SUMMARY
Updates on Positioning IBD Therapies and Comparative Efficacy

Biologics & Small Molecules for IBD "Which One based on the scenario"

The 'naïve patient'

Many insurances require anti-TNF first (FDA note: Tofa only after antiTNF)

UC severe (hospitalized or "pending" hospitalization)

- Tofa/Upa (if eligible) vs Infliximab (up to 10mg/kg) with AZA (MTX young males) vs Cyclosporine

UC: outpatient moderate/severe (not "impending" hospitalization)

- > 60 years or comorbid cancer/infection or Cardiac: 1st Vedolizumab or UST monotherapy
- < 60 years without comorbidity: 1st Vedolizumab, UST, Ozanimod

CD:

- > 60 years or comorbid cancer/infection: Vedolizumab, Ustekinumab, Risa monotherapy
- < 60 years without comorbidity: *still* 1st Vedolizumab or Ustekinumab, Risa

SUMMARY
Updates on Positioning IBD Therapies and Comparative Efficacy

Biologics & Small Molecules for IBD "Which One based on the scenario"
The 'Experienced patient'
Many insurances require anti-TNF first (FDA note: Tofa only after antiTNF)

Treatment history and other considerations

- **Loss of response to an anti-TNF (if anti-TNF was first):**
  - Secondary LOR (immunogenicity):
    - ***LOR to SQ*** - switch to IFX/UST/Tofa/Upa/Vedo
    - ***LOR to* IFX** – switch to Tofa/UPA (if is UC) or UST/Risa or Vedo (note: Failing weight based inflix in general I do not switch from IV to SQ anti-TNF)
  - Primary LOR (no antibodies, good levels): switch class to Tofa/UPA(UC) or UST/ Risa or Vedo

SUMMARY
Updates on Positioning IBD Therapies and Comparative Efficacy

Biologics & Small Molecules for IBD "Which One based on the scenario"
Naïve or experienced

Treatment history and other considerations

- Secondary to bowel inflammation (peripheral arthritis, iritis, EN): any that heal inflammation will tend to improve arthritis
- Pyoderma gangrenosum, Uveitis, Central Arthritis: anti-TNF/*MTX* (Ustekinumab/Risa? or Tofa/UPA?)

- **Pregnancy**
  - Any monoclonal Ab is ok, I treat straight through pregnancy
  - ***Stop*** MTX > 3 mos
  - We have very limited data on new small molecules (Tofa/Upa/Ozanimod)
  - If anticipating pregnancy in near future consider biologic rather than small molecule

SUMMARY
Updates on Positioning IBD Therapies and Comparative Efficacy

For most patients safety will be most critical

Comparative efficacy (we have limited data and probably should not compare trial results that are not head to head studies)

Assess for other specific factors

- Comorbid conditions
- Treatment history
- Disease burden (fixed dose SQ may not be ideal for severe disease)
  - High CRP and Low albumin predict rapid biologic clearance – consider small molecules vs well optimized biologic

Then of course insurance authorization

For the majority of patients and medications we have no good predictors of response/remission regardless of MOA. So treat early and assess for endoscopic remission

IBDH
EDUCATION

Thank You