GI ReConnect

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Napa Valley, California

GI Health Foundation

GI ReConnect

Current Treatment Algorithms & Management of Comorbidities

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Faculty Disclosures

Anita Afzali, MD

- Consultant/Advisor/Speakers Bureau: Abbvie, Janssen, Takeda, Pfizer, Bristol Myers Squibb
- Consultant: Lilly, Gilead, DiaSorin, Arena Pharmaceuticals, TLL Pharma
- Founder, Board Member: IBD Horizons

Learning Objectives

- Identify key factors to consider when treating IBD in a diverse population
- Summarize clinical features of IBD associated with high versus low risks of progression
- Discuss practical treatment algorithm considerations for management of disease and comorbidities

Approved Biologics and Small Molecule Agents

- **Tumor Necrosis Factor antagonists**
  - Infliximab: CD and UC
  - Adalimumab: CD and UC
  - Certolizumab: CD
  - Golimumab: UC
- **Integrin antagonists**
  - Natalizumab: CD
  - Vedolizumab: CD and UC
- **Interleukin 12/23 antagonists**
  - Ustekinumab: CD and UC
- **Small molecule:**
  - Tofacitinib (JAK inhibitor): UC
  - Ozanimod (S1P1): UC (June 2021)
- **Immunomodulator**
  - Thiopurine
  - Methotrexate
- **Others**
  - Tacrolimus
  - Cyclosporine

How Do We Put Together the Puzzle of Therapy Selection?

DRUG

Efficacy

Indication
Rapidity of onset
Durability
Pharmacokinetics/TDM
Combination vs. monotherapy
Positioning and sequence

Safety

Infection
Cancer
Specific concerns by agent or mechanism

PATIENT

Individual Characteristics

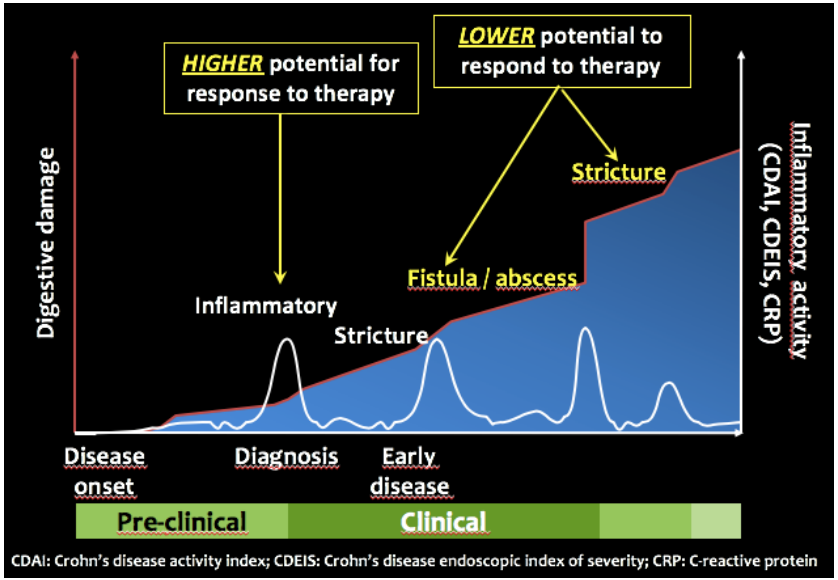
Age
Comorbidities
Preferences (IV/SQ/PO)
Insurance
Costs
Access to care

Disease Characteristics

CD vs. UC
Disease behavior/complication
Disease severity
Early vs. late
EIMs
Prior treatment success or failure

EIMs = extraintestinal manifestations; TDM = therapeutic drug monitoring

Defining Crohn's Disease ACTIVITY vs. SEVERITY



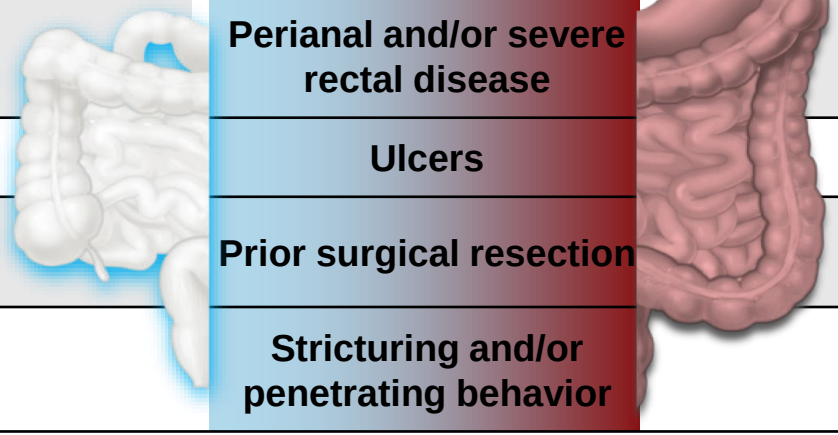
Successful monitoring strategies begin with appropriate treatment selection at diagnosis.

- **ACTIVITY** → inflammatory burden and impact at single point in time
  - **MONITOR** with clinical assessments, labs, colonoscopy, imaging
- **SEVERITY** → Cumulative impact of inflammatory burden over time
  - Risk stratification based on **likelihood of progression**
  - **Severity determines treatment strategy**

Pariente B et al. *Inflamm Bowel Dis*. 2010.

Treatment Selection for Crohn's Disease: Characterizing Risk

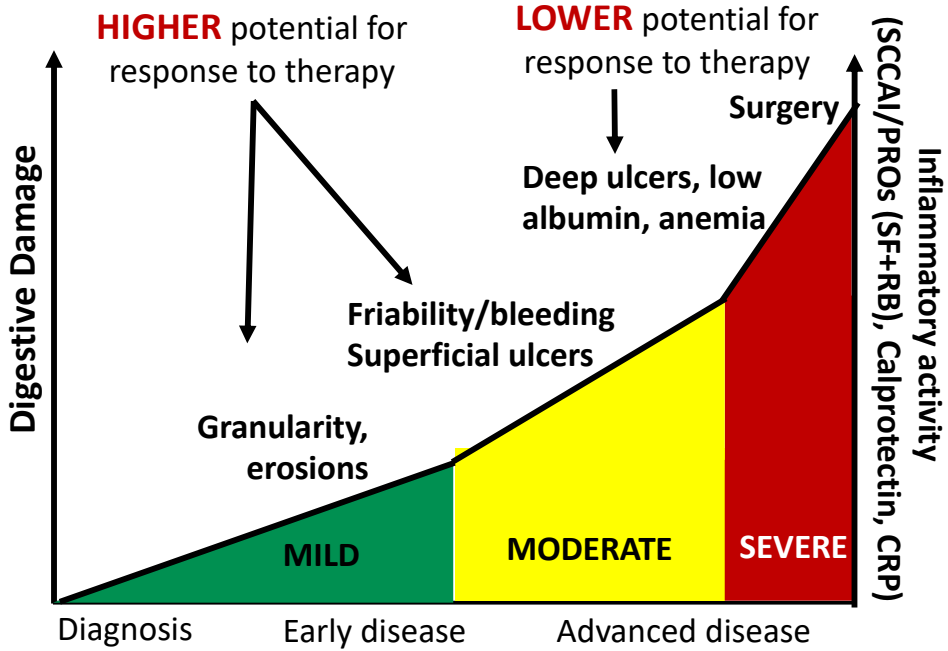
Low-Risk		High-Risk
>30 years	**Age at diagnosis**	**<30 years**
Limited	**Anatomic involvement**	**Extensive**
No	**Perianal and/or severe rectal disease**	**Yes**
Superficial	**Ulcers**	**Deep**
No	**Prior surgical resection**	**Yes**
No	**Stricturing and/or penetrating behavior**	**Yes**



ACG Clinical Guidelines: Management of Crohn's disease in adults. *Am J Gastroenterol*. 2018; 113: 481-517.

Defining UC Disease ACTIVITY vs. SEVERITY

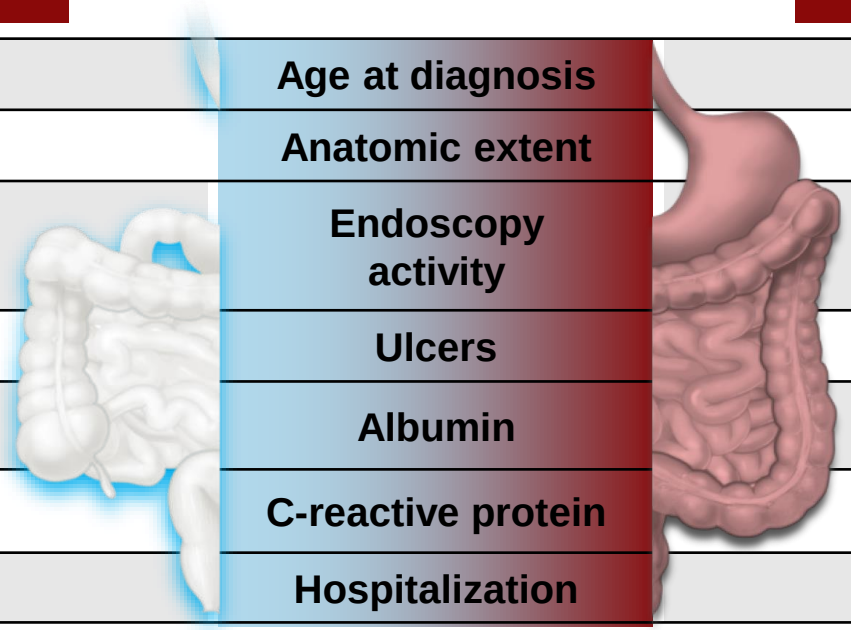
Successful monitoring strategies begin with appropriate treatment selection at diagnosis



SCCAI: Simple Colitis Clinical Activity Index; PROs: patient reported outcomes, CRP: C-reactive protein.

Treatment Selection for Ulcerative Colitis: Characterizing Risk

Low-Risk		High-Risk
>40 years	**Age at diagnosis**	**<40 years**
Proctitis	**Anatomic extent**	**Extensive**
Mayo 1	**Endoscopy activity**	**Mayo 3 UCEIS ≥ 7**
Superficial	**Ulcers**	**Deep**
Normal	**Albumin**	**Low**
Normal	**C-reactive protein**	**Elevated**
No	**Hospitalization**	**Yes**



ACG Clinical Guidelines: Ulcerative Colitis disease in adults. *Am J Gastroenterol*. 2019; 114: 384-413.

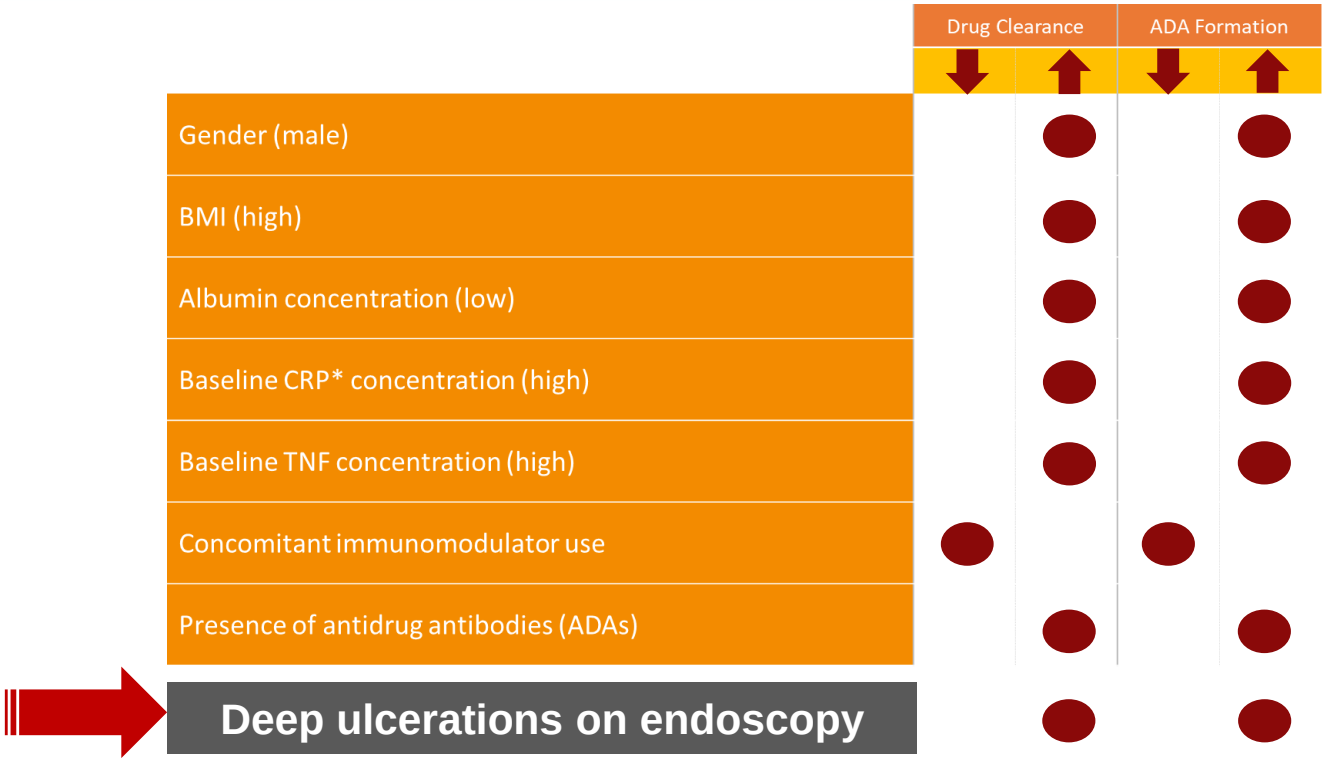
Treatment Algorithms Based:
Early Appropriate Therapy and Proactive Disease Monitoring

- Early *appropriate* therapy based on *aggressive* disease factors
- Define timeframe for response to initial or change in treatment
- Objective proactive evaluation should be performed to confirm subjective improvement
- Continued symptoms → Diagnostic evaluation, Dose adjustment or Change in therapy

Communicate Goals of Treatment with the Patient and Care Team

ACG Clinical Guidelines: Ulcerative Colitis disease in adults. *Am J Gastroenterol*. 2019; 114: 384-413;
ACG Clinical Guidelines: Management of Crohn's disease in adults. *Am J Gastroenterol*. 2018; 113: 481-517.

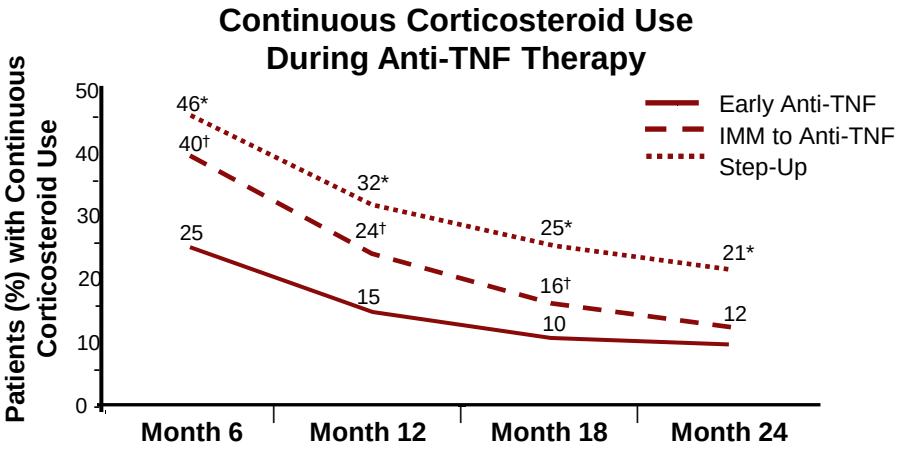
Factors Impacting Pharmacokinetics (pK)

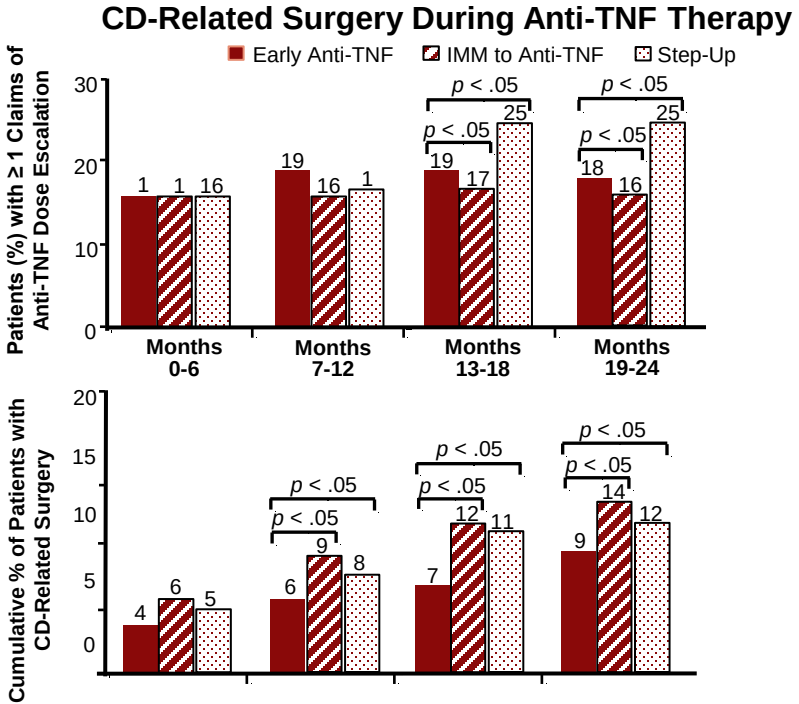


Adapted from Ordas I et al. *Clin Pharmacol Ther*. 2012.

Earlier Use of Anti-TNF Biologic Therapy in CD Results in Better Outcomes

- Claims data assessment
- > 3,700 patients; all received anti-TNF at some point

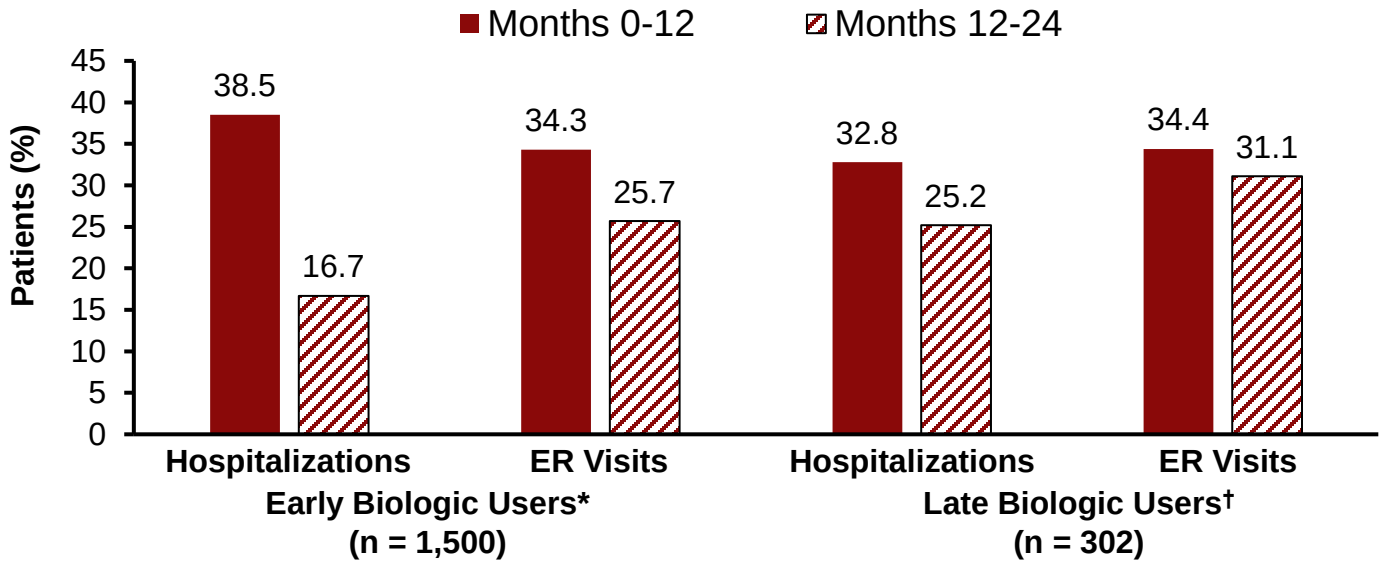




IMM = immunomodulator
*$p < .05$ for early anti-TNF groups vs. other groups
†$p < .05$ for IS to anti-TNF group vs. other groups
Rubin DT et al. *Inflamm Bowel Dis*. 2012; 18(12): 2225-2231.

Effects of Early Biologic Initiation on ER Visits and Hospitalizations

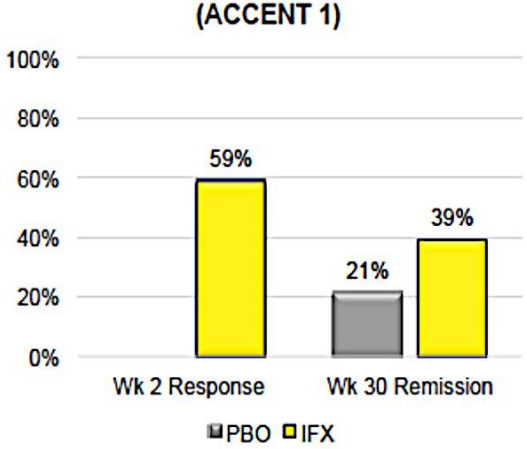
Retrospective Observational Cohort Study of Medical and Pharmacy Claims in Patients with Moderate-Severe CD



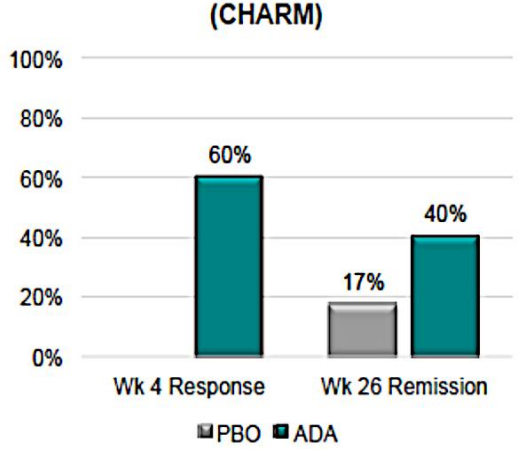
*≥ 1 biologic claim ≤ 12 months post CD diagnosis; †≥ 1 biologic claim 12-24 months post CD diagnosis;
Ungaro RC et al. *Gastroenterology.* 2020; 158(6): S-725.

Overall Similar Remission Rates:
TNF Antagonists

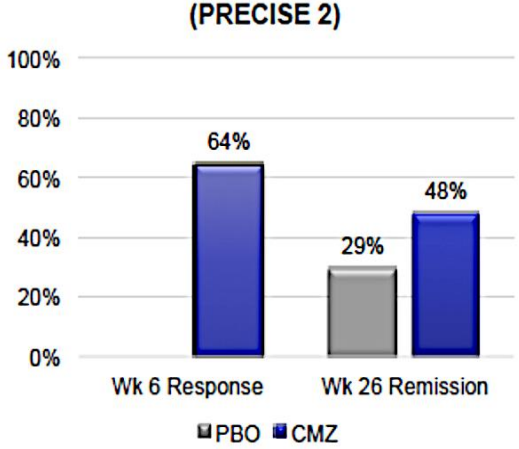
Infliximab Maintenance



Adalimumab Maintenance



Certolizumab Maintenance

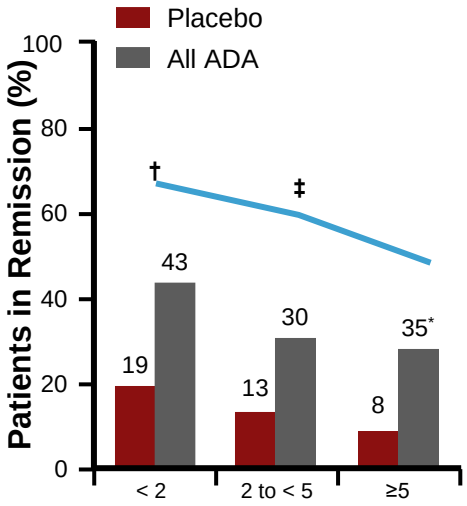


- ACCENT I, CHARM and PRECISE 2 have similar overall response and remission rates when including all enrolled patients

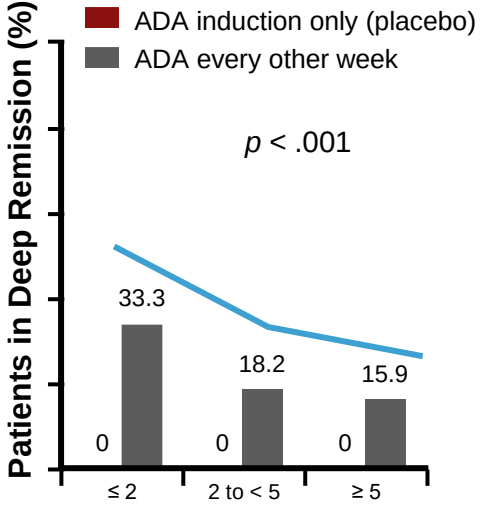
Hanauer SB et al. *Lancet.* 2002; Colombel JF et al. *Gastro*. 2007; Schreiber S et al. *N Engl J Med.* 2007.

Post-Hoc Sub-Analyses of Disease Duration on Rates of Remission in CD: Early Appropriate Therapy

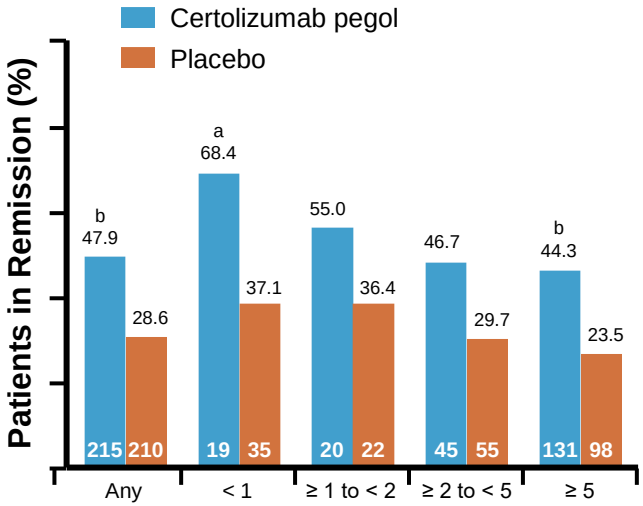
CHARM Week 56[1]
Patients in Remission



EXTEND Week 52[2]
Patients in Deep Remission



PRECISE 2 Week 26[3]
Patients in Remission

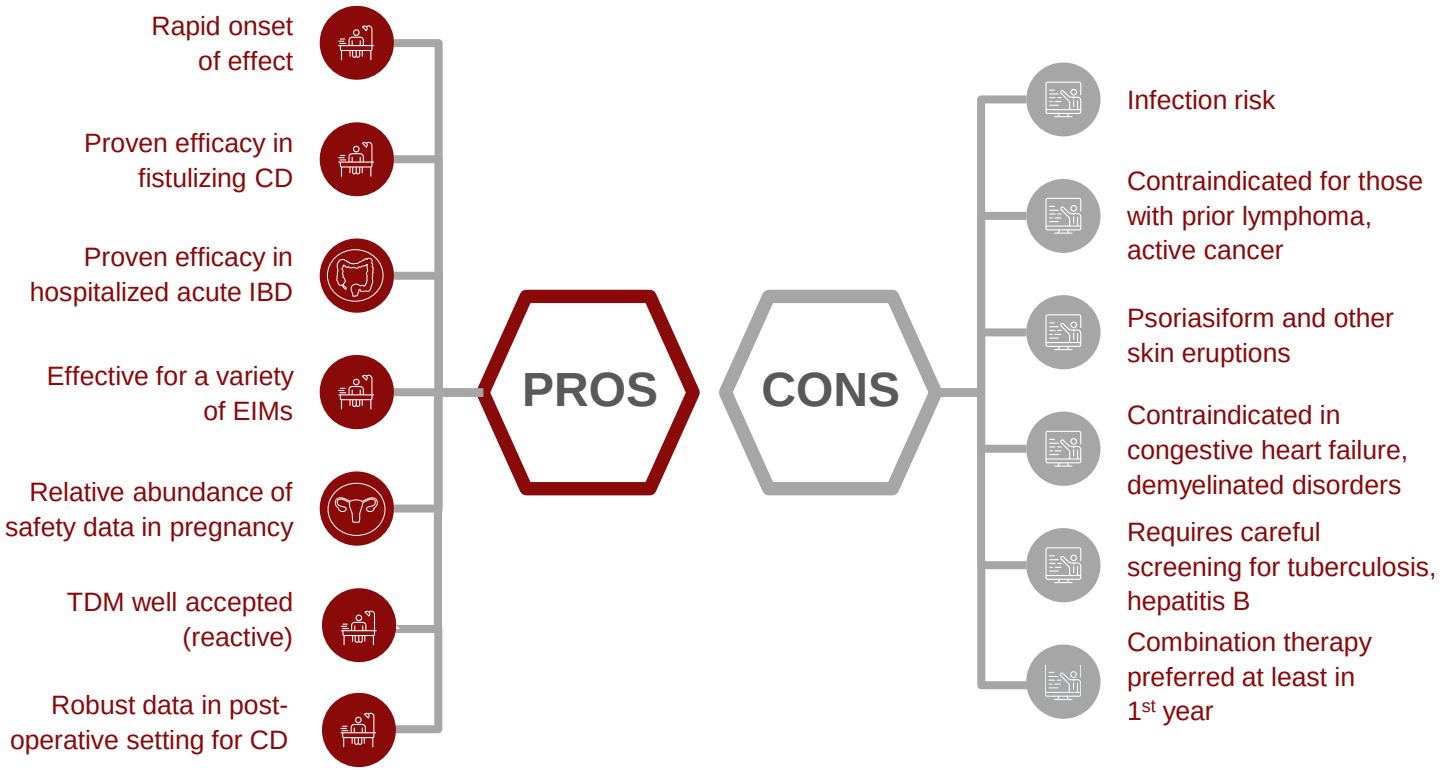


Time Since Disease Diagnosis (Years)

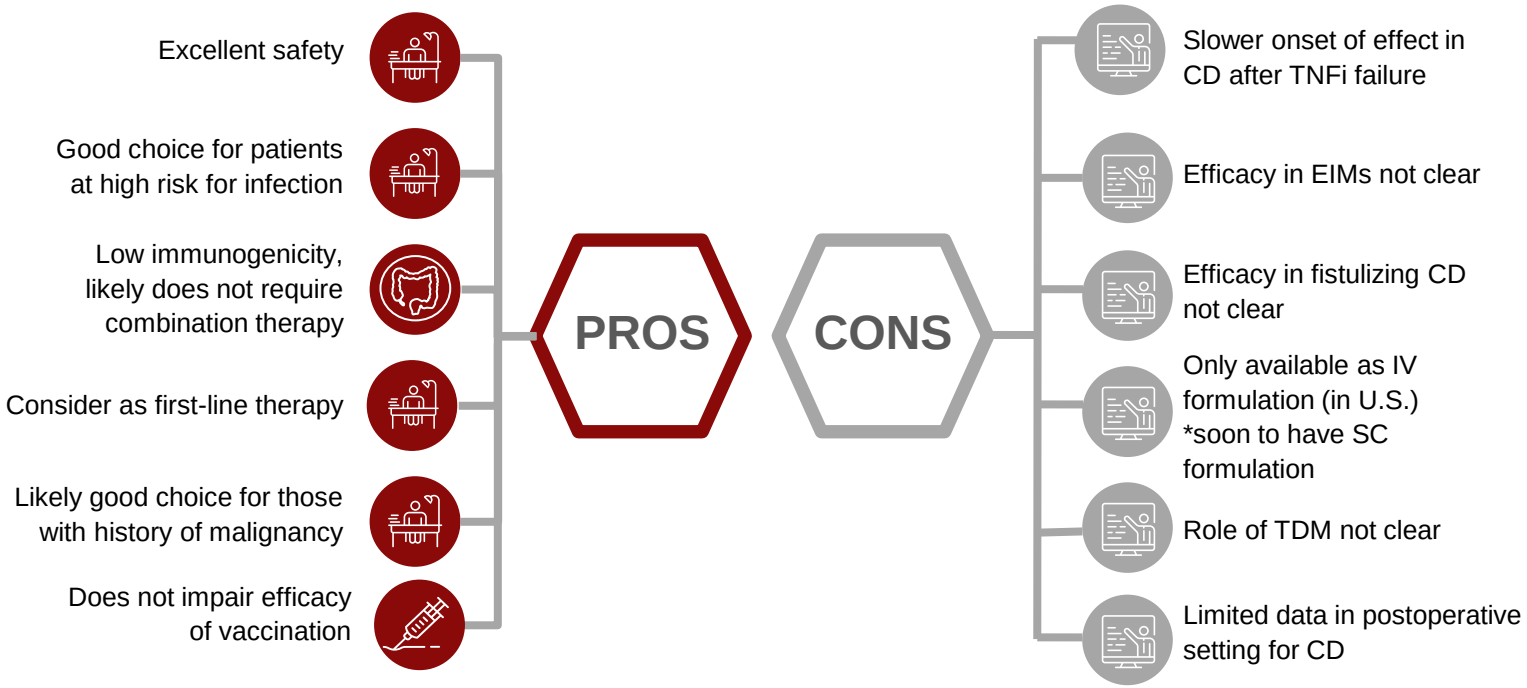
*p < .001; †p = .024; ‡p = .028 vs. placebo ; ap < .05; bp < .001 vs. Placebo
ADA = adalimumab

1. Schreiber S et al. *J Crohns Colitis.* 2013; 7: 213-221; 2. Colombel JF et al. *Gut.* 2010; 59 (Suppl 3): A80. Abstract OP371;
3. Schreiber S et al. *Aliment Pharmacol Ther*. 2011; 33: 185-193.

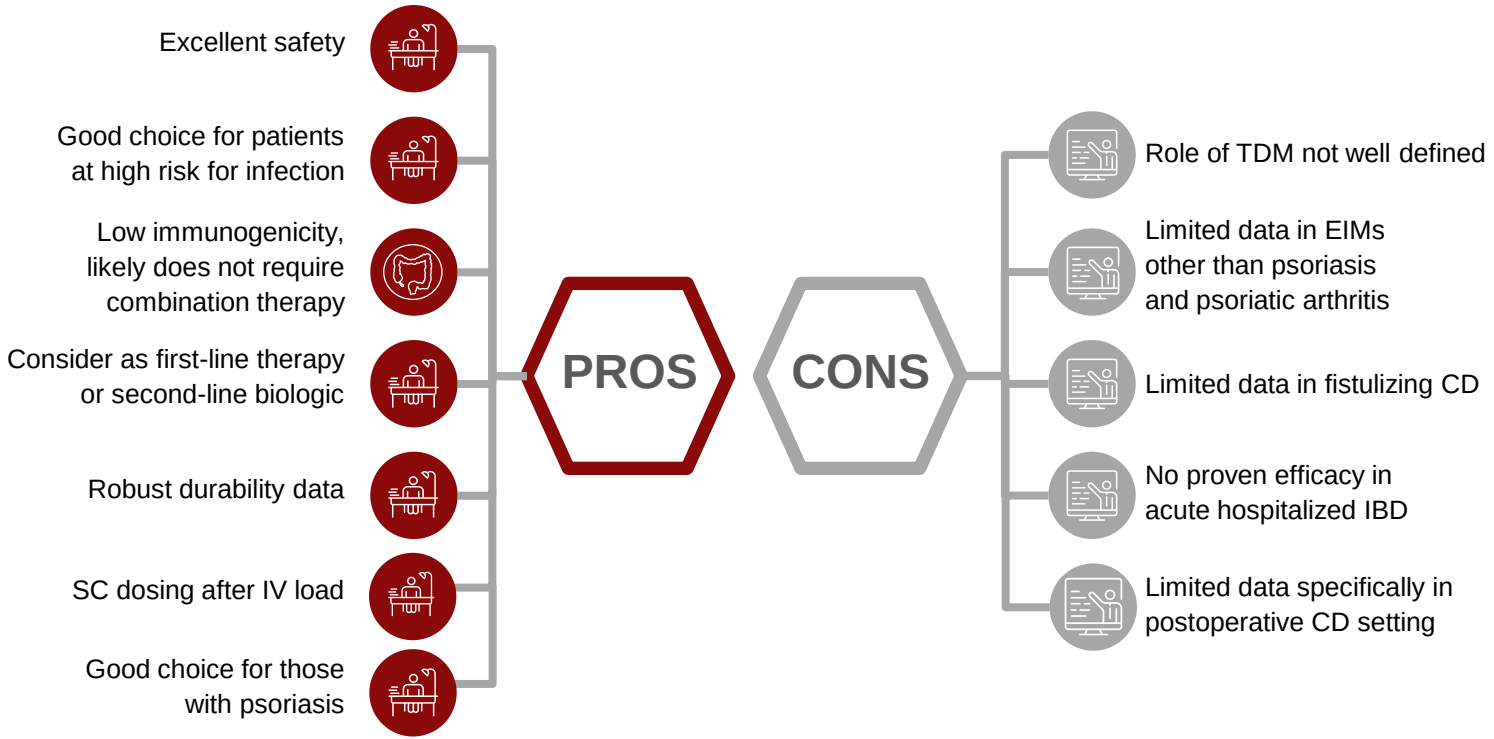
TNF Inhibitors
Considerations



Vedolizumab
Considerations



Ustekinumab
Considerations



Anti-TNF Therapy: Overall Safety, Efficacy

- Dose and duration related adverse effects
  - Psoriasiform rash
    - 50% chance of recurrence with 2nd anti-TNF
    - 50% chance can treat through
  - Sensitization reactions
    - If + ADA, can use 2nd or 3rd agent but decreasing efficacy, increased risk ADA
    - Switch to out of class
- Relative contraindications:
  - Opportunistic infections (TB, histo, etc..)
  - Heart Failure NY class III or IV
  - Demyelinating disease

Afzali A. et al. *J Crohns Colitis*. 2014; 8: 480-488; Tiderington E, Afzali A. *JCOM*. 2018; 5: 219-228.

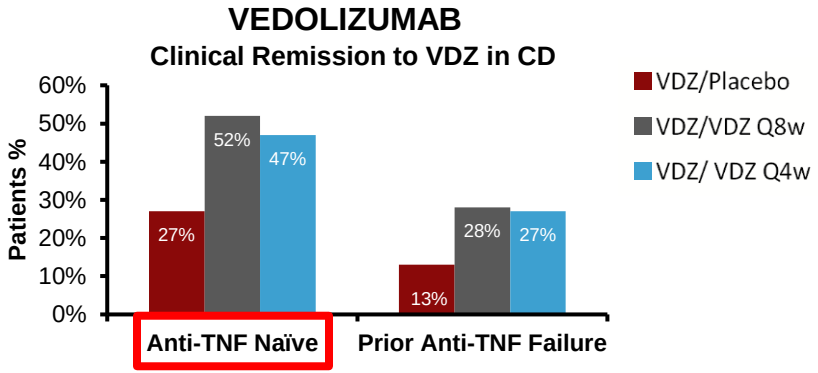
Anti-TNF Therapy

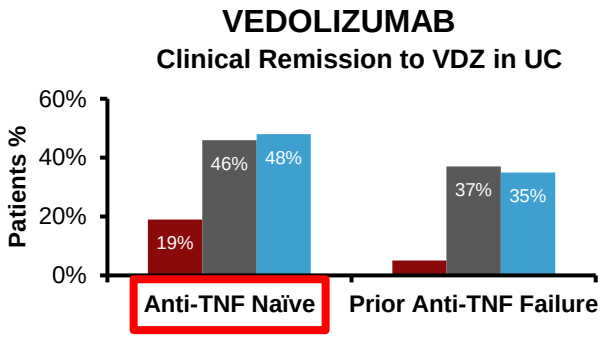
- 30-40% will fail to have initial response to anti-TNF therapy = Primary Non-Responder (PNR)
  - PNR are ~25% less likely to achieve remission with 2nd biologic (non-TNF)
- ~50% may develop loss of response in first year of therapy = Secondary Loss of Response

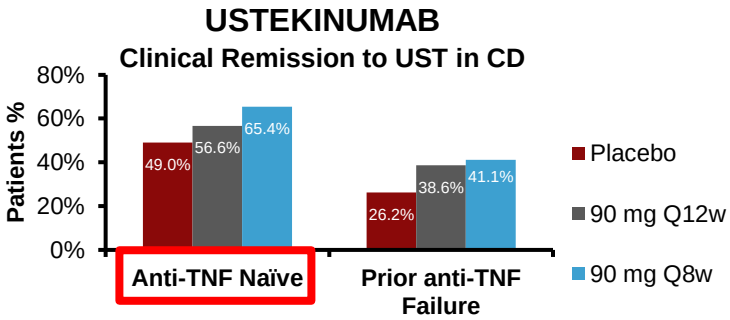
The TNF naïve patient vs the TNF exposed patient is different

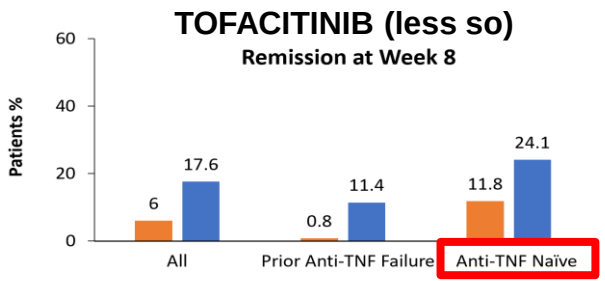
Fausel R, Afzali A. *Ther Clin Risk Man*. 2015 11: 63-73; Singh S et al. *J Crohns Colitis*. 2018; 12: 635-643.

Anti-TNF Naïve Patients Do Better With Other MOAs









Sandborn WJ et al. *N Engl J Med*. 2013; 369: 711-721; Feagan BG et al. *N Engl J Med*. 2013; 369: 699-710;
Sandborn W et al. *Gastroenterology*. 2016; 150(4 Suppl 1): S157-S158; Data on file. Pfizer Inc, New York, NY.

Proposed Treatment Algorithm:
LOW-RISK Moderate to Severe Disease

Low Risk

- Diagnosed > 30 yrs
- Limited anatomic involvement
- No perianal or severe rectal dz
- Superficial ulcers or erosions
- No prior surgical resection
- No stricturing or penetrating behavior
- Normal albumin
- Normal C-reactive protein

→

- Vedolizumab
- Anti-TNFs (injections or infusions)* ± IMM
  - Bio-naïve UC → infusion >> injections
- Ustekinumab

- Monitor response to induction by week 12
- Vedolizumab ***LESS EFFECTIVE AFTER*** anti-TNF
- Injectable anti-TNFs ***LESS EFFECTIVE*** after IFX
- Proactive monitoring may not be warranted
- ***REACTIVE MONITORING*** if Sx during maintenance
- Discontinue 5-ASAs

AGA Guidelines Moderate to severe CD. *Gastroenterology*. 2021 (preprint);
AGA Guidelines Moderate to severe UC. *Gastroenterology*. 2020; 158: 1450-61.

Proposed Treatment Algorithm:
HIGH-RISK Moderate to Severe Disease

High Risk

- Diagnosed < 30 yrs
- Extensive anatomic involvement
- Perianal or severe rectal dz
- Deep ulcers
- Prior surgical resection
- Stricturing or penetrating dz
- Low albumin
- Elevated C-reactive protein
- Prior anti-TNF exposure

→

- Anti-TNFs (+ IMM), **INFUSION** >>> injections
- Ustekinumab
- Tofacitinib
- Cyclosporine

} Crohn's Disease

} Ulcerative Colitis

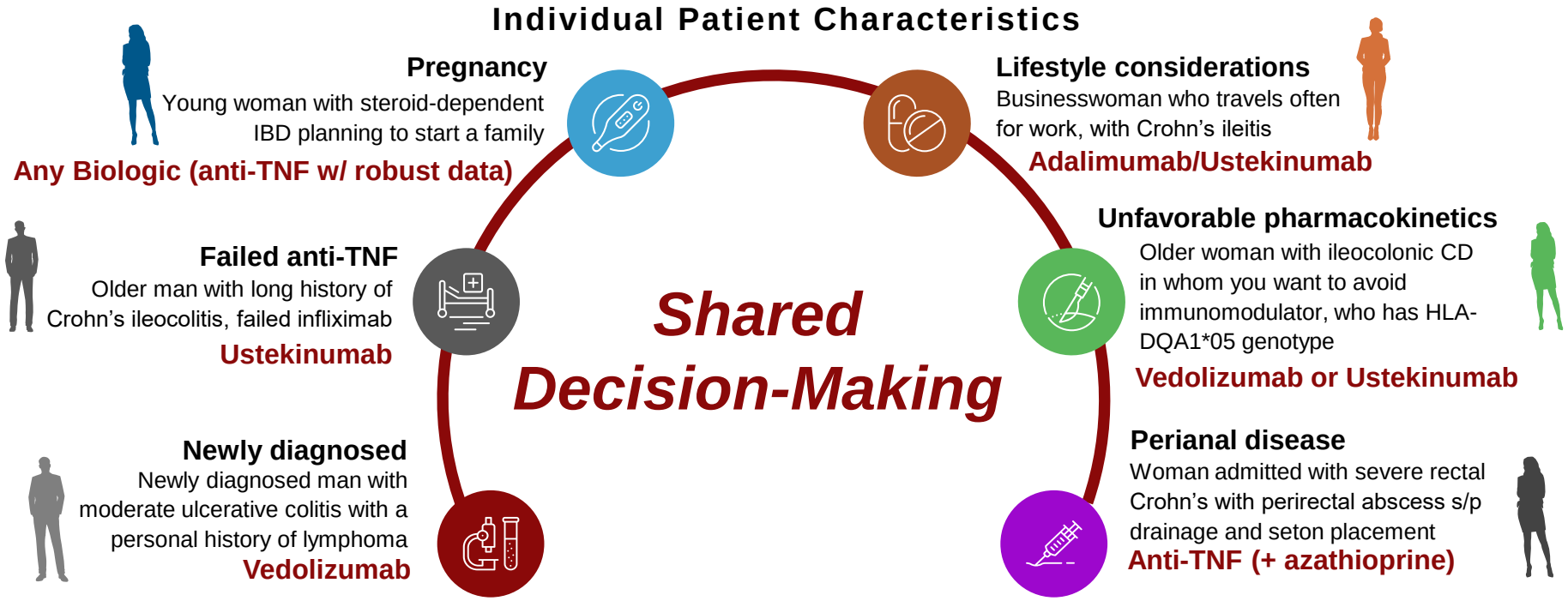
- Monitor response to induction by week 12
- ***PROACTIVE MONITORING*** for immunogenicity/ therapeutic levels (anti-TNF)
  - Post induction TDM for IFX
  - Aim for higher levels
- Earlier potential dose escalation (anti-TNF)
- Potential reinduction dosing (UST)
- Extending to 16-week induction (TOFA)
- ? Combo therapy w/dual biologics, biologics + Jakinhibs

AGA Guidelines Moderate to severe CD. Gastroenterology. 2021 (preprint);
AGA Guidelines Moderate to severe UC. Gastroenterology. 2020;158:1450-61.

Suggested *First* IBD Therapy Consideration

Disease	Modifier	First Drug	Reason
IBD	Psoriasis	Ustekinumab	On label
IBD	WoCBA, Pregnancy	Certolizumab pegol *Any biologic agent	CTZ No placental transfer
IBD	• Older age (>60yrs) • Prior hx of malignancy	Vedolizumab Ustekinumab	• Older pts higher risk of infections • Less associated risk of malignancy
UC	Synovitis Arthritis	TNF antagonists Tofacitinib	On label
UC	Low albumin	Cyclosporine Tofacitinib	Small molecules Absorption

Biologic Choice in the Absence of Head-to-Head Data



Treatment Considerations in Your IBD Patient
(Assume insurance not an issue)

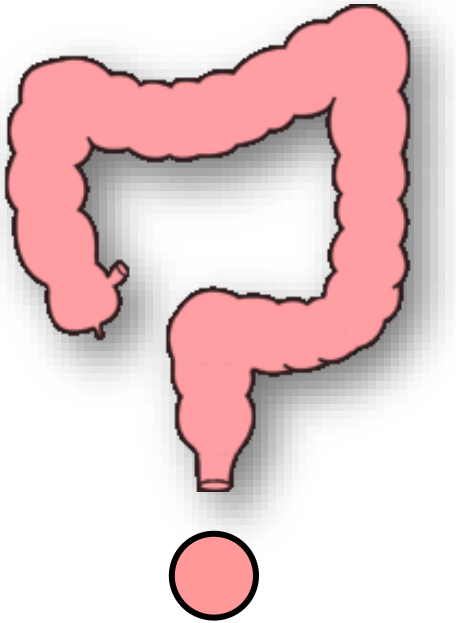
- If choosing based on **safety**:
  - VDZ and UST best safety (age, prior malignancy, infection risk, etc.)
  - Anti-TNF and JAK associated with higher risk of infections
  - Anti-TNF relative contraindication in CHF, MS, endemic areas of opportunistic infections
  - CTZ no placental transfer
  - Tofa associated with VTE/PE (RA patients)
- If based on **efficacy**:
  - Difficult to determine which is ‘superior’ – more head-to-head studies
- If choosing on ‘**convenience**’:
  - Some will prefer infusion to injection
  - Many likely to prefer oral formulation
- If choosing based on **sensitization (non-adherence)**:
  - Tofa not associated with sensitization
  - UST has lowest (to date) immunogenicity

Current Treatment Algorithms & Management of Comorbidities

- Start the early appropriate therapy based on risk stratification
- Avoid recurrent courses of steroids before starting steroid-sparing strategy (ask - steroids bridge to what)
- Assess factors which influence pharmacokinetics of biologic agents
- Consider potential need for escalated treatment regimens
- Always think ahead → which agents can also work “2nd line”
- Agent selection must factor both Drug and Individual Patient factors
- Treat to target strategy recommended with defined timeframe for response to treatment (up next)

GI ReConnect

Thank You



IBD_Afzali

The Ohio State University
Wexner Medical Center