GI ReConnect

June 17-19, 2021

Napa Valley, California

GI Health Foundation

GI ReConnect

Relevance of Real-World Data in IBD

Millie D. Long MD, MPH
Associate Professor of Medicine
Vice-Chief for Education
Director, Gastroenterology
and Hepatology Fellowship Program
Inflammatory Bowel Diseases Center
University of North Carolina-Chapel Hill

Disclaimer

All faculty and staff involved in the planning or presentation of continuing education activities provided by the University of Cincinnati are required to disclose to the audience any real or apparent commercial financial affiliations related to the content of the presentation or enduring material. Full disclosure of all commercial relationships must be made in writing to the audience prior to the activity.

All additional planning committee members, the University of Cincinnati staff and the Gi Health Foundation staff have no relationships to disclose.

Faculty Disclosure

Millie D. Long MD, MPH

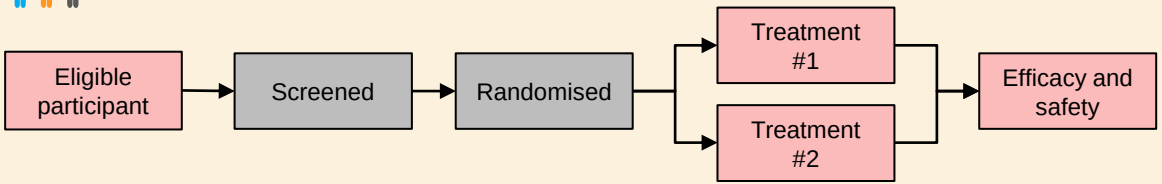
- Consultant: Abbvie, Takeda, Pfizer, Janssen, BMS, Lilly, Theravance, Target Pharmasolutions, Salix, Calibr
- Research Support: Pfizer, Takeda

Outline: Real World Data in IBD

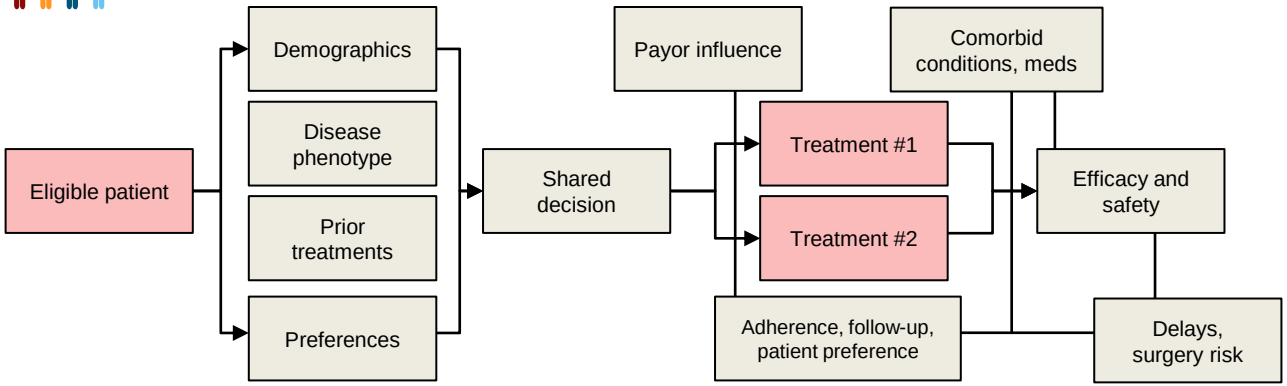
- Definitions
- Biologics in the real world
  - Effectiveness
  - Safety
  - Optimization (combination therapy)
  - Withdrawal of therapy
- Small molecules in the real world
  - Effectiveness
  - Safety
- Putting it all together for your clinical practice

What Is Real World Data?

Randomized controlled trial: population is screened for eligibility, randomly assigned to alternative interventions and observed for outcomes of interest[1]



Observational study: population is assigned to alternative interventions based on patient/provider factors and local guidelines, and observed for outcomes of interest



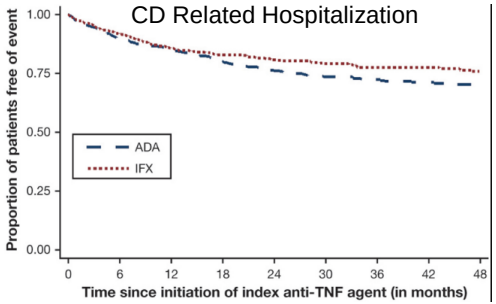
Armstrong K et al. *J Clin Oncol.* 2012;30:4208-14.

What Is Real World Data Best For?

- Identify *exposures* or risk factors that increase or decrease the risk of a disease (incidence)
- Study *natural history* of disease
  - Factors that increase the risk of a disease can be very different than those that affect prognosis
- Investigate the *effect of a treatment on a disease or condition*
  - Particularly useful when studying something where patients would not want to participate in a RCT
  - May be susceptible to **confounding or selection bias**
- Understanding *safety associated with a therapy* (need very large numbers to assess rare complications)
  - Some complications are only recognized after decades of use

Biologics: Selecting Anti-TNF Therapy in Crohn's Disease

- Nationwide cohort in Denmark of 2908 biologic naïve patients with CD between 2005-2014: IFX and ADA comparable over median 2.3 yrs
  - CD related hospitalization HR 0.81 (0.55-1.20)
  - Major surgery HR 1.24 (0.66-2.33)
  - Serious infections HR 1.06 (0.26-4.21)
- US claims study of 3205 new anti-TNF users (IFX, ADA, CZP) with CD 2006-2014
  - IFX with lower CD related hospitalization than ADA (HR 0.80)
  - IFX with lower abdominal surgery than ADA (HR 0.76)
  - IFX with lower steroid use than ADA (HR 0.85)
  - IFX also better than CZP for all outcomes
  - Comparable serious infections in all groups



Singh S et al. *Aliment Pharmacol Ther.* 2018 Mar; 47 (5): 596-604; Singh S et al. *Clin Gastroenterol Hepatol.* 2016 Aug; 14 (8):1120-1129.

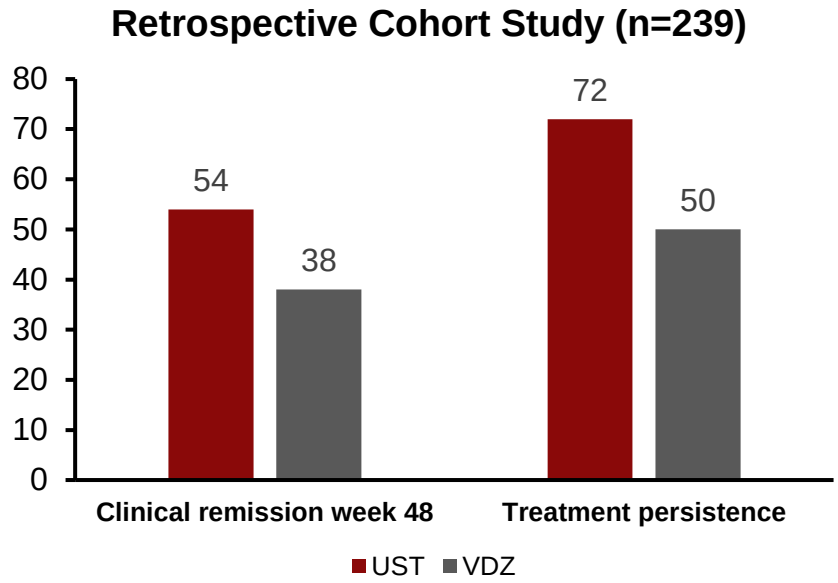
Biologics: Selecting Anti-TNF vs. Anti-Integrin in Crohn's Disease

- VICTORY consortium retrospective cohort study VDZ vs. anti-TNF in CD (n=538)
  - Similar rates of clinical remission 38% vs. 34% HR 1.27 (0.91-1.78)
  - Similar rates of steroid free remission 26% vs 18% HR 1.75 (0.90-3.43)
  - VDZ with improved rates of remission in colonic vs. ileal disease (HR 1.51)
- VICTORY consortium initial 212 patients with CD on VDZ
  - Clinical remission at 12 months 35%
  - Prior TNF exposure (HR 0.40), smoking history (HR 0.47), perianal disease (HR 0.49), severe disease (HR 0.54) were less likely to achieve clinical remission
- Retrospective cohort study of anti-TNF vs. VDZ in IBD, age ≥ 60 yrs; 131 anti-TNF and 103 VDZ, 50% with CD
  - Infections at one year similar, 20% with anti-TNF and 17% VDZ (p=0.54)
  - Similar efficacy of both classes at 6 and 12 months in CD

Bohm M et al. *(OP025 J Crohns Colitis, 12 (Suppl. 1).* 2018; Dulai PS et al. *Am J Gastroenterol.* 2016 Aug; 111 (8): 1147-55; Adar T et al. *Aliment Pharmacol Ther.* 2019 Apr; 49 (7): 873-879.

Biologics: Comparing VDZ and UST Post Anti-TNF in Crohn's Disease

- Retrospective cohort of 239 patients with CD refractory or intolerant to TNF
  - 107 UST and 132 VDZ
- Clinical remission rate at week 48:
  - 54% UST vs. 38% VDZ
  - OR 1.92 (95% CI 1.1-3.4)
- Subgroups with UST superiority in ileal inflammation and penetrating behavior



Alric H et al. *APT.* 2020 May; 51(10):948-957.

Biologics: Anti-TNF Safety in Crohn's Disease

- TREAT registry: prospective registry of 6273 patients with CD, 3420 on IFX and 2853 comparator population, over 5 years of follow up
  - IFX patients with more severe disease, higher rates of prior surgery, hospitalization, prednisone, narcotics use
  - Mortality similar for IFX and other treatments (0.58 vs 0.59/100 p-y)
  - Increased mortality linked to prednisone (HR 2.1), narcotics (HR 1.79) and age (HR 1.08)

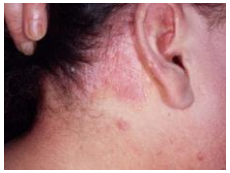
- PYRAMID registry: prospective registry of 5025 patients with CD, followed for 6 yrs
  - Lymphoma rate lower than background rate; ruled out a doubling of lymphoma with ADA
  - Total of 556 serious infections (11.1%, 4.7 E/ 100 PY)

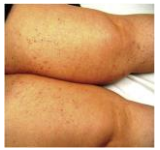
- Population based study in Denmark of 52,392 patient with IBD, of whom 4300 were treated with anti-TNF
  - HR 1.63 for serious infection in the first 90 days of therapy
  - Subsequent decline in infection risk

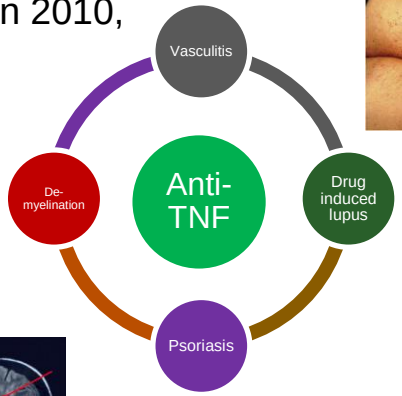
Lichtenstein GR et al. *Am J Gastroenterol.* 2012 Sep; 107 (9):1409-22; D'Haens G et al. *Am J Gastroenterol.* 2018 Jun; 113 (6):872-882; Anderson NN et al. *BMJ.* 2015; 350: h2809.

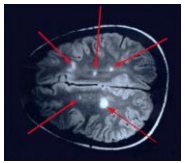
Biologics: Anti-TNF Safety in IBD – Complications Recognized in Long-Term

- Paradoxical inflammation associated with biologics
  - Not seen/recognized in clinical trials or in initial phase 4 registries
  - Observational data show association b/t anti-TNF and paradoxical reactions
  - Infliximab approved in 1999, first reports of paradoxical psoriasis in 2010, now recognized to occur in 5-10% of anti-TNF treated patients
- Paradoxical reactions reported with anti-TNF
  - Unclear why this was recognized later in treatment course
  - Not associated with anti-TNF level
  - Not associated with cumulative dosing
  - Often requires discontinuation of anti-TNF therapy
  - Can recur with treatment in the same class





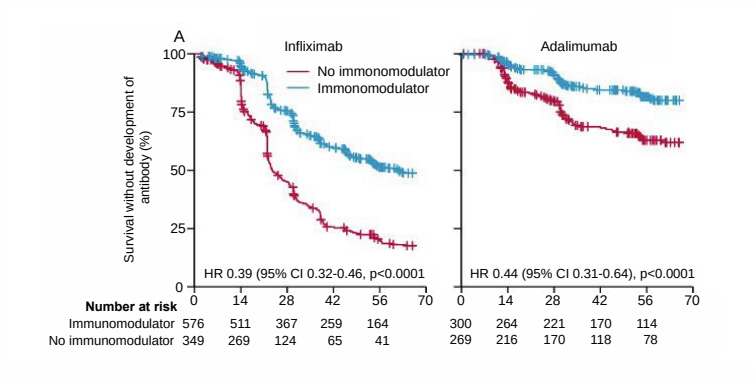


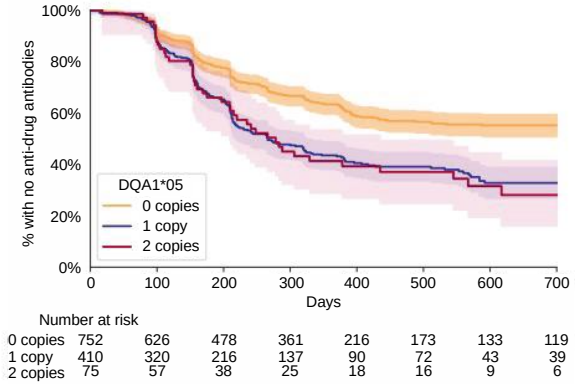


Cleynen I, Vermeire S. *Nat Rev Gastroenterol Hepatol.* 2012;9:496-503; Fiorino G, Danese S et al. *Autoimmun Rev.* 2014;13:15-9.

Biologics: Effectiveness of Combination vs. Monotherapy

- PANTS prospective cohort of anti-TNF naïve patients age ≥6 yrs
- 955 on IFX and 655 on ADA:
  - Primary non-response to anti-TNF 23%, non remission in 63%
  - Optimal week 14 levels: 7 mg/dL IFX, 12 mg/dL ADA, associated with remission
  - HLA-DQA105 allele associated with development of immunogenicity

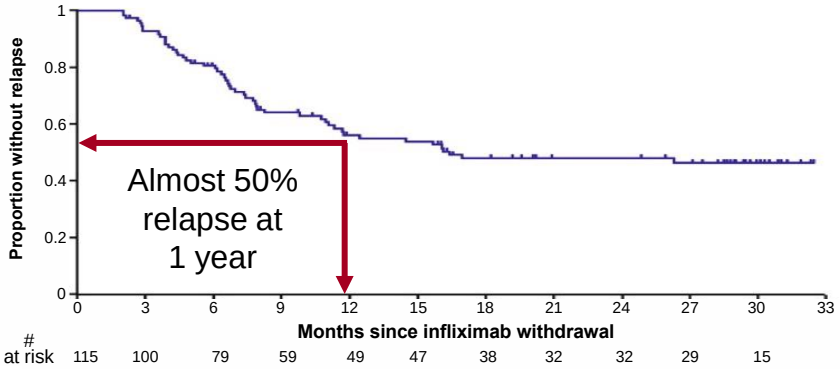




Kennedy NA et al. *Lance*t 4. 2019; 341-353; Sazonovs A et al. *Gastro.* 2020 Jan; 158 (1):189-199.

Biologics: Stopping Therapy With Anti-TNF

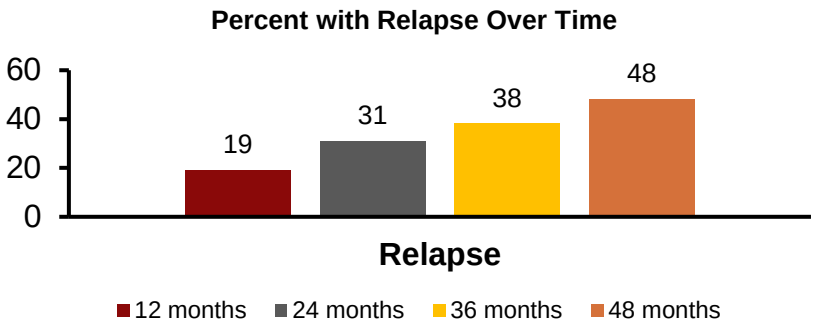
- STORI: 115 patients on IFX + immunomodulator for >1 year, clinical remission and steroid free for 6 months
- IFX withdrawn and median 28 months follow up
- Factors associated with time to relapse: male, Hgb <14.5, Leukocytes >6, CRP >5, calpro > 300, no prior resection

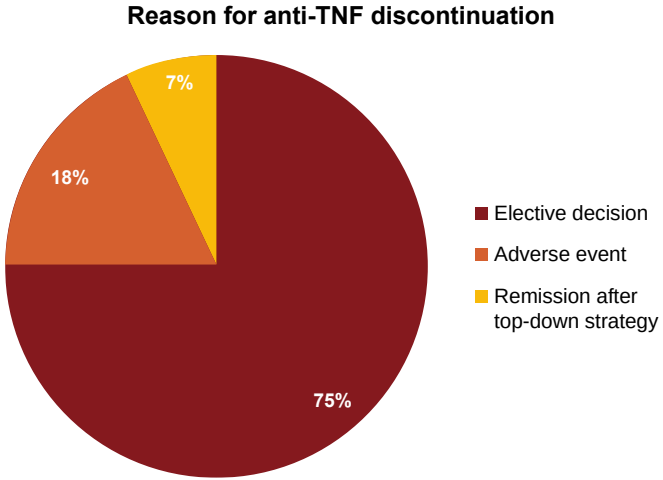


Louis et al. *Gastro.* 2012.

Biologics: Stopping Therapy With Anti-TNF

- EVODIS: Retrospective multicenter Spanish cohort of n=1055 IBD patients in clinical remission, longitudinal follow up after d/c of anti-TNF
- Majority (71%) remained on immunomodulator
- Relapse rate of 12% per py median time to relapse of 17 months
- Factors protective of relapse: IMM use and age
- 60% retreated with same anti-TNF after relapse
  - 73% regained remission (29% of these relapsed)
  - 16% with AEs, mostly mild (most frequently infusion reactions)

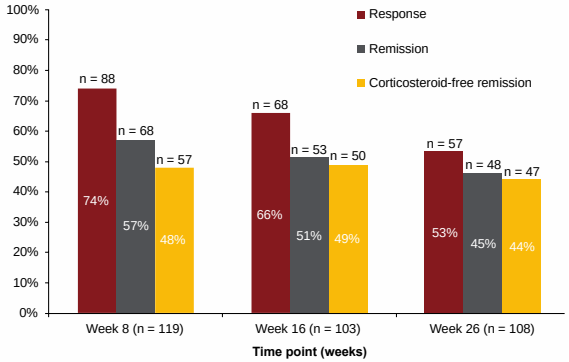


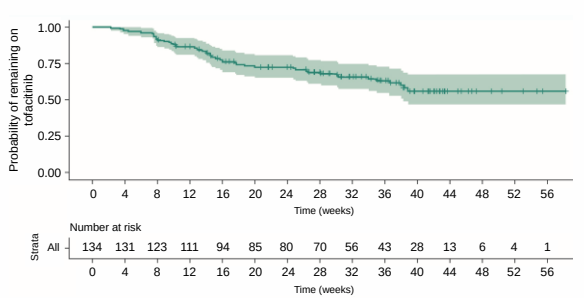


Casanova MJ et al. *UEG.* 2020. OP119.

Small Molecules: Effectiveness From Real World Data

- Real world retrospective multicenter UK study of 134 patients w/ UC on TOFA
- 74% responded week 8, steroid free remission in 44% at week 26
- Factors associated with primary non response: younger age, higher CRP, no effect by prior biologic exposure
- After dose reduction, 32% of patients had a recurrence (median 41 days)
  - 47% of these recaptured response with dose escalation

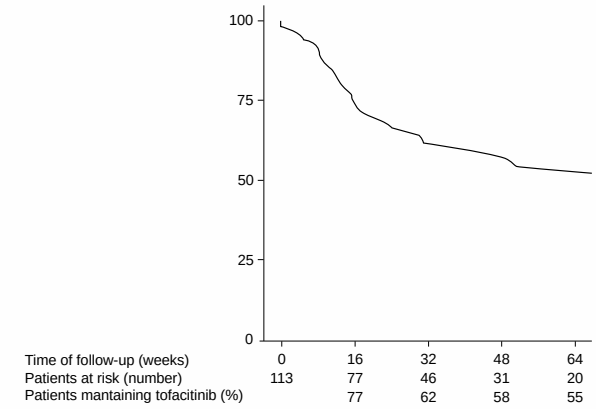


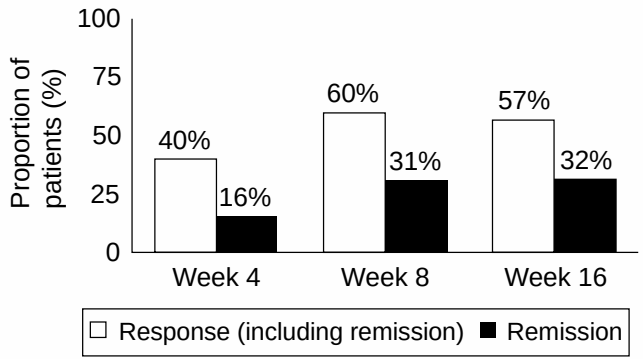


Honap S et al. *J Crohns Colitis*. 2020 Oct 5; 14 (10): 1385-1393.

Small Molecules: Effectiveness From Real World Data

- ENEIDA 113 patients treated with TOFA (median of 44 weeks), highly refractory cohort
- Response and remission at week 8 were 60% and 31%
- Higher partial mayo at week 4 associated with reduced likelihood of achieving remission
- Total of 45 (40%) discontinued TOFA over time
- Of those with remission at week 8, 65% relapsed after dose reduction

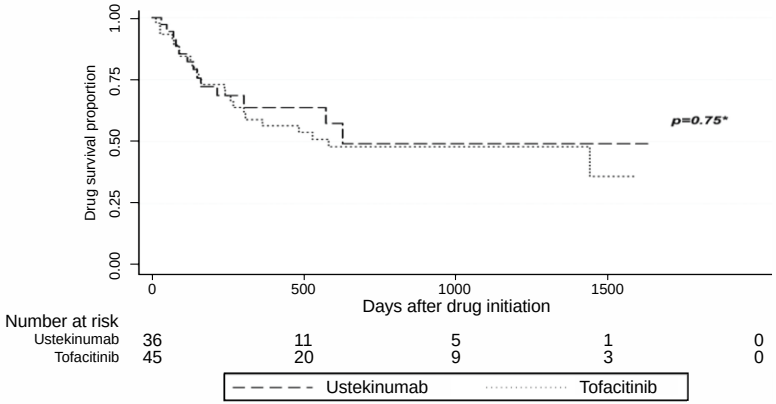




Chapparo M et al. *J Crohns Coltiis.* 2020 Sep 24 [epub].

Comparative Effectiveness: Tofacitinib vs. Ustekinumab in UC

- Single center retrospective study of patients with UC, prior failure of both anti-TNF and anti-integrin (n=45 tofacitinib, n=36 ustekinumab)
- Outcome: steroid free clinical remission at 12 to 16 weeks, SCCAI <=2, no prednisone
- Steroid free clinical remission
  - 44% tofacitinib
  - 40% ustekinumab
- Adverse events similar
  - 11% tofacitinib
  - 6% ustekinumab



Dalal RS et al. *Inflamm Bowel Dis.* 2021 May 14 [epub ahead of print].

Small Molecules: Safety From Real World Data

- ENEIDA: Overall 17 patients with adverse events (15%)
  - 4 high cholesterol
  - 1 HZ
  - 1 Herpes simplex
  - 3 infections (2 salmonella GI infections, anorectal abscess)
  - 1 neoplasia (metastatic breast cancer)
- UK Study
  - Worsening of UC in 11%
  - Alterations in lipid panels seen in 20%
  - No VTE/thromboembolic/CV events
  - 7 serious infections
  - 3 non disseminated HZ
- US comparative study
  - 1 DVT
  - 1 HZ

SAFETY:
Need large registries with ample follow up

Chapparo M et al. *J Crohns Coltiis*. 2020 Sep 24 [epub]; Verstockt B et al. *UEG.* 2020.

Summary: Some Tips From Real World Data for Your Practice

- Anti-TNF – when targeting effectiveness, use combination therapy
- Don’t stop an anti-TNF therapy, even if in deep remission
- Recognize that some complications can occur late (paradoxical reactions), lack of data ≠ safety data
- Emphasize the biggest risks for patients are steroids, narcotics and uncontrolled disease
- VDZ has excellent safety, not necessarily better than anti-TNF in older patients, as control of disease and use of steroids weighs heavily in infection risk
- When using TOFA in a refractory UC patient, think carefully about dose reduction for maintenance
- Need more head to head comparison studies in the post-anti TNF space; for UC TOFA and UST may be comparable, real world data may show benefit of UST > VDZ in subgroups of CD

UNC Multidisciplinary IBD Center