

10TH ANNUAL ***DIGESTIVE DISEASES: NEW ADVANCES***

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IBD: Difficult to Treat Populations

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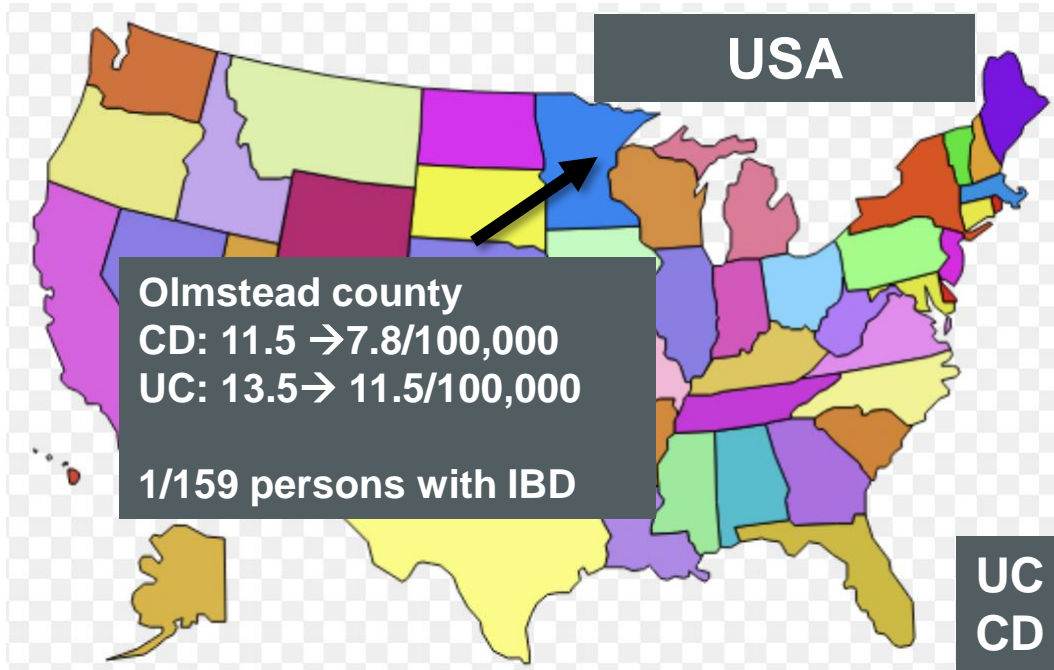
Outline

- Brief update
- Medication History
- Predicting severe disease
- Prior biologic failures
- Perianal disease
- Disease in pregnancy



IBD Brief Update

IBD: Changing Population Data



Increasing in Denmark, New Zealand, and Hungary

UC 1.2 million
CD 1.1 million

1. Lewis JD et al. Presented at DDW. May 2022. Abstract Sa1570;
2. Bakhshi Z et al. Presented at DDW. May 2022. Abstract 403;
3. Agarwal M et al. Presented at DDW. May 2022. Abstract Sa 1558;
4. Seleg S et al. Presented at DDW. May 2022. Abstract EP1295;
5. Lakatos L et al. Presented at DDW. May 2022. Abstract Sa1574/1575

Risk and Protective Factors for IBD

Risk factors

- Mebendazole (< 5 yo)¹
- Asthma + allergic rhinitis²
- Antibiotic exposure³
- EBV infection⁴
- Abuse as a child⁵

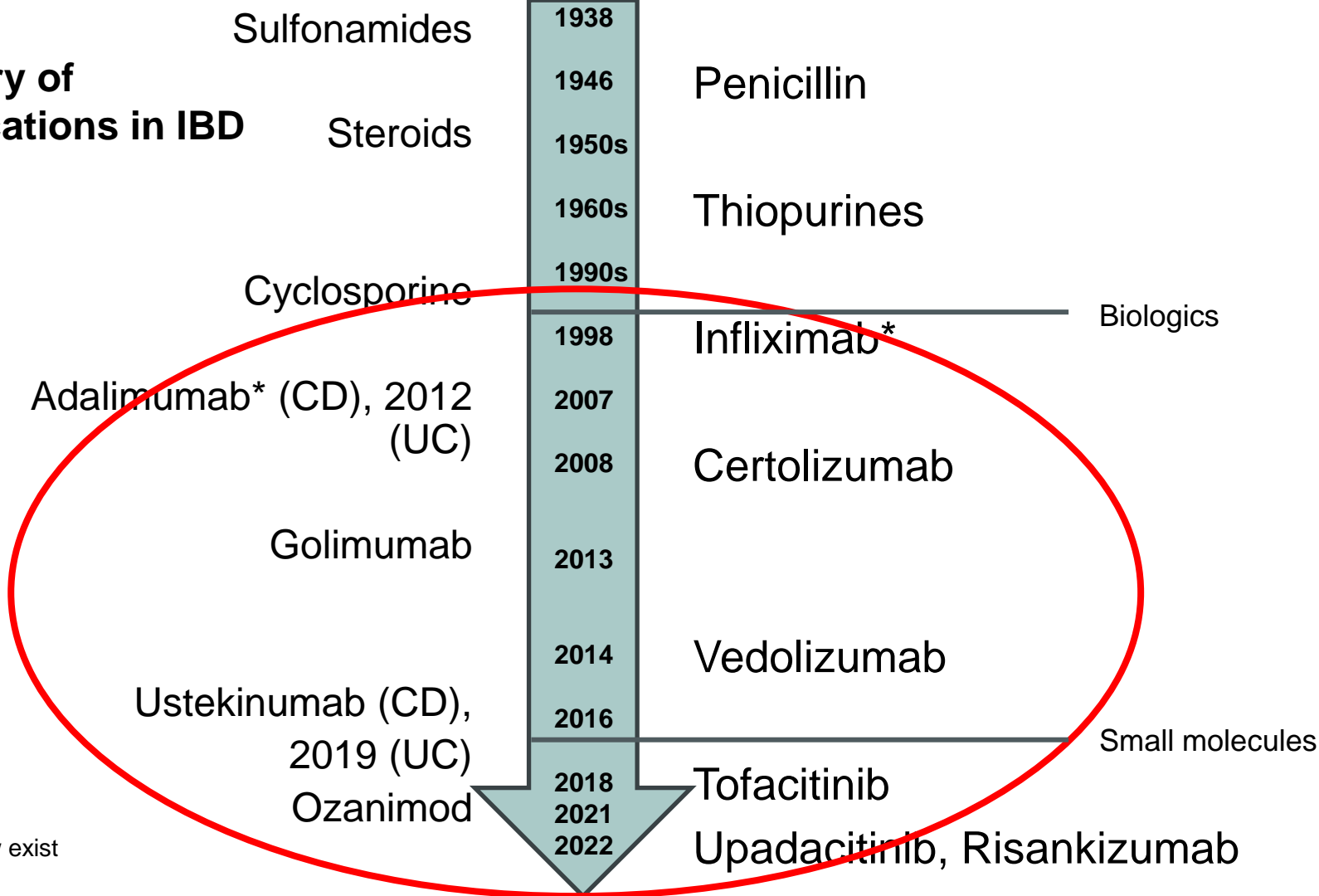
Protective factors

- Living with a dog⁶
- Being in a large family⁶



Medication History

History of Medications in IBD



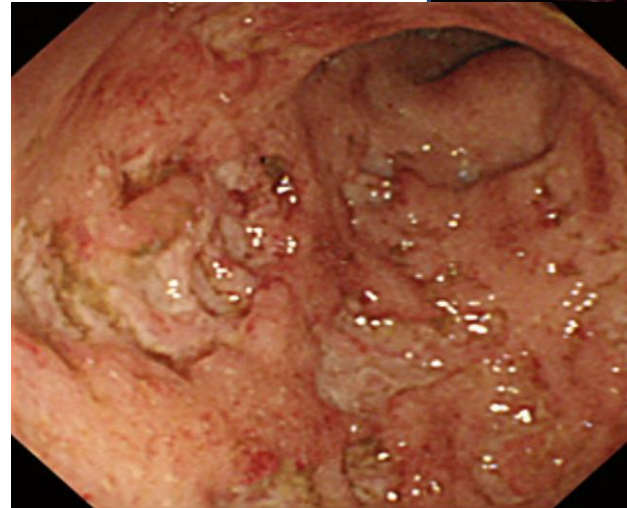
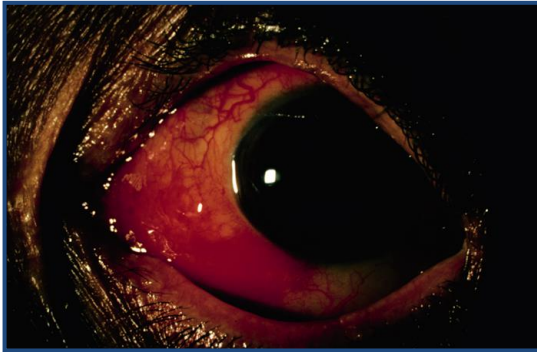
*biosimilars now exist



Predicting Severe Disease

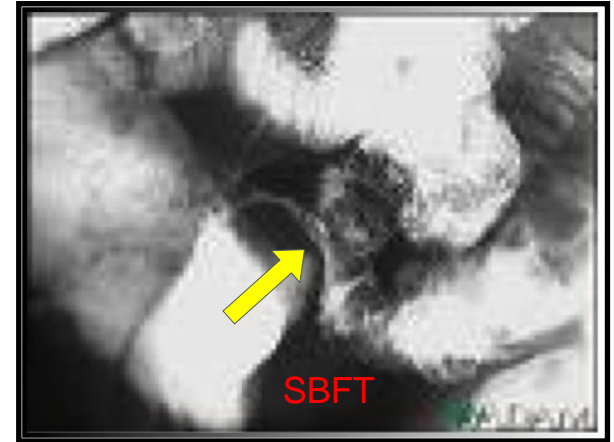
Predictors of Severe Disease and Colectomy in Ulcerative Colitis

- Young age at diagnosis (< 40 years old)
- Presence of large and/or deep ulcers
- Presence of extra-intestinal manifestations (EIM)
- Early need for steroids
- Elevated inflammatory markers



Predictors of severe Crohn's disease

- Early age at diagnosis (< 40 years old)
- Upper GI tract involvement
- Perianal disease
- Strictureing and/or penetrating disease
- Early steroid use
- Post operative complications
- Genetics



Prediction Tools: CD PATH

- Time from diagnosis
- Disease location
- Serologic factors
 - ASCA IgA and IgG
 - pANCA IFA
 - Anti-CBir1 IgG
- Genetic factor
 - NOD2 mutation
- Who is eligible?
 - ≥ 18 years old
 - Within 10 years of diagnosis
 - NO serious CD complications
 - Commercial insurance or uninsured



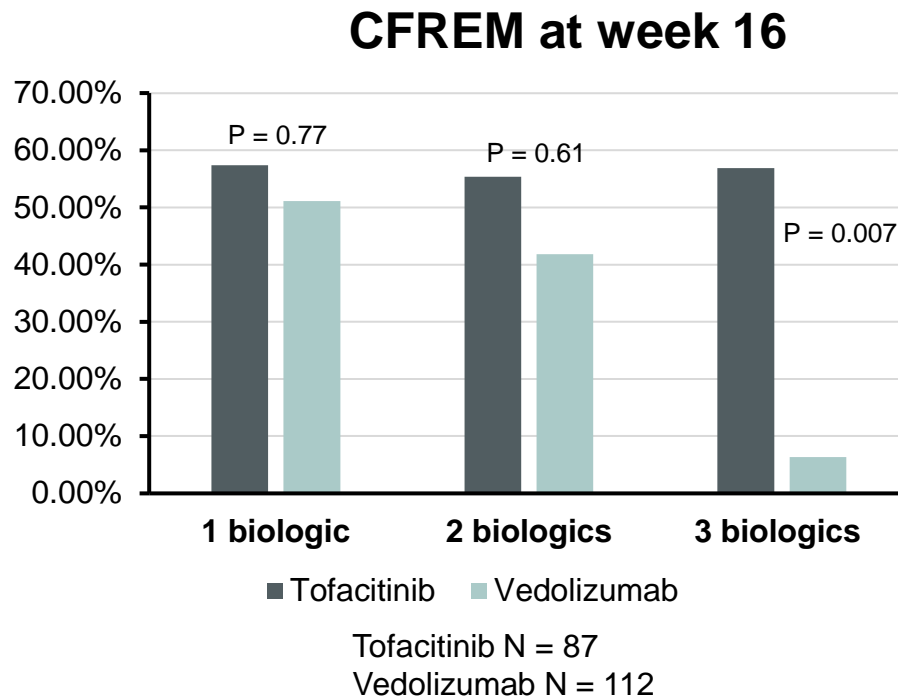
Prior Biologic Failures

What We Know

- It may be due to inadequate dosing
- Prior failure to anti-TNF therapy may indicate more refractory disease
- BUT – there's hope!

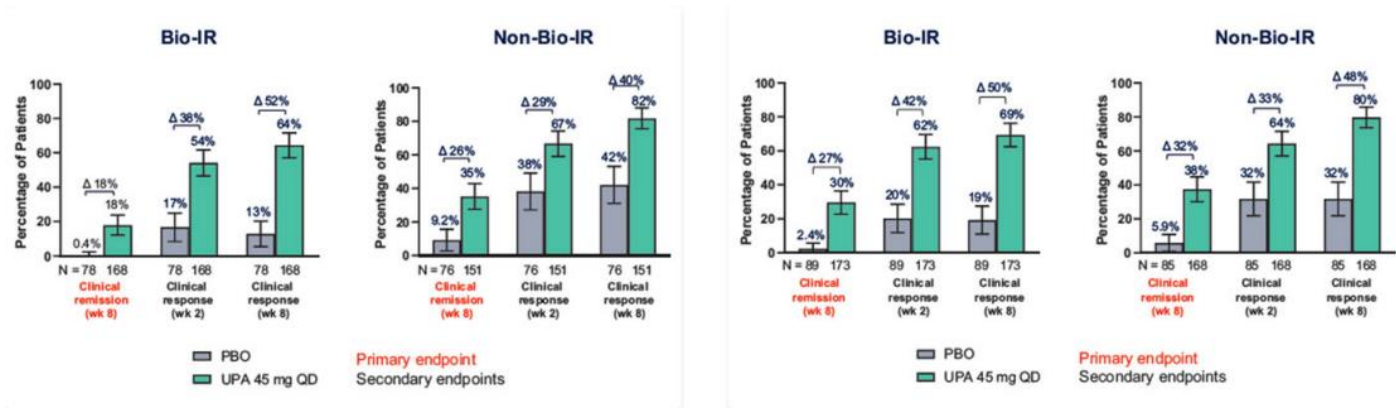
Tofacitinib > Vedolizumab in UC With Failure to ≥ 1 Biologic

- Multicenter retrospective evaluation of UC patients with prior biologic failure *including* at least 1 anti-TNF
- Assess corticosteroid free clinical remission (CFREM)
 - Secondary to assess endoscopic response and mucosal healing



Upadacitinib: Prior Biologic Failure

Upadacitinib in Induction by Bio-IR Status (U-ACHIEVE and U-ACCOMPLISH Phase 3 Induction Trials)



Bio-IR: experienced previous biologic failure (inadequate response, loss of response, or intolerance)

Clinical Trials

- [Clinicaltrials.gov](https://clinicaltrials.gov)
- New mechanisms of action
- Dual therapy



Perianal Disease

Choosing Therapy: Crohn's Disease

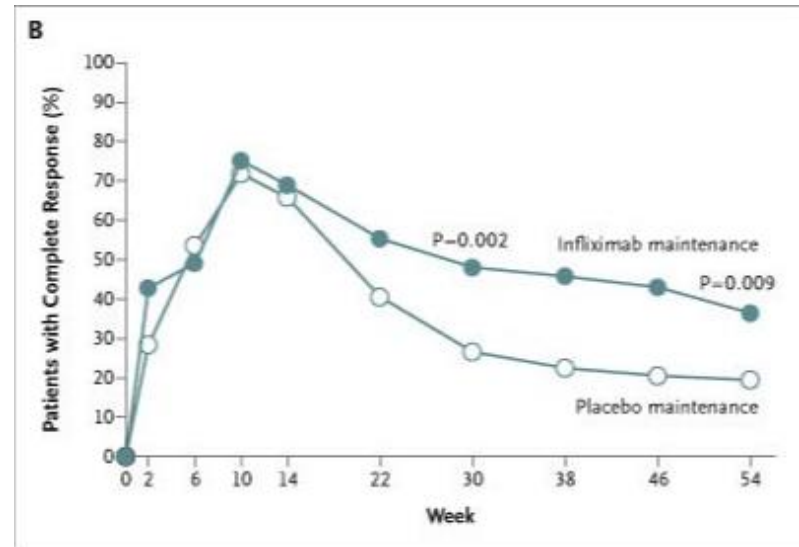
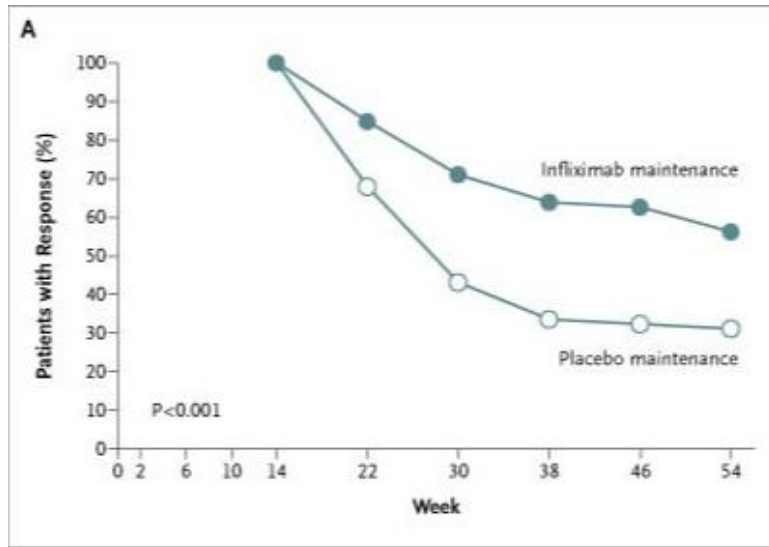
- Disease behavior
 - Fistulizing
 - Minimal data



Variable	Placebo		Infliximab	
	# patients	% primary responders	# patients	% primary responders
All patients	31	26	63	62
# EC fistulas				
1	13	8	29	52
>1	18	39	34	71
Dose of steroid				
20mg/day	5	20	6	67
< 20mg/day	6	17	15	53
None	20	30	42	64
MTX or Aza				
Yes	9	44	29	59
No	22	18	34	65
Antibiotics				
Yes	11	27	17	65
No	20	25	46	61

Choosing Therapy: Crohn's Disease

- Perianal disease

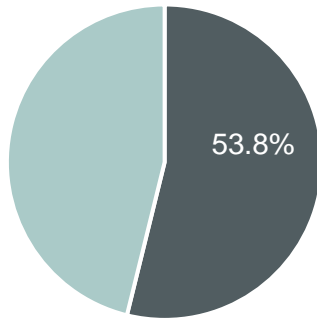


Perianal Disease: Response to Ustekinumab

SEAVUE

- Biologic naïve
- Evaluation at baseline + week 52

Fistula Resolution

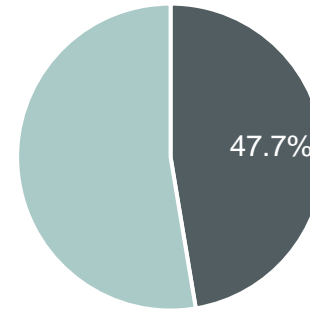


■ Yes ■ No

STARDUST

- Biologic naïve or failed 1 biologic
- Evaluation at baseline + week 48

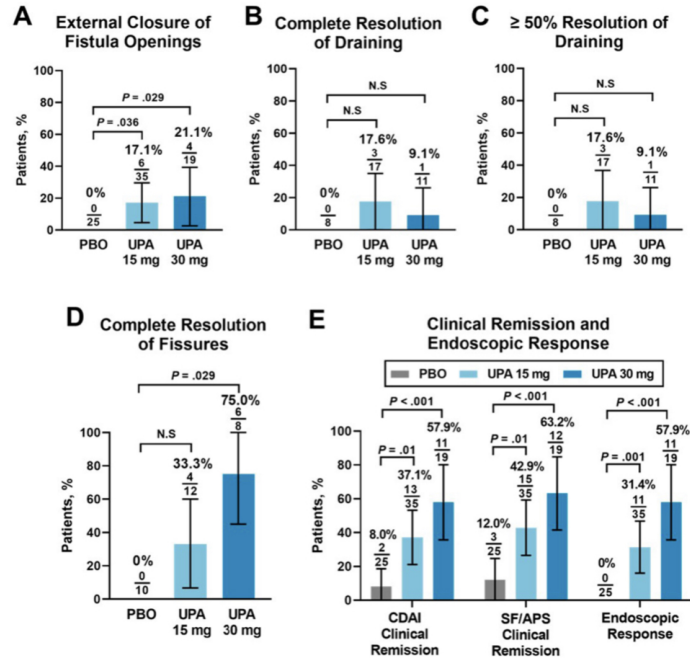
Fistula Resolution

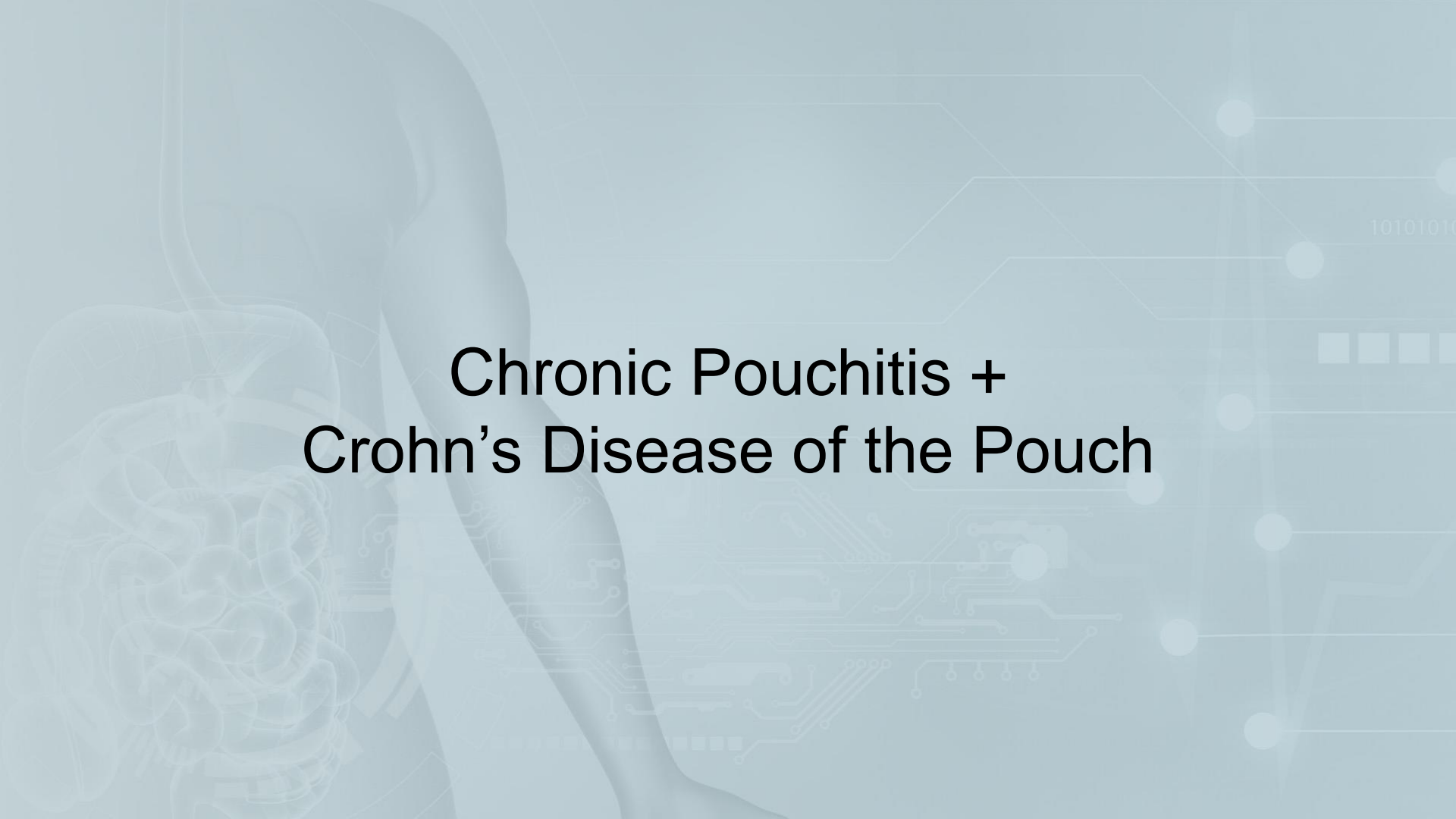


■ Yes ■ No

Upadacitinib: Fistulas

Figure 2. Proportion of Patients Who Achieved Fistula, Draining, Fissure, Clinical, and Endoscopic Outcomes at Week 52 of Maintenance





Chronic Pouchitis + Crohn's Disease of the Pouch

Pouchitis

- Mainstay of treatment

- Antibiotic course

→ Works for many BUT what about...

- Chronic antibiotic refractory pouchitis (CARP)

- Crohn's disease of the pouch

Chronic Antibiotic Refractory Pouchitis (CARP)

- Other antibiotics
- Steroids
 - Oral and rectal budesonide
- Advanced therapies
 - Biologics
 - Small molecules

Crohn's Disease of the Pouch

- Data has shown that biologics are effective
 - Choice dependent on prior exposures, disease history
- Recent study assessing efficacy of UST and VDZ
 - N = 101, majority bio-exposed
 - Clinical and histologic response favorable (Clinical >> histologic)



Disease in Pregnancy

Choosing Therapy: Women of Childbearing Age

- AGA pregnancy pathway
- IBD Parenthood Project 

Choosing Therapy: Pregnancy Considerations

- Discontinue MTX *prior* to conception
 - At least 3 months
- Avoid steroids if possible
 - 1st trimester, ↑ cleft palate risk

IBD + Pregnancy: Mediations to Continue

- Mesalamines*
 - All phthalate free except Azulfadine EN
 - SFZ concerns
- Thiopurines*
 - Continue if monotherapy
 - Consider stopping if combination therapy
 - Don't start during pregnancy

IBD + Pregnancy: The [Classic] Medications

- Infliximab*
- Adalimumab*
- Certolizumab
 - Pegylated
 - Does not cross placenta
- Golimumab

IBD + Pregnancy: The [Classic] Medications

Timing of administration

- Adjust timing of dose in attempt to deliver at trough
- Resume after delivery
 - 24 hours after vaginal
 - 48 hours after c-section

Adjustments prior to estimated delivery date

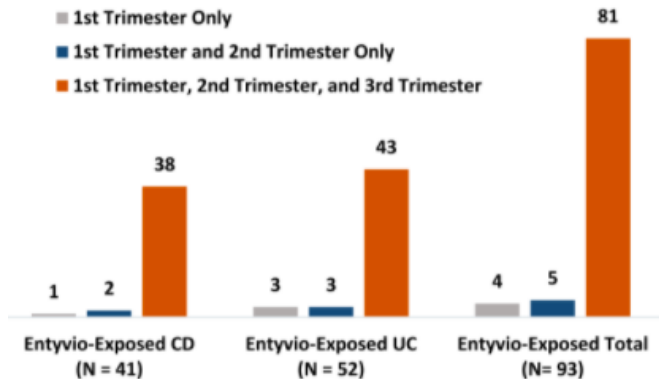
- Infliximab
 - 6-10 weeks prior (4-6 weeks if Q4week dosing)
- Adalimumab
 - 2-3 weeks prior (1-2 weeks if weekly dosing)
- Golimumab
 - 4-6 weeks prior
- *Certolizumab: continue regular dosing

IBD + Pregnancy: The [Newer] Medications

Anti-integrin: vedolizumab

- Vedolizumab Pregnancy Exposure Registry

Figure 1. Gestational Timing of Vedolizumab Use in Pregnancy



Chambers CD et al. Abstract presented at: ACG October 25, 2021.

	Vedolizumab exposed (N = 93)	Disease matched (N = 104)	Healthy controls (N = 98)
Live born infant n/N (%)	88/93 (94.6)	99/104 (95.2)	85/98 (86.7)
Spontaneous abortion n/N (%)	3 (9.4)	3 (6.1)	1 (5.7)
Termination; n/N (%)	0/93 (0)	0/104 (0)	0/98 (0)
Still birth; n/N (%)	0/93 (0)	1/104 (1.0)	0/98 (0)
Preterm rate	13 (15.3)	6 (6.1)	6 (7.3)
Mean birthweight (g)	3405.4	3427.9	3307.4
Major birth defects; n/N (%)	5/91 (5.5)	7/103 (6.8)	4/86 (4.7)
Serious infections (≤ 1 y/o); n/N (%)	3/92 (3.3)	1/99 (1.0)	1/88 (1.1)
Screening with concern (up to 1 y/o); n/N (%)	9/48 (18.8)	19/85 (22.4)	8/56 (14.3)

IBD + Pregnancy: The [Newer] Medications

Anti-IL-12/IL-23: Ustekinumab

Safety data through 2019

- Active pregnancy registry
- Literature demonstrates similar birth outcomes as compared to the general population

	Live Birth	Elective/ Induced Abortion	Spontaneous Abortion	Live Birth with Congenital AEs
All Cases	68.8%	9.0%	18.4%	2.7%
Prospective Cases	75.7%	7.8%	13.5%	2.7%
Retrospective Cases	57.7%	11.0%	26.4%	2.7%
General Population	62.9%	19.4%	17.9%	4.0%

Tikhonov I, Volger S, Lin CB, et al. Poster presented at: American Academy of Dermatology; June 2020; Abraham B, Ott E, Busse C, et al. Abstract presented at: Digestive Disease Week; May 2021.

IBD + Pregnancy: The [Newer] Medications

JAK inhibitor: Tofacitinib

- Other agents preferred
 - At least avoid during 1st trimester
- Animal studies show in utero fetal harm
- Limited data
 - 11/1157 pregnancies with maternal exposure
- Pregnancy registry

	Maternal Exposure (11/1157) No. (%)	Paternal Exposure (14/1157) No. (%)
Healthy newborn	4 (36.4)	11 (78.6)
Medical termination	2 (18.2)	0 (0.0)
Neonatal death	0 (0.0)	0 (0.0)
Fetal death	0 (0.0)	0 (0.0)
Congenital malformations	0 (0.0)	0 (0.0)
Spontaneous abortion	2 (18.2)	0 (0.0)
Pending or lost to follow up	3 (27.3)	3 (21.4)

IBD + Pregnancy: The [Newer] Medications

S1P receptor modulator: Ozanimod

- Other agents preferred
- Animal studies have shown in-utero exposure may cause fetal harm
- Data from MS trial
 - 42 pregnancies/1868 females
- Elimination takes approximately 3 months

	Ozanimod exposed pregnancies (N = 42)
Live born infant n/N (%)	27/42 (64.3)
Spontaneous abortion n/N (%)	6/42** (14.3)
Termination n/N (%)	9/42 (21.4)
Preterm rate n/N (%)	3/27 (11.1)

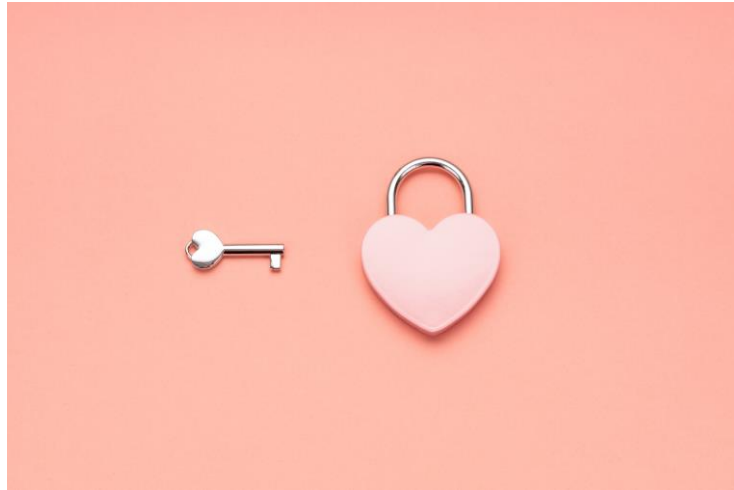
Outcome, n	UC	CD
Pregnancies	9	3
Healthy live birth	2	1
Congenital abnormality	0	0
Premature	0	0
Ongoing	2	2
Spontaneous early loss	2	0
Elective termination	3	0

*loss of one twin

+ Rate of spontaneous abortion in general population 12-22%
 Minton N, Henry A, et al. *Neurology*. 2021;
 Dubinsky et al. *J Crohn's and Colitis*. 2021.

Key Points

- Monitor disease
- Treat aggressively
- Growing armamentarium of options!





Thank You!

Questions?