Updates in IBD

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OUTLINE

- Updates in IBD: Fernando Velayos MD
- Updates in Pregnancy in IBD: Uma Mahadevan
- Case Discussions

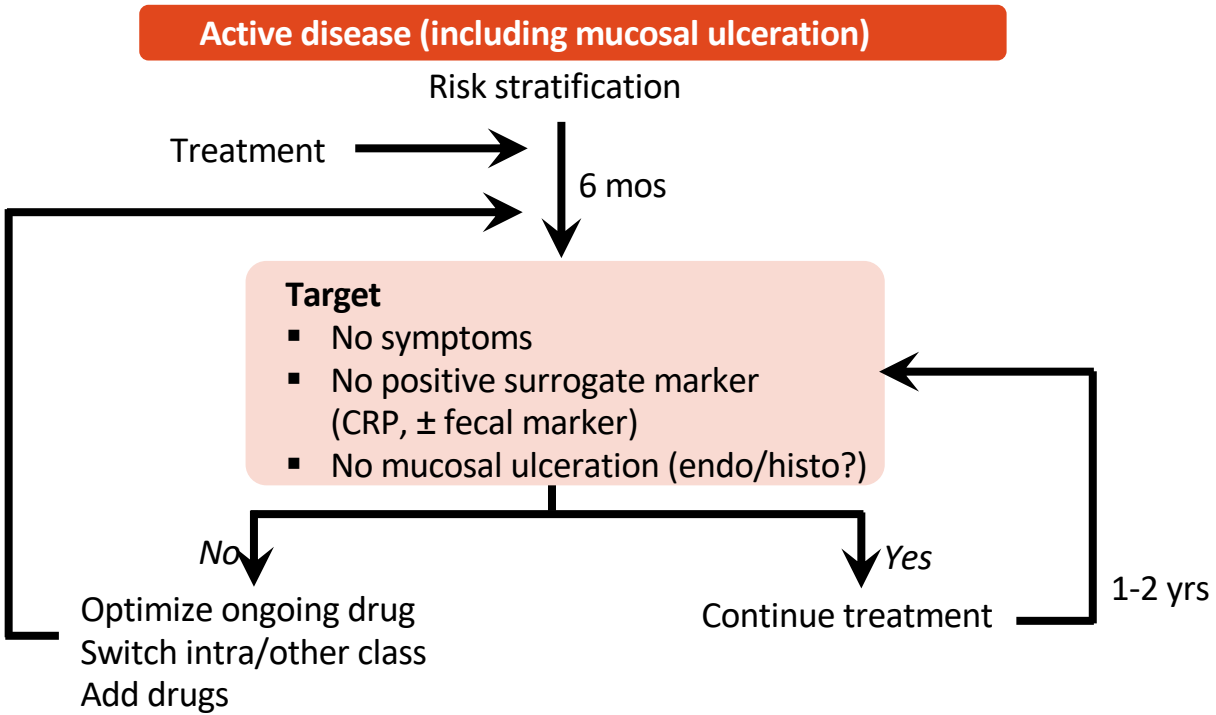
Treat to Target: What Is the Target?

	Type of Remission				
Disease	**Clinical[1-3]**	**Steroid Free[3,4]**	**Biologic[5]**	**Endoscopic[1,3,6]**	**Histologic[7,8]**
CD	▪ CDAI < 150 ▪ HBI < 5	**Steroid free +** ▪ CDAI < 150 ▪ HBI < 5	▪ CRP < 5.0 mg/L ▪ Calprotectin < 50 µg/g	▪ CDEIS score < 4 ▪ SES-CD ≤ 4 ▪ Frøslie score 0	▪ GHAS ▪ Nancy Index ▪ Robarts Histopathology Index
UC	▪ SCCAI score ≤ 4 ▪ Mayo score ≤ 1	**Steroid free +** ▪ SCCAI score ≤ 4 ▪ Mayo score ≤ 1		▪ **Mayo endoscopy subscore 0 or 1**	▪ **Geboes score** ▪ Nancy Index ▪ Robarts Histopathology Index

- New UC endpoint (used in UNIFI study)[9]:
  - **Histo-endoscopic mucosal healing** = **endoscopic** plus **histologic** remission

1. Peyrin-Biroulet. Clin Gastroenterol Hepatol. 2016;14:348. 2. Kappelman. Clin Gastroenterol Hepatol. 2014;12:1315. 3. FDA. Ulcerative colitis: clinical trial endpoints guidance for industry. August 2016. 4. Panaccione. Can J Gastroenterol. 2011;25:419. 5. Pittet. J Crohns Colitis. 2013;7:820. 6. Frøslie. Gastroenterology. 2007;133:412. 7. Löwenberg. Gastroenterology. 2019;157:997. 8. Mosli. Cochrane Database Syst Rev. 2017;5:CD011256. 9. Sands. NEJM. 2019;381:1201.

Proposed Algorithm in IBD



Guideline Recommendations for Optimizing UC Therapy

AGA: Induction of Remission in Moderate to Severe UC for Biologic Naive Patients

- AGA suggests **early use of biologic agents** (with or without immunomodulator therapy) **rather than gradual step-up** after failure of 5-ASA

	Recommendation
Recommended Therapy	**Biologic Naive**
TNF inhibitor	**Infliximab** preferred over adalimumab based on relative efficacy
Vedolizumab	**Vedolizumab** preferred over adalimumab based on relative efficacy
Ustekinumab	Effective but not ranked in guidelines
Tofacitinib	Effective but not FDA approved for TNF naive

No induction with thiopurine monotherapy or MTX.

Feuerstein. Gastroenterology.2020;158:1450.

Slide credit: clinicaloptions.com

AGA: Induction of Remission in Moderate to Severe UC for Biologic Naive or TNF-Experienced Patients

- AGA suggests **early use of biologic agents** (with or without immunomodulator therapy) **rather than gradual step-up** after failure of 5-ASA

	Recommendation	
Recommended Therapy	**Biologic Naive**	**Previous Infliximab**
TNF inhibitor	**Infliximab** preferred over adalimumab based on relative efficacy	
Vedolizumab	**Vedolizumab** preferred over adalimumab based on relative efficacy	
Ustekinumab	Effective but not ranked in guidelines	**Ustekinumab** preferred over adalimumab or vedolizumab
Tofacitinib	Effective but not FDA approved for TNF naive	**Tofacitinib** preferred over adalimumab or vedolizumab

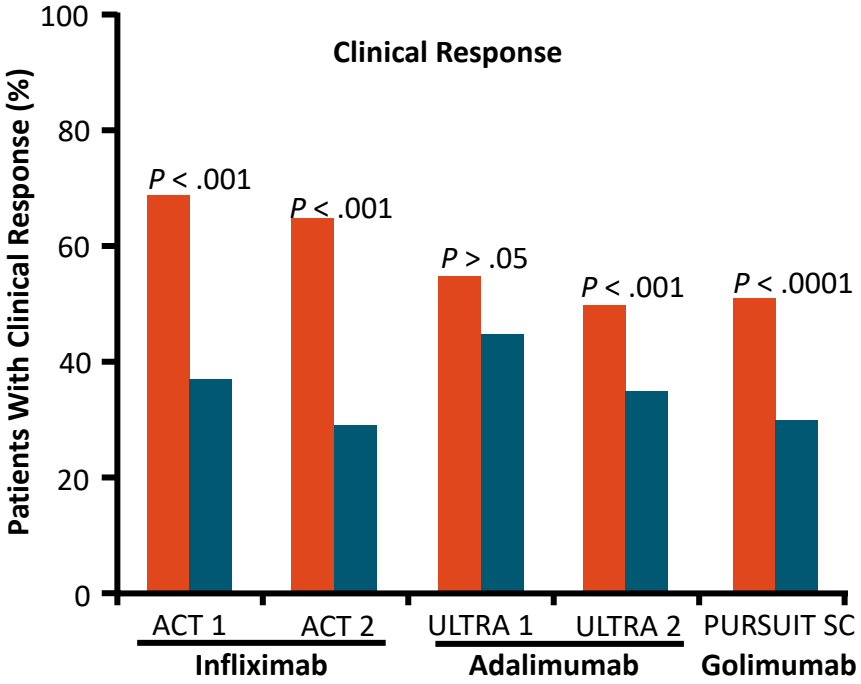
No induction with thiopurine monotherapy or MTX.

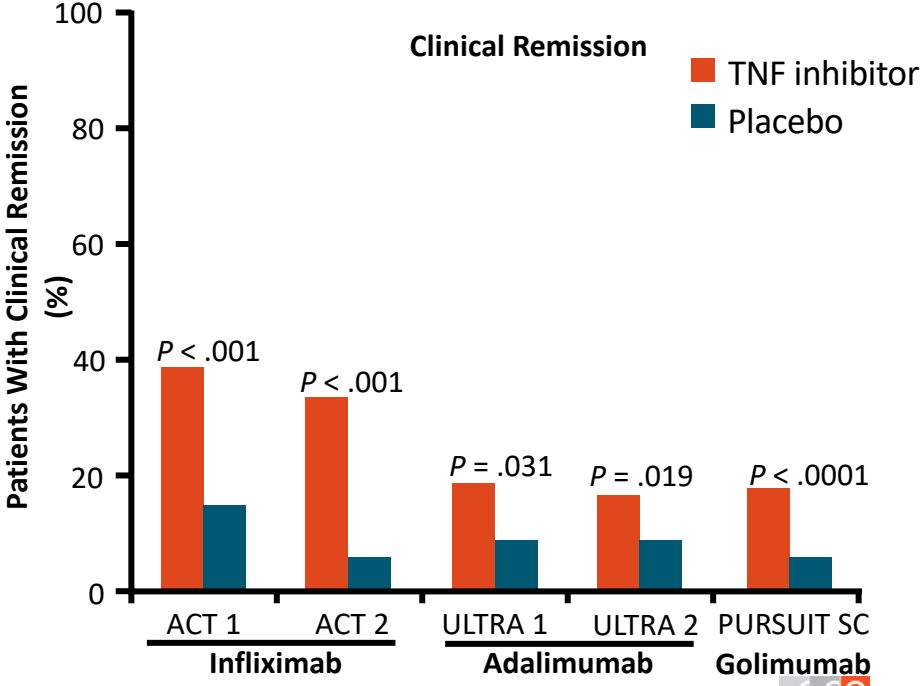
Feuerstein. Gastroenterology.2020;158:1450.

Slide credit: clinicaloptions.com

TNF Inhibitor Therapy in UC

- Non–head-to-head studies support efficacy of TNF inhibitors in UC





Fausel. Ther Clin Risk Manag. 2015;11:63.

Slide credit: clinicaloptions.com

SERENE: High-Dose Adalimumab in UC

- Double-blind, multicenter study of **high-dose** (160 mg weekly for 4 wks followed by 40 mg weekly for 2 wks) vs **standard-dose** adalimumab in patients with moderate to severe UC

Patients With Outcome, %	High-Dose Adalimumab (n = 512)	Standard-Dose Adalimumab (n = 340)	*P* Value
Clinical remission, Wk 8	13.3	10.9	.273
Endoscopic improvement	31.1	27.1	.182
Fecal calprotectin < 150 mg/kg	22.5	19.8	.283
IBDQ response	66.8	60.9	.063
Clinical response per full Mayo Score*	47.1	40.0	.034
Endoscopic remission	13.1	10.0	.162

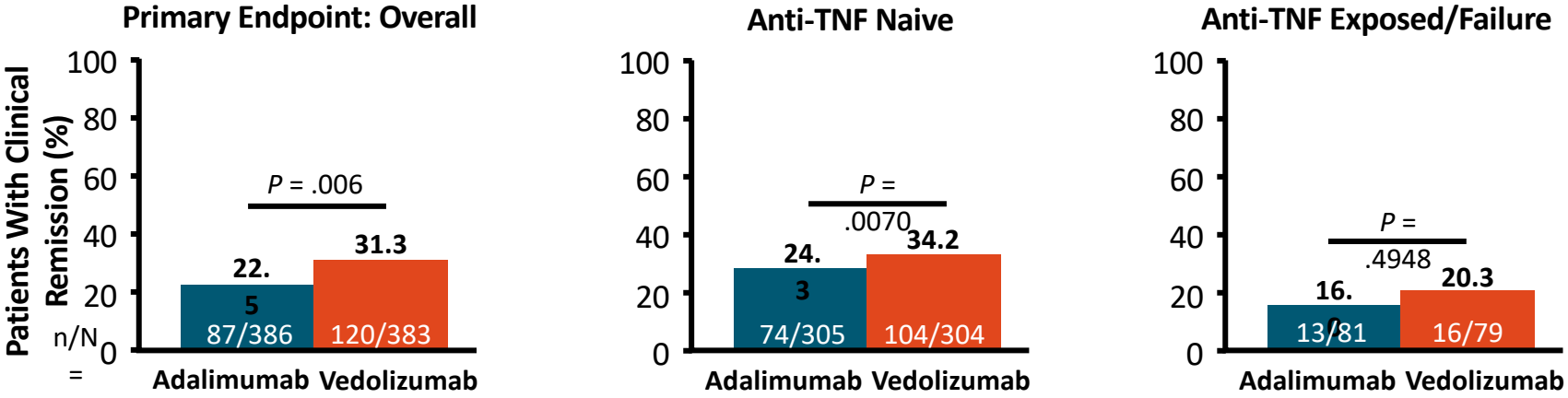
*Decrease from baseline in the full Mayo Score ≥ 3 points and ≥ 30% from baseline, plus a decrease in rectal bleeding score ≥ 1 or an absolute score ≥ 1.

Panes. United European Gastroenterology Week 2019. Abstr OP216.

Slide credit: clinicaloptions.com

VARSITY: Efficacy of Vedolizumab vs Adalimumab in UC at Wk 52

- Double-blind, randomized phase IIIb study in N = 769 adults with moderate to severe UC (up to 25% with prior non-adalimumab TNF inhibitor)



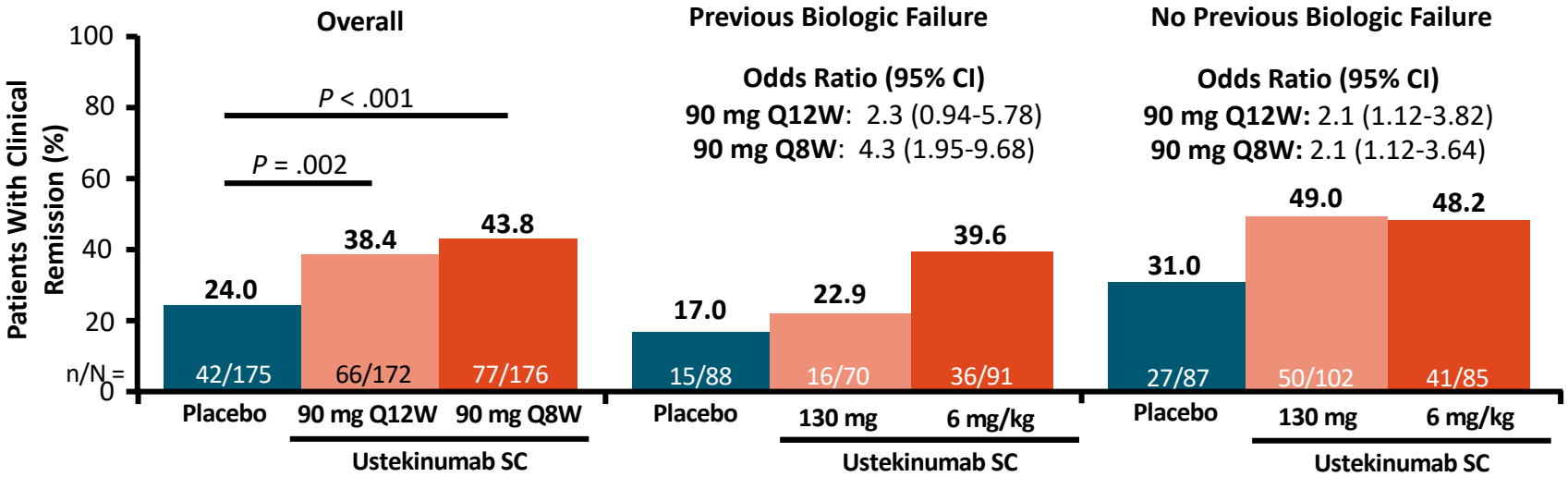
- At Wk 52, vedolizumab was superior to adalimumab for clinical remission and endoscopic improvement, but not corticosteroid-free clinical remission

Sands. NEJM. 2019;381:1215. Schreiber. ECCO 2019. Abstr OP34.

Slide credit: clinicaloptions.com

UNIFI: Ustekinumab Efficacy in UC at Wk 44

- Randomized, double-blind, placebo-controlled phase III studies in adults with moderate to severe UC
  - Patients had inadequate response or intolerance to previous treatment

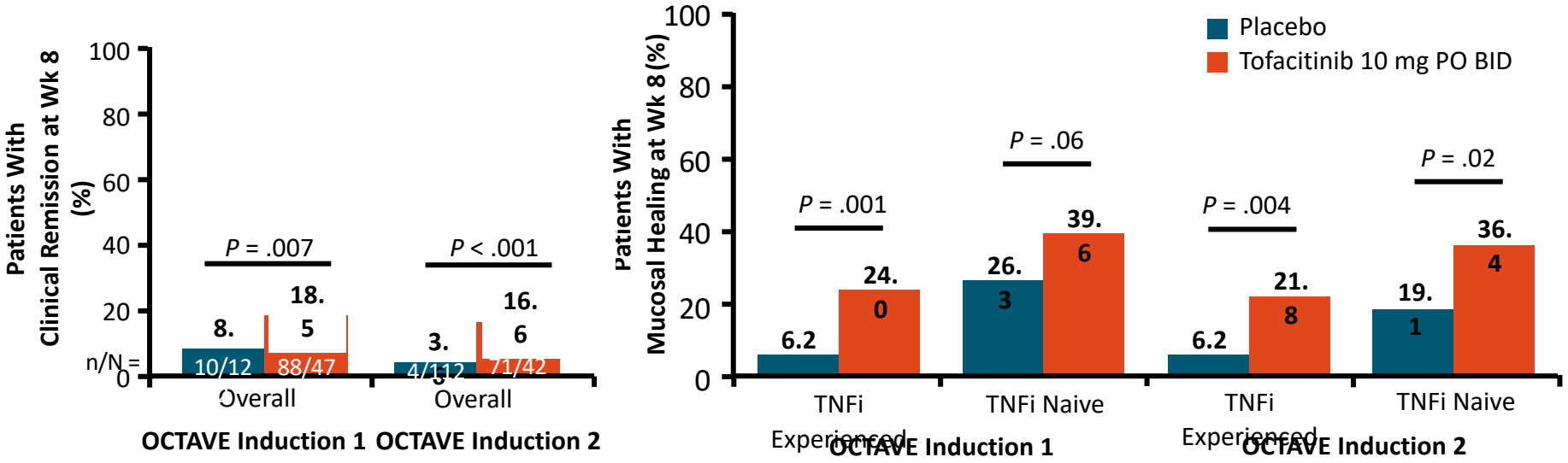


Sands. NEJM. 2019;381:1201.

Slide credit: clinicaloptions.com

OCTAVE: Tofacitinib Efficacy in UC

- Randomized, double-blind, placebo-controlled, multicenter phase III studies in adults with moderate to severe UC
  - 46% to 58% of patients TNF inhibitor experienced, depending on treatment arm



Sandborn. NEJM. 2017;376:1723.

Slide credit: clinicaloptions.com

Combination Therapy With Immunomodulators and Biologics in Moderate to Severe UC

AGA

- **Combine TNF inhibitors** with **thiopurines or methotrexate,** rather than biologic monotherapy[1]
  - Conditional recommendation, low quality evidence

Our Opinion

- Emerging evidence suggests **vedolizumab** and **ustekinumab** can be used as **monotherapy**
  - Antidrug antibodies found in only **4% of patients in vedolizumab** registry trials[2] and **< 3% of patients in ustekinumab** CD registry trials[3]

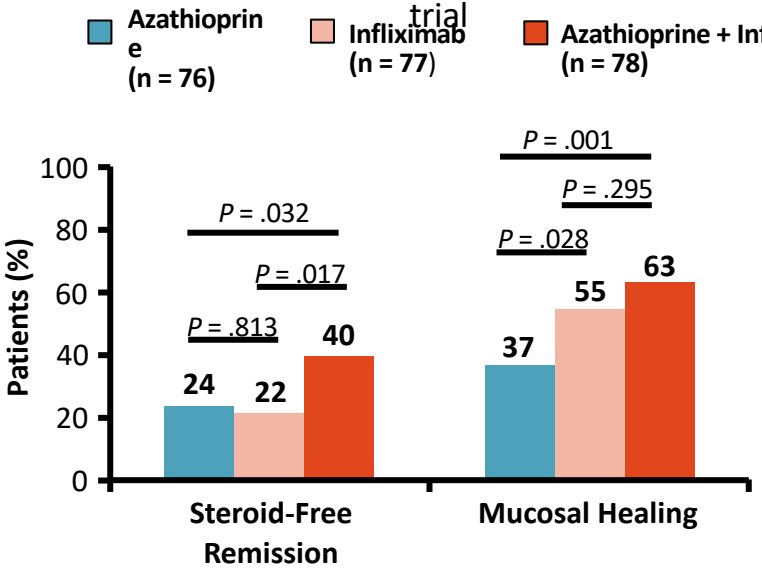
1. Feuerstein. Gastroenterology. 2020;158:1450. 2. Vedolizumab PI. 3. Ustekinumab PI.

Slide credit: clinicaloptions.com

Adding Immunomodulator to TNF Inhibitor in CD or UC: Benefit

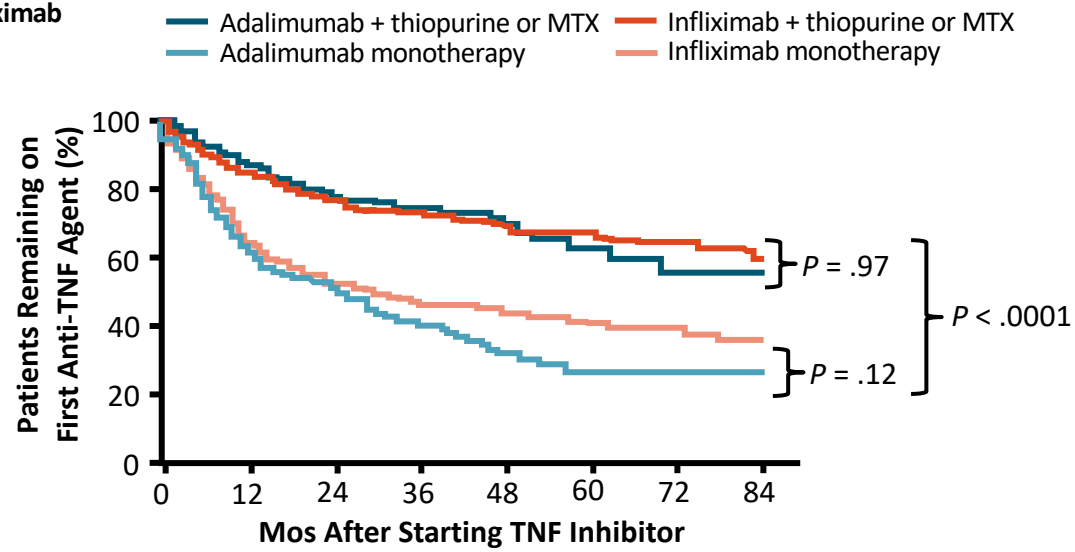
UC SUCCESS[1]

Patients naive to TNF inhibitor and azathioprine or > 3 mos discontinuation of azathioprine before trial



Retrospective Study of Initial Combination Therapy in Biologic-Naive CD Patients (N = 906)[2]

Patients remaining on first TNF inhibitor

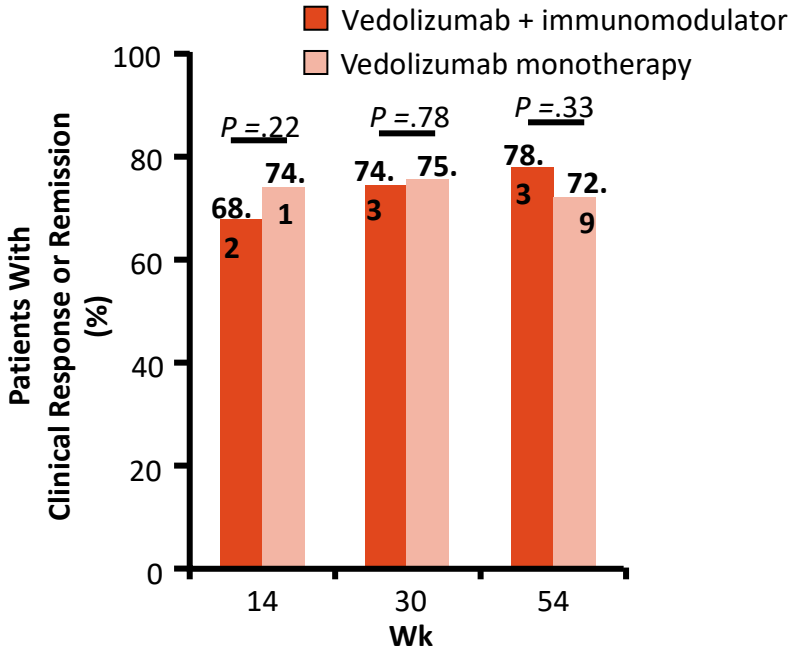


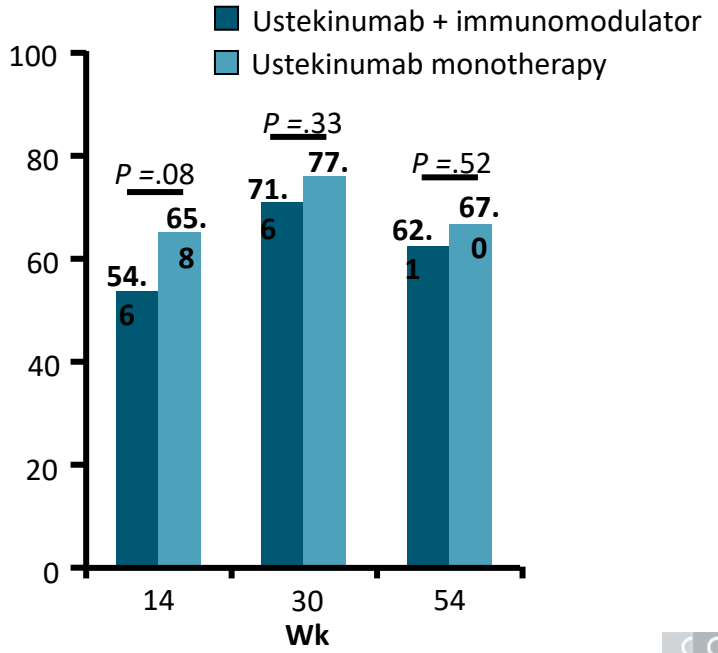
1. Panaccione. Gastroenterology. 2014;146:392. 2. Cosnes. Aliment Pharmacol Ther. 2016;44:1102.

Slide credit: clinicaloptions.com

Adding Immunomodulator to Vedolizumab or Ustekinumab in CD and UC: No Benefit

- Retrospective study of N = 549 patients with UC or CD receiving vedolizumab and N = 363 patients (mostly with CD) receiving ustekinumab





Hu. Clin Gastroenterol Hepatol. 2020;[Epub].

Slide credit: clinicaloptions.com

Guideline Recommendations for Optimizing CD Therapy

AGA Clinical Pathway: Induction Therapy for Moderate to Severe CD

Moderate- or High-Risk CD

- Age at diagnosis < 30 yrs
- Extensive anatomic involvement (eg, ileal/ileocolonic involvement)
- Perianal and/or severe rectal disease
- Deep ulcers
- Previous surgical resection
- Stricturing and/or penetrating behavior

Initial Treatment Options

- **TNF inhibitor + thiopurine** preferred over thiopurine monotherapy or TNF inhibitor monotherapy
- **TNF inhibitor monotherapy** preferred over no therapy or thiopurine monotherapy
- **Methotrexate** for patients who do not tolerate purine analog in combination with TNF inhibitor

Sandborn. Gastroenterology. 2014;147:702.

Slide credit: clinicaloptions.com

SERENE CD Study Design

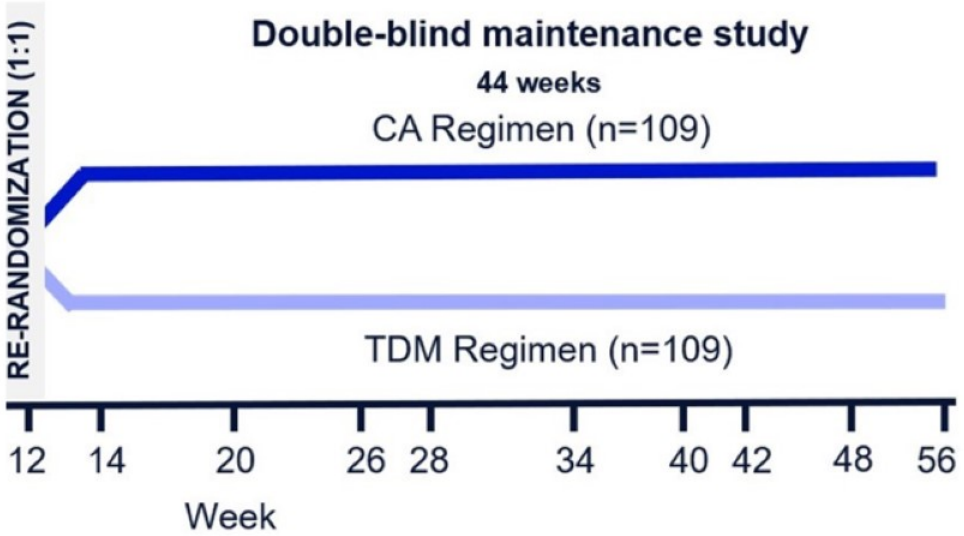
Wk 12 re-randomization stratified by:

- Induction regimen
- Response status[a] at Wk 12
- Decrease in SES-CD > 50% from baseline at Wk 12

Efficacy analysis performed in **Wk 12 responders[a]**

Safety analyses were performed using all subjects who took at least one dose of maintenance study drug

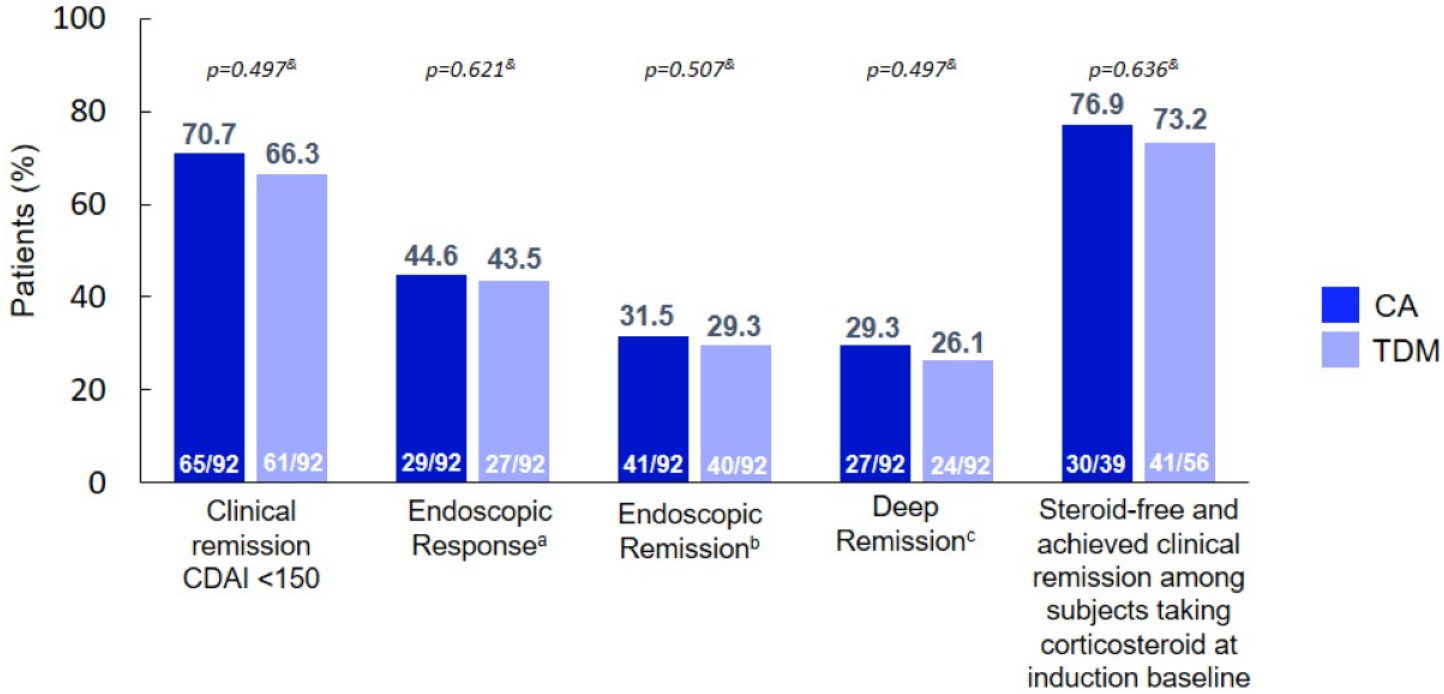
Endoscopy readings were centrally read



[a] Clinical response (CR-70) defined as decrease in CDAI from baseline by ≥ 70 points

Key Efficacy Endpoints (Wk 12 responders) at Wk 56

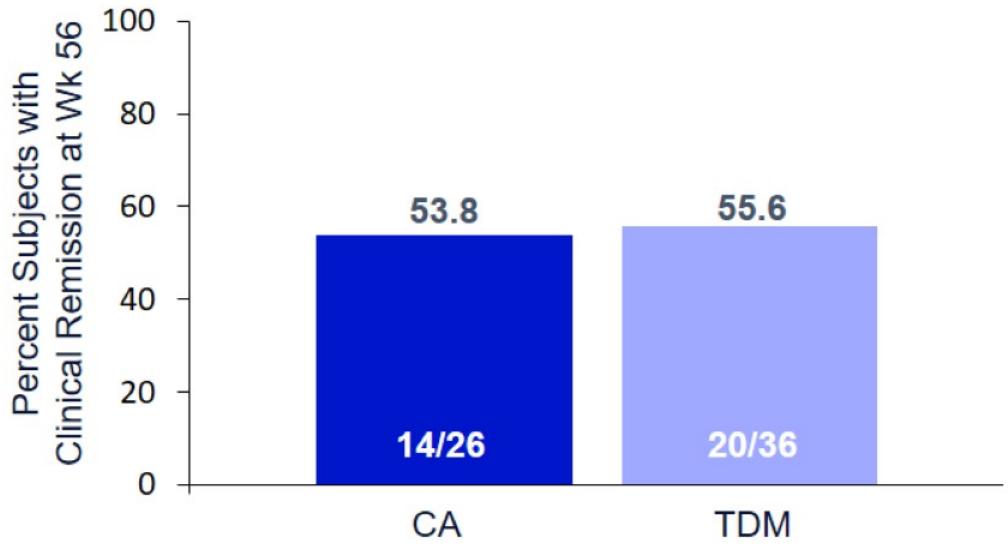
No statistical difference observed between the two treatment regimens for key efficacy endpoints



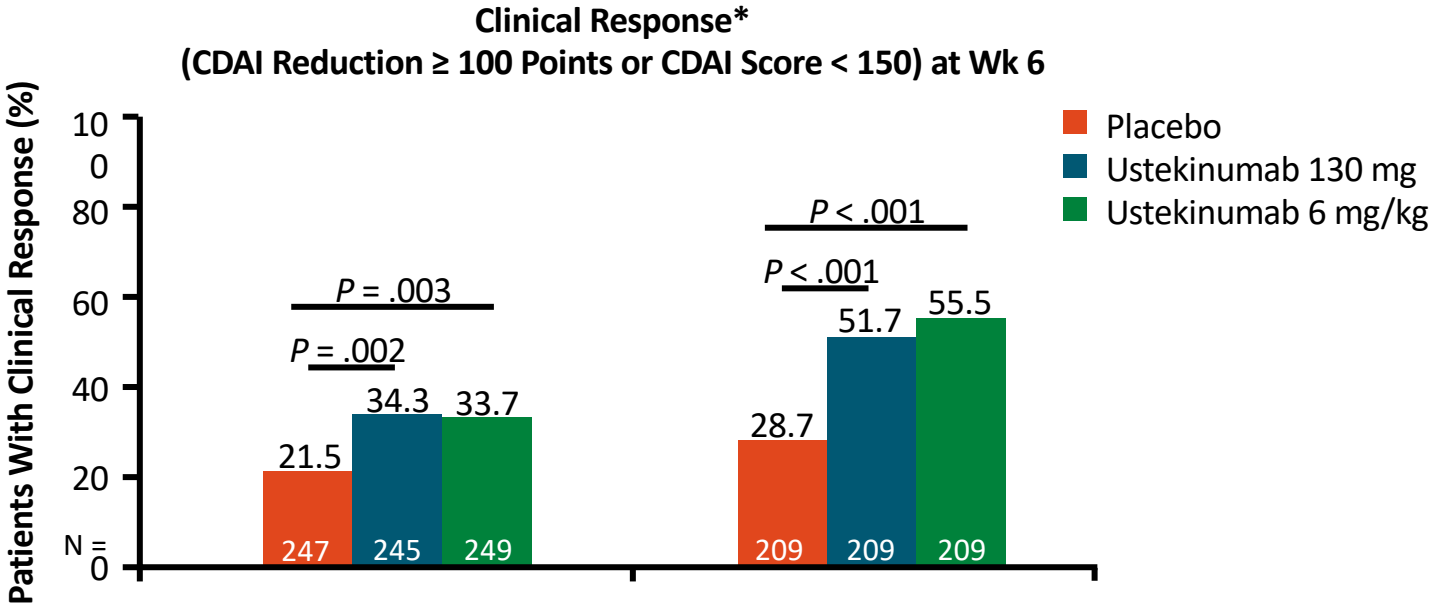
[&]p-values are nominal
[a]Defined as decrease in SES-CD > 50% from Induction Baseline (or for an Induction Baseline SES-CD of 4, ≥ 2-point reduction from Induction Baseline)
[b]Defined as SES-CD ≤ 4 and at least a 2-point reduction from Induction Baseline and no subscore greater than 1 in any individual variable
[c]Defined as CDAI <150 and endoscopic remission

Clinical Remission at Wk 56 in Subjects who Dose Escalated

Among those who escalated to ew dosing, over half achieved clinical remission at Wk 56



UNITI-1 and -2: Ustekinumab in CD



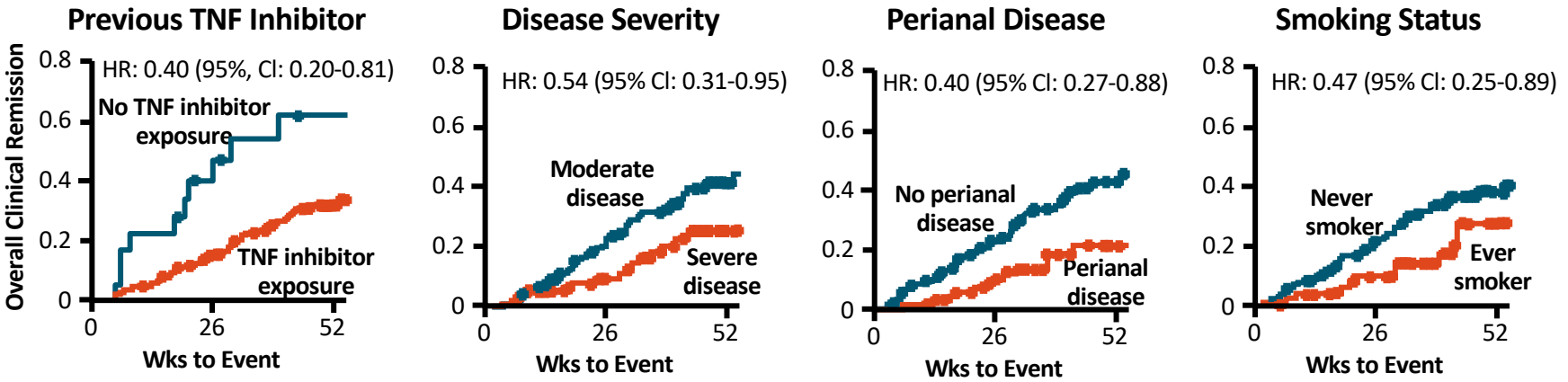
*Patients not considered to be in clinical response or remission if had undergone CD-related surgery, prohibited change in concomitant CD medications, started prohibited concomitant CD medication, or who had insufficient data for calculating CDAI.

Feagan. NEJM. 2016;375:1946.

Slide credit: clinicaloptions.com

US VICTORY Consortium of Vedolizumab in CD: Retrospective Analysis of Real-World Clinical Remission

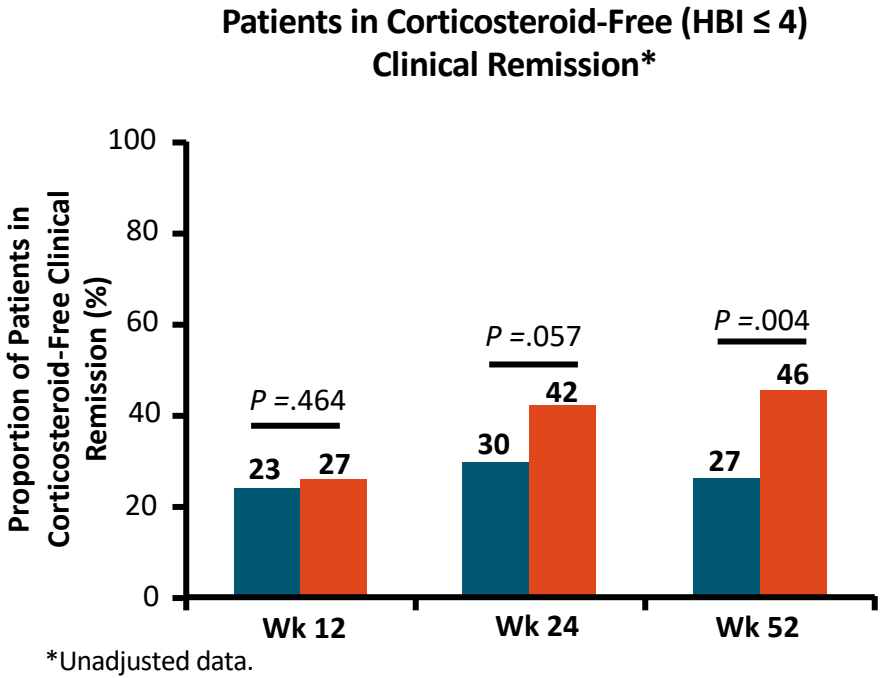
- 12-mo cumulative clinical remission rate: **35%**
  - Remission more likely in those with no previous TNF inhibitor, baseline moderate (vs severe) disease, no perianal disease, or no previous or current smoker status

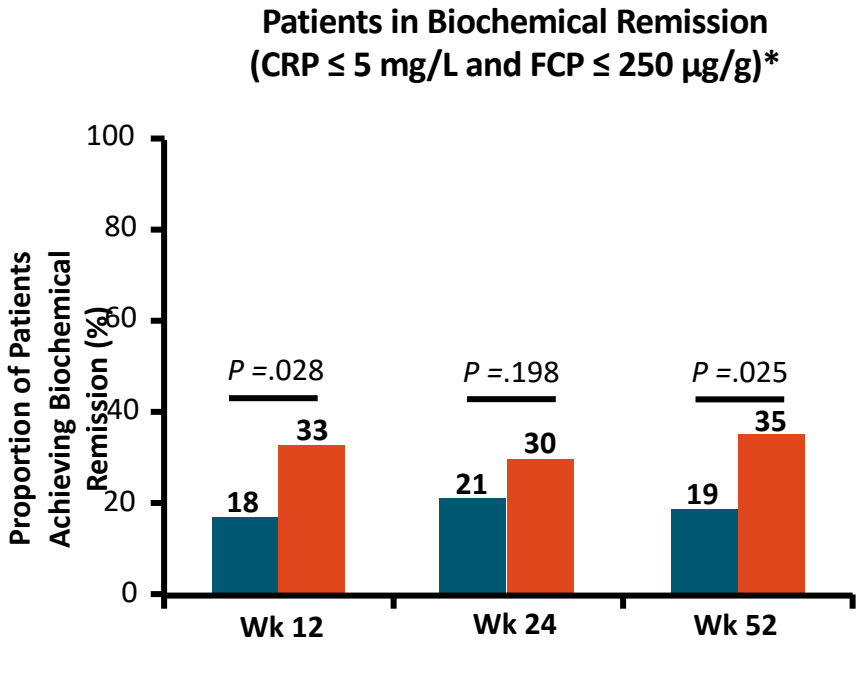


Dulai. Am J Gastroenterol. 2016;111:1147.

Slide credit: clinicaloptions.com

Ustekinumab Associated With Superior Effectiveness vs Vedolizumab in CD With Prior TNF Inhibitor Failure





Vedolizumab Ustekinumab

Biemans. Aliment Pharmacol Ther. 2020;52:123.

Slide credit: clinicaloptions.com

Safety in IBD

Therapy	Common AEs	Boxed Warning
TNF inhibitors[1-5]	Injection-site or infusion-related reactions, headache, rash, infections **Rare:** Lupus-like syndrome	Serious infections, malignancy
Ustekinumab[6]	Vomiting, injection-site reactions, nasopharyngitis, sinusitis, bronchitis, pruritis **Rare:** Reversible posterior leukoencephalopathy syndrome	None
Vedolizumab[7]	Fatigue, headache, nausea, upper respiratory tract infection	None
Tofacitinib[8]	Nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, herpes zoster	Serious infections, mortality, malignancy, thrombosis (including DVT/PE)

1. Infliximab PI. 2. Adalimumab PI. 3. Golimumab PI. 4. Certolizumab PI. 5. Etanercept PI. 6. Ustekinumab PI. 7. Vedolizumab PI. 8. Tofacitinib PI.

Selecting Biologics in Patients With IBD: Our Approach

Efficacy

- **Severe hospitalized patient or severe fistulizing disease:**
  Data support infliximab
- **Moderate to severe UC:**
  TNF inhibitor, ustekinumab (not ranked in AGA guidelines), vedolizumab
- **Moderate to severe CD:**
  TNF inhibitor, ustekinumab, vedolizumab
- **TNF failure:**
  Ustekinumab, tofacitinib for UC; ustekinumab for CD

Safety

- Vedolizumab has the best safety profile followed by ustekinumab
- TNF inhibitors and tofacitinib have similar safety profiles

Special Situations

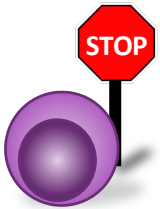
- Older patient
- Patient considering conception
- Comorbidities: history of VTE, demyelination, spondyloarthropathy

Slide credit: clinicaloptions.com

Emerging Therapies With New Data

S1P Receptor Modulators

Target	Agent	Current Phase
S1PR1/4/5	Etrasimod[1]	**Phase III** in UC, **phase II** in CD[2,3]
S1PR1/5	Ozanimod[4]	**Phase III** in UC, CD[5]



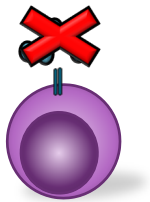
S1P receptor modulators block lymphocyte egress from lymph nodes

1. Adams. Pharmacology. 2017;31:993.11. 2. NCT03945188. 3. NCT04173273. 4. Park. Biomol Ther. 2017;25:80. 5. NCT02435992.

Slide credit: clinicaloptions.com

Interleukin Inhibitors

Target	Agent	Current Phase
IL-12/23	Ustekinumab	FDA approved in CD (2016),[1,2] and UC[3]
IL-23	Guselkumab	Phase II/III in CD[4]
IL-23	Mirikizumab	Phase III in UC[5,6] and CD[7,8]
IL-23	Risankizumab	Phase III in CD[9,10] and phase III in UC[11]

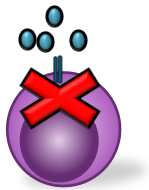


Interleukin inhibitors block extracellular signals that activate and differentiate lymphocytes

1. Ustekinumab PI. 2. Feagan. Lancet. 2017;389:1699. 3. NCT02407236. 4. NCT03466411. 5. Sandborn. Gastroenterol. 2018;154:S1360. 6. NCT03524092. 7. NCT03105128. 8. NCT03104413. 9. NCT03926130. 10. NCT02891226. 11. NCT03398135.

JAK Inhibitors

Target	Agent	Current Phase
JAK1/2/3	Tofacitinib (PO)[1]	FDA approved in UC
JAK1	Filgotinib (PO)[2]	Phase III in CD,[3] UC[4]
JAK1	Upadacitinib (PO)[5,6]	Phase III in CD,[7] UC[8]
JAK1/2/3	TD-1473 (topical)[9]	Phase II in CD,[10] phase II/III in UC[11]



JAK inhibitors block extracellular signals that activate and differentiate lymphocytes

1. Tofacitinib PI. 2. Vermeire. Lancet. 2017;389:266. 3. NCT02914561. 4. NCT02914522. 5. Upadacitinib PI. 6. Sandborn. Gastroenterology. 2020;158:2139. 7. NCT03345849. 8. NCT02819635. 9. Sandborn. J Crohns Colitis. 2020;[Epub]. 10. NCT03635112. 11. NCT03758443.

Conclusions

- Significant unmet needs still exist despite currently approved therapies
- Agents in phase III trials include a multitude of novel targets:
  - S1P receptor modulators
  - Anti–IL-12/23 antibodies
  - JAK inhibitors
- Algorithms and comparative trials will be essential guiding a wealth of upcoming new therapies

Managing the Preconception and Pregnant Patient with Inflammatory Bowel Disease

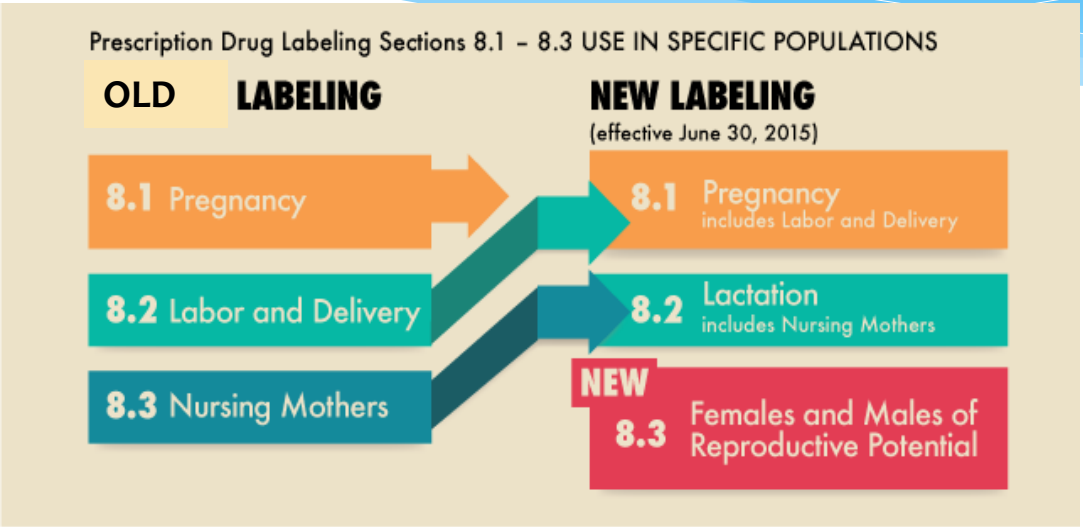
Uma Mahadevan MD
Professor of Medicine
UCSF Center for Colitis and Crohn's Disease
Twitter @UmaMahadevanIBD

What is unique about pregnancy in IBD?

* Women with IBD have higher rates of pregnancy complications
  * Spontaneous Abortion
  * Preterm birth, low birth weight
  * Complications of labor and delivery
* Active disease increases the likelihood of adverse events
* Medications, with limited safety data, are required to maintain remission during conception, pregnancy and lactation

G.Nguyen. Gastroenterology 2016 Mar;150(3):734-757

Pregnancy and Lactation Labeling (Drugs) Final Rule



1. Pregnancy exposure registry data will be in section 8.1
2. Section 8.3 includes information about pregnancy testing, contraception, infertility
3. Changes went into effect June 30, 2015.
   - Drugs submitted after will use new format
   - Drugs approved after June 30, 2001 will be phased in gradually

Joint Statement for Providers and Patients

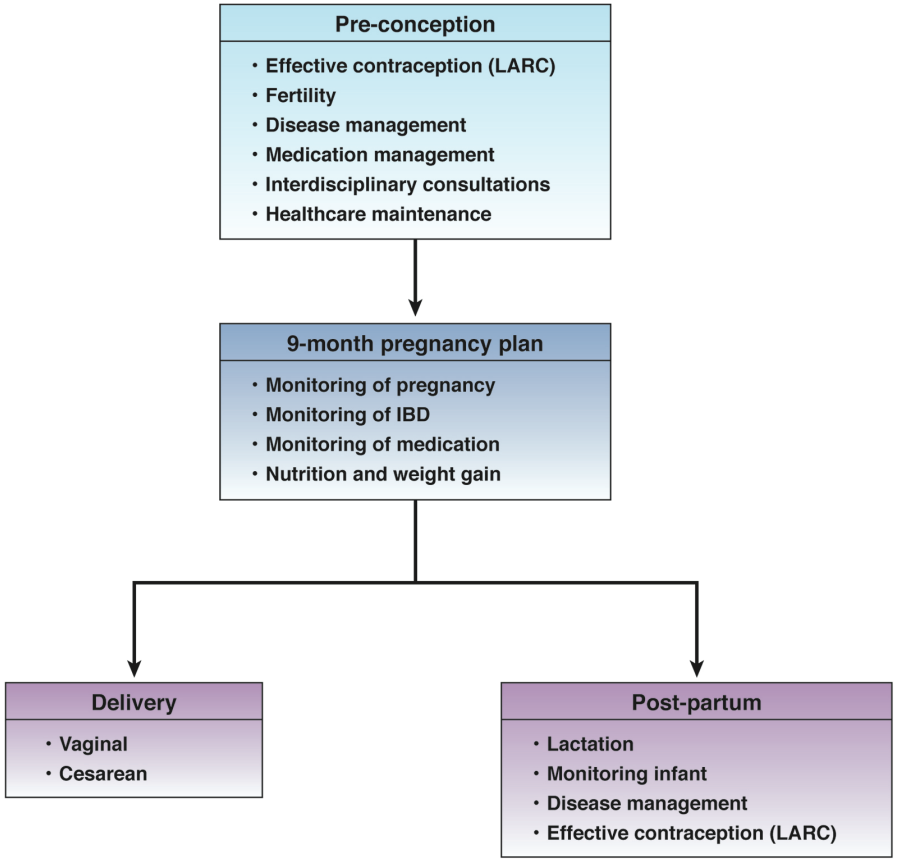
* Clinical Care Pathway for Pregnancy in IBD
  * Joint Statement among American Gastroenterological Association, Society for Maternal Fetal Medicine and the Crohns Colitis Foundation

* **IBDparenthoodproject.org**

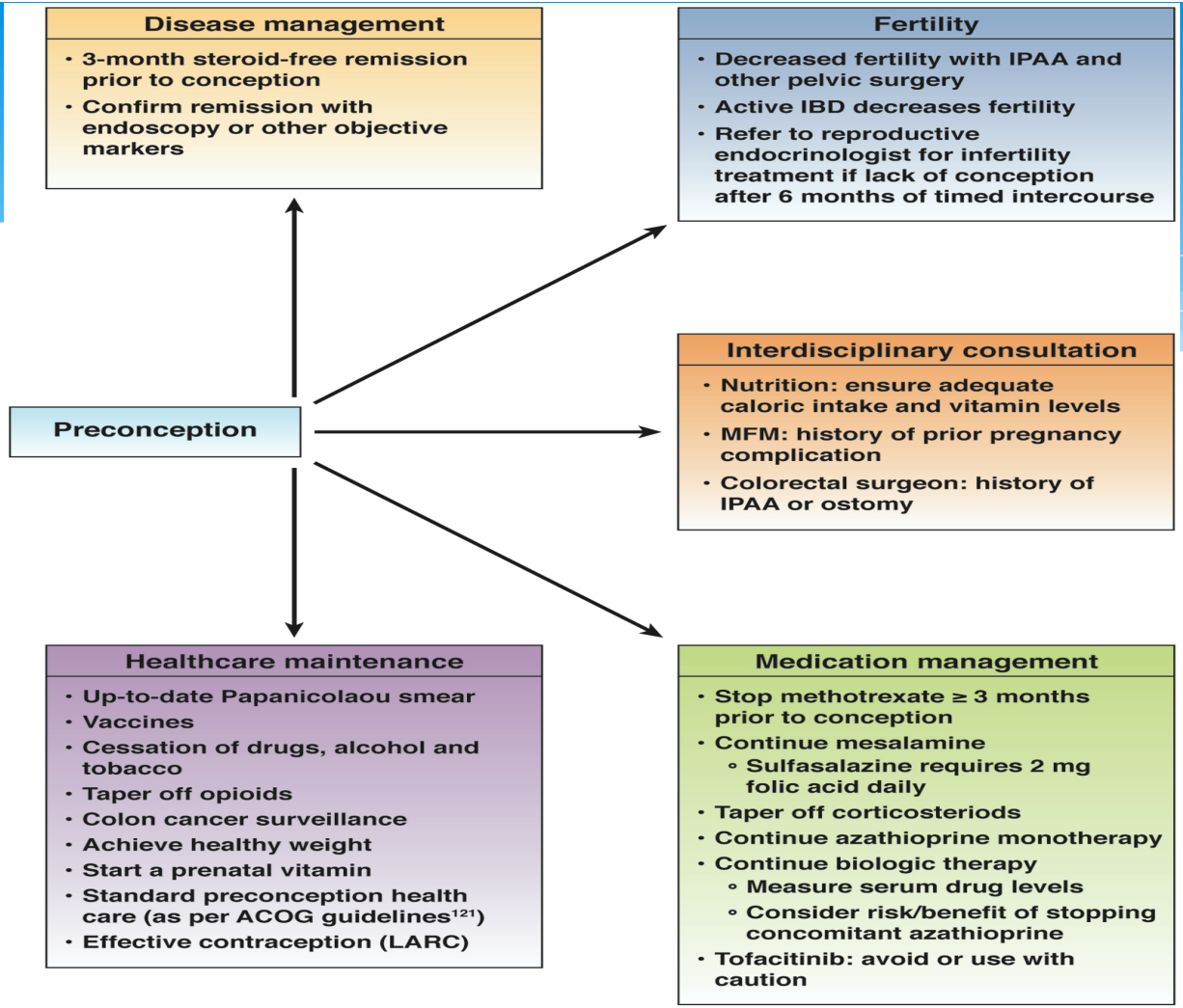
Mahadevan et al Gastroenterology. 2019 Jan 16. pii: S0016-5085(18)35437-4
Am J Obstet Gynecol. 2019 Apr;220(4):308-323..

AGA Institute Guideline on Inflammatory Bowel Disease (IBD) in Pregnancy

Clinical Decision Support Tool



ibd PARENTHOOD PROJECT



ibd PARENTHOOD PROJECT

Preconception care leads to less disease relapse during pregnancy

* Prospective study; 2008-2013
  * Females of reproductive age with IBD attending IBD Pregnancy Outpatient Clinic (POC)
  * Study group (n=149): preconception IBD POC counseling (30 minute consult)
  * Control group (n=105): patients attending IBD POC when already pregnant

N= 254	Control group (105)	Study group (149)	P value
Folate intake	46	87	0.0001
Smoking cessation	1	19	0.0001
Discontinuation of IBD meds due to concerns of side effects	8	0	0.0033
Periconceptual disease activity	16	12	0.68
Disease activity during pregnancy	34	20	0.04

De lima. Clin Gastroenterol Hepatol. 2016 Sep;14(9):1285-1292

Contraception

* Ideally, contraception should minimize use of oral contraceptives and estrogen
  * Variable absorption in Crohn's patients with small bowel disease
  * **Estrogen increases risks of VTE**
* Long-acting reversible contraceptives (LARC), are the most effective reversible contraceptive methods
  * Progesterone implants
  * Intrauterine devices
  * Depot medroxyprogesterone acetate injection

Fertility

* Rates of voluntary childlessness 17%[1]
* With both UC and CD, the risk of infertility prior to surgery appears to be similar to the general population [2]
  * Infertility in NE Scotland population based study
    * 15% UC (n= 138) *vs* 14% general population
    * 14% CD (n= 177) *vs* 14% general population
      * Surgical therapy:20% Medical therapy: 8%
* Olsen: 290 women with UC with IPAA[3]
  * After diagnosis of UC: FR = 1.01
  * After surgery IPAA: FR*= 0 .20

1. Selinger, J of Crohn's Colitis 2016 1151-8
2. Hudson, Int J Gynaecol Obstet 1997;58:229-37.
3. Olsen KØ, et al. *Gastroenterology.* 2002;122:15-19

Does laparoscopic IPAA reduce infertility compared with open approach?

* Cleveland Clinic: standardized fertility questionnaire all 18-44F with IPAA
* Infertility: 1 year
* 519/830 (58%) response rate
* 161: attempted pregnancy
* 18 lap IPAA and 143 open IPAA
* No difference in infertility (61% vs. 65%)
* Median time to pregnancy (3.5 monts vs. 9 months, p=0.01) reduced in pts with lap IPAA

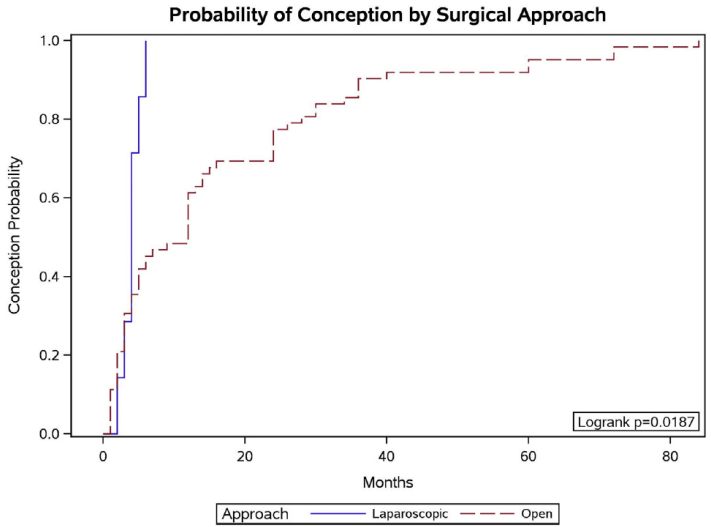


Figure. Kaplan-Meier curve for time to pregnancy for those attempting to conceive after laparoscopic and open IPAA.

Gorgun E Surgery. 2019 Oct;166(4):670-677. doi: 10.1016/j.surg.2019.04.045. Epub 2019 Aug 14

Fertility Treatment Less Successful in Women with IBD

* Nationwide cohort study Danish Health registries: Women with embryo transfer 1994-2013
  * 1360 ART in 432 UC, 554 ART in 182 with CD, 148,540 in 52, 489 without IBD
* Chance of live birth reduced in **UC** (OR = 0.73, 0.58-0.92) but not CD(0.77, 0.52, 1.14)
* Surgery for **CD** before ART treatment significantly reduced the chance of live birth for each embryo transfer (OR=0.51, 95% CI 0.29 to 0.91) [Not in UC]
* Children conceived through ART treatment by women with **UC**, increased Preterm birth
  * OR 5.29 (95% CI 2.41 to 11.63) in analyses including singletons and multiple births
  * OR 1.80 (95% CI 0.49 to 6.62) with only singletons

Norgard. .Gut 2016 May;65(5):767-76

Cannabis and Pregnancy

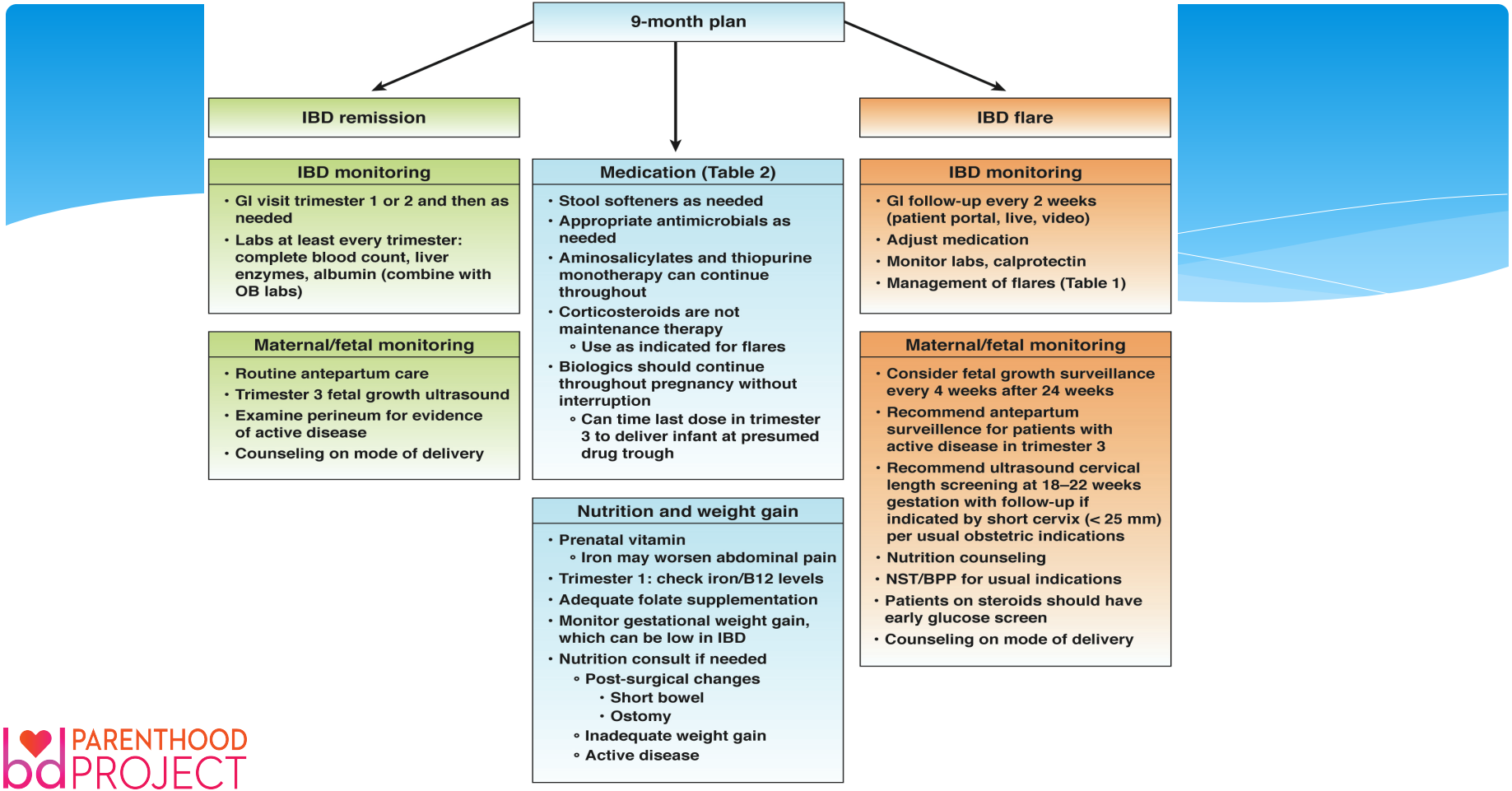
* The American College of Obstetricians and Gynecologists does not recommend or endorse the use of cannabis in pregnant patients because observational data show that cannabis use was associated with low birth weight and preterm delivery.[71]
* Meta-analysis that compiled data from 31 observational studies looking at maternal cannabis use found no difference in rates of low birth weight, preterm delivery, or perinatal death when controlling for tobacco use and other confounding variables. The authors concluded that maternal cannabis use is not an independent risk factor for adverse fetal outcomes, citing tobacco use as the main driver for poor outcomes.[72]
* Analysis of breast milk from mothers using cannabis detected THC up to 6 days after last use; the concentrations were directly related to the intensity and frequency of use, and the authors suggested that this may influence brain development during this period.

Swaminath Inflamm Bowel Dis 2018

ACOG Opinion: Use of Low Dose Aspirin

* Low-dose aspirin (81 mg/day) prophylaxis is recommended in women at high risk of preeclampsia
  * Initiated between 12 weeks and 28 weeks of gestation (optimally before 16 weeks) until delivery
* Low-dose aspirin prophylaxis should be considered for women with risk factors for preeclampsia
  * One high risk factor for preeclampsia
    * history of preeclampsia, multifetal gestation, renal disease, autoimmune disease, type 1 or type 2 diabetes, and chronic hypertension
  * Or more than one of several moderate-risk factors
    * first pregnancy, maternal age of 35 years or older, a body mass index greater than 30, family history of preeclampsia, sociodemographic characteristics, and personal history factors)
* In the absence of high risk factors for preeclampsia, current evidence does not support the use of prophylactic low-dose aspirin for the prevention of early pregnancy loss, fetal growth restriction, stillbirth, or preterm birth.

ACOG Committee Obstet Gynecol. 2018 Jul;132(1):e44-e52
Rolnik, August 17, 2017 N Engl J Med 2017; 377:613-622



ibd PARENTHOOD PROJECT

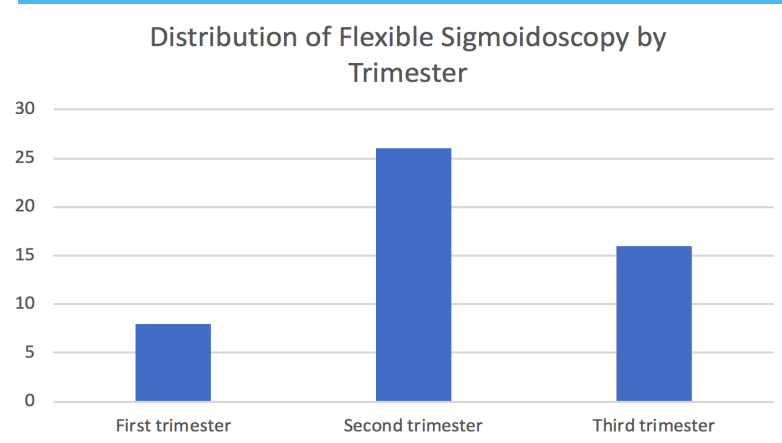
Abbreviations used: NST, Nonstress test; BPP, Biophysical profile

Managing Flares

Laboratory Values	Endoscopy	Radiologic imaging	Surgery	Medication

• Standard IBD labs checked
• Trends for CRP and ESR may be helpful
• Fecal calprotectin
• Serum drug concentrations
• Possibly elevated in pregnancy:
  ○ ESR
  ○ CRP
  ○ Alkaline phosphatase (also elevated in lactation)
• Reduced in pregnancy:
  ○ Hemoglobin
  ○ Albumin
	• Perform for strong indications:
	  ○ Determining IBD disease activity
	  ○ When result will change management
	• Flexible sigmoidoscopy is preferred over pan-colonoscopy when possible; can be performed unsedated, unprepped, and in any trimester
		• MRI and CT have similar diagnostic accuracy for assessing IBD
		• Gadolinium should be avoided in pregnancy
		• The cumulative radiation exposure of a single CT scan (about 50mGy) is below the level of concern
		• Ultrasound, where available is appropriate for terminal ileal disease
			• Surgical intervention may be needed for:
			  ○ acute refractory colitis
			  ○ perforation
			  ○ abscess
			  ○ severe hemorrhage
			  ○ bowel obstruction
				• Manage similar to non-pregnant IBD patients
				<u>Exceptions:</u>
				• Thiopurine-naïve patients: avoid first start in pregnancy due to concerns for distinctive rare adverse reactions
				• Methotrexate contraindicated
				• Tofacitinib – Avoid due to limited human data

Safety of Flexible Sigmoidoscopy in Pregnant Women with IBD



Median age (years)	33 [interquartile range 30.1 – 35]	
Median gestational Age (weeks) [Range]	23 [1-36]	
Median scope insertion [Range]	30 cm [15-40]	
Hospitalizations or Adverse Events within 4 weeks of Lower Endoscopy	Crohn's Disease	0
	Ulcerative Colitis	0
	Non-IBD	0

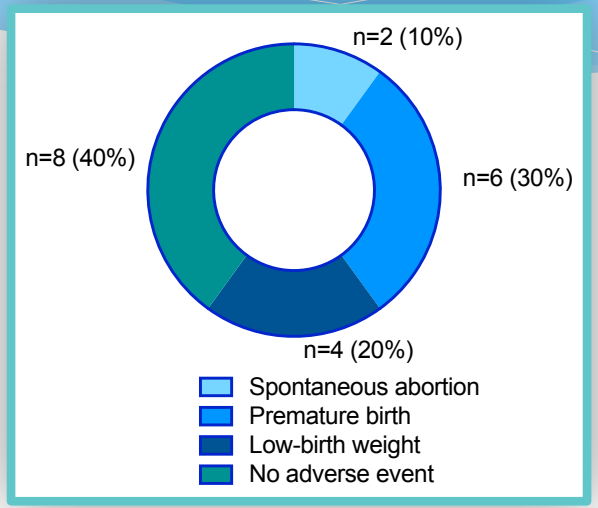
Impact of Endoscopic Findings

	N (%)	Added Systemic Steroids	Increased biologic dose	New biologic start	Switched biologic
Total	43	7 (16.3%)	1 (2.3%)	14 (33%)	1 (2.3%)
Remission	5 (11.6%)	0	0	0	0
Mild	11 (25.6%)	0	0	2 (18.2%)	0
Moderate	7 (16.2%)	1 (14.3%)	0	1 (14.3%)	0
Severe	20 (46.5%)	6 (30.0%)	1 (5.0%)	11 (55.0%)	1 (5.0%)

Ko et al. Dig Dis Sci. 2020 Feb 7.

Acute Severe UC responds to conventional steroid and anti-TNF therapy in pregnancy

- **Method**
  - Retrospective study 2003-2018
  - Primary end-point colectomy free survival
  - Secondary endpoints management and outcomes
- **Results**
  - Colectomy free survival (n=20)
    - 90% at 6 months
    - 84% at 1 year
    - 64% at 4 years
  - All treated with iv corticosteroids
  - 50% inpatient anti-TNF
  - Adverse pregnancy outcomes were seen in 60%
  - This data pooled with two case series identified by systematic review indicates a **colectomy rate at index admission of 7.7% (3/39)**
- **Conclusion**
  - Conventional therapy is safe and effective in pregnancy



Ollech J et al. Presented at DDW. Abstract Su1940

IFX: infliximab HR: Hazard ratio CI: Confidence interval

COVID-19 not increased in IBD

* NYC matched case-control analysis reveals IBD patients did not experience more severe COVID-19.
  * **Older age** was a risk for emergency care or hospitalization.
  * **UC** was associated with greater risk of severe disease
  * Baseline IBD activity nor biologic medication predicted need for higher level of care.
* IBD pts less dyspnea or severe outcomes than matched non-IBD controls (less obesity and COPD)
* Increased prevalence of GI manifestations of COVID-19 with the IBD population
* **Similar overall infection rates** in IBD patients and the general pandemic epicenter population
  * moderate-to-severe **IBD activity and corticosteroid use** associated with higher rates of COVID-19.

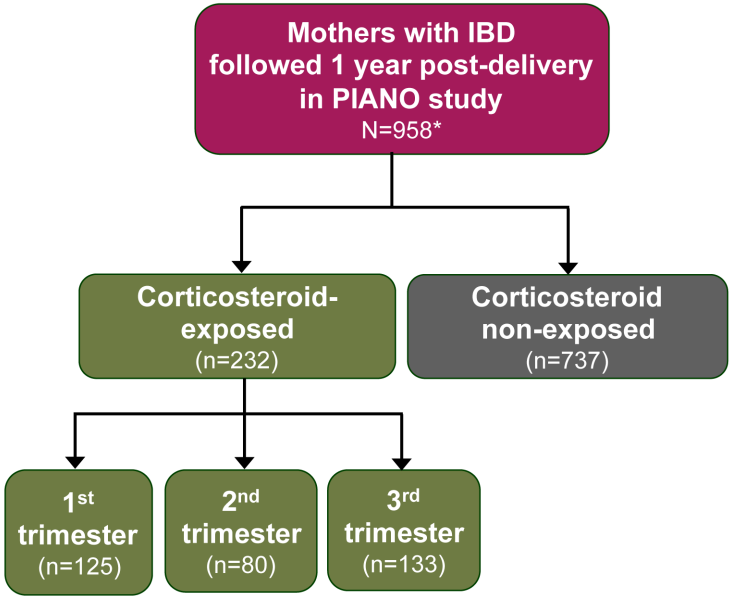
* **Acute severe UC during first trimester of pregnancy with concurrent COVID-19.**
  * Treated with IV methylprednisolone, transitioned to oral prednisone.
    Readmitted 2 days later, RT-PCR positive for SARS-CoV-2 by nasopharyngeal swab
  * Day 5, pleuritic chest pain, treated with azithromycin, hydroxychloroquine, initiated cyclosporin.
  * Day 9 fetal demise.

Lukin D et al Gastro 2020
Rosen M Inflamm Bowel Dis. 2020 May 1

COVID-19 Pregnancy Summary for Patients

* IBD patients on biologic therapy do not seem to be at increased risk of COVID compared to others their age
  * Older age, comorbidities, steroids, disease activity increase risk
* Pregnant women are at increased risk of COVID related adverse outcomes
  * Continue your pregnancy appropriate IBD therapy to maintain remission
  * Increase precautions and social distancing during pregnancy

PIANO: Pregnancy Outcomes Amongst Mothers With IBD Exposed to Systemic Corticosteroids (CS)



*417 completed 1-year questionnaire

Outcomes Significantly Associated with Corticosteroid Exposure During Pregnancy

Outcome	Odds Ratio (95% CI)
Preterm birth	1.8 (1.0–3.1)
Low birth weight	2.8 (1.3–6.1)
Gestational diabetes	2.8 (1.3–6.0)

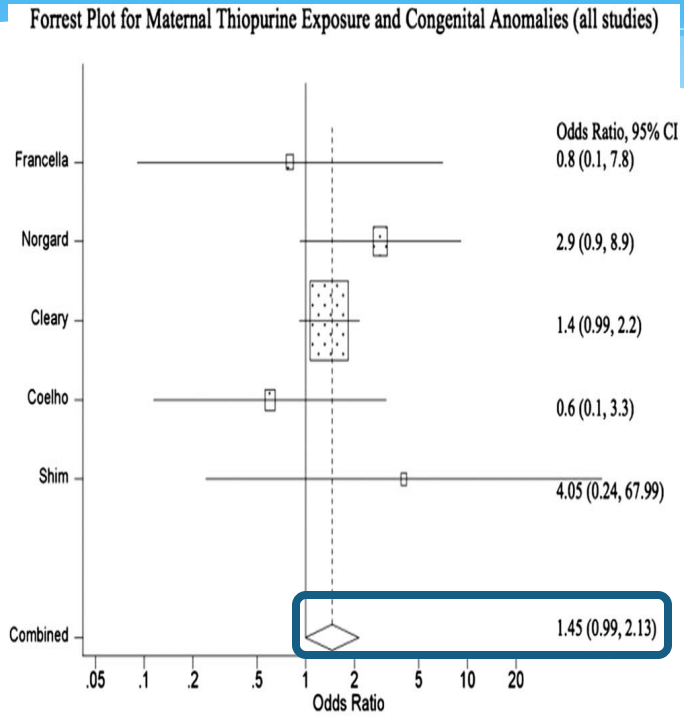
Outcomes *Not* Significantly Associated with Corticosteroid Exposure During Pregnancy

Outcome
Infections
Congenital malformations • Analyzed as any corticosteroid exposure vs unexposed and 1st-trimester exposed vs 1st-trimester unexposed • 4 cleft palates reported in non-steroid group only
Developmental delay

Lin K, et al. Presented at DDW; May 3, 2014 Abstract 2.

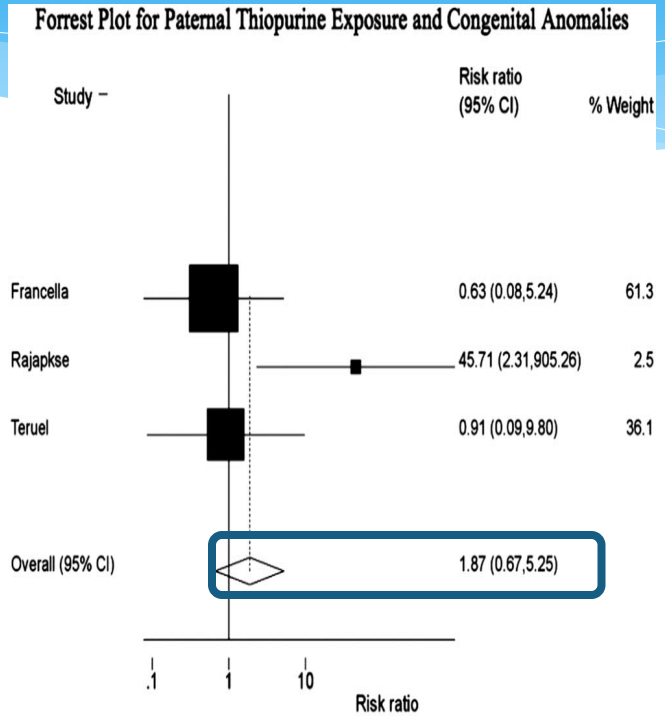
Thiopurines and Congenital Malformations: Meta-Analysis

Maternal



Test for heterogeneity: Q = 3.315, df = 4 (p value = 0.506), I^2 = 0%

Paternal



Test of heterogeneity: χ^2 5.76, df = 2 (p-value 0.056)

Akbari et al Inflamm Bowel Dis 2013;19:15–22

PIANO:

A 1700 Patient Prospective Registry of Pregnancy Outcomes in Women with IBD

Uma Mahadevan, Millie Long, Sunanda V. Kane MD, Abhik Roy MD, Marla C. Dubinsky MD, Bruce E. Sands MD, Russell D. Cohen MD, Christina D. Chambers PhD, William J. Sandborn MD &

Crohn's Colitis Foundation Clinical Research Alliance

CCF Clinical Research Alliance

PIANO@UCSF.EDU

Adverse Pregnancy Outcomes

	N	Group A AoR (CI)	Group B	Group AB
Any Complication	364	1.21 (0.78,1.87)	1.09 (0.76, 1.56)	1.38 (0.87, 2.17)
Spontaneous Abortion	61	1.07 (0.40,2.84)	1.25 (0.56, 2.72)	1.00 (0.34, 2.97)
Preterm Birth	203	1.21 (0.70, 2.07)	0.74 (0.50, 1.18)	1.68 (0.98, 2.9)*
Low Birth Weight	123	0.94 (0.46, 1.93)	0.94 (0.53, 1.66)	1.22 (0.60, 2.51)
IUGR	51	0.64 (0.19, 2.13)	1.12 (0.48, 2.61)	1.12 (0.37, 3.41)
Cesarean section	558	1.20 (0.84, 1.7)	1.25 (0.95, 1.66)	1.58 (1.09, 2.29)**
NICU	178	1.35 (0.74, 2.4)	1.21 (0.74, 1.98)	1.49 (0.81, 2.76)
Congenital Anomaly	103	1.08 (0.61, 1.92)	0.89 (0.55, 1.45)	1.10 (0.59, 2.06)

Adjusted for none/mild vs. mod/severe disease activity
Similar results when B=atnf only

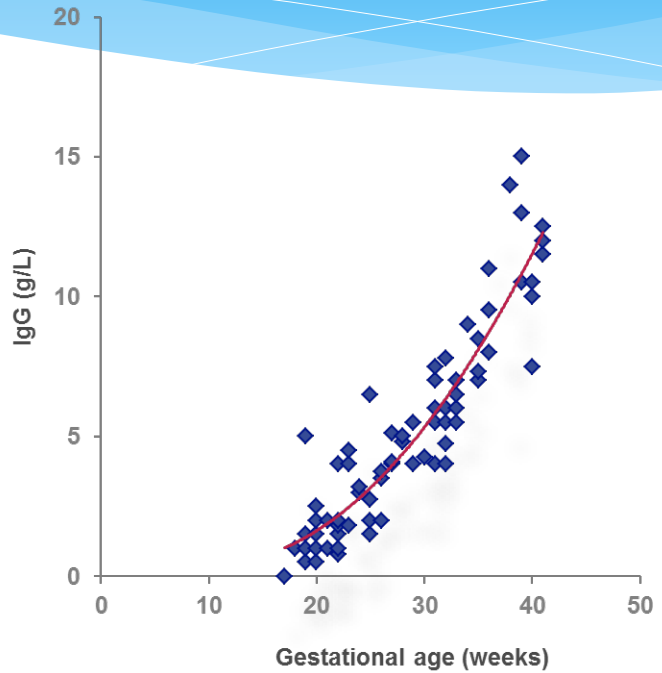
*P <0.058; **P.016

Biologics

Human Placental Transfer

- Active transport of IgG one way across the placenta by the neonatal FcRn receptor which binds to the CH2 and CH3 domain of the Fc
  - All 4 subclasses of IgG can pass to the foetus
- Preferential transfer of IgG1
  - 3rd trimester: IgG represents a major component of the umbilical venous blood[1] with the majority of transfer occurring in the 3rd trimester
- IgG transferred via the placenta will persist longer in the newborn than the mother
  - Half-life of IgG in newborns is twice as long as the mother at 48.4 days[2]

Distribution of IgG concentration during gestation in the umbilical vein[1]



[1]Malek et al. Am J Reprod Immunol. 1994;32(1):8-14
[2]Sarvas et al. J Clin Immunol. 1993;13:145-151

Slide Courtesy of Andrew Nesbitt

Placental Transfer of Biologic Therapy

Drug	N	Mean Infant: Maternal Ratio at Birth mcg/ml	% infants with >10 mcg/ml at birth
Infliximab	68	2.4 [0-6.3]	91%
Adalimumab	44	1.4 [0-3.5]	41%
Certolizumab	17	0	0
Vedolizumab	7	0.7 [0.4-1.4]	29%
Natalizumab	4	0.5 [0-0.7]	0
Ustekinumab	3	1.4 [1.4-1.4]	0

Risk of Infections

* **There was no significant association between risk of infection and drug levels at birth**
  * Infant, maternal or cord levels
  * Infection risk at 4, 9,12 months
  * Including or excluding otitis media (most common infection)
  * Drug level as continuous variable or by category

What is the data on TNF in pregnancy?

Study	Study Design	Number
TREAT	Prospective North American registry 1999-2012	99
EVASION	Retrospective study of French national health database 2011-2014	1457
TEDDY	Retrospective multicentre European cohort study 1999-2014	388
PIANO	Prospective USA registry	799

- Anti-TNF use may be associated with increased maternal complications including infection,confounded by disease activity.
- No association with anti-TNF use and congenital abnormalities, infant infections or lack of vaccine response
- Discontinuation of anti-TNF before week 24 increases the risk of disease flare.

Lichtenstein G et al Am J Gastro 2018; Luu et al *Am J Gastro* 2018; Chaparro et al Am J Gastro 2018;

Stopping TNF INCREASES Maternal Disease but No Impact On Infant infections

* Retrospective cohort French National Health Database (SNIRAM)
* IBD Pregnancies 2011-2014 (n= 8726), 12.9% (n=1457) TNF exposed
  * Adjusted for disease severity, steroids, age, IBD type, duration and use of 6mp

1073 Exposed versus 7523 Not Exposed					
	Composite	**All Infections (mom)**	In-hospital infections (mom)	Child Infection	Child In-hospital infection
Anti-TNF in T3	**1.66 [1.40-1.95]**	**1.42 [1.24-1.64]**	**1.31 [1.09-1.59]**	0.89 [0.76-1.05]	0.85 [0.64-1.13]
Severe Disease	**2.95 [2.18-3.99]**	**1.63 [1.20-2.20]**	1.35 [0.92—1.99]	1.04 [0.72-1.51]	1.35 [0.75-2.41]
Disease Relapse T3	**1.40 [1.09-1.81]**	**1.82 [1.48-2.25]**	1.15 [0.86-1.54]	**1.32 [1.04-1.69]**	**1.54 [1.08-2.21]**

Luu M, Am J Gastroenterol. 2018 Jul [epub]

Early Withdrawal of Adalimumab During Pregnancy is Associated with Increased Risk of Flare in IBD

- **Methods**
  - Retrospective study of all deliveries recorded in the Truven Health Analytics MarketScan® database 2011-2015
  - Compared pregnancy outcomes between IBD patients who discontinued adalimumab (ADA) 90 days or more before delivery (**"Early ADA"**) and those who continued ADA closer to the delivery date or throughout the pregnancy (**"Late ADA"**)

- Results
  - 551 deliveries included
  - There was no difference in the number of flares requiring emergency room visits or hospitalization
  - There were significantly more steroid prescriptions filled among patients in the Early ADA group after ADA discontinuation
  - No significant difference was noted in neonatal outcomes
  - Rates of major congenital anomalies were 11% in the Late ADA group vs 8% in the Early ADA group (*P*=0.2)*

Outcomes in the Late ADA and Early ADA groups

	Late ADA group N= 406 (74.2%)	Early ADA group N=142 (25.8%)	p-value
Age (SD) years	29.1 (5.1)	29.7 (4.5)	0.16
Inpatient flare	0	0	n/a
Emergency room admissions	0	0	n/a
New steroid prescriptions	11(1.7)	24(16.9)	<.001
Preterm birth	29 (7.09)	12(8.45)	.56
Intrauterine retardation	66(16.4)	26 (18.31)	.55
Stillbirth	4 (0.98)	1 (.7)	.08
Fetal abnormalities*	157 (38.39)	55(38.73)	.94

*

CONCLUSION

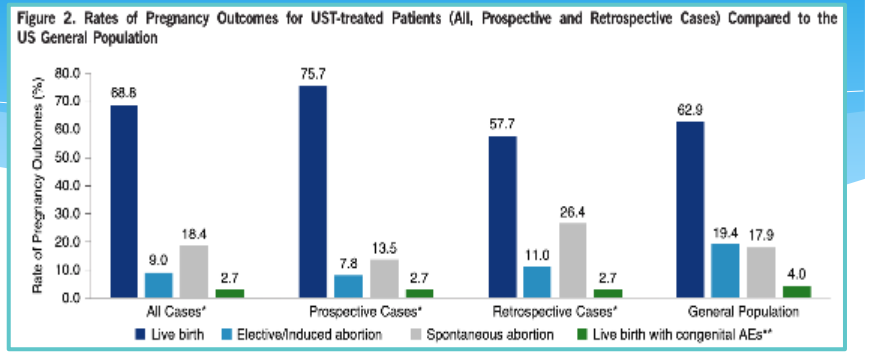
- Early withdrawal of ADA during pregnancy is associated with an increased risk of flare in IBD
- The continuation of ADA closer to delivery appears safe

Truta, *et al.* Presented at DDW. May 2020. Abstract Sa1857. *B. Truta, personal communication, May 13, 2020

ADA, adalimumab; IUGR, intrauterine growth retardation; SGA, small for gestational age

Exposure to Ustekinumab During Pregnancy Appears Low Risk

- **Methods**
  - Pregnancies with exposure to ustekinumab during pregnancy or within 3 months prior to conception reported to the manufacturer through April 2019
  - Data:spontaneous reporting, clinical studies, registries



- **Results**
  - 478 pregnancies (334 PsO, 124 CD, 11 UC, 9 PsA) were reported
  - 71.7% resulted in live births
  - The rate of spontaneous abortion (SA) was 18.4%
  - The rate of congenital anomalies (CA) was 3.9%
  - Pregnancy outcome rates in women with CD/UC and PsO/PsA were similar

	Total Cases (N=478)	
	n/N (%)	Congenital Anomaly
Live Birth[a]	341/478 (71.3%)[b]	12
Elective/Induced Abortion[c]	42/478 (9.0%)	1
Spontaneous Abortion[d]	88/478 (18.4%)	3
Ectopic pregnancy	3/478 (0.63%)	0
Still birth	2/478 (0.42%)	1
Ongoing (fetal congenital anomaly)	1/478 (0.21%)	1
Total	100%	18

- **Conclusion**
  - **Pregnancy outcome data following maternal exposure to UST show that the prevalence of live births, SA and major CA are consistent with the general population**
  - **Exposure throughout pregnancy was not associated with apparent safety signals**

Volger, *et al*. Presented at DDW. May 2020. Abstract

CA, congenital anomaly; PsO, psoriasis; CD, Crohn's disease; UC, ulcerative colitis; PsA, psoriatic arthritis; SA, spontaneous abortion; UST, ustekinumab

Vedolizumab

- Half-life 25 days
- VDZ clinical development program: 27 June 2013
  - 27 pregnancies in females
    - 25 in patients with UC or CD
    - 2 in healthy volunteers
    - 24 VDZ-treated females, 12 resulted in live births (2 PTB)
    - congenital anomaly: agenesis of the corpus callosum reported in healthy volunteer conceived 79 days after receiving single dose VDZ
  - 20 pregnancies in the partners of male patients
    - 16 VDZ-exposed partner pregnancies: 9 live births, 2 SAB, 2 EAB, and 3 undocumented outcomes at the last follow-up.

Mahadevan Aliment Pharm Therap 2017 Apr;45(7):941-95

- Retrospective multicenter study (CONCEIVE)
- 79 VDZ; 186 TNF; 184 unexposed
- VDZ group had more disease activity at conception
- No difference in spontaneous abortion, preterm birth, low birth weight and congenital anomalies among groups

Moens, A. APT Nov 6, 2019 epub

Tofacitinib

* Oral, small molecule janus kinase inhibitor
  * Feticidal and teratogenic in rats and rabbits at exposures 73 times and 6.3 times greater, respectively, than the human dose of 10 mg BID
* Across indications:
  * 158 cases of maternal/paternal exposure in clinical trials
    * 96 healthy newborns
    * 1 congenital malformation (pulmonary valve stenosis)
    * 19 spontaneous abortions and 13 TAB
  * 28 (RA) and 17 (?) post-marketing exposure during pregnancy
    * 5 healthy newborns
    * 1 congenital malformations of ventricular septal defect
    * 3 spontaneous abortions; 1 TAB
* In IBD Clinical trials: 11 maternal, 14 paternal exposure
  * Maternal: 2 SAB, 2 TAB, 4 healthy newborn, 3 pending
  * Paternal: 11 healthy newborn, 3 pending

Mahadevan, et al Inflamm Bowel Dis 2018

Method of Delivery

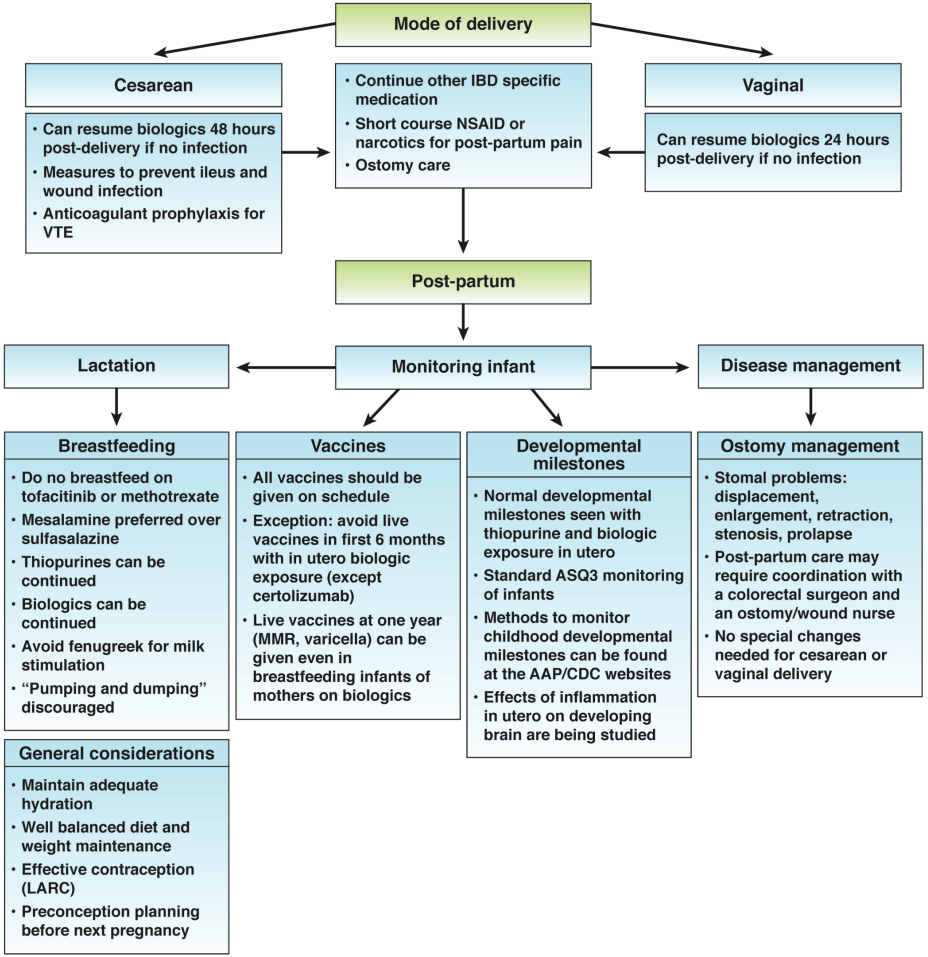
- Delivery should be at the discretion of the obstetrician
  - Most women with IBD can have an uncomplicated vaginal delivery
  - In nulliparous women, induction at week 39 led to lower rates of Caesarean section[1] [ARRIVE Study. 18.6% vs. 22.2%; relative risk, 0.84; 95% CI, 0.76 to 0.93]
- Exceptions:
  - Women with active perianal disease should have a cesarean section.
    - Women with inactive perianal disease may deliver vaginally without increased complications[2]
    - Rectovaginal fistulas?
  - Women with an ileoanal J pouch should consider cesarean section, though vaginal delivery is possible[3]
    - Preserve sphincter function and continence later in life

1. Grobman **N Engl J Med 2018;379:513-23.**
2. Cheng **Inflamm Bowel Dis. 2014 Aug;20(8):1391-8**
3. Juhasz ES et al. Dis Colon Rectum. 1995;38:159-165..

Induction at 39 weeks gestation

* ARRIVE: multicenter trial, randomized low-risk nulliparous women who at 38 weeks 0 days to 38 weeks 6 days of gestation to labor induction at 39 weeks 0 days to 39 weeks 4 days or to expectant management.
  * Primary outcome composite of perinatal death or severe neonatal complications
  * Secondary outcome was cesarean delivery.
* 3062 women labor induction vs 3044 assigned to expectant management.
* Primary outcome: 4.3% induction vs 5.4% expectant-management (RR, 0.80; 95% CI, 0.64 to 1.00)p=0.049
  * **Respiratory support** 3% vs. 4.2% 0.71 (0.55–0.93)
* Frequency of **cesarean delivery was significantly lower** in the induction group than in the expectant-management group (18.6% vs. 22.2%; relative risk, 0.84; 95% CI, 0.76 to 0.93).

Grobman August 9, 2018
N Engl J Med 2018; 379:513-523



Abbreviations used: IBD, inflammatory bowel disease; NSAID, nonsteroidal anti-inflammatory drugs; MMR, measles, mumps, rubella; AAP, American Academy of Pediatrics; CDC, Centers for Disease Control and Prevention

Breast Feeding While Taking AZA/6MP

* 8 lactating women received Aza 75-200 QD
  * Milk and plasma at 30, 60 min and every hour x 5
* Variation in bioavailability reflected in wide range in milk an plasma first 3 hours
* Major excretion in breast milk within 4 hours of drug intake
* Worst case scenario: max concentration 0.0075 mg/kg
  * In most cases, will be <10% of maximum concentration

Christensen S et al. *Aliment Pharmacol Ther*. 2008:28, 1209-1213.

Very Low Levels of Biologics Are Detected in Breast Milk, But Do Not Adversely Affect Infant Outcomes: PIANO Registry

Methods

- 1-year post-partum follow-up (N=787 women)
  - 75% breastfed

Results

- Disease activity and immunomodulator use, but not biologic use, inversely associated with likelihood of breast feeding

Detection of Biologics in Breast Milk

Biologic	N Detectable in Breast Milk (%)	Peak Time After Infusion (hr)	Range (µg/ml)
Infliximab	18/27 (67)	24-96	0–.680
Adalimumab	2/15 (13)	12-24	0–.710
Certolizumab	3/10 (30)	12-48	0–0.29
Ustekinumab	1/3 (33)	24	0–1.57
Golimumab	0/1 (0)	—	
Natalizumab	0/1 (0)	—	

Breastfeeding while on biologics does not inversely affect infant growth, developmental milestones and infection rate

Matro, R Gastroenterology 2018

Vedolizumab Present in Low Levels in Human Breast Milk[1]

Background: Vedolizumab has been previously detected in breast milk in two small studies and, moreover, is thought to be further degraded by intestinal proteolytic activity[2]

Figure 1: Mean VDZ Milk Concentration Over Time

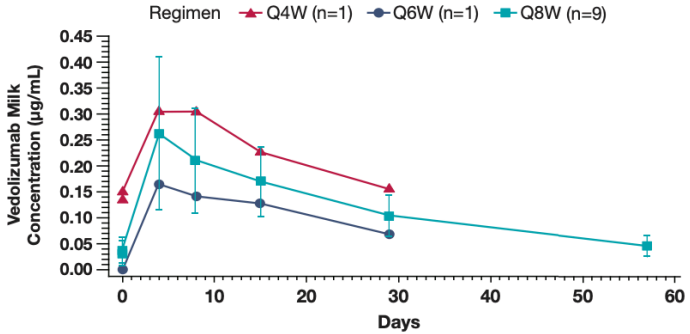


Table 1: Pharmacokinetics on q8 week dosing	C_{max}	Daily Infant Dose (mg/kg/d)	% Maternal Dose
N	9	7	7
Median (Range)	0.21 (0.10-0.56)	0.02 (0.01-0.03)	23.5 (11.4-30.0)

1. Sun W, et al. Presented at DDW. May 2020. Sa1831.
2. Lahat A, et al. JCC. 2018; 12(1):120-123.

Methods

- Open-label, multicenter, post-marketing milk-only study
- ELISA concentration of VDZ in breast milk in women exclusively breastfeeding while on VDZ maintenance

Results

- N=11
- Mean vedolizumab concentrations rose after administration with median time to peak at 3-4 days with subsequent exponential drop (Figure 1)
- Estimated daily dose on 8-week dosing interval was 20.9% of maternal dose (Table 1)
- Estimated ratio of mean VDZ milk to serum concentration (0.4%-2%) is similar to other IBD monoclonal antibodies

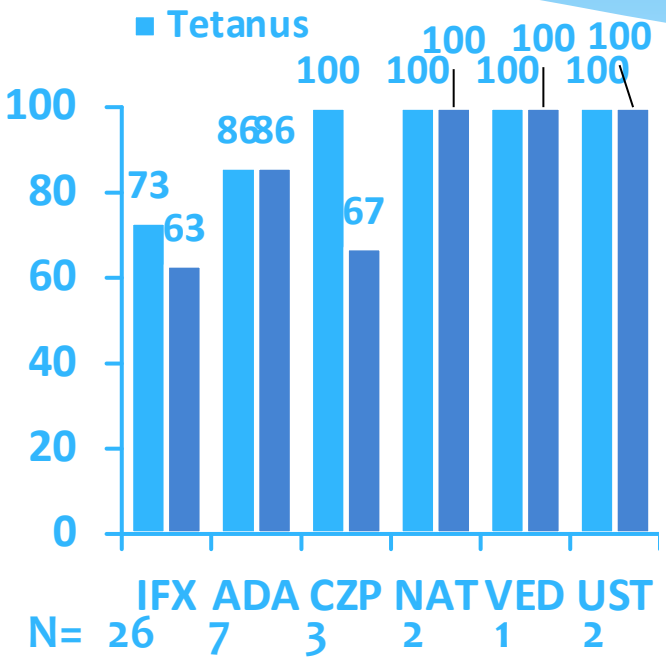
Conclusion

- Vedolizumab is present in human breast milk at a low level

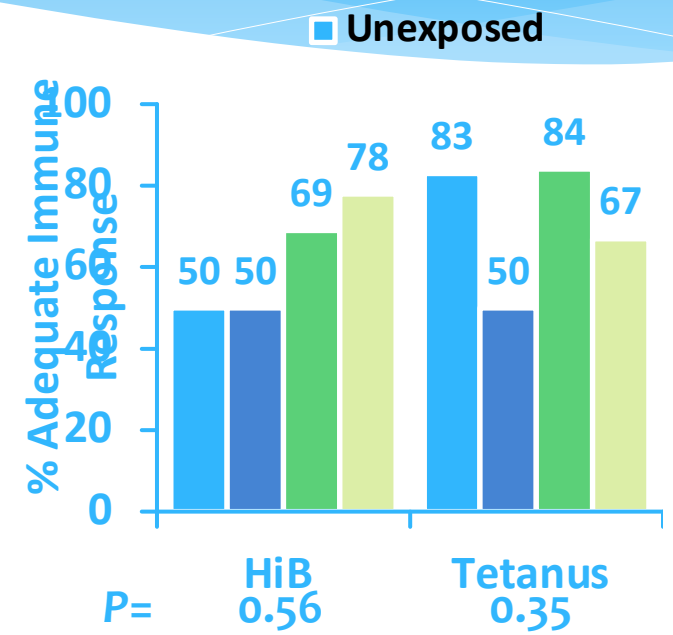
VDZ, vedolizumab; ELISA, enzyme-linked immunosorbent assay

PIANO Registry: Maternal Immunomodulators or Biologics Do Not Impact Vaccine Response

No Difference in Vaccine Response Rate Across Different Biologics



No Difference in Rates of Serologic Response to HiB or Tetanus Groups



Beaulieu, Ananthakrishnan, et al. Clin Gastro Hep, 2017

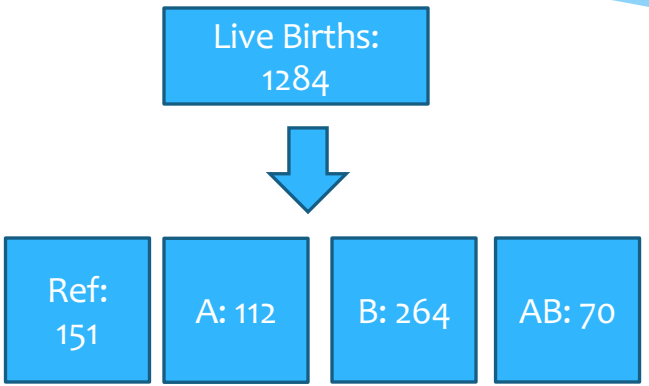
Rotavirus Vaccination

* 43 biologic exposed infants
  * 2 ADA, 1 CZP reaction unknown
  * 7/40 (17.5%) reaction

Drug	N	Reaction	Type	Levels (µg/ml)
Infliximab	19	6 (32%)	Fever (5) Diarrhea (1)	Diarrhea: 72 (0), 5 (3) NR: 44, 11, 42,28,22. 69
Adalimumab	7	1 (14%)	Fever	No reaction: 14, 7
Certolizumab	12	0	None	No rxn: BLOQ x 5
IFX/CZP	1	0	None	--
Ustekinumab	1	0	None	40

PIANO: Achievement of Developmental Milestones Among Offspring of Women with IBD

In utero exposure to immunomodulator and biologic therapy was not associated with developmental delay compared to unexposed infants or general population

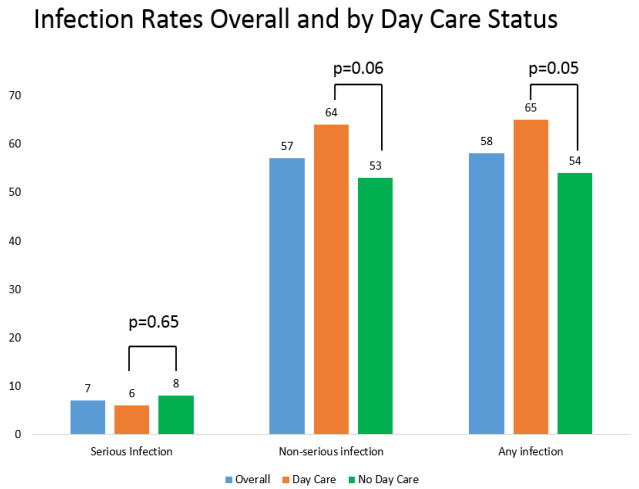


- Compared to IBD Reference Population:
  - Group A and B infants scored similarly to unexposed at 12, 24, 36, and 48 months
  - Group AB infants statistically higher 12, 48m communication, lower 24m fine motor scores
- Compared to Population means
  - Group A and AB were similar or higher through 48 months
  - Group B: statistically higher scores across all ASQ3 domains at all time points

Roy, A. DDW 2017

Daycare?

* 310 maternal-child pairs from PIANO
* 39% attended day care in year 1
* Characteristics of mothers and infants were similar by day care status
* Children in day care had a higher rate of any infection
  * No difference in serious infection vs. those not in day care
* Biologic use was not associated with any infection in children in day care



Long, M. ACG 2019

Summary

* Pre-conception planning and education is key
  * Patients should be in remission prior to pregnancy
  * Discussion on fertility, medication, delivery plan
  * Multidisciplinary: OB, MFM, Pediatrics
* Immunomodulators and Biologics allow refractory patients to achieve remission and conceive
  * Adverse events do not seem to be greater than in unexposed pregnant women with IBD
  * Can be continued through pregnancy and postpartum
* Children
  * Excellent developmental milestones
  * No live vaccines for 6 months if biologics but all other vaccines can and should be given

PIANO@UCSF.EDU

2018 NCSCG 15TH ANNUAL POST-DDW SYMPOSIUM

Case Vignettes

Case 1: Moderate to Severe UC

- 42M with newly diagnosed panulcerative colitis.
  - 6-8 BM per day with blood
  - Colonoscopy with Mayo 2 disease throughout the colon
  - Failed mesalamine 4.8 gm
- What would be your next step?
  - Prednisone 40 mg daily with taper and maintain on mesalamine
  - Azathioprine 2.5 mg/kg
  - Infliximab (+/- immunomodulator?)
  - Adalimumab (+/- immunomodulator?)
  - Vedolizumab (+/- immunomodulator?)
  - Ustekinumab (+/- immunomodulator?)
  - Tofacitinib (+/- immunomodulator?)

- Patient achieved clinical remission on vedolizumab monotherapy
  - Flex sig at 12 weeks showed Mayo 0
  - Histology showed mild activity and calprotectin was mildly elevated at 190
  - Patient is asymptomatic
- What would you do?
  - Nothing
  - Check a vedolizumab level and optimize
  - Add an immunomodulator
  - Switch to another therapy

- You chose to continue vedolizumab monotherapy (level 16 mcg/ml)
- The patient works in a school and is concerned about coronavirus. He wants to stop his therapy
- What do you tell him?
  - By all means, stop therapy!
  - Don’t go to work
  - Continue vedolizumab and observe social distancing and mask precautions. If the work place follows these guidelines he can return

- Though you told him he can continue, he chose to stop therapy. He now has a severe flare and was hospitalized. He was started on infliximab plus azathioprine and achieved endoscopic and clinical remission.
- Unfortunately, he lost his job and was without insurance for 6 months. During this time he was on no therapy and now again presents with a flare. Fortunately, he was re-hired by his school. What would you offer him?
  - Restart infliximab plus azathioprine every 8 weeks, no loading dose
  - Switch to ustekinumab
  - Switch to tofacitinib
  - Go back to vedolizumab

Case 2

- A 25F presents with a history of Crohn's ileocolitis for 8 years. She has been successfully managed on adalimumab monotherapy for the last 4 years. She now has developed perianal fistulas and on query notes her symptoms worsen in the few days before her injection.
  - Colonoscopy demonstrates mild to moderate inflammation of the ileum and moderate ulceration of the rectum
  - Serum drug level for adalimumab is 10 mcg/ml
- What is your next step?
  - Increase adalimumab to 40 mg weekly and add an immunomodulator
  - Switch to infliximab and immunomodulator
  - Switch to ustekinumab
  - Switch to vedolizumab
  - Switch to tofacitinib

- She was able to each endoscopic and symptomatic remission on adalimumab 40 mg weekly and azathioprine 2.5 mg/kg daily. Her fistulas healed with the aid of EUA, antibiotics and the above therapy. She now wants to conceive. What do you tell her?
  - She will need to stop azathioprine
  - She will need to stop adalimumab
  - She can continue both medications during pregnancy and lactation
  - She should switch to certolizumab