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Disclosures

Dr. Rubin: Consultant and/or Grant Support




- AbbVie
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- Bristol-Myers Squibb
- Celgene Corp/Syneos
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- Gilead Sciences
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- GSK (GlaxoSmithKline Services)
- Janssen Pharmaceuticals
- Lilly
- Mahana Therapeutics
- Narrow River Mgmt
- Pfizer
- Prometheus Laboratories
- Reistone
- Seres Therapeutics
- Shire
- Takeda
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- Techlab, Inc

Dr. Shah has indicated no relevant financial relationships.

1

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Positioning of Old and New Therapies in IBD

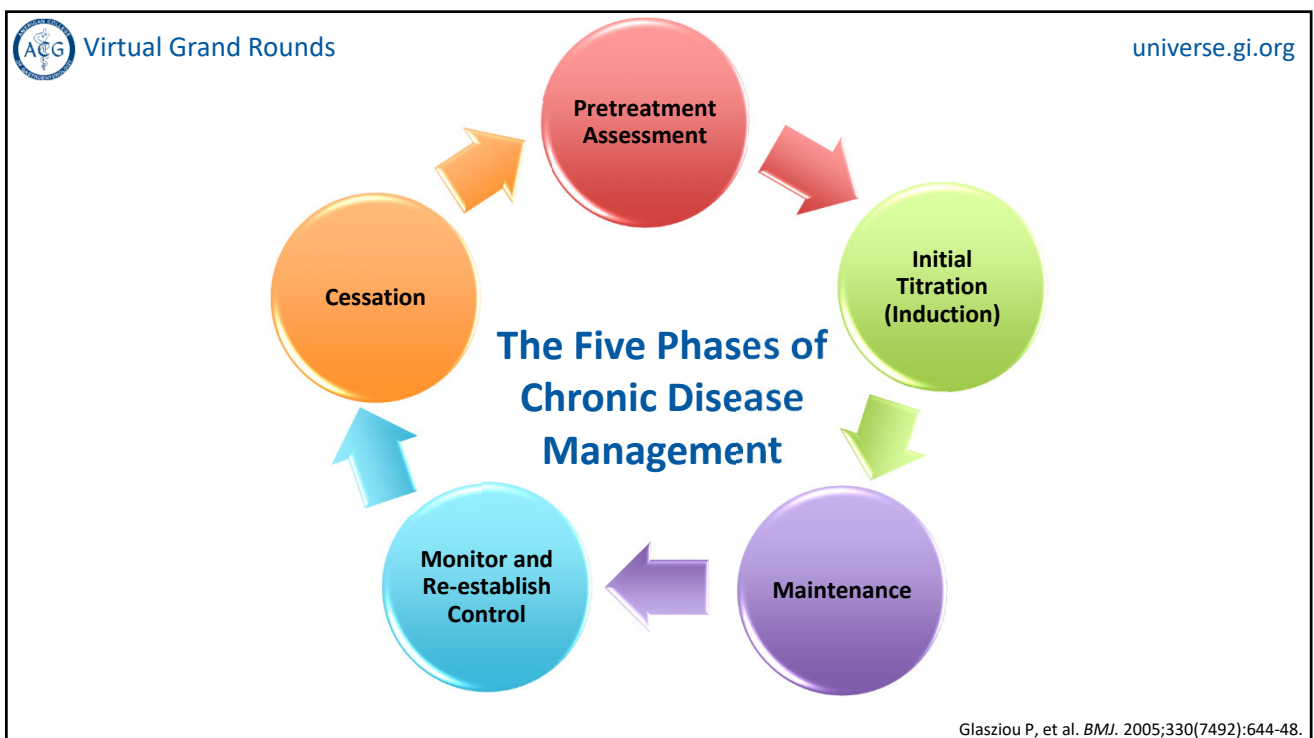
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 University of Chicago

 @IBDMD
 RubinLab.uchicago.edu

2



3



4



Prior Treatments for IBD: The “Really Old”

- Intracolonic insufflation of oxygen
- Gentian violet
- Tincture of iodine
- Sodium lauryl sulfate detergent to “destroy” trypsin or lysozyme
- Vaccines
- Azochloramid (“antibacterial” agent)
- Horse serum
- Copper sulfate
- Liver extracts
- Artificial fever therapy
- Hot (120°F) water enemas
- “Extracts” of hog intestine, stomach, and colon to “restore” an “intestinal protective agent”
- Zinc peroxide rectally
- Thiouracil drugs
- Hypnosis
- Neuroanalysis



From Kirsner, JB. Origins of the inflammatory bowel diseases, Oxford 2001.

5



Positioning Therapies in IBD c1950-1980s



Prednisone → Sulfasalazine

Sulfasalazine → Prednisone

6



Personalized Therapy with Old Drugs!

The New England Journal of Medicine

Volume 289

SEPTEMBER 6, 1973

Number 10

ADVERSE REACTIONS DURING SALICYLAZOSULFAPYRIDINE THERAPY AND THE RELATION WITH DRUG METABOLISM AND ACETYLATOR PHENOTYPE

K. M. DAS, M.D., M.R.C.P., M. A. EASTWOOD, M.Sc., F.R.C.P.E., J. P. A. McMANUS, F.R.C.P.E.,
AND W. SIRCUS, M.D., Ph.D., F.R.C.P. (London & Edin.)

GASTROENTEROLOGY 2000;118:859-866

Expression of Glucocorticoid Receptor β in Lymphocytes of Patients With Glucocorticoid-Resistant Ulcerative Colitis

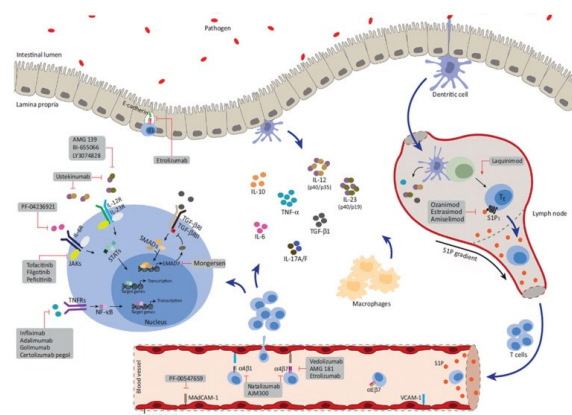
MITSUNORI HONDA, FUMIKA ORII, TOKIYOSHI AYABE, SHINJIRO IMAI,
TOSHIFUMI ASHIDA, TAKESHI OBARA, and YUTAKA KOHGO

7



Theory of Mechanistic Targeting in IBD Management

- Inflammation is a defense reaction to real or perceived threats to preserve self
 - Layered, duplicitous and redundant
- Targeting a dominant pathway (or more than one) may reduce the inflammatory response and “reset” homeostatic control (**healing**)
 - Persistent drive (antigenic?) may override this approach and result in **“mechanistic escape”** and loss of response to a specific target



Weissshof R, et al. *Adv Ther.* 2018;35(11):1746-62.

8



Modern Treatments for IBD

Immune modification/suppression

- 5-ASA (?)
- Steroids
- Thiopurines/methotrexate
- Anti-TNF α therapies
- Anti-integrin therapies
- Anti-IL12/23
- JAK inhibitors

Microbiota manipulation

- Dietary therapies (exclusion diets)
- Antibiotics
- Prebiotics
- Probiotics
- Intestinal microbiota transfer
- Bacterial derived proteins

Surgery

- Resection of fibrostenosis
- Resection in medically resistant disease

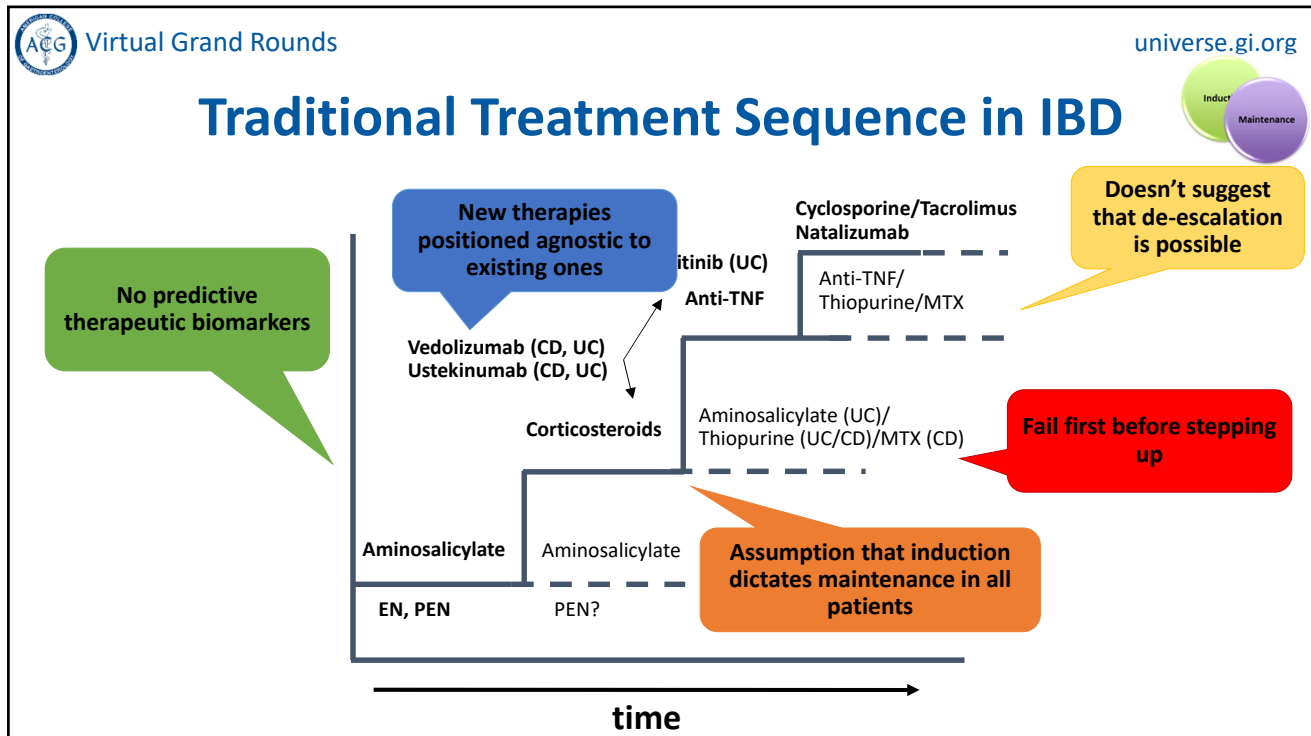
9



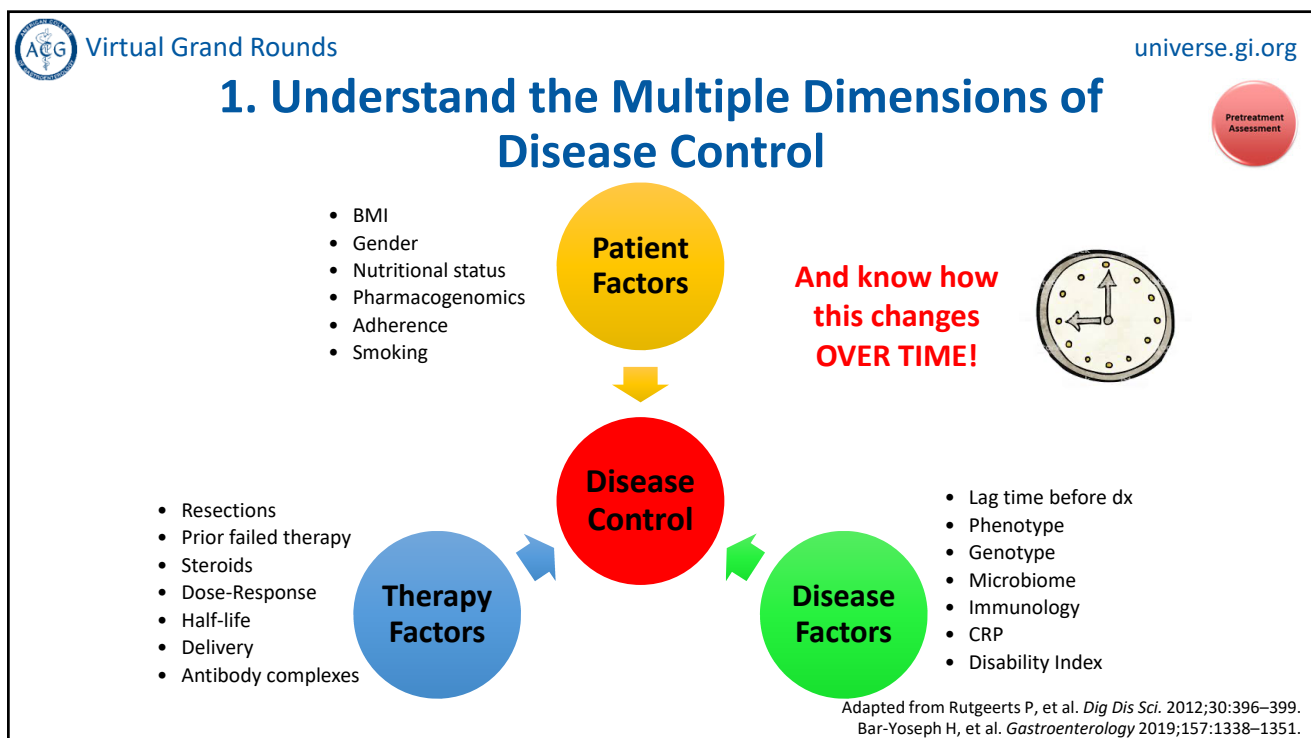
Treatment Options for Moderate-to-Severe IBD

Treatment	Induction	Maintenance	Other Indications
Steroids	CD, UC	X	
Thiopurines	X	CD, UC	
Methotrexate	CD	CD	
Anti-integrin (natalizumab, vedolizumab)	Natalizumab CD Vedolizumab CD, UC	Natalizumab CD Vedolizumab CD, UC	Natalizumab MS
Anti-p40 (ustekinumab)	CD, UC	CD, UC	Psoriasis, PsA
Anti-TNF (adalimumab ¹ , certolizumab pegol ² , golimumab ³ , infliximab ⁴)	CD, UC	CD, UC	PsA, SpA, RA, uveitis, etc
JAK inhibitor (tofacitinib)	UC	UC	RA, PsA

10



11



12

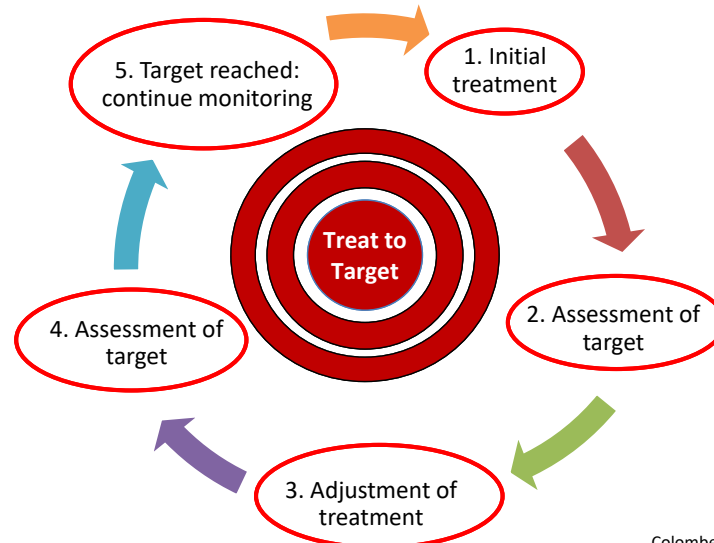


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2. Employ Treat to Target

Colombel JF, et al. *Lancet*. 2018;390:2779-2789.

13

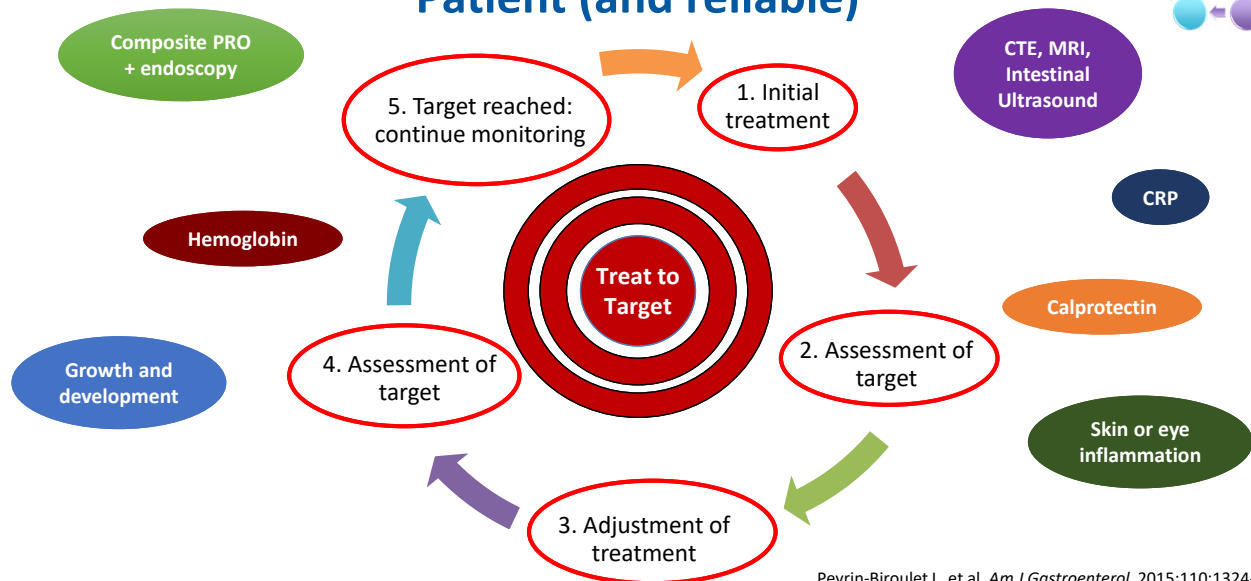


Virtual Grand Rounds

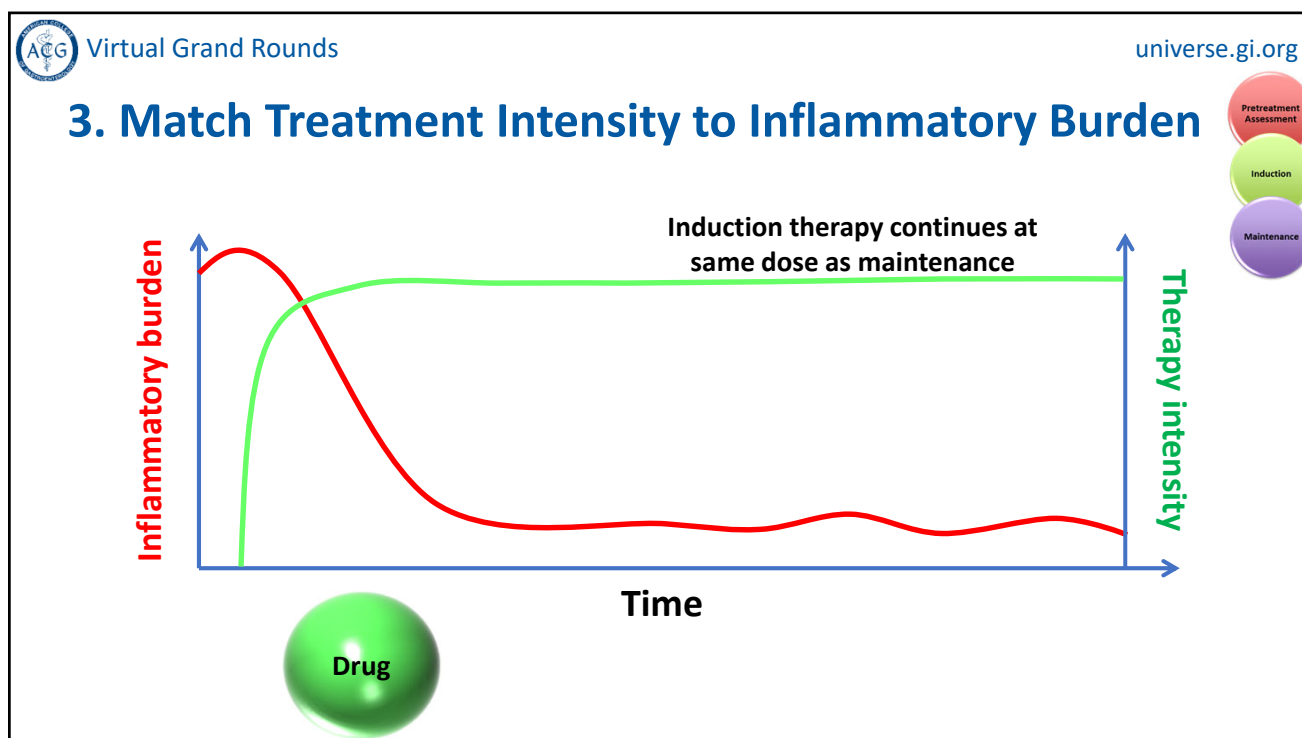
universe.gi.org



2. Choose a Target that Is Individualized for Your Patient (and reliable)

Peyrin-Biroulet L, et al. *Am J Gastroenterol*. 2015;110:1324-38.

14



15

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4. Choose Induction Therapies Wisely

- Based on disease activity and risk for bad outcomes
- Would surgery be best? (LIR!C)¹
- Based on likelihood of rapid clearance or absorption issues (BMI, gender, CRP, albumin, prior immunogenicity)²
- Use organ-selective therapies before systemic therapies³
- Based on prior treatment history that worked or did not (Cycle vs. Swap)⁴
- Based on co-morbid illnesses (RA? Psoriasis? SpA? PsA? DM?)

¹Ponsioen CY, et al. *Lancet Gastroenterol Hepatol.* 2017;2(11):785-792.
²Ordas I, et al. *Clin Pharmacol Ther.* 2012;91:635.
³Rubin DT, et al. *Am J Gastroenterol.* 2019;114:384-413.
⁴Yarur AJ and Rubin DT. *Inflamm Bowel Dis.* 2015;21(7):1709-18.

16



Specific Scenarios for Choice of First IBD Therapy

Disease	Modifier	First drug consideration	Reason
CD	Perianal	Anti-TNF	Best studied, on label (IFX)
IBD	Psoriasis	Ustekinumab	On label
IBD	>60 yo	Vedolizumab Ustekinumab	Older patients have higher risk of infections
UC	Synovitis Arthritis	Anti-TNF or Tofacitinib	On label
UC	Low albumin	Cyclosporine Tacrolimus Tofacitinib	Non-protein-based therapies



17



5. Optimize Treatment

- **Combine therapies:**
 - Anti-TNF with IMMs
 - Anti-TNF with antibiotics in perianal disease
- **Judicious use of proactive therapeutic drug monitoring:**
 - Post-loading drug levels in high-risk patients (infliximab week 8, adalimumab week 4)
 - Pediatrics: proactive monitoring of adalimumab beneficial (PAILOT)¹
 - 6-thioguanine metabolites to assess thiopurines
- **Match therapy to disease activity!**



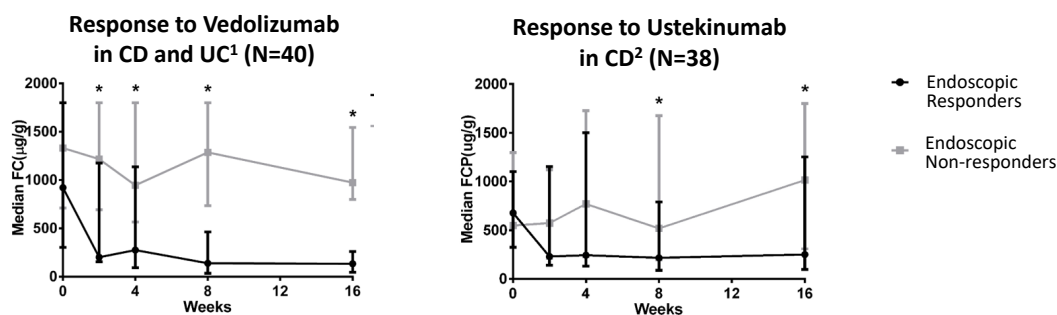
¹Assa A, et al. *Gastroenterology*. 2019;157(4):985-996.

18



Fecal Calprotectin Predicts Endoscopic Response to Therapy with VDZ and UST

- FC levels decreased as early as week 2 in responders
- FC < 250 $\mu\text{g/g}$ at week 8 predicts endoscopic response at week 16



¹Pauwels RWM, et al. *Gastroenterology*. 2019;156(6 Suppl_1):S-110.

²Pauwels RWM, et al. *Gastroenterology*. 2019;156(6 Suppl_1):S-874–S-875.

19



Optimizing Response to Thiopurines

Understand TMPT and NUDT15

6-TG	6-MMP	Possible cause	Recommendation
Undetectable	Undetectable	Non-adherent or underdosed	Understand why pt not taking med or increase dose
Low (<230)	Low or undetectable	Non-adherent or underdosed	Discuss adherence, increase dose
Low (<230)	High (>5700)	6-MMP shunter	1. Consider allopurinol, or 2. Switch agents
“Therapeutic” (>230-<400) or High (>400)	Normal range or high	Primary non-responder	1. Assess disease 2. Switch agents

Sparrow MP, et al. *Clin Gastroenterol Hepatol*. 2007;5(2):209-14.
Dubinsky MC. *Curr Gastroenterol Rep*. 2003;5(6):506-11.

20



Optimizing Response to Thiopurines

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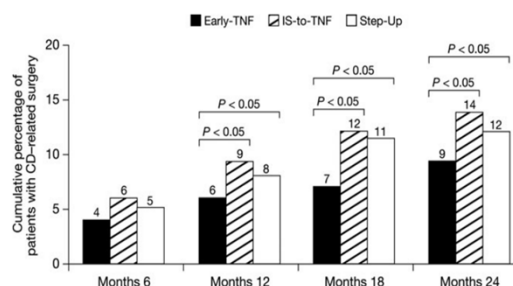
Sparrow MP, et al. *Clin Gastroenterol Hepatol.* 2007;5(2):209-14.
Dubinsky MC. *Curr Gastroenterol Rep.* 2003;5(6):506-11.

21



Optimizing Response to Biologics

- CD patients with short disease duration treated with anti-TNF:
 - Respond better¹
 - Lose response less often²
 - Have less surgery³
- Your first therapy will work better
 - Vedolizumab
 - Ustekinumab
 - Tofacitinib



¹Schreiber S, et al. *J Crohns Colitis.* 2013;7(3):213-21.

²Schreiber S, et al. *Am J Gastroenterol.* 2010;105(7):1574-82.

³Rubin DT, et al. *Inflamm Bowel Dis.* 2012;18(12):2225-2231.

⁴Sandborn WJ, et al. *N Engl J Med.* 2013;369(8):711-721.

⁵Feagan BG, et al. *N Engl J Med.* 2013;369(8):699-710.

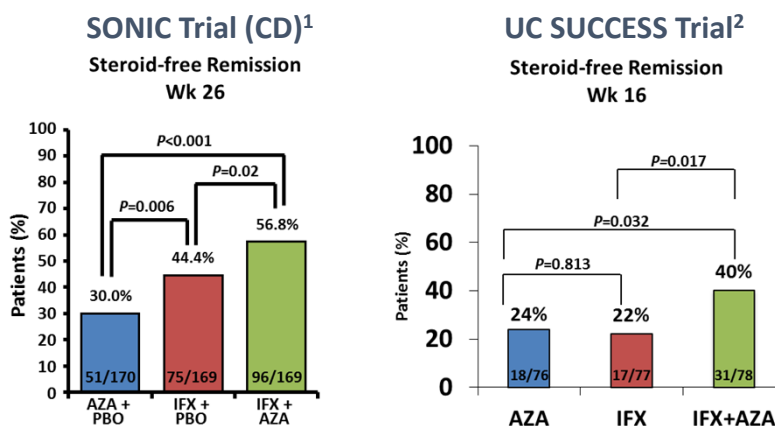
⁶Sandborn W, et al. *Gastroenterology.* 2016;150(4 Suppl 1):S157-S158.

⁷Paschos P, et al. *Ann Gastroenterol.* 2018;31(5):572-82.

22



Comparative Effectiveness Studies in IBD Favor Anti-TNF (mostly infliximab) Combined with IMM...



¹Colombel JF, et al. *N Engl J Med.* 2010;362(15):1383-95.

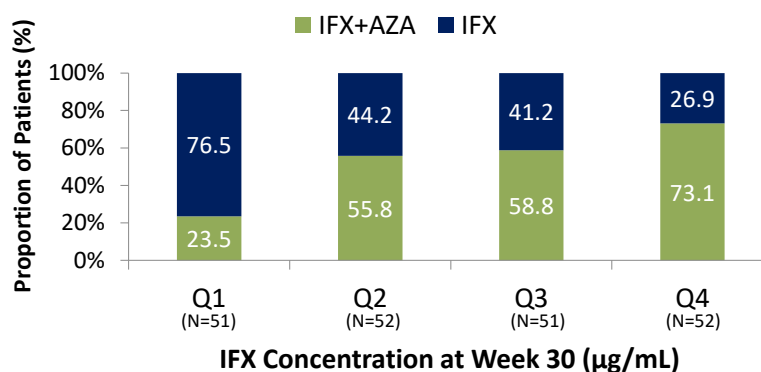
²Panaccione R, et al. *Gastroenterology.* 2014;146(2):392-400.

23



...BUT, Infliximab Level is A More Important Predictor of Remission Than Combination Therapy

SONIC Post-hoc Analysis



Q1: <0.84 µg/mL; Q2: 0.84-2.36 µg/mL; Q3: 2.36-5.02 µg/mL; Q4 ≥5.02 µg/mL.

Colombel JF, et al. *Gastroenterology.* 2017;152(5):S37-38.

24



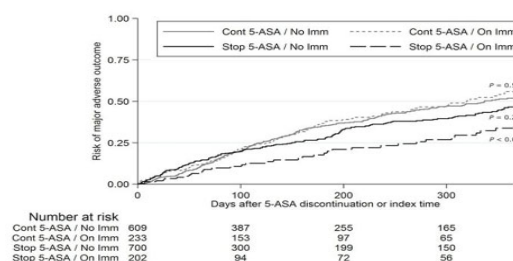
It is Safe to Stop 5-ASA in Patients Escalated to Biological Therapy

- Analysis of clinical trials of infliximab and golimumab in moderate-severe UC¹
- Health claims data of UC and CD^{2,3}

5-ASA vs. no concomitant 5-ASA in TNFi-treated patients

Outcome	Adjusted OR (95% CI)	p-value	Outcome
Clinical Remission	0.67 (0.45-1.01)	0.06	Clinical Remission
Clinical Response	0.89 (0.60-1.33)	0.58	Clinical Response
Endoscopic Remission	1.12 (0.82-1.51)	0.48	Endoscopic Remission
Biochemical Remission	0.94 (0.61-1.46)	0.79	Biochemical Remission

Risk of major adverse outcomes according to 5-ASA use



¹Singh S, et al. *Am J Gastroenterol*. 2018;113(8):1197-1205.

²Ungaro RC, et al. *Gut*. 2019;68(6):977-84.

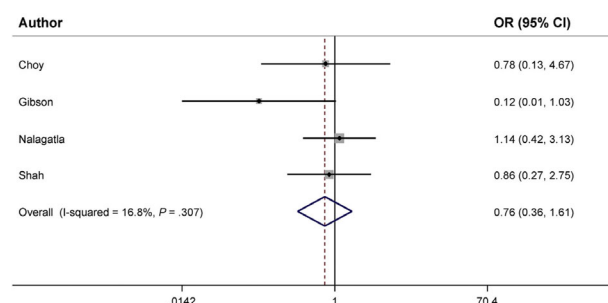
³Ungaro RC, et al. *Clin Gastroenterol Hepatol*. 2019. [Epub ahead of print].

25



More Anti-TNF is Not Always Better

- Meta-analysis: accelerated dosing of infliximab in acute severe UC does not prevent colectomy¹
- High-dose adalimumab (160 mg qw x 4) not better than standard dosing (160 mg week 0 then 80 mg week 2) in induction of remission in UC²



¹Nalagatla N, et al. *Clin Gastroenterol Hepatol*. 2019;17:502-509.

²Panes J, et al. United European Gastroenterology Week 2019. Abstract OP216.

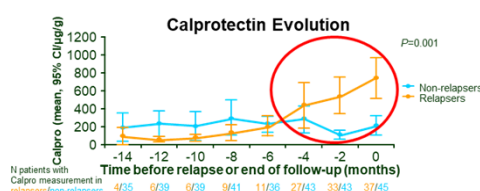
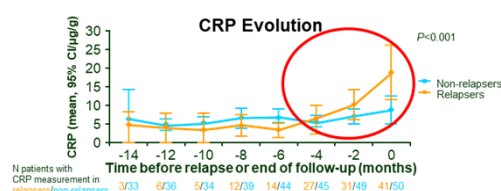
26



6. Choose Maintenance Therapies Wisely



- Based on induction therapy
- Don't forget adherence issues!
- Don't forget changes that may occur over time: **MONITOR** for LOR
 - Are symptoms stable between doses?
 - Objective assessment over time

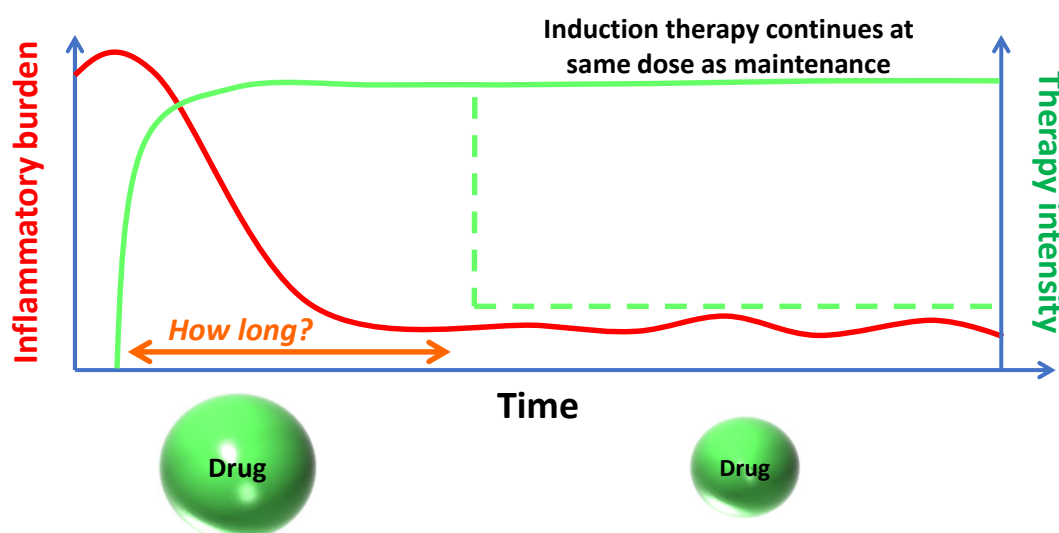


Louis E, et al. *Gastroenterology*. 2012;142(1):63-70.
De Suray N, et al. *Gastroenterology*. 2012;142(5):S-149.

27



Can You De-intensify Therapy?



28



Examples of “De-Intensification” of Therapy

- **Steroid induction → steroid-sparing maintenance therapy**
- **5-ASA**
 - 4.8 g induction can be reduced to 2.4 g maintenance (IF ENDOSCOPIC IMPROVEMENT)¹
- **Concomitant IMM + anti-TNF therapy**
 - Possibility of withdrawing IMM (IMM experienced)²
 - Possibility of withdrawing anti-TNF (Crohn’s disease)³ (IF DEEP REMISSION)

¹Rubin DT, et al. *J Crohns Colitis*. 2016;10(8):925-33.

²Van Assche G, et al. *Gastroenterol*. 2008;134(7):1861-8.

³Louis E, et al. *Gastroenterol*. 2012;142(1):63-70.

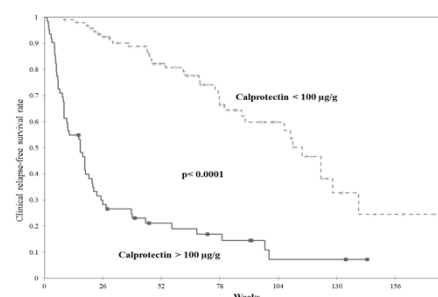
29



7. Planning for De-escalation in IBD



1. Discuss WHY this might be reasonable (Is the patient healthy because of your therapy or in spite of it?)
2. Confirm deep remission (mucosal healing), preferably for >1 year
3. Confirm optimization of drug (make SURE it’s working)
4. De-escalate
5. Have a monitoring strategy (Serial labs, fecal calprotectin, scope)
6. Know your rescue plan (Resume prior therapy or Move on to next strategy)



Buisson A, et al. *J Crohns Colitis*. 2019;13(8):1012-24.

30



8. Reasons to Switch Therapies and What to Choose

Monitor and
Re-establish
Control

Disease	Modifier	First drug consideration	Reason
UC/CD	Anti-TNF-induced lupoid reaction	Non-anti-TNF	Not reported with non-anti-TNF drugs
UC/CD	Joint pain+ vedolizumab	Anti-TNF (UC+CD) Tofacitinib (UC)	On label
UC/CD	Anti-TNF-induced psoriasis or palmar plantar pustulosis	Ustekinumab (CD) Tofacitinib (UC) Vedolizumab (UC+CD)	On label Not reported Case Reports ¹
UC/CD	Cancer (solid tumor)	None during Chemo Vedolizumab Ustekinumab	Safety

¹Rubin DT. *Gastroenterol Hepatol.* 2017;13(11):688-90.

31



9. Be Smart About Loss of Response

Monitor and
Re-establish
Control

1. Confirm adherence
2. Rule out infection
3. Confirm inflammation
4. Assess drug
5. If anti-drug antibodies, take precautions on the next treatment (use combination therapy)

Roblin X, et al. *Inflamm Bowel Dis.* 2018;24(9):2078-85.
Kennedy NA, et al. *Lancet Gastroenterol Hepatol.* 2019;4(5):341-53.

32



Can you Go Back to a Therapy That Had Worked and Stopped Working?

Circling Backwards

- If the inflammatory pathway is reactivated: **YES**
- If prior loss of response was due to anti-drug antibodies: **NO**
- After surgery:
 - Did the patient just need surgery anyway, and that was the reason for the lack of response to therapy? **YES**
 - Did the patient progress right through the prior therapy? **NO**



33



Novel Treatment Considerations – 1 Two Step Management

INDUCTION	MAINTENANCE
Cytokine inhibition: • TNFi • IL23 • JAKinib	Cellular inhibition: • Anti-integrin • S1P1 receptor modulator • Thiopurine
Microbiota “pre-treatment”: • Intestinal microbiota transfer¹ • Antibiotics²	Microbiota maintenance: • Diet • Prebiotics • Bacterial products • Antibiotics?
Surgery: • Ileocectomy “curative resection” • Diverting ileostomy	

¹Ananthakrishnan AN, et al. *Cell Host Microbe*. 2017;21(5):603-610.

²Lombardo M, et al. *Open Forum Infect Dis*. 2015;2(Suppl_1):S149.

34

Novel Treatment Considerations – 2 Combination Approaches



- Biological combinations
- Small molecule and biological combinations
 - To prevent immunogenicity
 - To combine mechanisms of action
- Antibiotics and immune suppressives
- Diet plus immunobiological therapies

Clinical Gastroenterology and Hepatology 2019;17:486–493

Safety and Efficacy of Combination Treatment With Calcineurin Inhibitors and Vedolizumab in Patients With Refractory Inflammatory Bowel Disease

Britt Christensen,^{*,†,§} Peter R. Gibson,[§] Dejan Micio,^{*} Ruben J. Colman,^{*}
Sarah R. Goeppinger,^{*} Olufemi Kassim,^{*} Andres Yarur,^{*} Christopher R. Weber,^{||}
Russell D. Cohen,^{*} and David T. Rubin^{*}



Biocycle. www.biocycle-project.eu. Accessed July 3 2018.
Clinical Trials. <https://clinicaltrials.gov> (NCT02764762) Accessed April 23 2019.
Yang E, et al. *Aliment Pharmacol Ther*. 2020. [In Press].

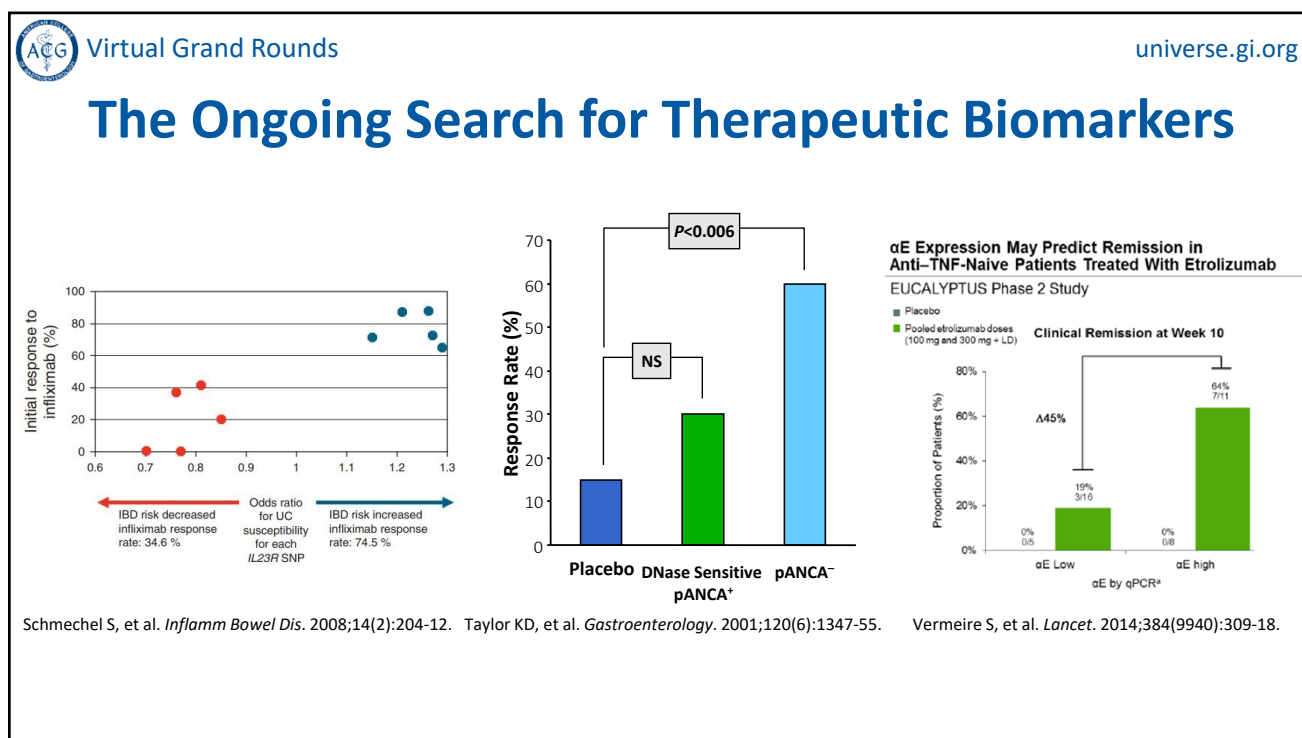
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Calcineurin Induction Therapy Followed by Maintenance on Vedolizumab in IBD

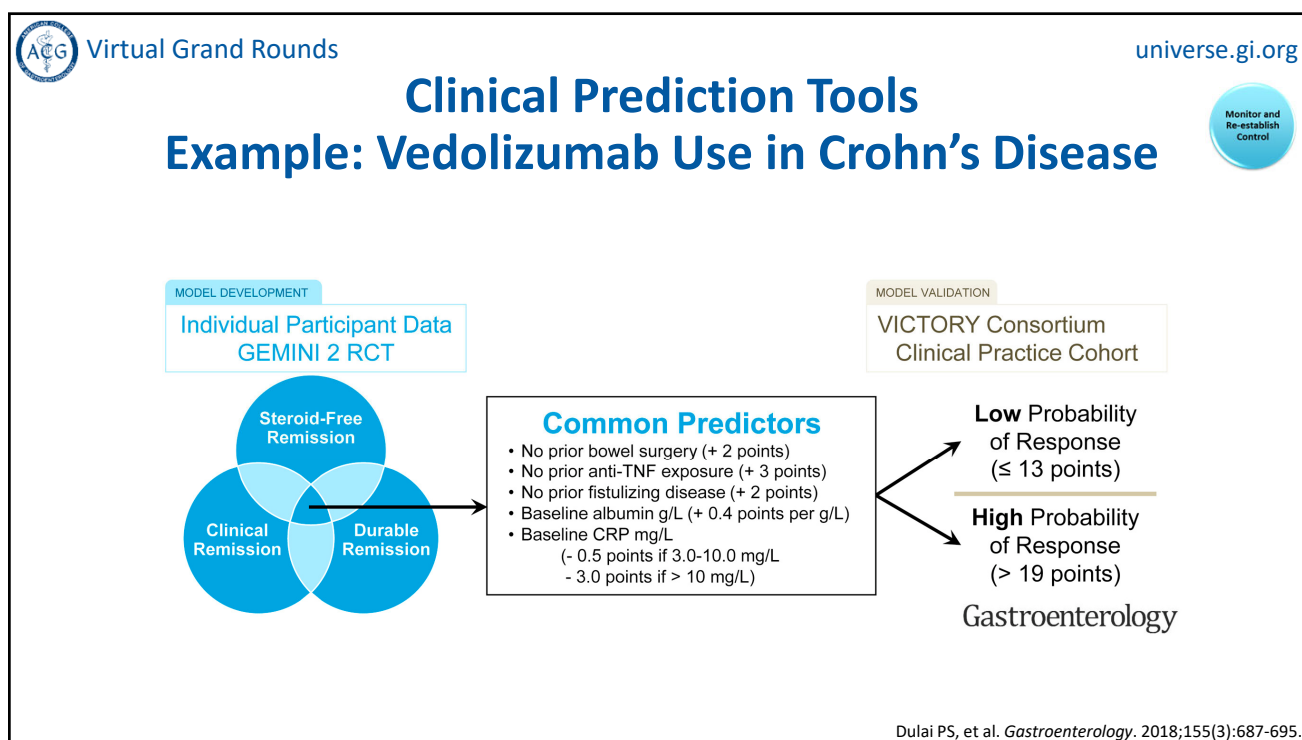
Author/Center	Design	N	Week 14 Clinical Remission	Week 52 Clinical Remission
Christensen B/UChicago CGH 2019	Retrospective	20	55%	45%
Ollech J/UChicago APT 2019		71	50%	43% (28% at 2 y)
Pellet G/GETAID CGH 2019	Retrospective	39	38%	--
Tarabar D/Serbia UEGW 2018	Prospective	17	93%	79%

Christensen B, et al. *Clin Gastroenterol Hepatol*. 2019;17(3):486–93.
Ollech J, et al. *Aliment Pharmacol Ther*. 2020 Mar;51(6):637–643.
Pellet G, et al. *Clin Gastroenterol Hepatol*. 2019;17(3):494–501.
Tarabar D, et al. *United European Gastroenterol J*. 2018;6(8S1):A457.

36



37



38



Future of Personalized Management of IBD

