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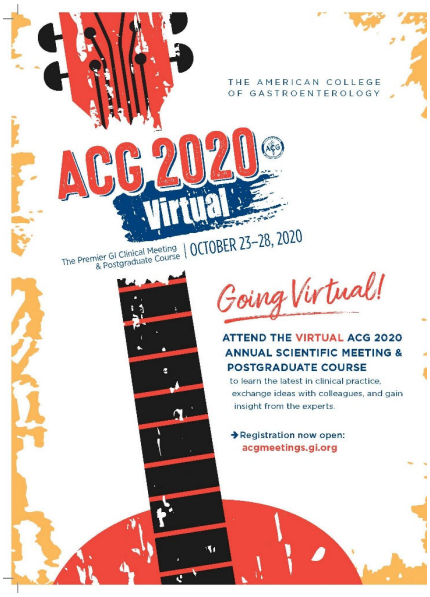

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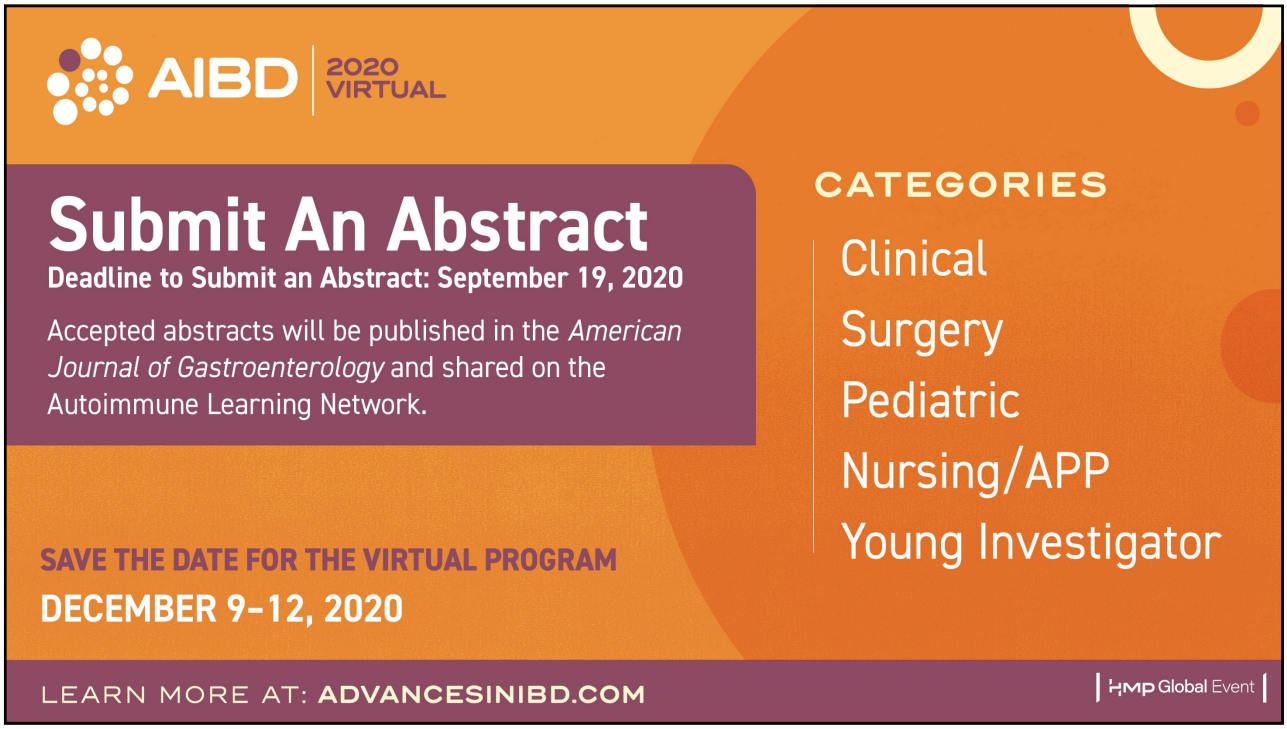
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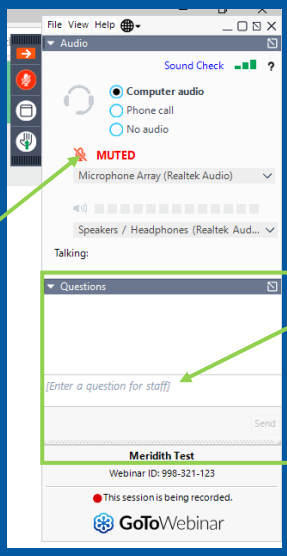
Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.



Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

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How to Receive CME and MOC Points

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ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2020 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2021 for this activity.

ACG will submit MOC points on the first of each month. Please allow 3-5 business days for your MOC credit to appear on your ABIM account.

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MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement.
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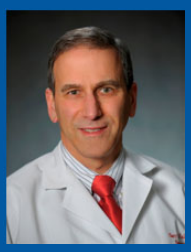

Week 25: Management of EoE With Topical Steroids: The When and How of Long Term Management
Gary W. Falk, MD, MS, FACG
September 10, 2020 at Noon EDT

Week 26: Current and Emerging Concepts in Irritable Bowel Syndrome
Brooks D. Cash, MD, FACG
September 17, 2020 at Noon EDT

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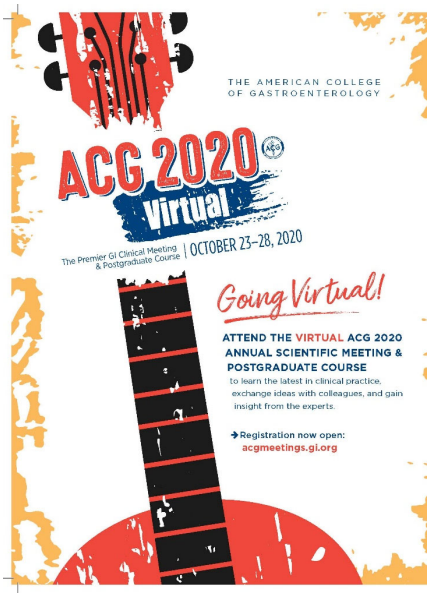

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Disclosures:

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Mark C. Mattar, MD, FACG

AbbVie: Consultant, Speakers Bureau
Janssen: Consultant, Speakers Bureau
Takeda: Consultant, Speakers Bureau
Pfizer: Consultant, Speakers Bureau

Off label Use: azathioprine/mercaptopurine/thioguanine, methotrexate

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Northwestern Medicine

Combination Therapies in IBD: Assessing the Evidence for and Against

Stephen B. Hanauer, MD, MACG
Clifford Joseph Barborka Professor of Medicine
Northwestern University Feinberg School of Medicine
Chicago

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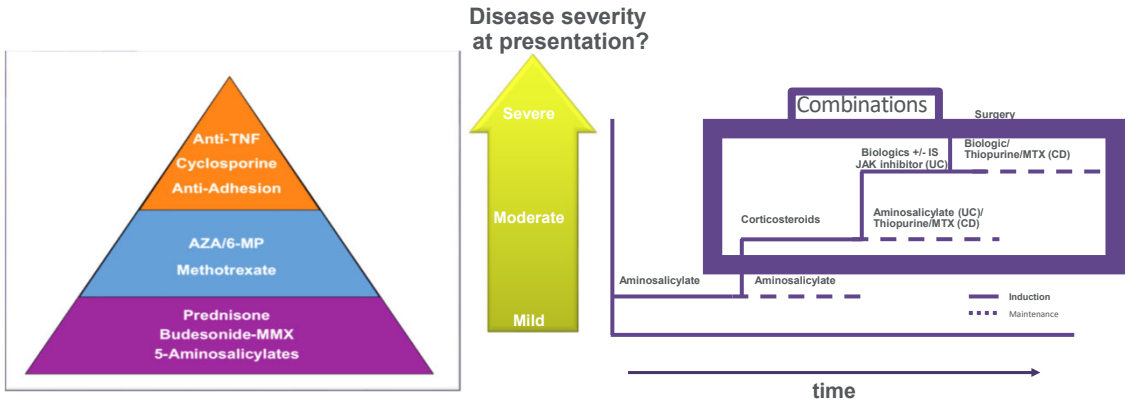
Outline

- Historical context of combination therapies in IBD
- Efficacy of Combination Biologics with Immunosuppressives
- Efficacy of Combination Biologics with Aminosalicylates
- Other Combinations
- Safety concerns
- Practical applications

Historical Context of Combination Therapies

- Ulcerative colitis
  - Aminosalicylates→Corticosteroids→Thiopurines
  - Cylcosporine→Thiopurines
- Crohn's disease
  - Corticosteroids→Thiopurines/Methotrexate

Concept of Step-Therapy is Flawed



Theoretical Advantages of Combined Therapy

- Prevention of immunogenicity with biologics
- Increased drug concentrations
- Targeting multiple mechanism- greater efficacy

- Disadvantages of combined therapy
  - Increased adverse effects (immunosuppression)
  - Complexity and cost of the regimen

Immunogenicity of TNF Antagonists in Patients With Detectable Antibodies to a TNF Antagonist

	Patients, %			
	Episodic Maintenance		Scheduled Maintenance	
	IMS-	IMS+	IMS-	IMS+
Infliximab[1] (CD 5 mg/kg)	38%	16%	11%	7%
(CD 10 mg/kg)			8%	4%
Infliximab[2] (UC 5 mg/kg)	No data		19%	2%
(UC 10 mg/kg)			9%	4%
Certolizumab[3] (PRECiSE I)			10%	4%
Certolizumab[4] (PRECiSE II)	24%	8%	12%	2%
Adalimumab[5] (RA, all doses)	No data		12%	1%
Adalimumab[6] (CLASSIC II)			4%	0%

IMS, immunosuppressant

1. Hanauer SB et al. *Clin Gastroenterol Hepatol*. 2004;2:542.
2. Lichtenstein GR et al. *Aliment Pharmacol Ther*. 2009;30:210.
3. Sandborn WJ et al. *N Engl J Med*. 2007;357:228;
4. Schreiber S et al. *N Engl J Med*. 2007;357:239.
5. Humira [package insert]. North Chicago, IL: Abbott Laboratories; 2011.
6. Sandborn WJ et al. *Gut*. 2007;56:1232.

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Factors that Influence PK of TNF Antagonists

	Impact on TNF antagonist PK
Presence of ADAs	Decreases drug concentration Increases clearance Worse clinical outcomes
Concomitant use of immunosuppressives	Reduces ADA formation Increases drug concentration Decreases drug clearance Better clinical outcomes
Low serum albumin concentration	Increases drug clearance Worse clinical outcome
High baseline CRP concentration	Increase drug clearance
High baseline TNF concentration	May decrease drug concentration by increasing clearance
High body size	May increase drug clearance
Sex	Males have higher clearance

Ordas I et. al. *Clin Gastroenterol Hepatol*. 2012; 10:1079-1087.

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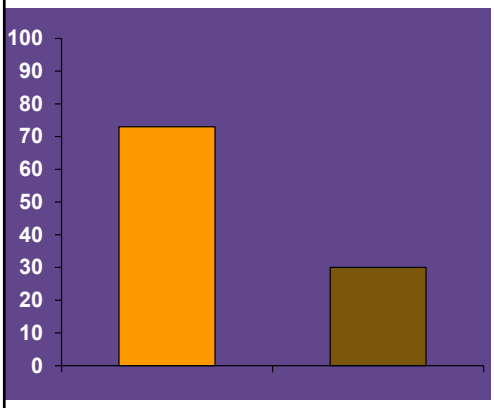
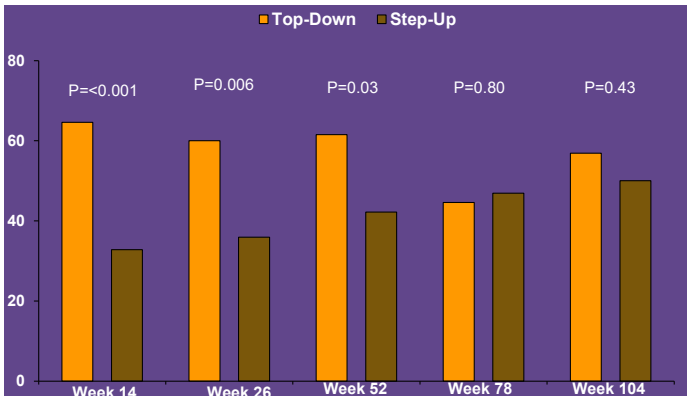
Prospective vs. Post-Hoc

TOP DOWN - Remission (CDAI<150) Corticosteroid Therapy

Complete Ulcer Disappearance



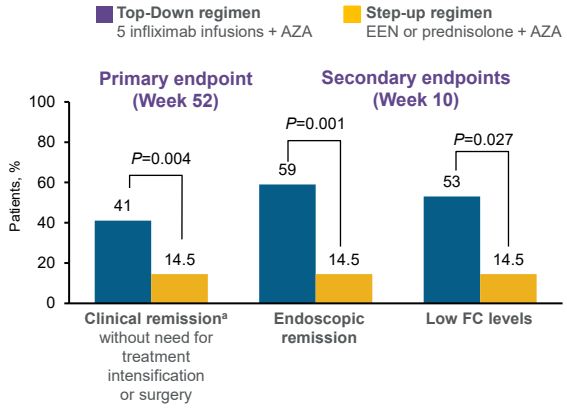
Percent Remission



D'Haens G et al. Lancet. 2008 Feb 23;371(9613):660-7

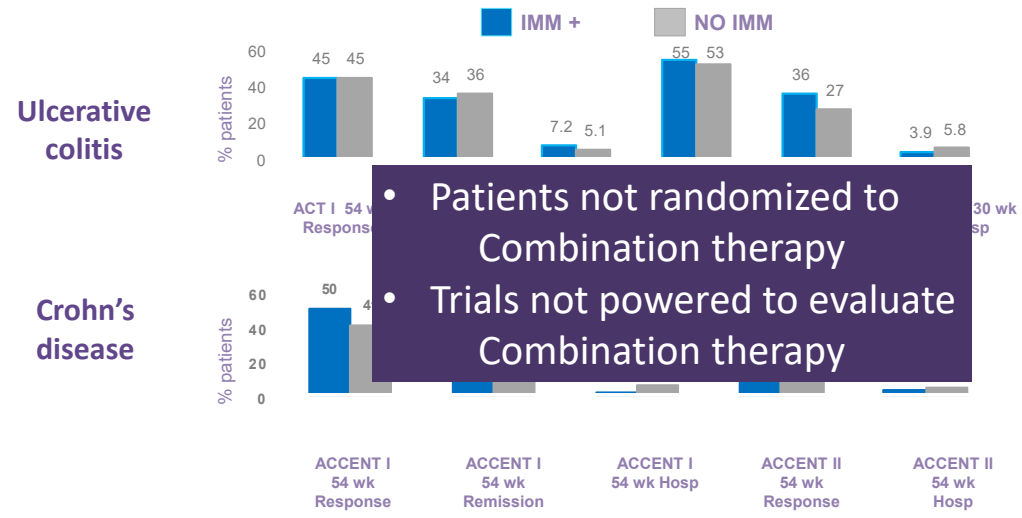
Top-Down Infliximab Superior to Step-Up in Children With Moderate to Severe CD: A Multicenter Randomized Trial

- International RCT at 12 centers
- 97 children aged 3-17 years with new-onset, untreated CD randomized to Top-Down or Step-Up therapy



Jongsma M et al. Presented at DDW Virtual Conference 2020. May 4, 2020. Abstract 947.

Efficacy of Infliximab with/without Immunomodulators in Pivotal Trials

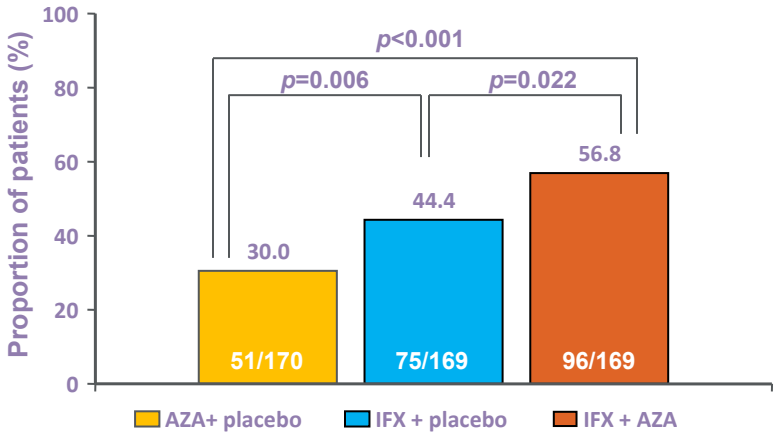


- Patients not randomized to Combination therapy
- Trials not powered to evaluate Combination therapy

Lichtenstein GR, et al. *Aliment Pharmacol Ther*. 2009:30;210.

Evidence for combination therapy in Crohn's Disease in immunosuppressive-naive patients: SONIC

Corticosteroid-free clinical remission at Week 26



Colombel JF, *et al. NEJM* 2010; 362:1383-95

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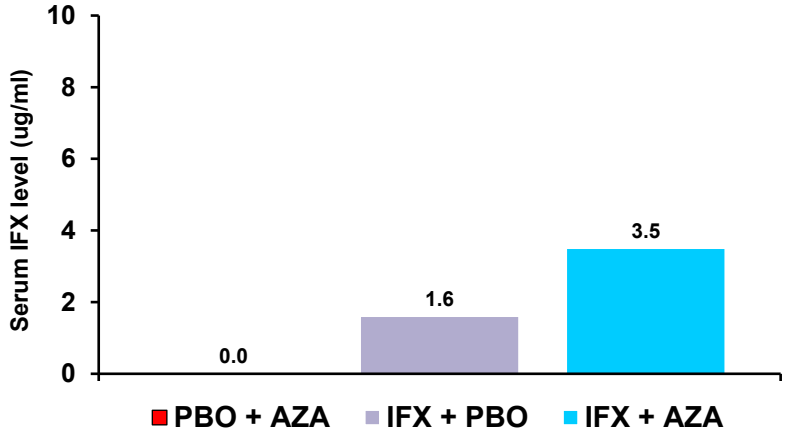
SONIC: Trough Levels at Week 30



Colombel JF. et al. N Engl J Med. 2010 362:1383-95

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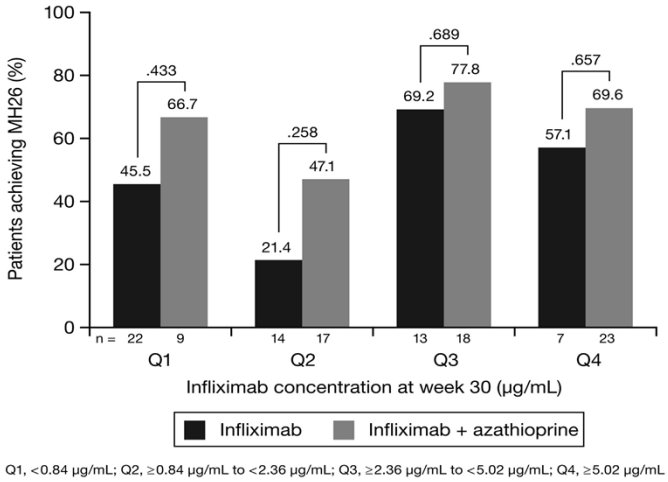
SONIC: Proportions achieving mucosal healing at week 26 by serum trough infliximab concentration at week 30

- SONIC re-analysis
  - Within quartiles, there was no statistically significant difference in proportions of patients achieving CSFR26 between treatment groups
  - No difference in ROC was observed between IFX monotherapy and IFX+AZA treatment groups



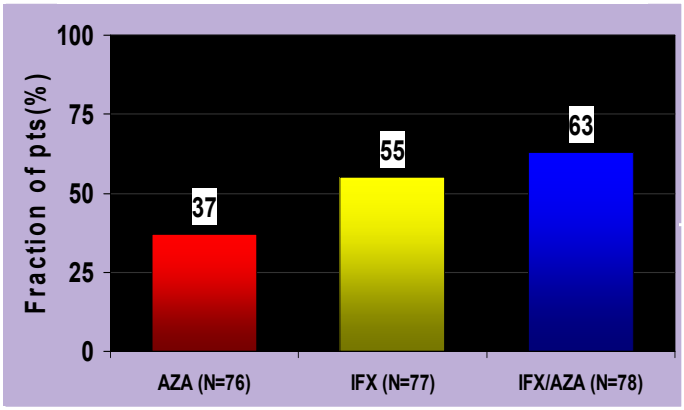
Q1, <0.84 µg/mL; Q2, ≥0.84 µg/mL to <2.36 µg/mL; Q3, ≥2.36 µg/mL to <5.02 µg/mL; Q4, ≥5.02 µg/mL

Colombel, J-F, CGH 2019 17:1525–1532

27

IFX+AZA is Superior to IFX Alone in Ambulatory UC (SUCCESS Trial)

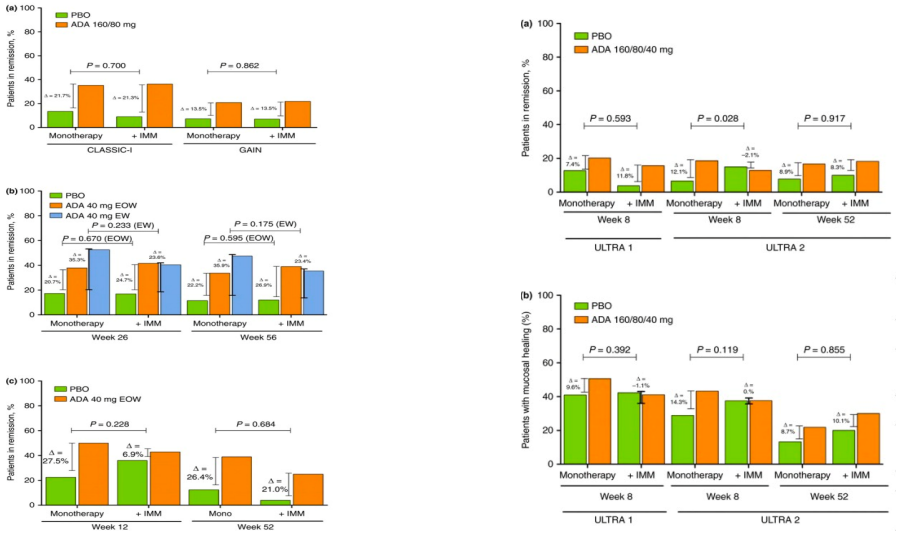
Mucosal Healing



Panaccione R, et al Gastroenterology. 2014 146:392-400

28

No Effects of Concomitant Immunomodulators on Efficacy and Safety of Adalimumab in Crohn's disease or Ulcerative Colitis Who had Failed Conventional Therapy



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Colombel, J-F, et al. APT 2017 45:50-62

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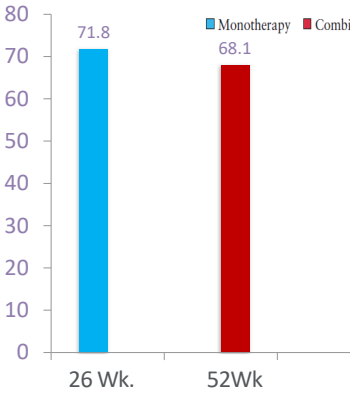
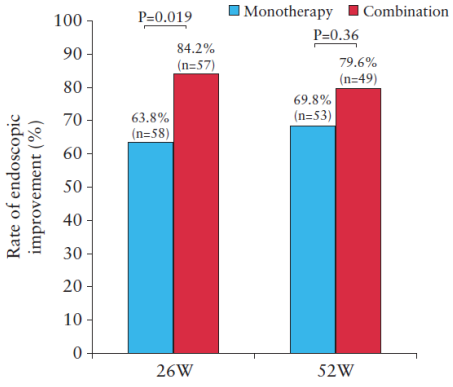
Adalimumab in Combination with AZA: Remission and Endoscopic Improvement at 26 wks CD (Diamond Study)

- Randomized (open-label)
- Active CD naïve to biologics and thiopurines
- Efficacy of adalimumab +/- AZA
- Primary endpoint: clinical remission at Wk 26

Clinical Remission



Endoscopic Healing



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Matsumoto T, et al. J Crohn's and Colitis 2016 10:1259-66

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Adalimumab Monotherapy and a Combination with Azathioprine for Crohn's Disease: Diamond

- Anti-ADA Ab positive:
  - 13.2% monotherapy group
  - 4.0% combination group [$p = 0.078$]
- ADA trough level
  - 6.5±3.9 µg/ml monotherapy group
  - 7.6±3.6 µg/ml combination group [$p = 0.084$].
- Not statistically significant with trends towards a higher ADA trough level and a lower positive rate of Anti-ADA Ab in combination group compared with monotherapy

Matusmoto, et al J Crohns Colitis. 2016;10 :1259-1266.

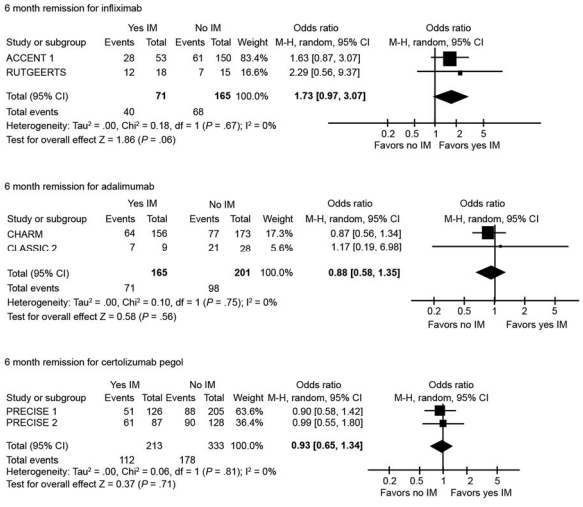
Effects of Concomitant Immunomodulator on Efficacy & Safety of TNFi for CD: Meta-analysis of Placebo-controlled Trials

Pooled summary estimate for adverse events:

infusion/injection reactions
Malignancy
Serious infections
Death

mono vs combo therapy not significantly different (OR, 0.71; 95% CI, 0.41–1.25).

Odds of infusion reaction with infliximab significantly reduced in subjects taking IM (OR, 0.46; 95% CI, 0.26–0.79)

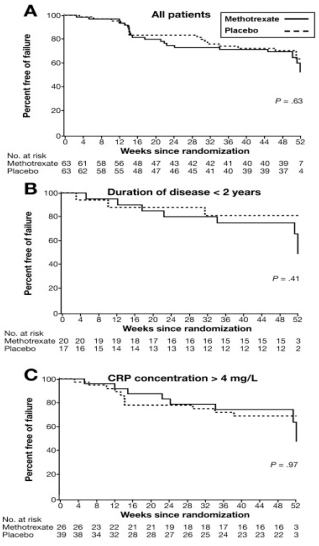


Jones, JL, et al. CGH (2015) 13:2233-2240

Methotrexate in Combination With Infliximab in Patients With Crohn's Disease*: COMMIT

50-week, d-b, p-c trial
Compared mtx and ifx with ifx alone
126 patients initiated prednisone within prior 6 weeks

MTX initial 10 mg/wk, escalating to 25 mg/week
IFX (5 mg/kg) at wks 1, 3, 7, and 14, and q 8 wks
Prednisone tapered beginning week 1 and d/c'd no later than week 14



Feagan, B, et al. Gastroenterology 2014:146;681-8

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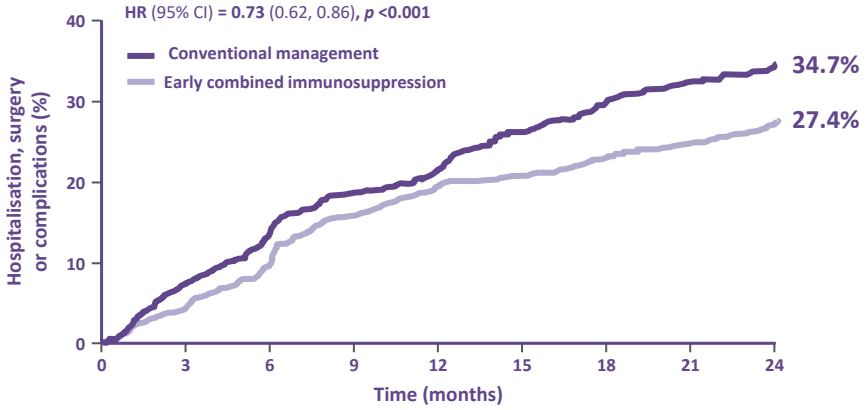
REACT: Time to First Hospitalization, Surgery or Complication

- Cluster randomized controlled trial
- Gastroenterology practices randomized to either implement a treatment algorithm or to continue with their usual care for the management of CD
- 40 practices randomized in a 1:1 ratio using a minimization procedure to balance treatment allocation for country and number of CD patients seen annually at the practice (<100 or ≥100)



Khanna R. et al. Lancet. 2015 386:1825-34

34

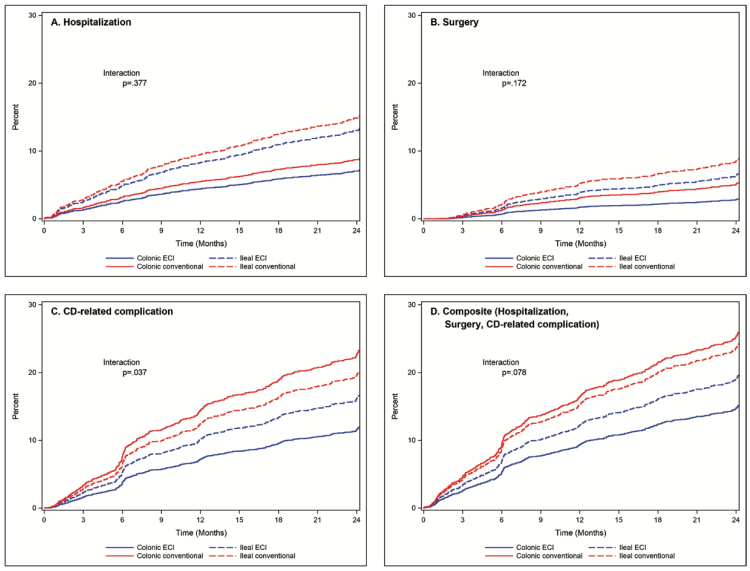
Early Combined Immunosuppression (ECI) Reduces Complications in Isolated Colonic- vs Ileal-Dominant Crohn Disease

Rates of complications stratified by treatment algorithm and disease location

Post-hoc analysis of REACT

ECI

Conventional



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Dulai et al. Inflamm Bowel Dis epub 6/20

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Benefit of TNFi + IS combination therapy depends on disease phenotype and duration in Crohn's disease

multicenter prospective cohort

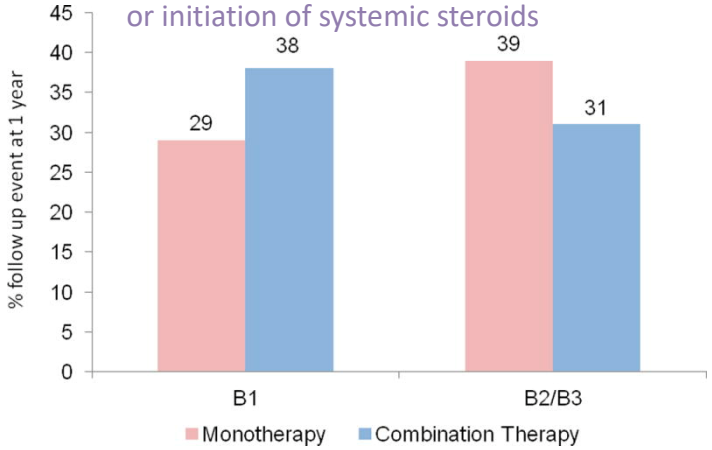
707 CD pts (45% combo therapy)
164 UC pts (38% combo therapy).
Combination therapy not associated with reduction in composite outcome in CD (OR: 0.87, 95% CI: 0.63-1.22) or UC (OR: 1.45, 95% CI: 0.63-3.38).

No difference with non-stricturing, nonpenetrating CD

Significant reduction in stricturing or penetrating CD (30% vs 39%, OR: 0.58, 95% CI: 0.37-0.90)

Stronger effect disease duration <5 years (OR: 0.35, 95% CI: 0.14-0.87) vs longer duration (OR: 0.75, 95% CI: 0.45-1.27

New CD-related hospitalization, surgery, change in biologic therapy, new fistula or abscess, or initiation of systemic steroids



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Ananthakrishnan, AN et al. APT 2017 46: 162-168

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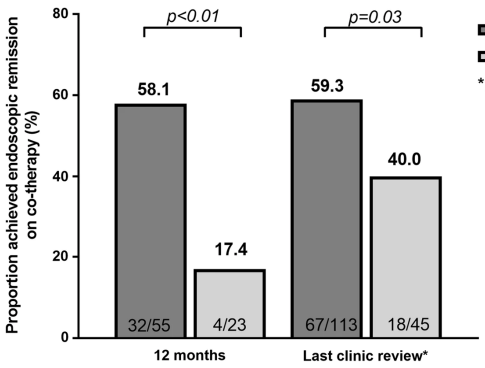
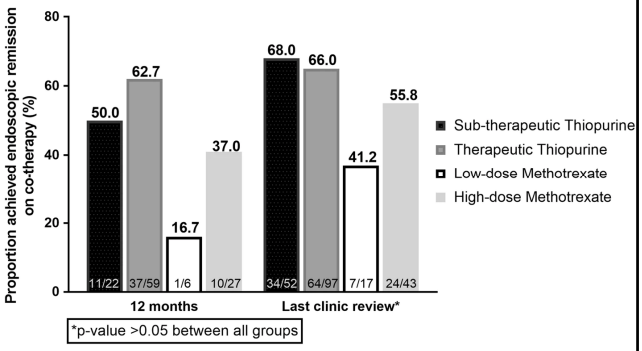
Higher Mucosal Healing Rates with TNFi's in Combination with Thiopurines Compared to Methotrexate in Crohn's Disease

Retrospective observational study at 2 tertiary centers (2010-2016)





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Vasudevan, A. et al. Dig Dis Sci 2019 64: 1622-1631

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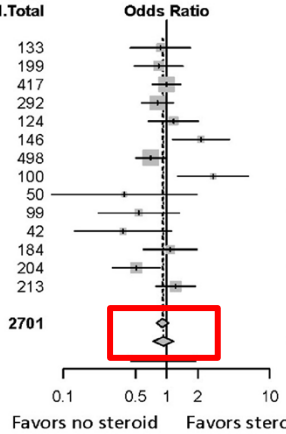
Concomitant Steroids Do Not Improve Crohn's Remission Rates with TNFi's

A

Study	SteroidYes N.Remission	SteroidYes N.Total	SteroidNo N.Remission	SteroidNo N.Total	OR	95%-CI	Weight (fixed)	Weight (random)
Schreiber et al.[23]	17	76	33	133	0.87	[0.45; 1.70]	4.2%	6.4%
Sandborn et al. (PRECISE 1)[24]	26	132	45	199	0.84	[0.49; 1.44]	6.5%	7.8%
Schreiber et al. (PRECISE 2)[25]	110	251	183	417	1.00	[0.73; 1.37]	17.5%	11.1%
Sandborn et al. (WELCOME)[26]	86	235	121	292	0.82	[0.57; 1.16]	15.5%	10.5%
Sandborn et al.[27]	35	98	40	124	1.17	[0.67; 2.04]	5.1%	7.6%
Hanauer et al. (CLASSIC 1)[28]	26	58	40	146	2.15	[1.14; 4.05]	2.8%	6.7%
Colombel et al. (CHARM)[29]	65	279	150	498	0.70	[0.50; 0.99]	18.7%	10.8%
Sandborn et al. (GAIN)[16]	18	54	15	100	2.83	[1.29; 6.23]	1.6%	5.2%
Watanabe et al.[30]	2	14	15	50	0.39	[0.08; 1.95]	1.3%	1.7%
Rutgeerts et al. (EXTEND)[31]	8	31	39	99	0.54	[0.22; 1.32]	3.1%	4.4%
Present et al.[32]	8	21	26	42	0.38	[0.13; 1.11]	2.4%	3.4%
Hanauer et al. (ACCENT 1)[33]	27	201	23	184	1.09	[0.60; 1.97]	4.7%	7.2%
Sands et al. (ACCENT 2)[34]	36	78	128	204	0.51	[0.30; 0.86]	8.6%	8.0%
Colombel et al. (SONIC)[35]	65	125	100	213	1.22	[0.79; 1.90]	8.0%	9.2%
Fixed effect model		**1653**		**2701**	**0.91**	**[0.80; 1.04]**	**100.0%**	--
Random effects model					**0.93**	**[0.74; 1.17]**	--	**100.0%**
Prediction interval						**[0.45; 1.91]**		

Heterogeneity: I^2 = 57%, τ^2 = 0.0955, P < .01



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Faleck,DM et al CGH Epub 2020 Jun 20;S1542-3565(20)30847-8.

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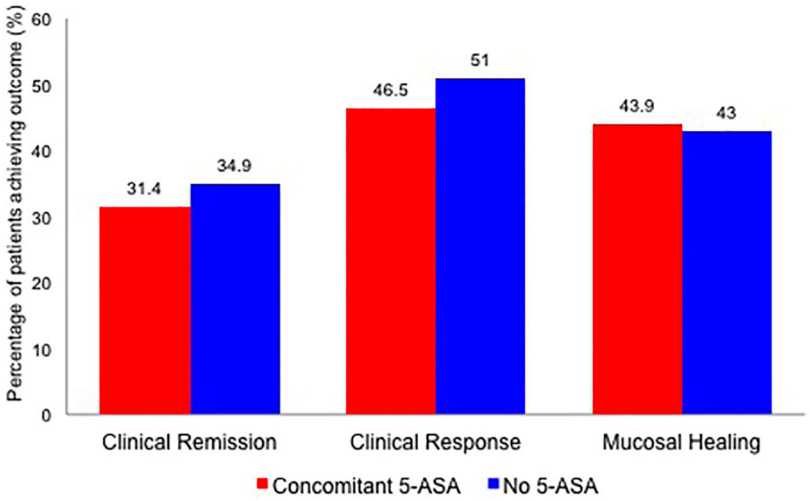
No Benefit of Concomitant Aminosalicylates in Patients with Ulcerative Colitis Escalated to TNFi Therapy

Individual patient data from 5 trials of infliximab and golimumab in moderate-severe UC



Singh,S. et al Am J Gastro 2018 113:1197-1205

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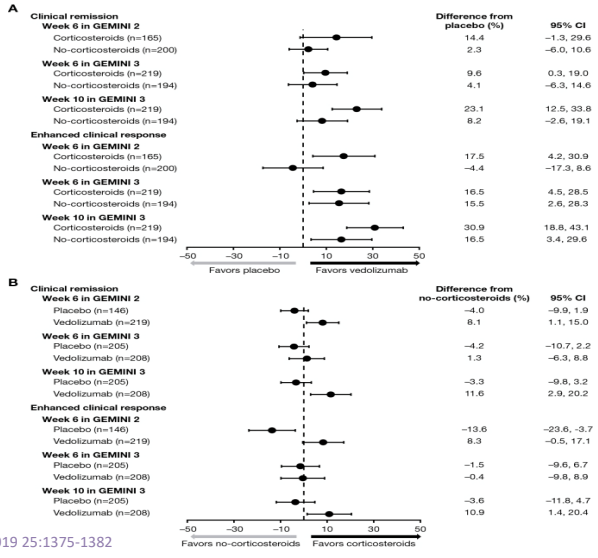
Vedolizumab in combination with stable corticosteroids

(Post Hoc Analysis of GEMINI 2/3)

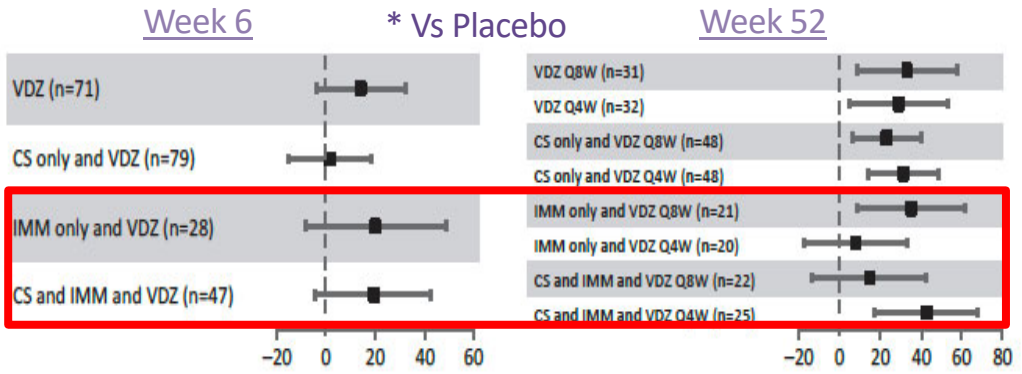
May improve induction of clinical response or remission in moderately-severely Crohn's disease



Sands, B IBD 2019 25:1375-1382

40

Percentage of Vedolizumab-Treated Patients in Clinical Remission*



- Gemini Trials in UC and CD
  - Immunosuppressives disallowed after 6 weeks in US, allowed in Europe
  - No difference in clinical response/remission in ~20% of patients with/without concomitant IS

C. Hedin, C. & Halfvarson, J Best Practice & Research Clinical Gastroenterology 32-33 (2018) 27e34

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Observational Studies Assessing Concomitant Immunomodulators & vedolizumab in UC & CD

Reference	Year	Country of origin	Number of patients	Comparison	Statistical estimate	Additional effect of combination therapy
Shelton [17]	2015	US	UC, n = 65 CD, n = 107	Concomitant use of immunomodulators and clinical response/remission at week 14	OR 0.56; 95% CI 0.19–1.66	No
Williet [15]	2016	France	UC, n = 16 CD, n = 31	Proportion of patients on combination therapy vs. monotherapy, who achieved sustained remission	7/17 (41.2%) vs. 13/30 (43.3%), p = NS	No
Amiot [10]	2016	France	UC, n = 121 CD, n = 173	Concomitant use of immunomodulators and steroid-free clinical remission at week 54	p = NS	No
Stallmach [14]	2016	Germany	UC, n = 60 CD, n = 67	Concomitant use of immunomodulators and clinical remission at week 54	UC, OR 0.20; 95% CI 0.02–1.66 CD, OR 0.38; 95% CI 0.04–3.25	No No
Baumgart [11]	2016	Germany	UC, n = 115 CD, n = 97	Concomitant use of immunomodulators and clinical remission at week 14	UC; p = 0.825 CD; p = 0.369	No
Kopylov [12]	2016	Israel	UC, n = 74 CD, n = 130	Concomitant use of immunomodulators and clinical remission at week 14	p = NS	No
Samaan [13]	2016	UK	UC, n = 20 CD, n = 27 IBD-U, n = 3	Proportion of patients on combination therapy vs. monotherapy, with active disease at initiation of VDZ, who achieved clinical remission at week 14	8/16 (50%) vs. 6/21 (29%)	No
Eriksson [16]	2017	Sweden	UC, n = 92; CD, n = 147 IBD-U, n = 7	Concomitant use of immunomodulators and drug discontinuation, because of lack of or loss of response, at the last follow-up	Adjusted HR 1.39; 95% CI 0.85–2.30	No
Allegretti [18]	2017	US	UC, n = 40 CD, n = 96	Concomitant use of immunomodulators at initiation of VDZ and response or remission at week 54 Initiation of immunomodulators after initiation of VDZ and response or remission at week 54	UC; OR 1.27; 95% CI: 0.27–5.96 CD; OR 1.89; 95% CI: 0.66–5.38 UC; OR 0.43; 95% CI 0.09–2.00 CD; OR 8.33; 95% CI 2.15–32.26	No No No Yes

VDZ, vedolizumab; UC, ulcerative colitis; CD, Crohn's disease; UK, United Kingdom; US, United States; OR, odds ratio; CI, confidence interval.

No Effect

C. Hedin, C. & Halfvarson, J Best Practice & Research Clinical Gastroenterology 32-33 (2018) 27e34

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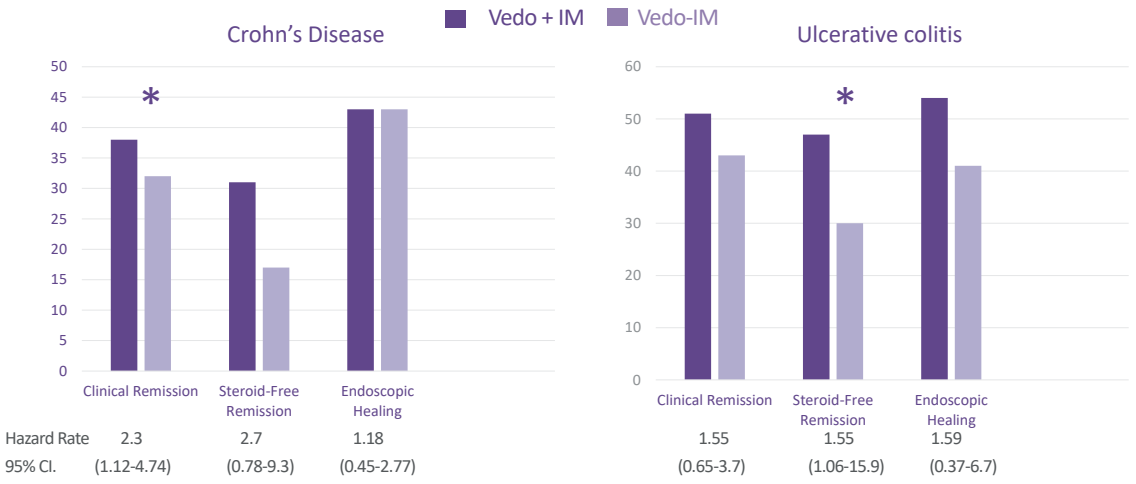
Impact of Concomitant Immunomodulator Use on Vedolizumab Effectiveness

Multicentre Consortium Propensity Score-matched Analysis



ACG Virtual Grand Rounds * Clinically Significant

Hudesman, D et al ECCO DOP 053 (s067) 2018

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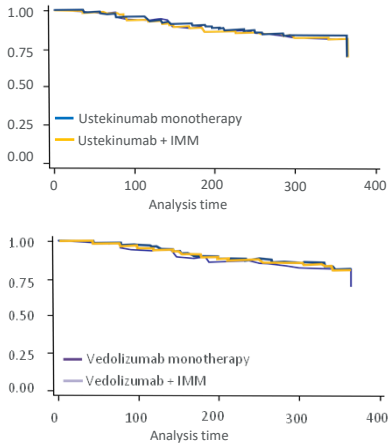
Combination Therapy Does Not Improve Clinical and Endoscopic Remission Rates with Vedolizumab or Ustekinumab in CD and UC

- Retrospective Study 3 academic sites in US, Canada, France
- Ustekinumab initiated in CD patients (n=291)
  - 44% on combination therapy with thiopurine/MTX
- Vedolizumab initiated in 381 patients (203 CD, 178 UC)
  - 25% on combination therapy with thiopurine/MTX
- Patients followed with DAIs (HBI, SCCAI, or pMayo Score)
- Primary outcomes were clinical remission or response at 14, 30, and 54 weeks

Kaplan-Meier survival curve comparing monotherapy vs combination therapy



ACG Virtual Grand Rounds

Hu, et CGH epub https://doi.org/10.1016/j.cgh.2020.07.012

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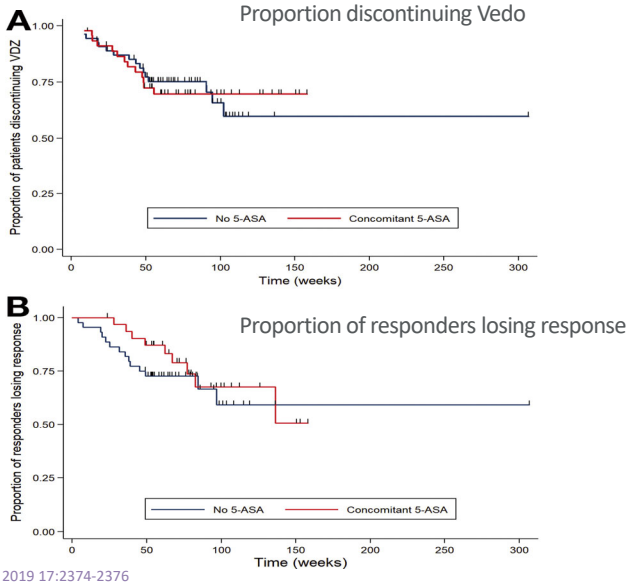
Concomitant Aminosalicylates Not Associated With Improved Outcomes in UC Patients Escalated to Vedolizumab

Retrospective observational cohort
109 UC pts receiving vedolizumab w (n=46) or w/o (n=63) concomitant aminosalicylates



Ma, C. et al. CGH 2019 17:2374-2376

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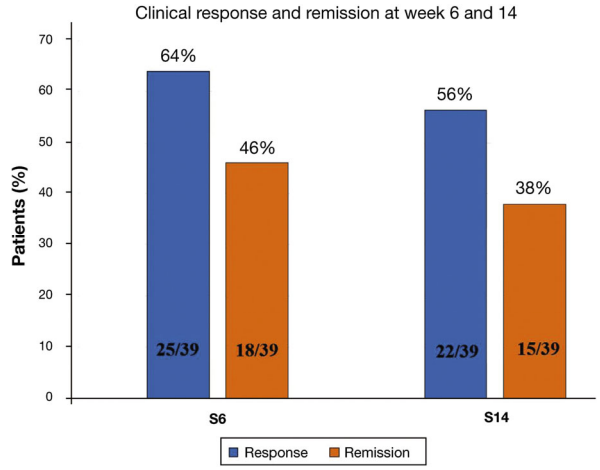
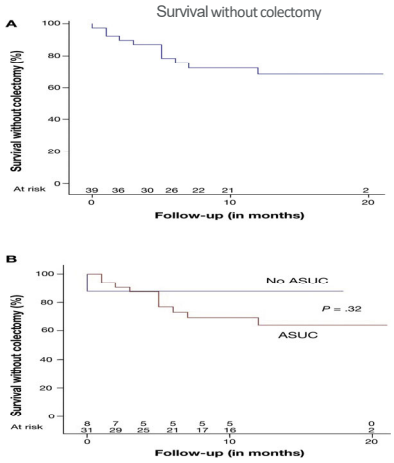
Calcineurin Inhibitors in Combination with Vedolizumab in Refractory UC

Retrospective study of induction therapy with cyclosporine or tacrolimus in combination with vedolizumab
39 pts with refractory UC (most of whom failed TNFi's





Pellet, G et al CGH 2019 17:494-501

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Efficacy Summary

- Combination therapy more effective than monotherapy for infliximab & adalimumab (?) in both CD and UC
  - Decreased sensitization \better PK \targeting multiple mechanisms (?)
- Co-administration of immunosuppressives is not necessary for vedolizumab/ustekinumab, if the intent is solely to prevent sensitization*
- Combination therapy may be the only way forward if we are to achieve high (>80%) rates of corticosteroid–free remission
- *Most KOLs recommend combination therapy for subsequent biologics for patients who have demonstrated prior immunogenicity

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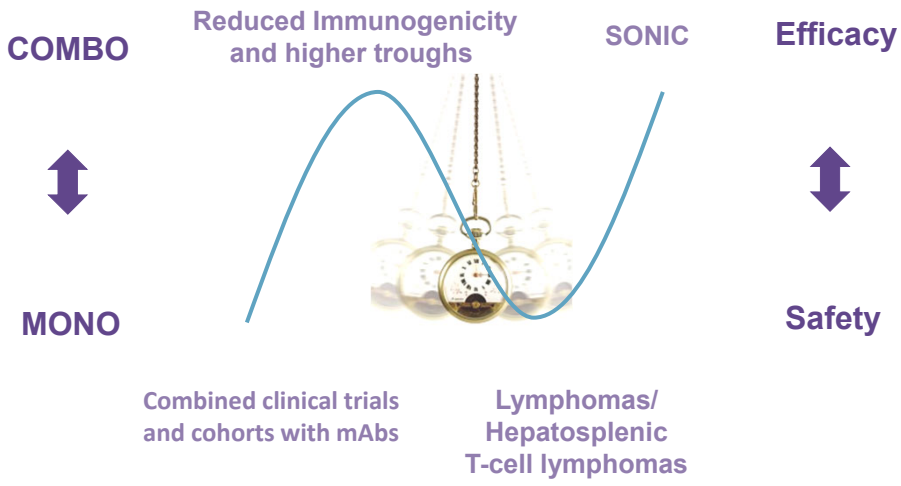
Mono or Combo: Why is the pendulum swinging?



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Risk factors for opportunistic infections The Mayo experience

Biologic + Azathioprine is Least Risky for Opportunistic Infection

Medication	OR (95%CI)	P-value
1	2.7 (1.5-4.8)	<0.002
2	9.7 (3.3-28.2)	<0.0001
3	infinite	
Steroids	2.2 (1.1-4.8)	0.037
AZA/6-MP	2.5 (1.2-5.1)	0.015
IFX	11.2 (0.8-153.3)	0.07
6-MP/aza + ster	15.7 (4.1-59.5)	<0.0001
6-MP+IFX	**1.6 (0.1-18.7)**	0.71
6-MP/Aza+IFX+ster.	infinite	

Toruner M Gastroenterology. 2008 134:929-36.

TREAT Registry: Serious Infections Logistic Regression Data (Multivariate)

Steroids are the biggest risk for infections

	Odds Ratio	95% CI
Age (years)	1.01	0.99-1.03
Female	1.24	0.81-1.90
Moderate or severe CD	2.11	1.10-4.05*
Current use of infliximab	1.40	0.95-2.07
Current use of 6MP/AZA/MTX	0.88	0.61- 1.27
Current use of corticosteroids	2.21	1.46- 3.34*
Current use of narcotic analgesics	2.38	1.56- 3.63*

Lichtenstein GR, et al. CGH 2006 4:621-630.

SONIC Summary of Adverse Events Through Week 50 – All Randomized Patients

	AZA + placebo (n=161)	IFX + placebo (n=163)	IFX + AZA (n=179)
Pts with ≥ 1 AE, n (%)	144 (89.4%)	145 (89.0%)	161 (89.9%)
Pts with ≥ 1 SAE, n (%)	43 (26.7%)	39 (23.9%)	27 (15.1%)
Serious infections	9 (5.6%)	8 (4.9%)	7 (3.9%)

Combination Therapy had Lowest Risk Of Infections

Colombel et al. N Engl J Med 2010 362: 1383-1395.

REACT: Safety-Deaths

	Conventional Management n	Early Combined Immunosuppression n
Cardiovascular	4	2
Thromboembolic	1	1
Cancer	2	3
Infection	1	1
Other**	2	0
Total	1 (1.1%)	7 (0.9%)

**"exhaustion" (age 96)
"unknown"

Khanna R. et al. Lancet 2015 386:1825-34.

Crohn's Disease Activity and Concomitant Immunosuppressants Affect Risk of Serious and Opportunistic Infections in Patients Treated With Adalimumab

- 2,266 patients treated with adalimumab in placebo-controlled trials
- Each 100-point increase in CDAI associated with >30% increased risk of serious or opportunistic infection.
- Concomitant immunomodulators associated with >3-fold decreased risk of serious infection by 1 year
- Concomitant corticosteroids associated with increased risk of serious infection (HR 2.40 (1.33–4.35), P=0.004)
- Concomitant use of either category of immmunosuppressant associated with numerically higher rates of opportunistic infection, 40% due to herpes zoster, compared with adalimumab monotherapy.

Osterman, M et al AJG 2016 111:1806–1815

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The Incidence of Pneumonia & Impact of Immunosuppressive Medications on Risk of Pneumonia Among Patients with IBD

- Nationwide cohort of IBD patients from VA, 2000 -2019
  - –56,398 patients with IBD
  - –9 years median follow-up
- 6.4 per 1000 patient-years of follow-up risk of developing pneumonia
- **Anti-TNF agents and corticosteroids associated with increased risk of pneumonia**

Cox model results adjusted for all covariates

	Adjusted HR	95% CI	P value
Charlson comorbidity index	1.16	1.14, 1.18	<0.001
Influenza vaccination	1.28	1.19, 1.38	<0.001
Narcotic within 60 days prior to index date	1.45	1.34, 1.57	<0.001
Prednisone cumulative (mg/day)	1.02	1.01, 1.03	<0.001
Prednisone within 30 days prior to index date	1.99	1.78, 2.22	<0.001
IBD flare	2.64	2.38, 2.93	<0.001
Medications (5-ASA reference)			
Thiopurines	0.92	0.81,1.04	0.173
Anti-TNF	1.21	1.05,1.40	0.01
Thiopurine/anti-TNF combination	1.12	0.84. 1.51	0.439
Vedolizumab	0.74	0.30, 1.80	0.508
PPSV23	1.15	1.07, 1.23	<0.001

Patel D et al. Presented at DDW Virtual Conference 2020. Abstract 282.

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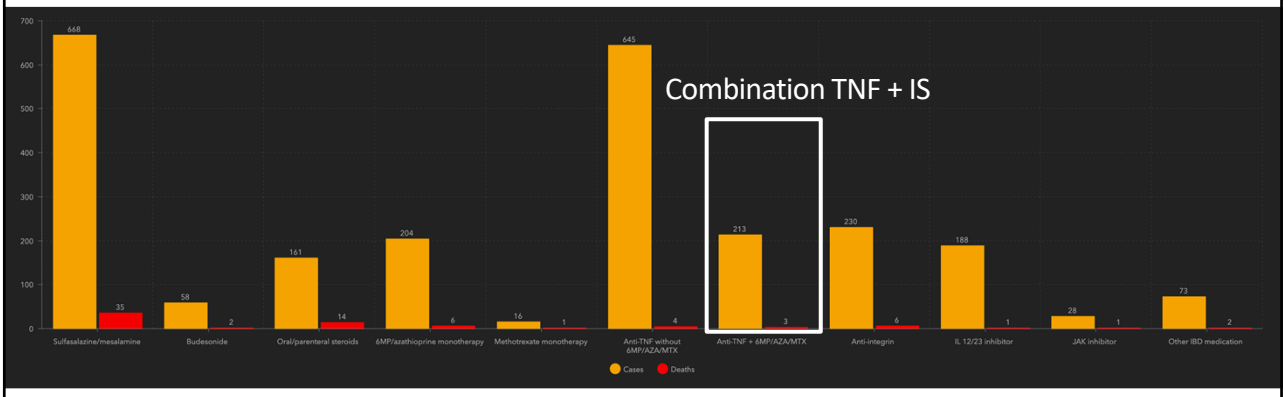
SECURE-IBD REGISTRY

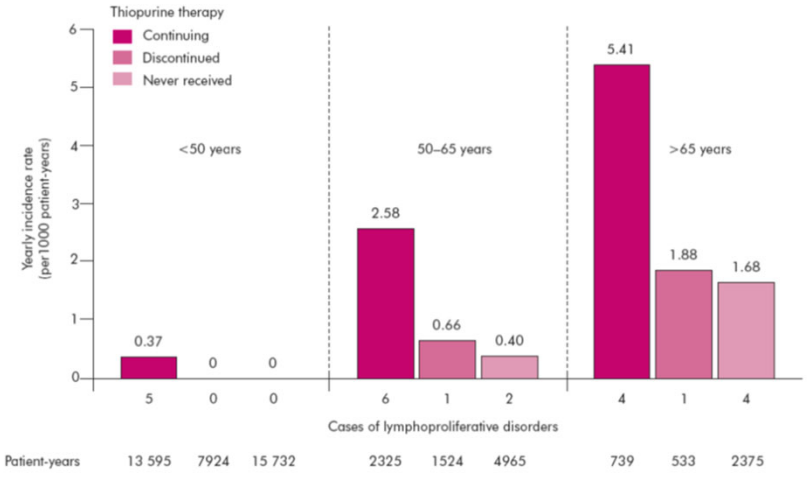


Accessed 8/29/90

2156 IBD Cases, 548 Hospitalization, 65 Deaths

Exposure to Thiopurines and Lymphomas in IBD

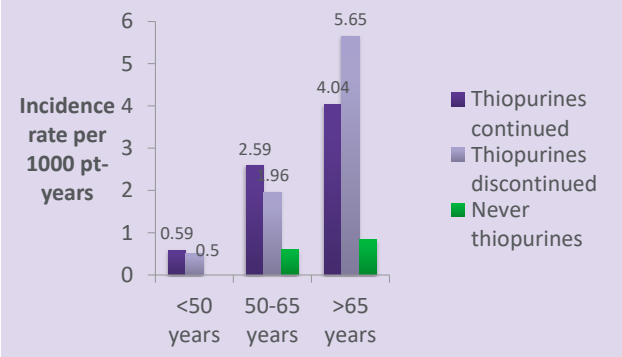
HR thiopurines = 5 [CI 95%: 2-14] Increases with Age



Beaugerie L et al., Lancet 2009 374:1617-25

Risk of Skin Cancer Associated with Thiopurines (CESAME)

- 19,486 IBD patients
- 32 cases of skin cancer (20 basal cell, 12 squamous)



Peyrin-Biroulet L, et al. Gastroenterology 2011 141:1621-28

Hepatosplenic T-cell lymphomas

- Main features
  - Rapidly fatal lymphoproliferations
  - Young men <35 yrs
  - Non EBV-related
  - Combo therapy thiopurines/anti-TNF, and less frequently monotherapy with thiopurines
  - Rare within the first two years of treatment
- Rare (<0.1 /1000 PY) – 20 cases with Combo and 16 with AZA/6-MP

Kotlyar D et al. CGH2011 9:36-41

Systematic review: hepatosplenic T-cell lymphoma on biologic therapy for inflammatory bowel disease

- 62 cases (identified from 2486 abstracts and 181 FDA AERS)
- Median age 28 years (12-81)
- 83% Male
- 84% Crohn's disease
- 5/62 No thiopurine exposure
- All cases with biologics had TNFi exposure
- 88% Mortality (median survival 5 months)

Shah, ED et al. Aliment Pharmacol Ther. 2020 51:527–533

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Risk of Serious/Opportunistic Infections & Lymphoma Associated with Treatment of IBD

French Administrative Databases (n=190,694)

Lymphoma

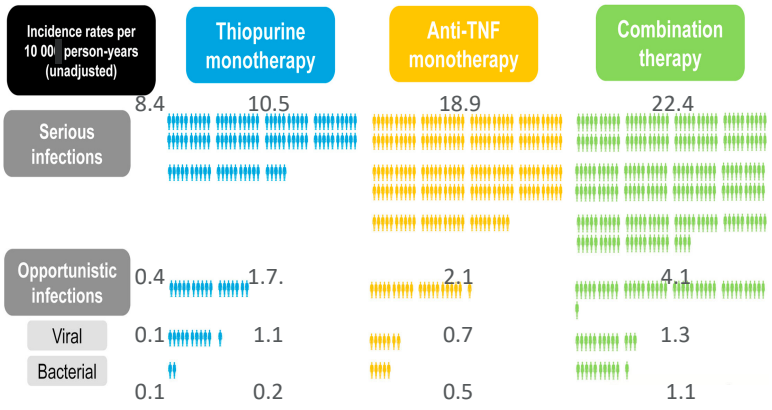
Incidence Rates per 1000 p/yrs

Unexposed 0.26

Thiopurine 0.54

Anti-TNF 0.41

Combined 0.95



Kirchgesner, J, et al Gastroenterology 2018 155, 337-346

Lemaitre, M et al JAMA 2017; 318: 1679–1686

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Combination therapy

positives

negatives

Pharmacokinetics

Higher drug levels

Optimizing 2 drugs?

Immunosuppression

Synergistic efficacy (?)

Infections (Steroids)
Malignancy (Thiopurines)

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Risk-Benefit of Stopping Combination Therapy

Benefits

- Reduced risk of lymphoma (?)

Risks

- Disease Flare
- Disease Progression

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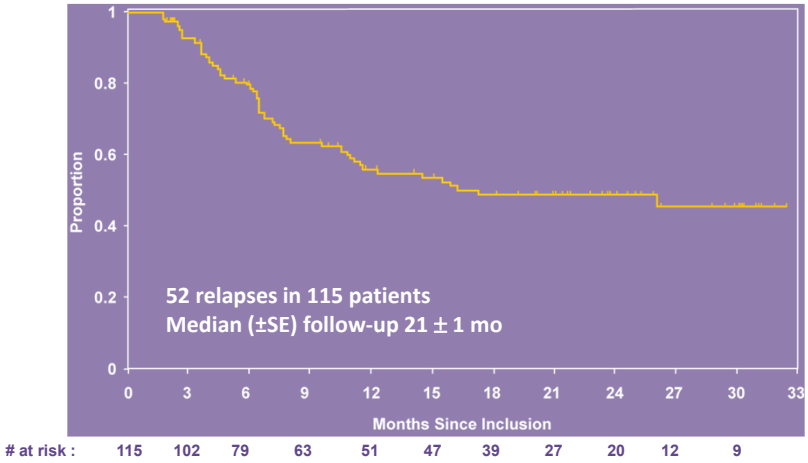
Can We Stop Biologic and Continue Immunomodulator?

Discontinuation of Infliximab in Patients in Stable Remission on Combination Therapy (Azathioprine Maintained, STORI trial)

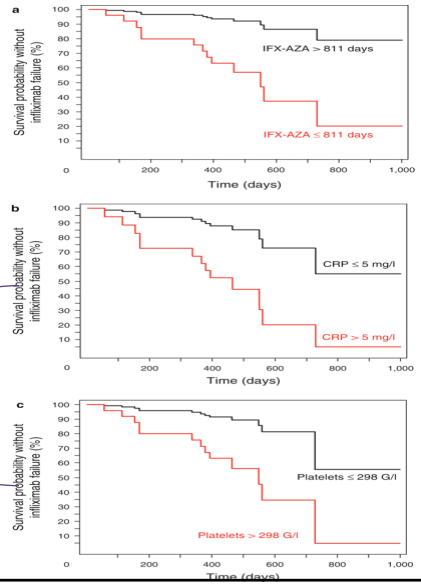


Louis, E. Gastroenterology. 2012 142:63-70

Probability of Crohn's Relapse on Azathioprine after Discontinuing Infliximab

Long-term response

"Deep Remission"



Oussalah, A, et al. Am J Gastro. 2010 105:1142-1149

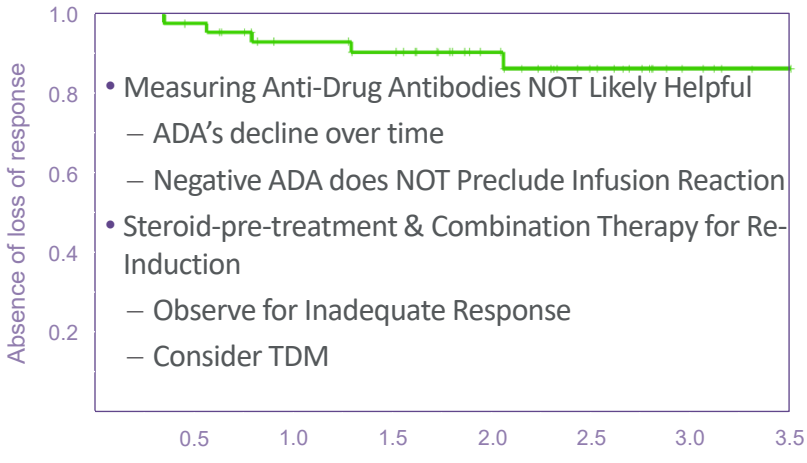
Pragmatic Approach to Stopping Immunomodulators

- Assure Deep Remission (Symptoms, Endoscopy, Biomarkers)
- Determine Trough Biologic Levels
  - Therapeutic Level→Stop IMM
  - Non-Therapeutic Level →Measure Thiopurine Level
    - Therapeutic Thioguanine → Consider Stopping Biologic (?) or Continue Combo (?)
    - Non-Therapeutic → Continue Combination (?)

Can Biologics be Restarted?

Long-term efficacy of Infliximab re-treatment (GETAID)

*Kaplan Meier **loss of response** over time in the STORI cohort*
52 retreated patients after 6.6 months drug holiday; 6/52 only loss of response over a median follow-up of 24 months



- Measuring Anti-Drug Antibodies NOT Likely Helpful
  - ADA's decline over time
  - Negative ADA does NOT Preclude Infusion Reaction
- Steroid-pre-treatment & Combination Therapy for Re-Induction
  - Observe for Inadequate Response
  - Consider TDM

Louis, E. Gastroenterology. 2012 142:63-70

Which Patients Should Receive Combination Biologic and Immunosuppressive Therapy?

- Patients Initiating TNF inhibitor
  - Continue for 6-12 months
  - Assess for Deep Remissions & Therapeutic Drug Levels
- Patients who have developed Immunogenicity with First Biologic starting Second Biologic
  - Continue for 6-12 months
  - Assess for Deep Remissions & Therapeutic Drug Levels
- Patients being treated without TDM

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Which Patients Should NOT Receive Combination Biologic and Immunosuppressive Therapy?

- Teenage and young adult males appear to have an increased relative risk of hepatosplenic T-cell lymphoma with combination anti-TNF agents and thiopurines
  - Consider EBV titers for young males
- Patients >65 years have an increased risk of serious infection with anti-TNF therapy and combination therapy
- Patients >65 years have an increased risk of non-Hodgkin's lymphoma with AZA therapy

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Summary

- **Higher rates of clinical response and remission demonstrated in IBD patients treated with TNFi combined with immunomodulators**:
  - Associated with higher trough serum TNFi concentration, Lower incidence of anti-drug antibodies
- **There are significant differences between TNFi anti-TNF drugs and vedolizumab/ustekinumab**
  - Different nature of the target molecule, Longer half-life, Not certain strategies that optimize anti-TNF effectiveness are applicable to vedolizumab/ustekinumab
- **Higher serum concentrations of vedolizumab and ustekinumab are associated with increased rates of clinical response and remission**
- **Currently available evidence suggests that concurrent treatment with immunomodulators does not result in higher serum vedolizumab/ustekinumab concentrations**
- **Anti-vedolizumab/Anti-ustekinumab antibodies are generated, although probably to a lesser extent and with less effect on vedolizumab/ustekinumab clearance compared with anti-TNF drugs**
- **No currently available studies that specifically assess additional benefit of adding immunomodulators to vedolizumab/Ustekinumab (most data do not suggest effect)**

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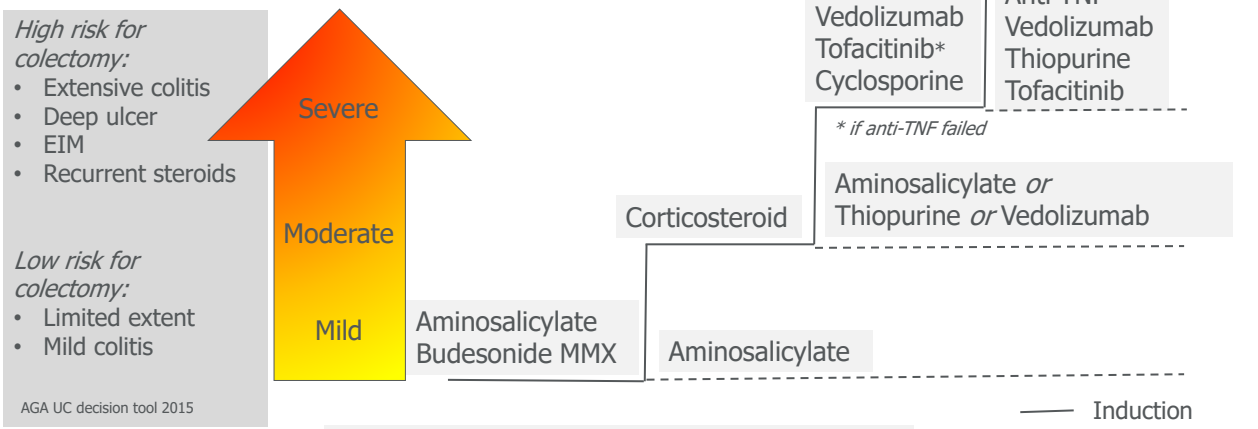
Future Treatment Strategy for Ulcerative Colitis

The AGA suggests early use of biologic agents with or without immunomodulator therapy, [or tofacitinib], rather than gradual step up after failure of 5-aminosalicylates.



Step-Up according to severity or failure at prior step

adapted from S. Hanauer

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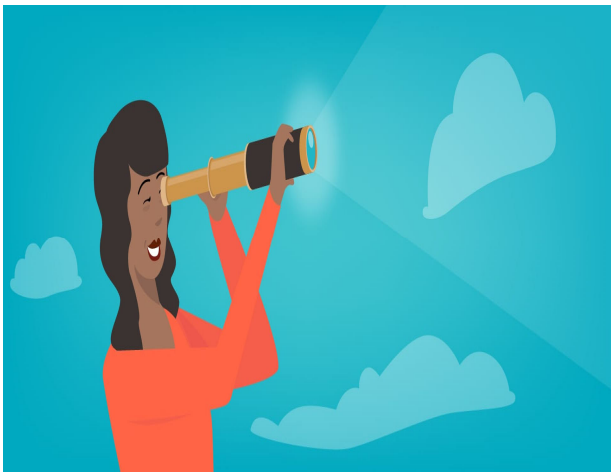
Looking Backwards

- Be cautious of post-hoc analyses!
  - They are often disproven in prospective studies

Looking Forward



- Prospective studies of ustekinumab & vedolizumab + IMM in bio-/IMM naive
- Comparative effectiveness trial
- Expanding Real-World data

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Questions?

Stephen B. Hanauer, MD, MACG

Mark C. Mattar, MD, FACG

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