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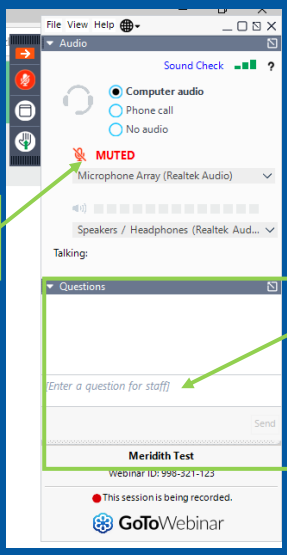
Participating in the Webinar

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

LIVE VIRTUAL GRAND ROUNDS WEBINAR

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, 2022 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, 2023 for this activity.

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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.
THESE ANSWERS WILL BE REVIEWED.

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SPECIAL EDITION: GIQuIC QuIC Bite Webinar – Wednesday, September 28, 2022
Screening Colonoscopy Updates: What They Mean for Your Practice
Wednesday, September 28, 2022 at 8pm Eastern

Week 39 – Thursday, September 29, 2022
Diagnosis and Management of Cancer Risk in the Gastrointestinal Hamartomatous Polyposis Syndromes: Recommendations from the US Multi-Society Task Force on Colorectal Cancer
Faculty: Gregory E. Idos, MD
Moderator: Veroushka Ballester, MD
Thursday, September 29, 2022 at Noon Eastern and **NEW! 8pm Eastern!**

Visit **gi.org/ACGVGR** to Register

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Disclosures

Andres J. Yarur, MD, FACG
Arena Pharmaceuticals: Consultant
Boehringer Ingelheim: Consultant
Bristol Myers Squibb: Consultant
Procise: Consultant

Ryan C. Ungaro, MD, MS
AbbVie: Advisory board, consultant
Bristol Myers Squibb: Advisory board, consultant
Janssen: Advisory board, consultant
Pfizer: Advisory board, consultant
Takeda: Advisory board, consultant

**All of the relevant financial relationships listed for these individuals have been mitigated*

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THERAPEUTIC DRUG MONITORING OF BIOLOGICS IN IBD: WHY, WHEN AND HOW?

Andres Yarur, MD FACG
Associate Professor of Medicine
Division of Gastroenterology
Cedars Sinai Medical Center
Los Angeles, California

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GOAL

- Understand what is therapeutic drug monitoring of therapies in IBD
- Why can be an important tool
- Review when and how to use it
- Answer a lot of questions!

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 26, 2019 VOL. 381 NO. 13

Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis

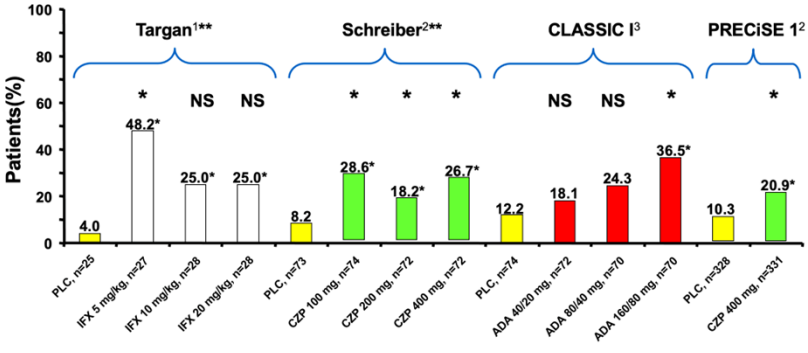
B.E. Sands, W.J. Sandborn, R. Panaccione, C.D. O'Brien, H. Zhang, J. Johanns, O.J. Adedokun, K. Li, L. Peyrin-Biroulet, G. Van Assche, S. Danese, S. Targan, M.T. Abreu, T. Hisamatsu, P. Szapary, and C. Marano, for the UNIFI Study Group*

Stephen B Hanauer, Brian G Feagan, Gary R Lichtenstein, Lloyd F Mayer, S Schreiber, Jean Frederic Colombel, Daniel Rachmilewitz, Douglas C Wolf, Allan Olson, Weihang Bao, Paul Rutgeerts, and the ACCENT I Study Group*

13

A HIGH NUMBER OF PATIENTS DO NOT RESPOND

Clinical remission in anti-TNFα naïve patients (ITT) (CDAI ≤ 150)
(for Targan study CDAI < 150)
REMISSION AT 4 WEEKS[1,2,3]



1. Targan et al. *N Engl J Med* 1997;337:1029-1035.
2. UCB Data on File.
3. Hanauer et al. *Gastroenterology* 2006;130:323-333.

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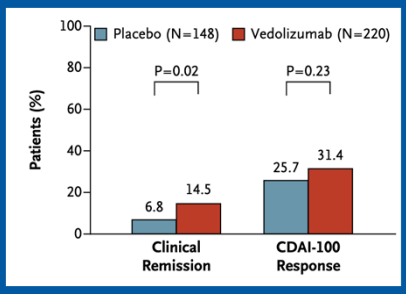
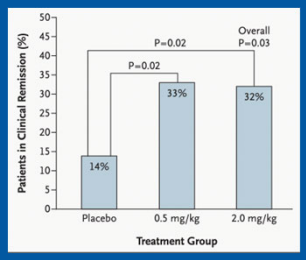
A HIGH NUMBER OF PATIENTS DO NOT RESPOND

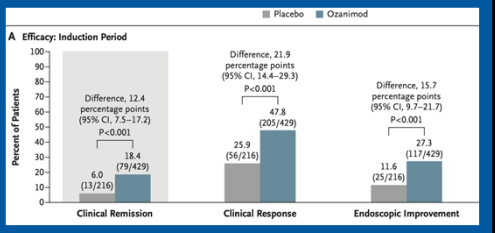
Vedolizumab in Crohn's Disease



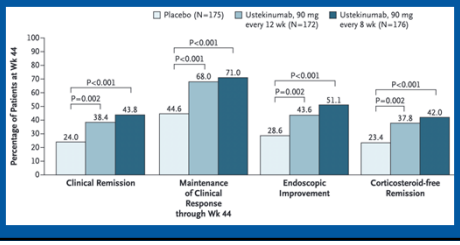
Vedolizumab in UC



Ozanimod in UC



Ustekinumab in UC



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A HIGH NUMBER OF PATIENTS DO NOT RESPOND

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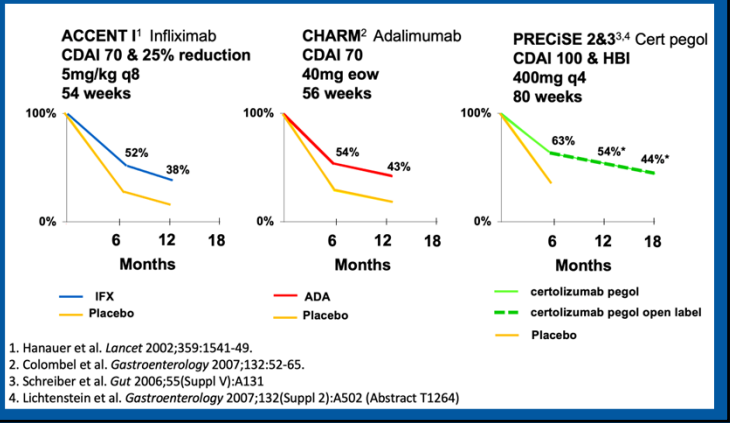
CHALLENGES WITH BIOLOGIC THERAPY

- Of those who do respond…
- A significant amount lose response



1. Hanauer et al. *Lancet* 2002;359:1541-49.
2. Colombel et al. *Gastroenterology* 2007;132:52-65.
3. Schreiber et al. *Gut* 2006;55(Suppl V):A131
4. Lichtenstein et al. *Gastroenterology* 2007;132(Suppl 2):A502 (Abstract T1264)

17

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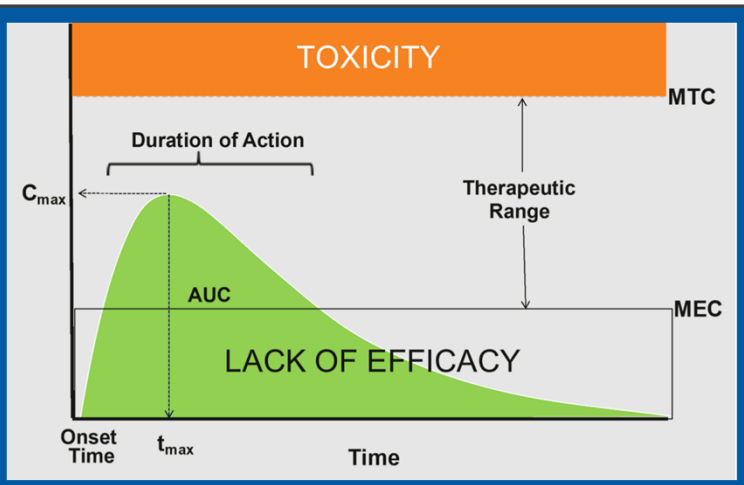
PHARMACOKINETIC PRINCIPLES: THERAPEUTIC DRUG MONITORING IN IBD



AUC = area under the curve
C_{max} = maximum concentration
MEC = minimum effective concentration
MTC = maximum tolerated concentration
t_{max} = time to Cmax.

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OBSERVATIONS THAT LED TO THE DEVELOPMENT OF TDM IN BIOLOGIC THERAPY FOR IBD

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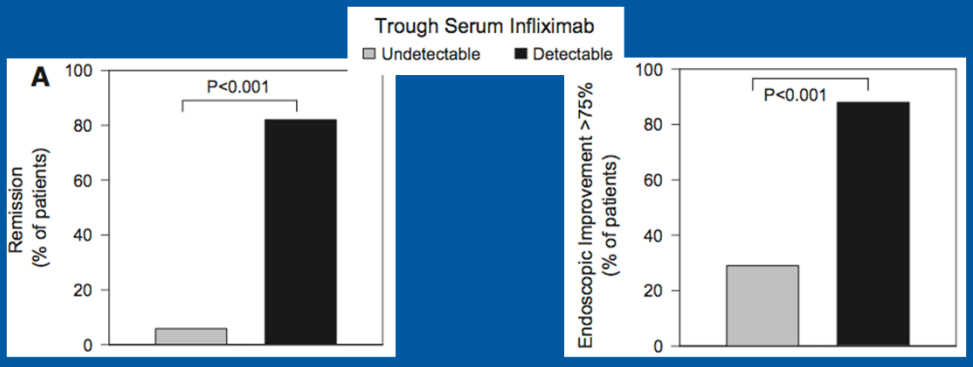
EXPOSURE-RESPONSE: INFLIXIMAB



Maser EA. Clinical Gastroenterology and Hepatology. 2006;4:1248–1254.

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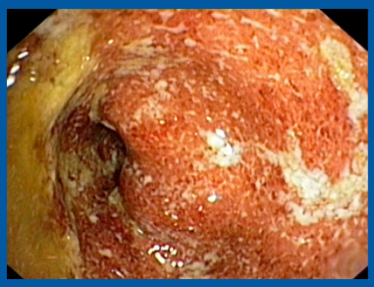
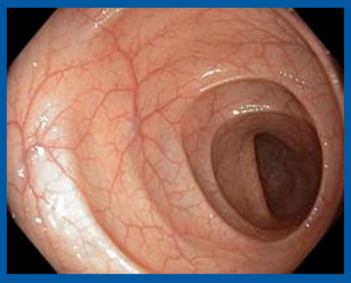
EXPOSURE-RESPONSE: ADALIMUMAB

Higher adalimumab levels correlate with higher efficacy



Mucosal Inflammation
Mean ADA level 8.5 µg/mL



Endoscopic Healing
Mean ADA level 13.3 µg/mL

P=0.02

Yarur A et al. Inflamm Bowel Dis. 2016

21

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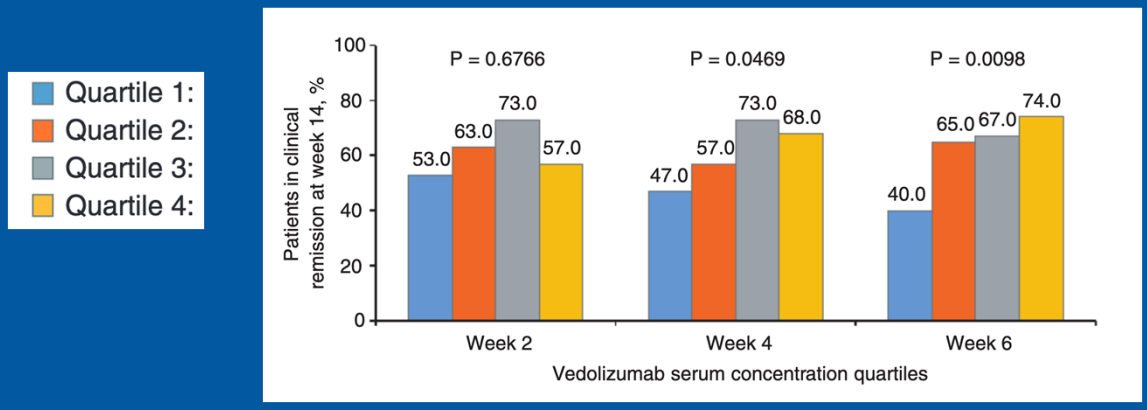
EXPOSURE-RESPONSE OF VEDOLIZUMAB

Post-hoc Gemini study



Osterman et al. Aliment Pharmacol Ther. 2019

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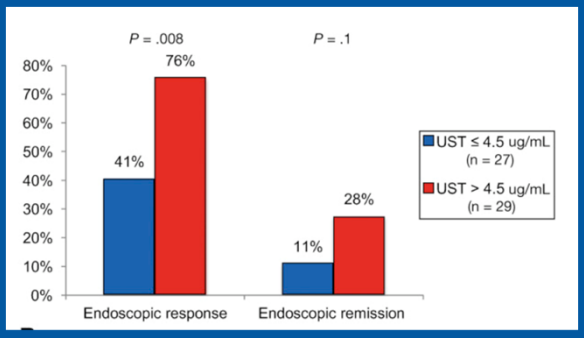
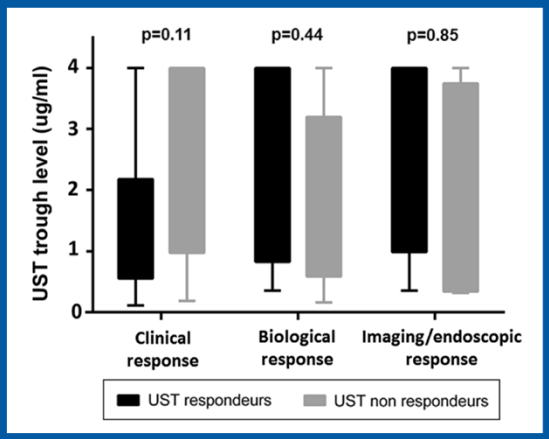
USTEKINUMAB…. SIMILAR STORY?

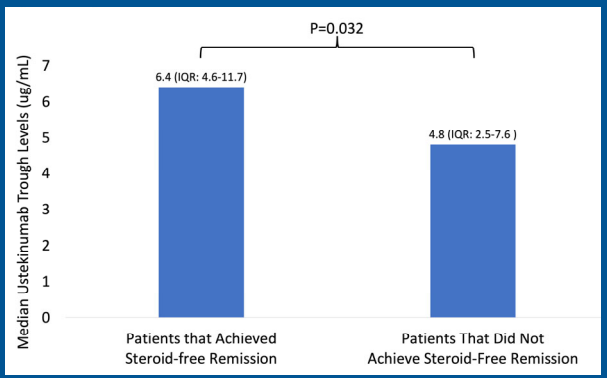


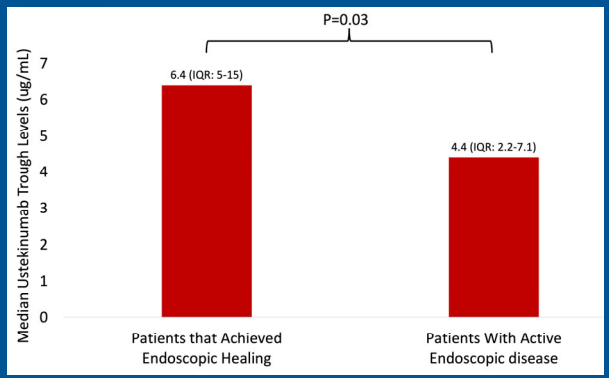


Battat et al. CGH 2017
Painchart I C et al. DDS 2020

23

USTEKINUMAB…. SIMILAR STORY?





Yarur et al. Presented at DDW 2022

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THE ROLE OF PHARMACOKINETICS IN NON-RESPONSE TO BIOLOGICS: ANTI-TNF

Higher drug levels = higher efficacy

Let's "fill the tank"

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CLINICAL TRANSLATION OF THESE FINDINGS

Measuring Drug Levels and the Presence of Anti-Drug Antibodies → Use to Guide Therapeutic Decisions

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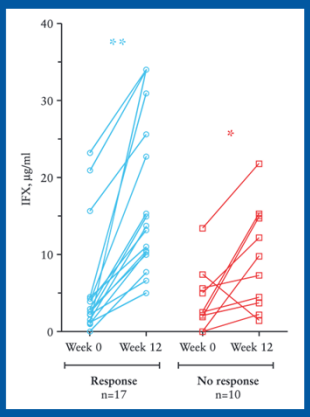
INCREASE IN INFLIXIMAB LEVELS IS ASSOCIATED WITH BETTER CLINICAL OUTCOMES

- Observations that higher anti-IFX levels are associated with lower disease activity raised the question if increasing drug levels may lead to better outcomes
- Dose-escalating patients with "low" drug levels translates only into a 50%-86% rate of response



C. Steenholdt et al. Journal of Crohn's and Colitis, 2015
Afif et al. Am Journal of Gastro, 2010.

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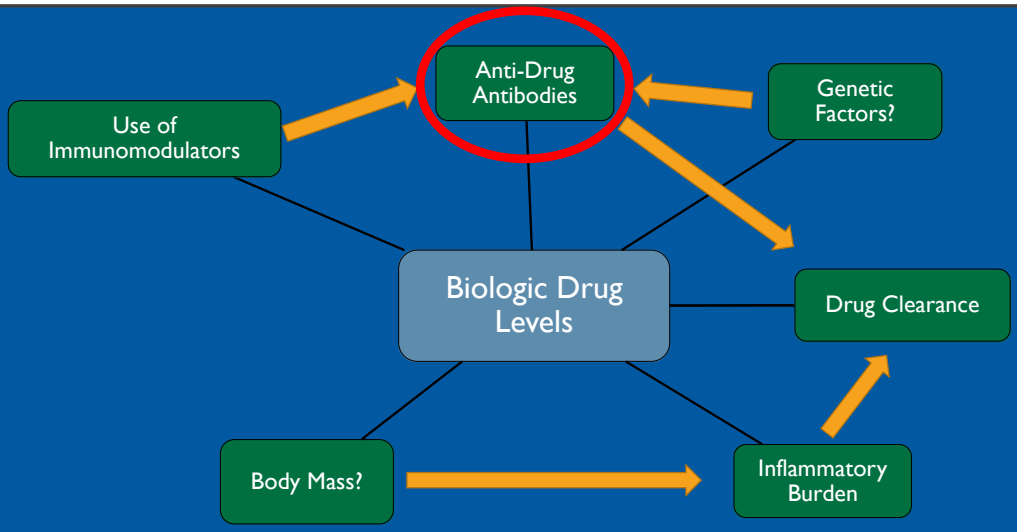
MULTIPLE FACTORS AFFECT THE PK OF ANTI-TNF



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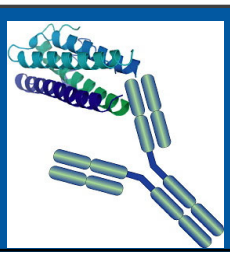
IMMUNOGENICITY AGAINST ANTI-TNF BIOLOGICS IS PREVALENT



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IMMUNOGENICITY TO ANTI-TNF: PREVALENCE

		Patients, %	
		Episodic Maintenance	Scheduled Maintenance
Infliximab[1]	(CD 5 mg/kg) (CD 10 mg/kg)	38%	11% 8%
Infliximab[2]	(UC 5 mg/kg) (UC 10 mg/kg)	No data	19% 9%
Certolizumab[3]	(PRECiSE I)		10%
Certolizumab[4]	(PRECiSE II)	24%	12%
Adalimumab[5]	(RA, all doses)	No data	12%
Adalimumab[6]	(CLASSIC II)		4%
Golimumab[7]	(RA)	No data	13.1%

[1]Hanauer S, et al. *Clin Gastroenterol Hepatol*. 2004;2(7):542-53.
[2]Sandborn WJ, et al. DDW 2007. Abstract T1273.
[3]Sandborn WJ, et al. *N Engl J Med*. 2007;357(3):228-38.
[4]Schreiber S, et al. *N Engl J Med*. 2007;357(3):239-50.
[5]Summary of Product Characteristics for adalimumab. Abbott Laboratories. July 2007.
[6]Sandborn WJ, et al. *Gut*. 2007;56(9):1232-9.
[7]Keystone EC, et al. *J Rheumatol*. 2013;40(7):1097-103.

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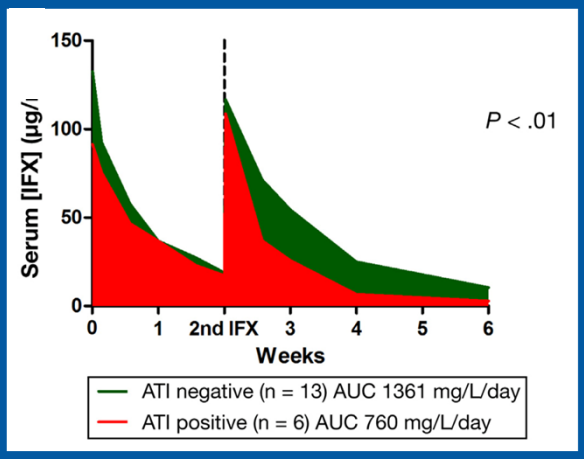
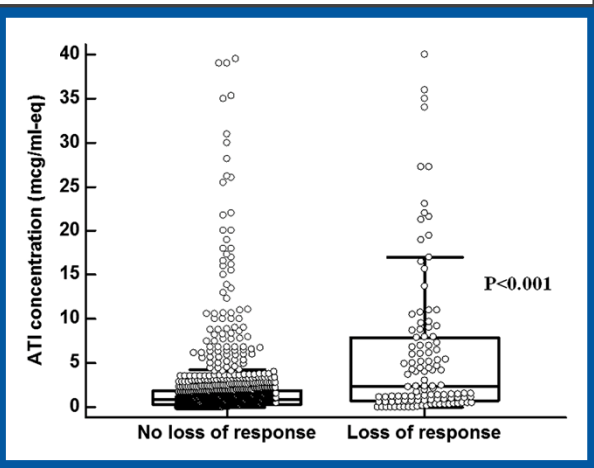
ANTI-DRUG ANTIBODIES ARE ASSOCIATED WITH LOWER DRUG LEVELS AND WORSE OUTCOMES





Brandse J. CGH. 2016
Ungar B. Gut. 2014

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ANTI-DRUG ANTIBODES ARE BAD NEWS (AT LEAST IN ANTI-TNFS)… HOW CAN WE AVOID THEM?

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CONCOMITANT USE OF IMMUNOMODULATORS

		Patients, %			
		Episodic Maintenance		Scheduled Maintenance	
		IMS-	IMS+	IMS-	IMS+
Infliximab[1]	(CD 5 mg/kg) (CD 10 mg/kg)	38%	16%	11% 8%	7% 4%
Infliximab[2]	(UC 5 mg/kg) (UC 10 mg/kg)	No data		19% 9%	2% 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%
Golimumab[7]	(RA)	No data		13.1%	4.3%

[1]Hanauer S, et al. *Clin Gastroenterol Hepatol*. 2004;2(7):542-53.
[2]Sandborn WJ, et al. DDW 2007. Abstract T1273.
[3]Sandborn WJ, et al. *N Engl J Med*. 2007;357(3):228-38.
[4]Schreiber S, et al. *N Engl J Med*. 2007;357(3):239-50.
[5]Summary of Product Characteristics for adalimumab. Abbott Laboratories. July 2007.
[6]Sandborn WJ, et al. *Gut*. 2007;56(9):1232-9.
[7]Keystone EC, et al. *J Rheumatol*. 2013;40(7):1097-103.

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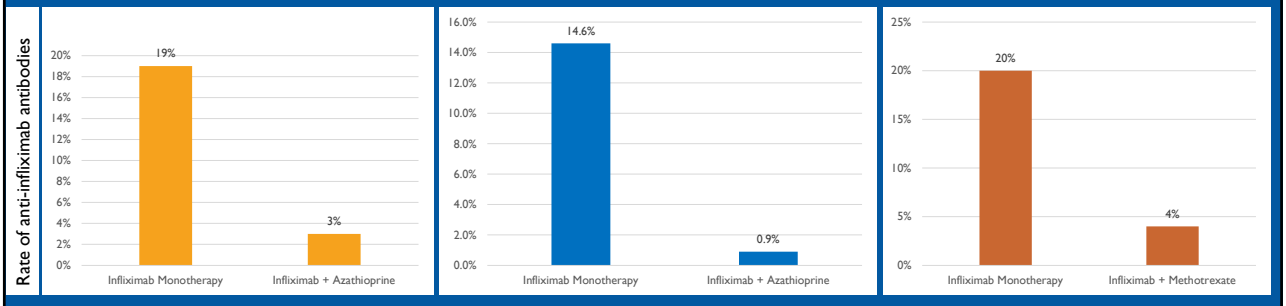
CONCOMITANT USE OF IMMUNOMODULATORS

- The concomitant use of immunomodulators are associated with higher anti-TNF drug levels and lower rate of anti-drug antibodies
- Thiopurines
- Methotrexate



UC SUCCESS
Panaccione et al. Gastroenterology 2014

SONIC
Colombel JF. NEJM 2010

COMMIT
Feagan B. Gastroenterology. 2014

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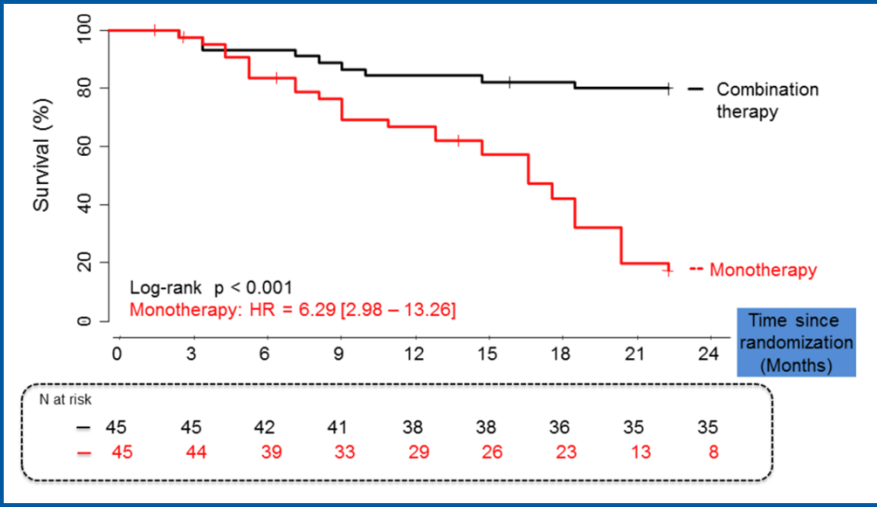
USING COMBINATION THERAPY WITH A SECOND A-TNF AFTER IMMUNE-MEDIATED LOSS OF RESPONSE TO A FIRST ANTI- TNF



Roblin X, et al. Gut 2020

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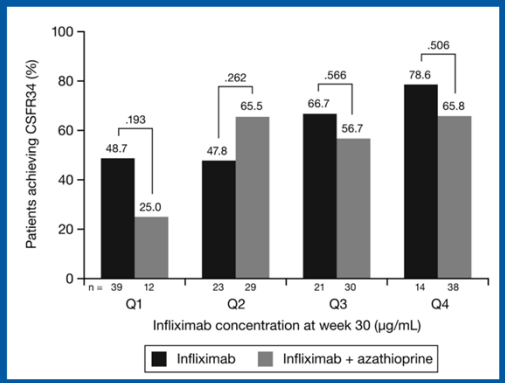
INFLIXIMAB+AZATHIOPRINE ASSOCIATED WITH BETTER PHARMACOKINETIC PROFILE

- Among patients with CD and similar serum concentrations of infliximab, combination therapy with azathioprine was not significantly more effective than infliximab monotherapy.



Colombel JF et al. Clinical Gastroenterology and Hepatology. 2019

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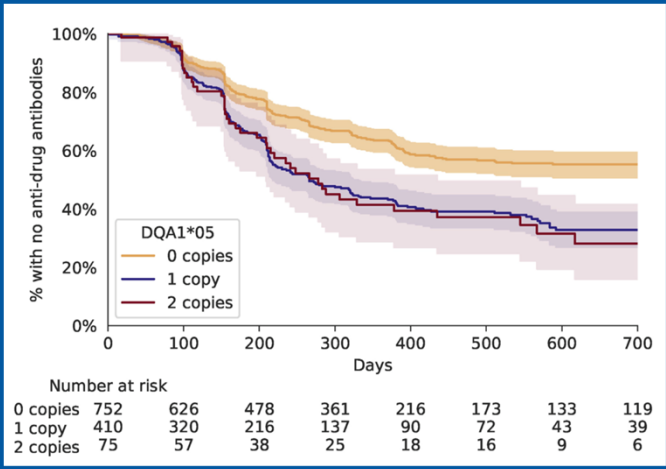
GENETICS
HLA-DQA1*05 CARRIAGE ASSOCIATED WITH IMMUNOGENICITY TO INFLIXIMAB AND ADALIMUMAB



Sazonovs et al. Gastroenterology 2020

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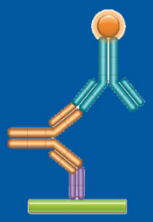
IMMUNOGENICITY IN VEDOLIZUMAB AND USTEKINUMAB

- The prevalence of anti-vedolizumab antibodies is lower than in Anti-TNF: 3-5%
- GEMINI I: 3.7%
- GEMINI II: 4.1%
- Similar with Ustekinumab (2.3% in UNITI)
- Most of them are transient and have no clinical significance



Rosario M et al. Clin Pharmacokinet 2017
Yarur A et al. DDS 2021
Ward MG et al. Therp. Adv. Gastro 2018

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HOW ABOUT THERAPEUTIC DRUG MONITORING FOR THIOPURINES?

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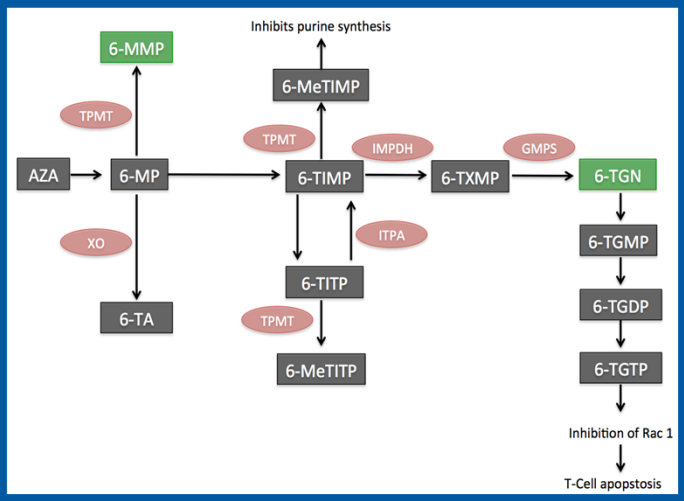
METABOLISM OF THIOPURINES

- Complex and not completely understood



Yarur AJ. WJG 2014 Apr 7;20(13):3475-84

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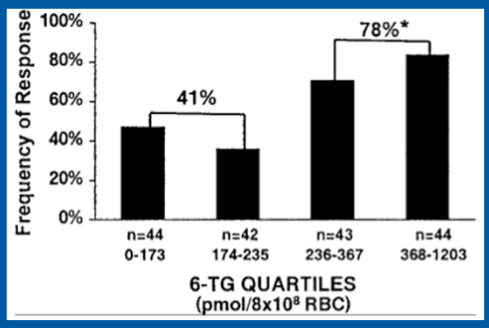
THIOPURINE METABOLITES

- 6-TGN Has been the metabolite most associated with treatment efficacy
- Its measurement has been proposed as a strategy to optimize treatment in patients with IBD receiving AZA/6-MP
- 6-TGN level >230 pmol/8 X 10^8 RBC has been correlated with clinical remission



Dubinsky MC, Gastroenterology. 2000;118:705–713.
Osterman MT, Gastroenterology. 2006;130:1047–1053.

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MEASURING THIOPURINE METABOLITES

- Non-response to monotherapy
- Compliance
- High liver enzymes

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COMBINATION THERAPY IMPROVES THE PHARMACOKINETICS OF ANTI-TNF AGENTS AND THIOPURINE SUB-METABOLITES ARE ASSOCIATED WITH EFFICACY

HOW ABOUT IF WE USE THIOPURINE METABOLITES TO GUIDE COMBINATION THERAPY?

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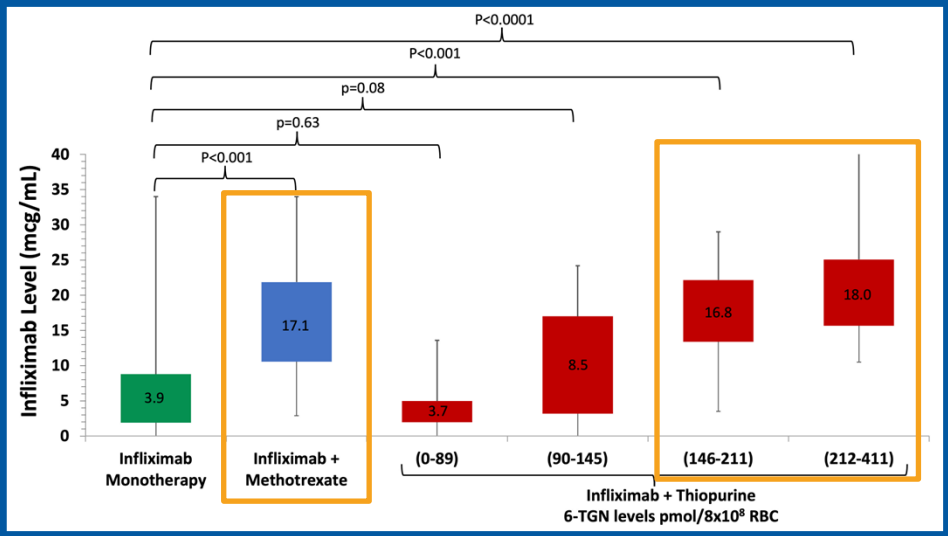
HIGHER 6-TGN IMPROVE THE PK OF INFLIXIMAB



Yarur et al. Presented at DDW 2022

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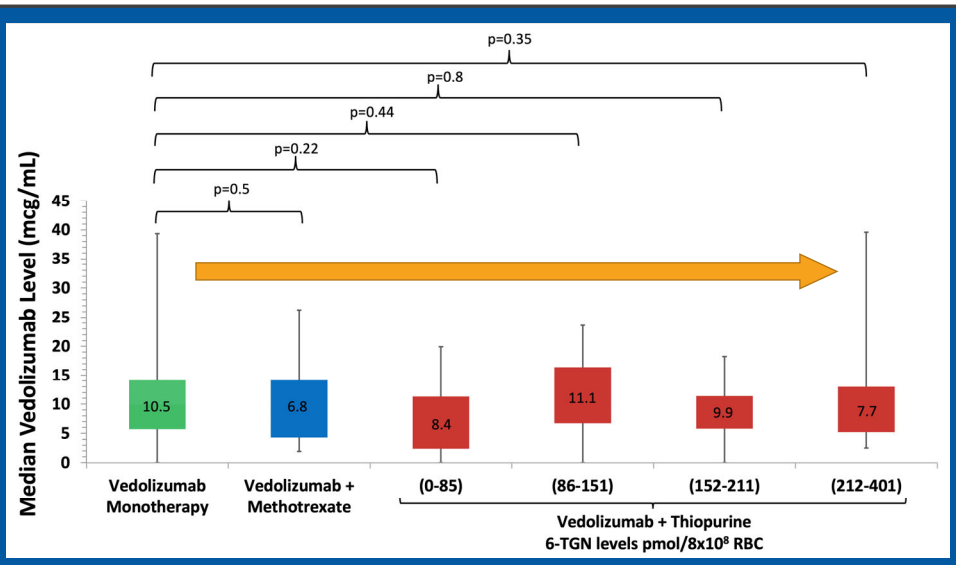
HIGHER 6-TGN DO NOT IMPROVE THE PK OF VEDOLIZUMAB



Yarur et al. Presented at DDW 2022

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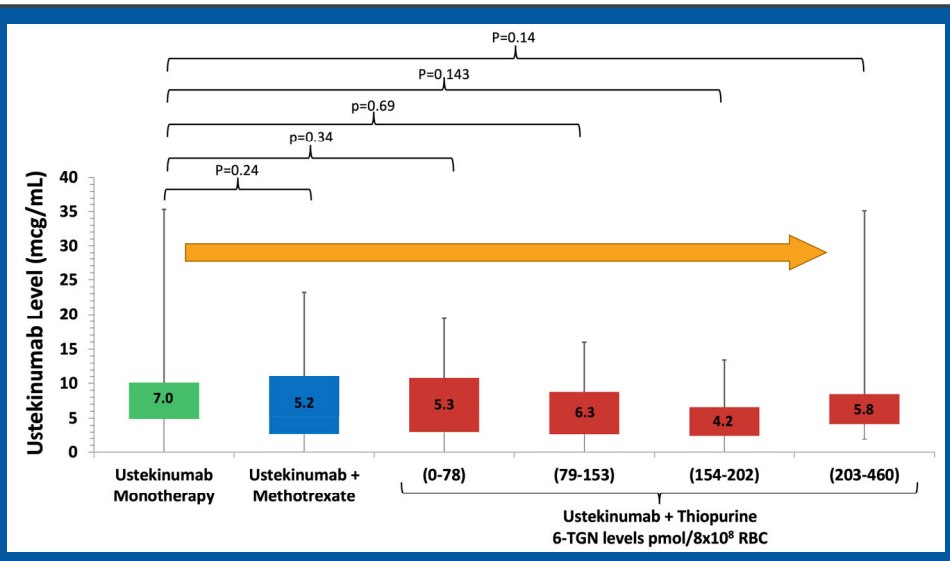
HIGHER 6-TGN DO NOT IMPROVE THE PK OF USTEKINUMAB



Yarur et al. Presented at DDW 2022

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WHEN TO PERFORM THERAPEUTIC DRUG MONITORING THE **PROACTIVE** VS **REACTIVE** DEBATE

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USE OF REACTIVE THERAPEUTIC DRUG MONITORING WITH BIOLOGICS

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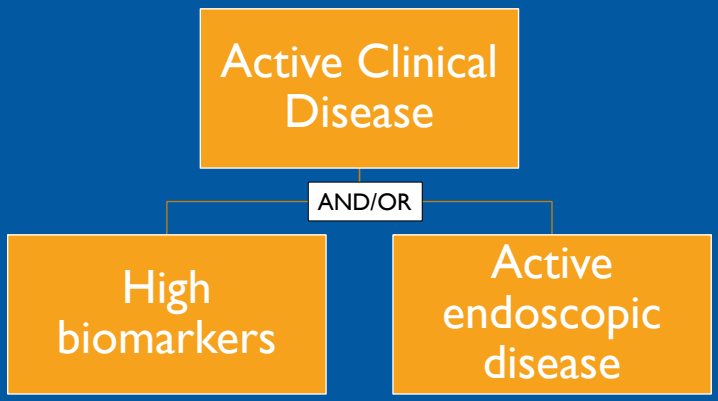
REACTIVE TDM

- Recommended after primary or secondary non-response
- Scenarios when to use reactive TDM:



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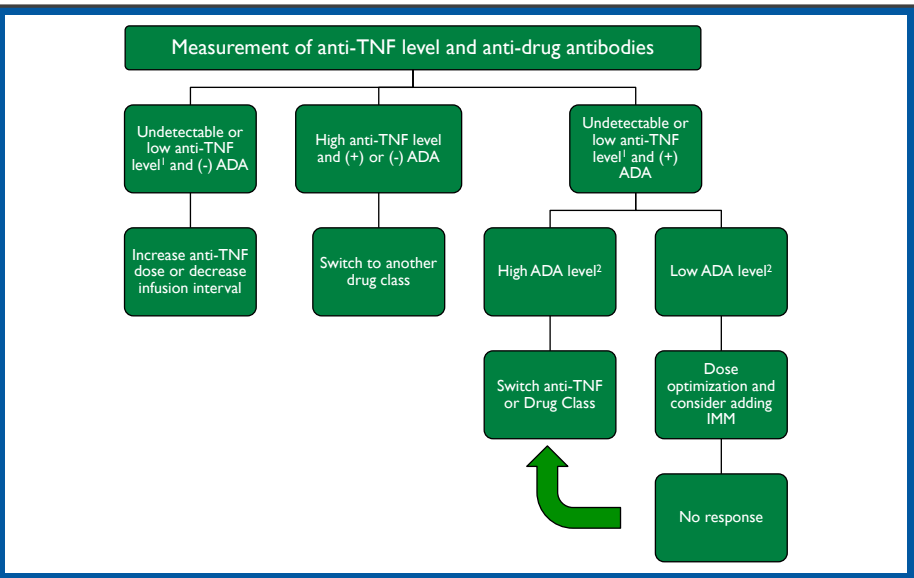
PATIENTS WITH LOSS OF RESPONSE ANTI-TNF



Yarur AJ & Rubin DT. Inflamm Bowel Dis. 2015 Jul;21(7):1709-182015

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HOW ABOUT REACTIVE TDM WITH VEDOLIZUMAB?

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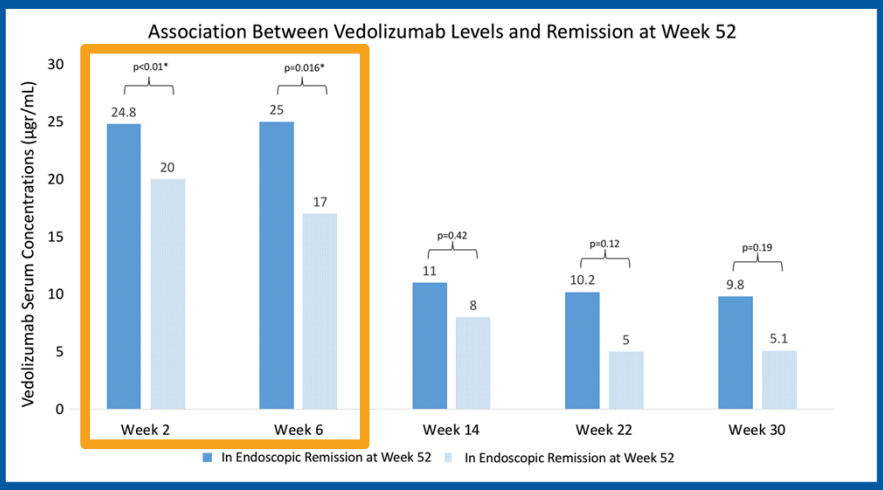
EXPOSURE-RESPONSE IN VEDOLIZUMAB



Yarur et al. DDS 2019

52

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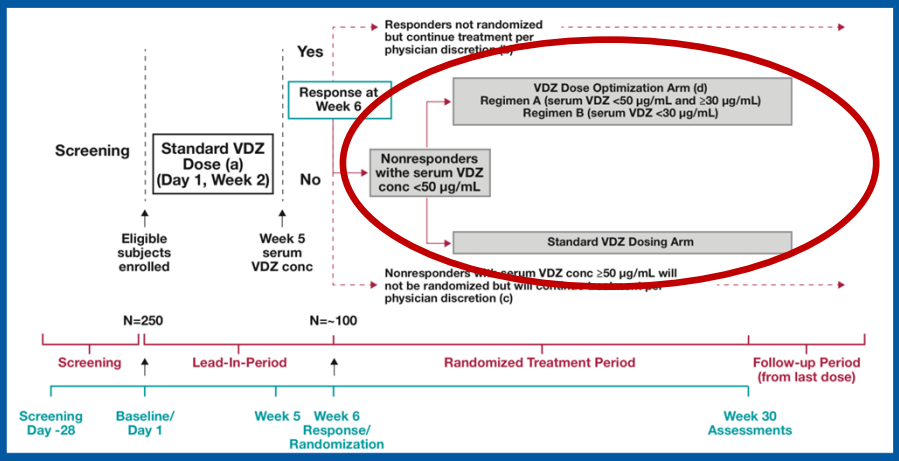
ASSOCIATION DOES NOT IMPLY CAUSATION

ENTERPRET Study: Increasing drug exposure in non-responderswith HIGH drug clearance

Moderate to Severe UC Starting Vedolizumab



Osterman et al. Presented at DDW 2022

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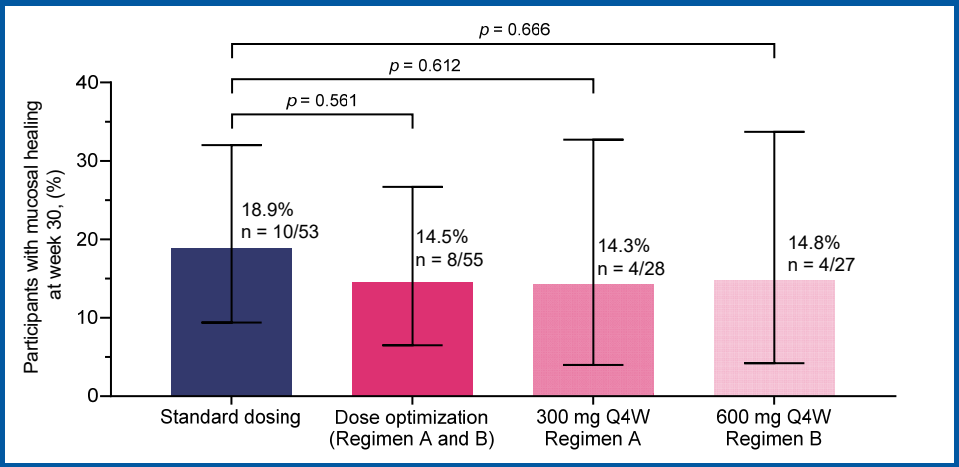
VEDOLIZUMAB DOSE ESCALATION IN PATIENTS WITH HIGH DRUG CLEARANCE DO NOT IMPROVE OUTCOMES

Full analysis set

Endoscopic mucosal healing at week 30

Mayo endoscopic subscore ≤ 1 by centrally read examination[a]



[A] Modified so a score of 1 does not include friability.

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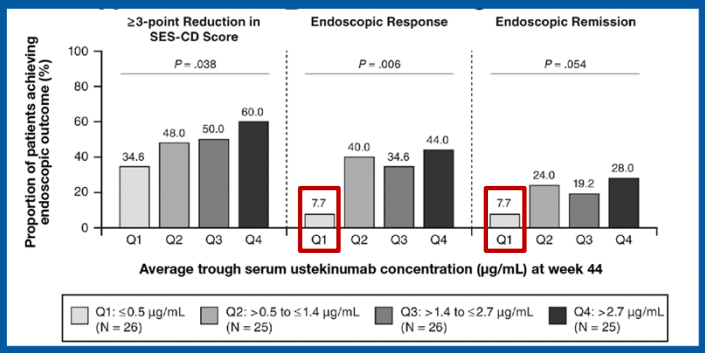
REACTIVE TDM: USTEKINUMAB

- The evidence is limited
- Antibodies are rare
- Common practice of increasing the dose
  - What is really a low level?



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BUT IS PROACTIVE TDM REALLY BETTER?

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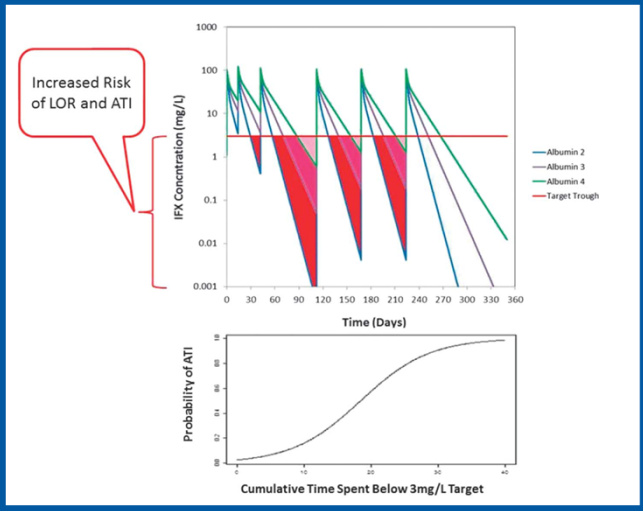
AVOID UNDER-EXPOSURE TO INFLIXIMAB

- Avoid under-exposure to infliximab
- IFX levels < 3 mcg/dL
- "pseudoepisodic treatment"



Brandse J. Inflammatory Bowel Disease Journal. 2017

57

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DOES IT MAKE SENSE TO BE PRO-ACTIVE?

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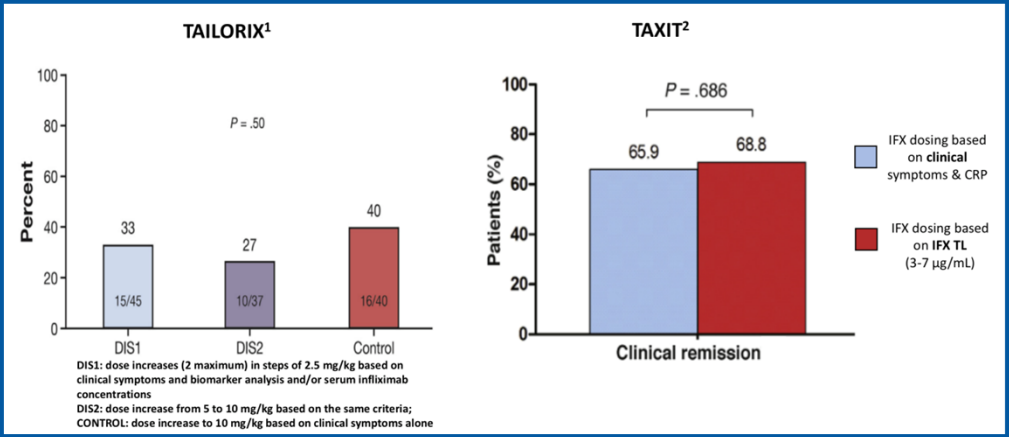
PRO-ACTIVE VS REACTIVE TDM WITH INFLIXIMAB



1) D'Haens G, et al. *Gastroenterol*. 2018;154:1343-1351.
2) Vande Casteele N, et al. *Gastroenterol*. 2015;148(7):1320-1329

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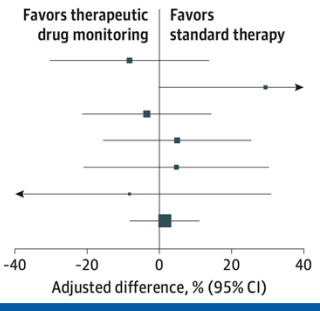
PRO-ACTIVE TDM WITH INFLIXIMAB: NORDRUM

- RCT- open label: Pro-active TDM vs. standard therapy

Disease subgroup	Remission rate, No./total (%)		Adjusted difference, % (95% CI)
	Therapeutic drug monitoring	Standard therapy	
Rheumatoid arthritis	21/38 (55.3)	21/42 (50.0)	-8.3 (-30.4 to 13.8)
Psoriatic arthritis	5/20 (25.0)	12/22 (54.5)	29.4 (-0.2 to 59.0)
Spondyloarthritis	23/59 (39.0)	21/58 (36.2)	-3.5 (-21.4 to 14.4)
Ulcerative colitis	25/39 (64.1)	29/41 (70.7)	4.9 (-15.6 to 25.5)
Crohn disease	17/29 (58.6)	17/28 (60.7)	4.7 (-21.1 to 30.4)
Psoriasis	9/13 (69.2)	6/9 (66.7)	-8.3 (-47.7 to 31.0)
Overall	100/198 (50.5)	106/200 (53.0)	1.5 (-8.2 to 11.1)



Watterdal Syversen et al. JAMA. 2021;325(17):1744-1754

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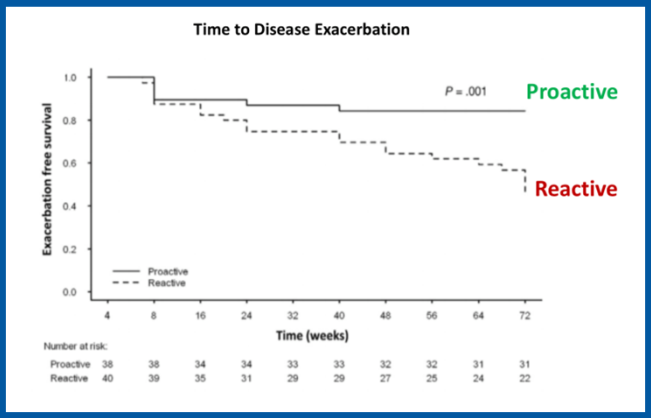
PRO-ACTIVE VS REACTIVE TDM WITH ADALIMUMAB

- Adalimumab-level-based optimization treatment in a multicenter, nonblinded trial
- Primary endpoint: sustained steroid-free clinical remission (PCDAI<10) from Weeks 8 to 72
- Proactive trough measurements + tight control based superior to reactive trough measurements + tight control
- Goal ADA level >5 mcg/ml



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

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PRO-ACTIVE TDM WITH BIOLOGICS: ANTI-TNF PRACTICAL IMPLICATIONS

- Consider in patients on anti-TNF, especially in:
  - ✓High drug clearance and/or severe disease
  - ✓Monotherapy
  - ✓After reactive TDM
  - ✓After anti-TNF dose reduction
- No evidence for pro-active TDM in biologics other than anti-TNF

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OPTIMAL THRESHOLD DRUG LEVELS: WHERE TO AIM?

- Multiple studies show multiple "target: threshold levels

Drug type	IBD type	TDM time point	Threshold (μg/mL)	Therapeutic outcome*	Therapeutic outcome time point
IFX[K]	CD	Week 2	>16.9	Clinical response	Week 14
			>20.4	Clinical remission	
	UC		>11.5	Clinical response	
			>15.3	Clinical remission	
IFX	UC	Week 14	≥5.1	Mucosal healing (MES<2)	Week 30
			≥6.7	Mucosal healing (MES = 0)	
IFX	CD	Week 14	≥2	CRP normalization	Week 14
			≥6.1	Complete fistula response	
			≥7.2	Complete fistula response and CRP normalization	
IFX	CD	Week 14	>9.4	FC < 250 μg/g	Week 14
			>11.5	FC < 100 μg/g	
IFX	CD	Maintenance	≥2.2	Normal CRP	Maintenance
			≥9.7	Endoscopic remission	
			≥9.8	Histologic remission	
IFX	CD	Maintenance	>0.6	Normal CRP[I]	Maintenance
			>1.1	Normal FC[J]	
			>4	Mucosal healing	
IFX	CD	Maintenance	>1.5	Clinical remission	Maintenance
			>3.4	Normal CRP	
			>5.7	Normal FC[K]	
IFX	UC	Maintenance	≥7.5	Endoscopic healing	Maintenance
			≥10.5	Histologic healing	
IFX	CD/UC	Maintenance	>2.1	Clinical remission	Maintenance
			>2.9	Clinical remission and normal CRP	
			>3.9	Clinical remission and FC < 250 μg/g	
			>4.9	Clinical remission, normal CRP, and FC < 50 μg/g	
ADM	CD	Maintenance	>5.6	Normal CRP[I]	Maintenance
			>7.9	Mucosal healing	
ADM	CD	Maintenance	>8.5	Normal CRP and FC < 250 μg/g	Maintenance
			>10.5	Normal CRP and FC < 100 μg/g	
ADM	CD	Maintenance	>6.8	Perianal fistula healing	Maintenance
			>9.8	Perianal fistula closure	
ADM	CD	Maintenance	>6.8	Normal CRP	Maintenance
			>9.8	Normal CRP and FC[J]	
ADM	CD/UC	Maintenance	>6.6	Normal CRP	Maintenance
			>7.1	Mucosal healing	

Cheifetz A et al. Am Journal of Gastroenterology, 2021

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OPTIMAL THRESHOLD DRUG LEVELS: WHERE TO AIM?

- Multiple studies show multiple "target: threshold levels
- The truth is there is no "magic number"
- Multiple variables can affect these targets:
  - Assay used in studies can be heterogeneus
  - Different phenotypes may require different targets
  - Especially with adalimumab, tissue levels not always correlate with serum levels.

Yarur et al. Gut 2016

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PRO-ACTIVE TDM WITH ANTI-TNF: WHERE TO AIM?

Biologic	Measurement Timepoint	Goal (mcg/mL)	Outcome
Infliximab	Week 2	>15-20	Clinical Remission at Week 14
	Week 14	>12	Mucosal Healing week 30 Normal Calprotectin Week 14
	Maintenance	> 8-10	Mucosal Healing
	Maintenance	>20	Fistula healing
Adalimumab	Maintenance	>8	Mucosal Healing
	Maintenance	>10	Fistula closure

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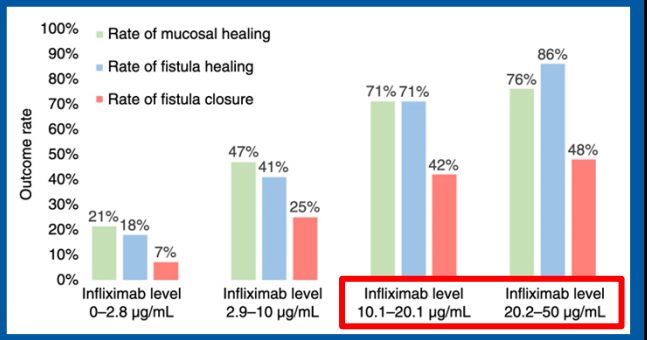
PRACTICAL RECOMMENDATIONS ON DRUG LEVEL TARGETS?

- Aim high
- Do not "give up" on anti-TNF if the dose can be escalated as long as there are no antibodies
- Some phenotypes may benefit from really "high" doses



Yarur A et al. AP&T 2017

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RE-STARTING TREATMENT AFTER A DRUG HOLIDAY

- Not uncommon
- Infliximab in the past may have not been optimized
- Known high risk of immunogenicity after re-exposure

  - Non-response
  - Infusion reaction

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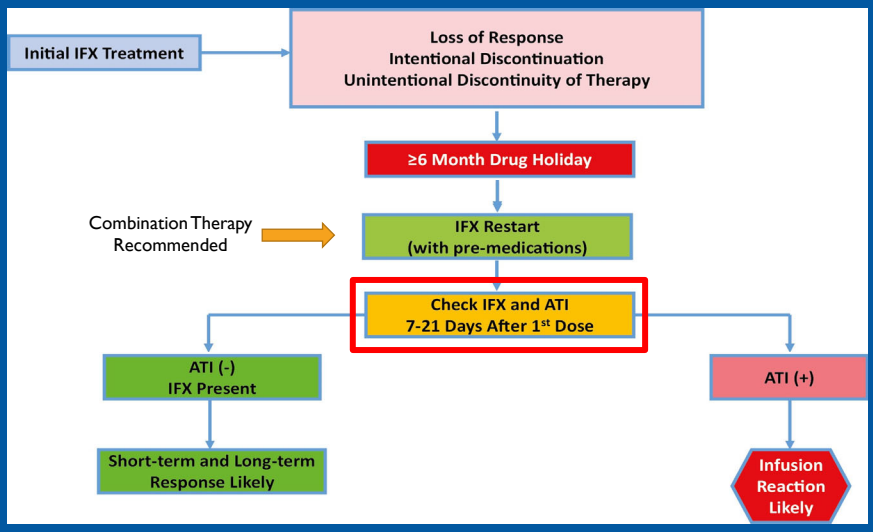
HOW TO USE TDM WHEN RE-STARTING INFLIXIMAB



Normatov I, et al. *Crohns Colitis 360*. 2021

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IN SUMMARY (I)

- Reactive drug monitoring is
  - Helpful when using anti-TNF
  - May be "too late" if just relying on symptoms
  - Reactive is not just for symptoms
- Have a monitoring strategy and don't rely only on symptoms
  - ✓Biomarkers
  - ✓Endoscopy
- Incorporate TDM in treat-to-target strategies

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IN SUMMARY (II)

- Evidence is limited but "makes sense" to use pro-active TDM with Anti-TNF, especially on:
  - ✓Aggressive disease
  - ✓Re-starting treatment with infliximab
- Vedolizumab and ustekinumab have very low immunogenicity and the significance of serum drug levels is not completely understood
- Just because TDM is useful with anti-TNF doesn't mean is useful with other biologics

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Los Angeles, California

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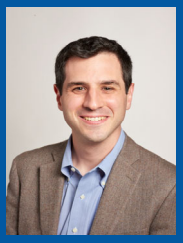
Questions and Answers

Andres J. Yarur, MD, FACG



Ryan C. Ungaro, MD, MS

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