1st Gulf Coast Symposium

Omni Royal Hotel New Orleans, Louisiana

October 15, 2022

IBDH

State of the Art in Drug and Disease Monitoring

ARS QUESTION 1

Which is TRUE regarding HLA-DQA1*05 allele in IBD

A. Present in 40% Caucasian patients
B. Associated with presence of anti-TNF drug antibody
C. Associated with anti-TNF therapy discontinuation
D. All of the above

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Which is TRUE regarding therapeutic drug monitoring

A. Antibodies to Infliximab cross react with Adalimumab
B. High BMI is associated with increased anti-TNF clearance
C. Combination therapy is associated with higher rates of anti-drug antibody
D. High CRP is associated with decreased clearance of biologics

Clinical Case 4

Patient with CD on infliximab 5 mg/kg due to prior disease breakthrough. Recent colonoscopy shows deep remission. Trough is 2.1 mcg/mL with low antibody titer detected.
You are considering the next steps

State of the Art in Drug and Disease Monitoring

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IBD_Afzali

University of CINCINNATI

Disclosures

Anita Afzali, MD, MPH, MHCM – Planner/Moderator/Course Director/Presenter

Research Ed Support – AbbVie, Janssen, Takeda, BMS, Pfizer

Advisory Board – Gilead, TLL Pharma, AbbVie, Janssen, Takeda, BMS, Pfizer

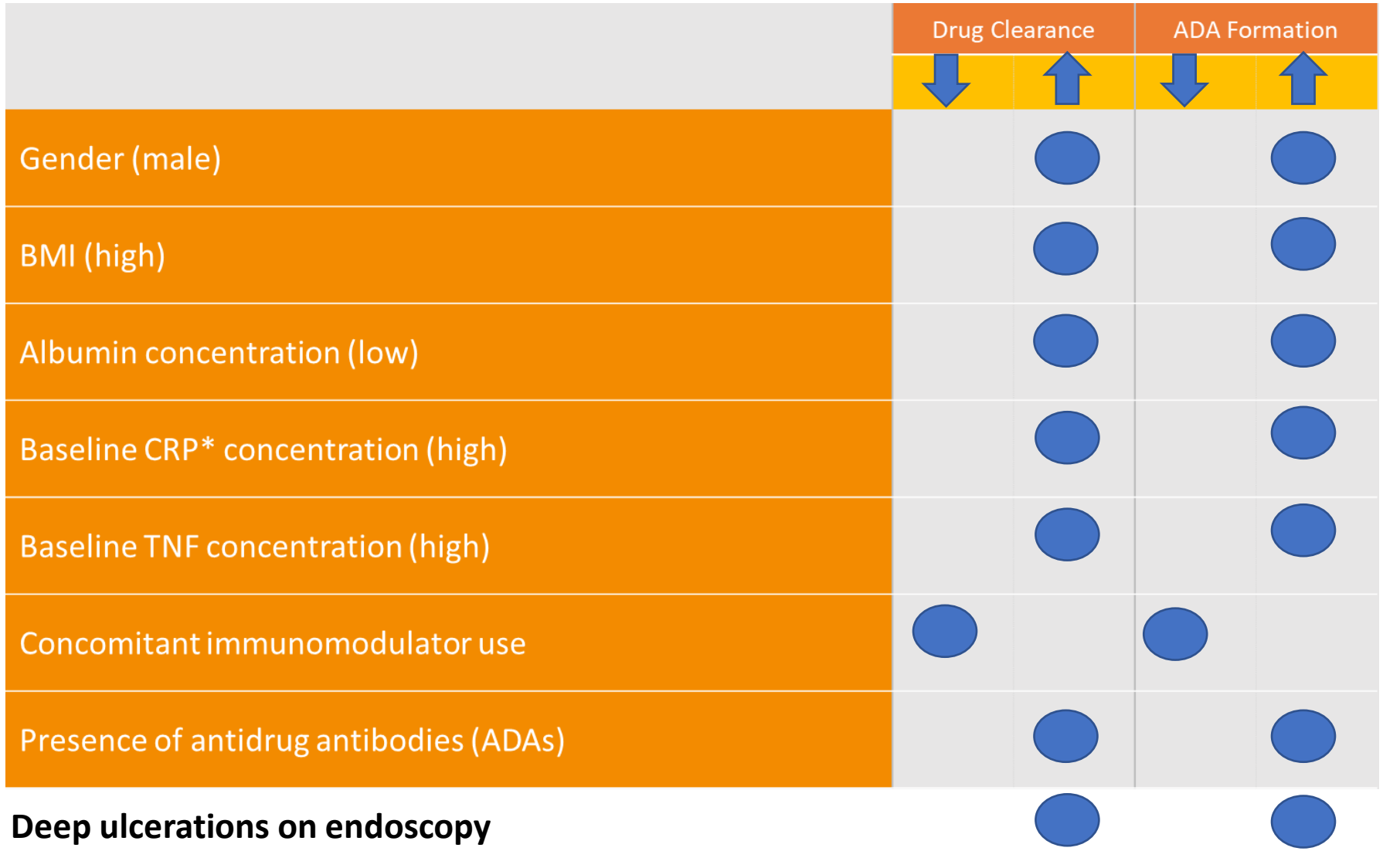
Consultant – Gilead, DiaSorin, Arena, AbbVie, Janssen, Takeda, BMS, Pfizer

Board Member and Co-Founder – IBD Horizons, Scrubs & Heels

Why Do We Need to Understand Therapeutic Drug Monitoring?

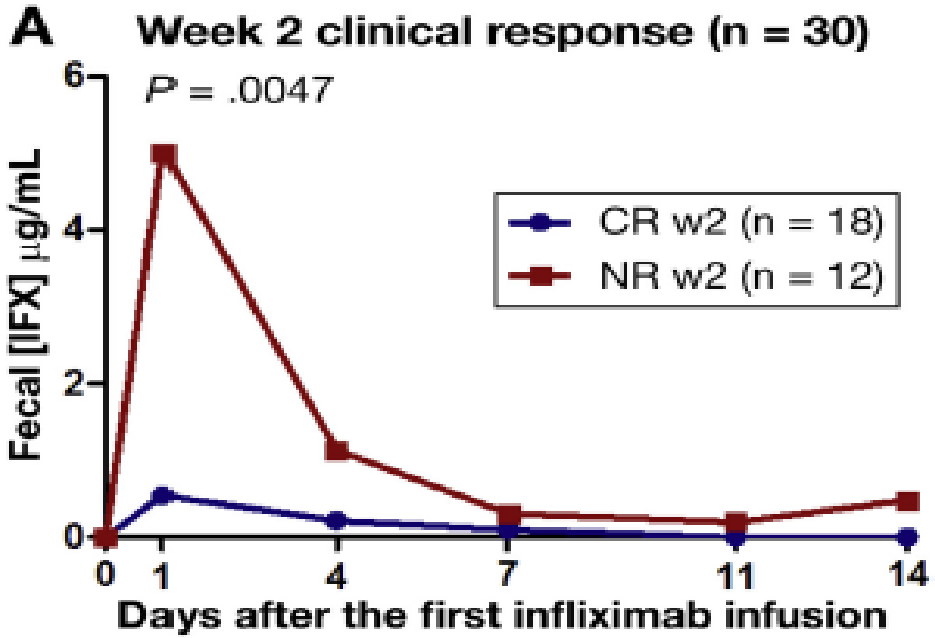
- To improve management of our patients with IBD
- To understand the heterogeneity of drug and patient characteristics which results in variation in drug
  - Delivery,
  - Metabolism,
  - Efficacy
  - Safety
- To provide insight into primary and secondary non-response
- To assist in treatment selection for each individual patient

Factors Impacting Pharmacokinetics



Adapted from Ordas I et al. Clin Pharmacol Ther 2012

Fecal Loss of IFX Resulting in Lack of Response



- Does fecal loss of IFX contribute to failure to respond to induction therapy in severe colitis?
- Fecal samples collected within 14d following IFX 5mg/kg, n=30
- **Non-responders** (compared to responders) to IFX:
  - Higher fecal IFX conc at day 1 (p=0.02)
  - Lower serum IFX conc day 14 (p=0.03)

Brandse JF et al. Gastroenterology 2015

Principles of Therapeutic Drug Monitoring in IBD

We CAN Assess Drug or Metabolites:

- **Thiopurines**
- **Biologics**
  - **Anti-TNF therapy**
  - Vedolizumab
  - Ustekinumab

We DO NOT Assess Drug or Metabolites:

- **Methotrexate**
- **5-ASA**
- **JAK inhibitors**
- **S1P receptor modulators**

REACTIVE

- Most common approach
- Await a bad occurrence (classically LOR) then attempt to fix it

PROACTIVE

- Preemptively change drug dosing prior to onset of bad occurrence to prevent a LOR

Commercially Available Drug Assays

Type	Methods	Drug Assays Available
Prometheus (Anser)[1]	Can measure drug concentration and antibody level simultaneously **(drug tolerant assay)**	IFX, ADA, CZP, VEDO, UST
ARUP Labs[2]	Test measures bioactivity using reported cells Method - Cell culture / Stimulated cell function assay / Chemiluminescent immunoassay, quantitative and semi-quantitative	IFX, ADA
Mayo Medical Laboratories[3]	Liquid Chromatography/Mass Spectrometry (LC/MS)	IFX, ADA, CZP, VEDO
Inform Diagnostics[4]	ELISA: Can measure drug concentration and antibody level	IFX, ADA, CZP, GOL, VEDO, UST
Esoterix (Labcorp)[5]	Electrochemiluminescence Assay **(note different units of results for antibody titers – ng/mL)**	IFX, ADA, CZP, GOL, VEDO, UST

1. https://www.prometheuslabs.com/anser/about-the-tests/
2. http://www.aruplab.com/
3. https://www.mayocliniclabs.com/index.html
4. http://www.informdx.com/
5. http://www.esoterix.com

Phases of Therapeutic Drug Monitoring

Treatment Selection

Prediction of Ongoing Response

Assessment of Loss of Response

Phases of Therapeutic Drug Monitoring

Treatment Selection

- Based on Mechanism or Label
- Dosing
- Combination Therapy

Prediction of Ongoing Response

Assessment of Loss of Response

Pre-Treatment Considerations Related to TDM: Thiopurines

TPMT

Frequency	Enzyme Activity	Allele
89%	Normal to High	$TPMT^{H}/TPMT^{H}$
11%	Intermediate	$TPMT^{H}/TPMT^{L}$
0.33%	Low to Absent	$TPMT^{L}/TPMT^{L}$

Beaugerie L, et al. *Lancet*. 2009;374(9701):1617-25.

NUDT15

p.Arg139Cys Allele Frequency

Chinese: 13%

Koreans: 10.4%

Japanese: 7%

Mixed American: 2%

Yang SK, et al. Nat Genet. 2014 Sept;46(9): 1017–1020.

Recommended:

- **TPMT testing prior to dosing thiopurines for IBD**

Suggested:

- **NUDT15 testing in some individuals**

Practical guidance:

- **Early CBC (1-2 weeks) prior to dose increase of thiopurine**

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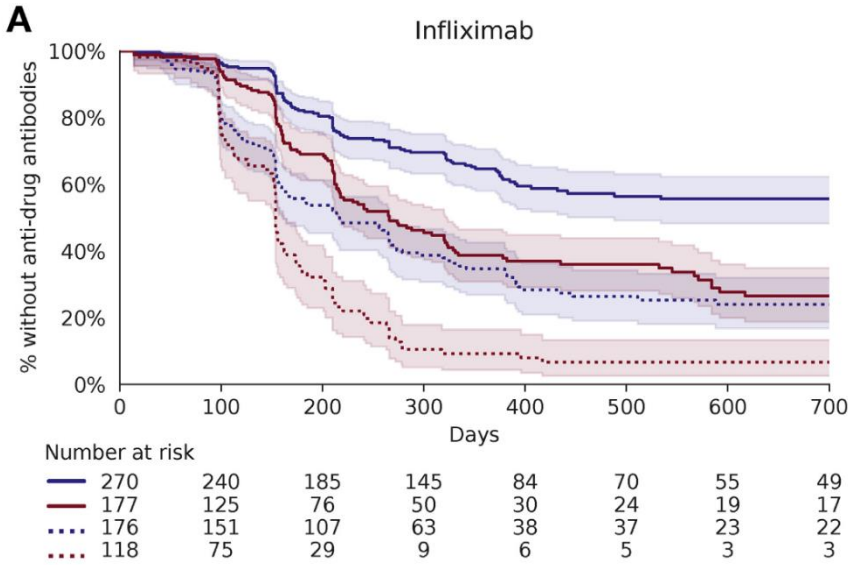
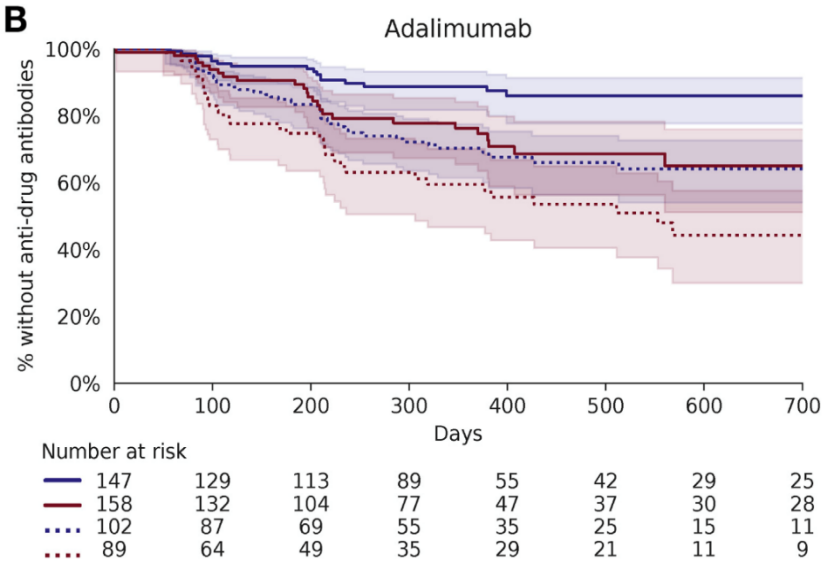
Pre-Treatment Considerations Related to TDM: Can we predict immunogenicity to Anti-TNF?

HLA-DQA1*05 Carriage Associated With Immunogenicity to Infliximab and Adalimumab

- **N = 1240**
- **Biologic-naïve CD patients starting infliximab or adalimumab**
- **Genome wide study**
- **HLA-DQA1*05 allele, significantly increased the rate of immunogenicity**

(HR 1.90; 95%CI 1.60–2.25)





Dotted lines: anti-TNF monotherapy
Solid lines: combination therapy with immunomodulators
Red: carriers of the HLA-DQA1*05 allele (1 or 2 copies)
Blue: non-carriers

Sazonovs A, et al. *Gastroenterol*. 2020;158(1):189-199.

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Unanswered Questions: Immunogenicity to Anti-TNFs

- **Did your patient already develop anti-drug antibodies (ADA) on a prior anti-TNF?**
- **Related to HLA DQ1*05:**
  - **If negative: would you use monotherapy with anti-TNF?**
  - **If positive: would you not consider proactive TDM or stopping IMM?**

Recommended:

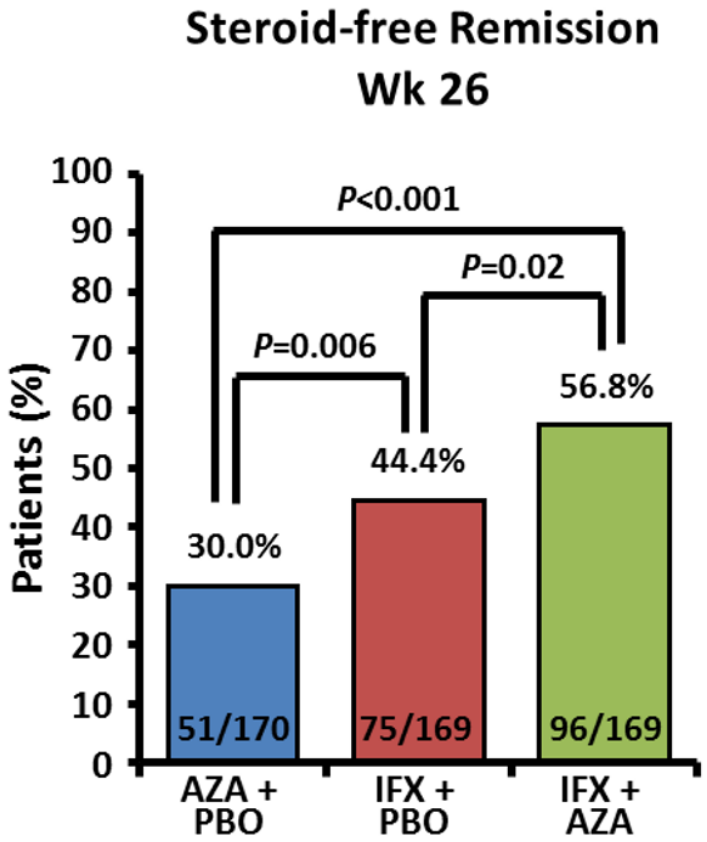
- **If prior ADAs to anti-TNF, and going to second anti-TNF use combination therapy and/or proactive TDM**

Consider:

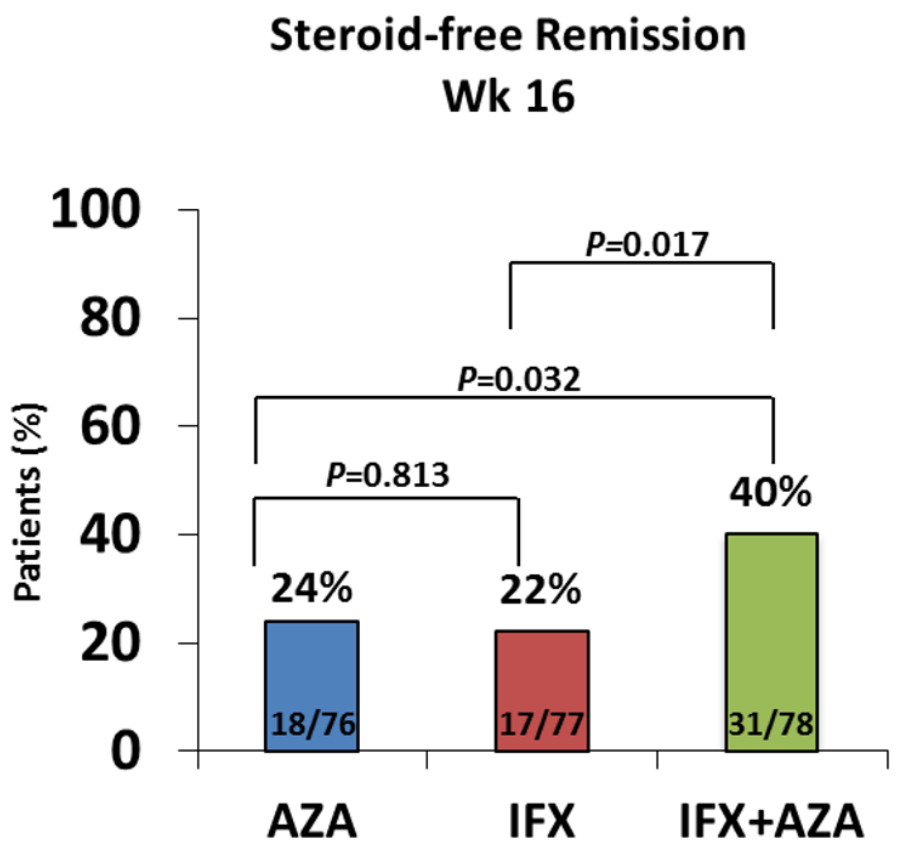
- **HLA DQ1*05 testing in the future (?)**

Combination Therapy with Anti-TNF is better Than Monotherapy

SONIC Trial (CD)[1]



SUCCESS Trial (UC)[2]

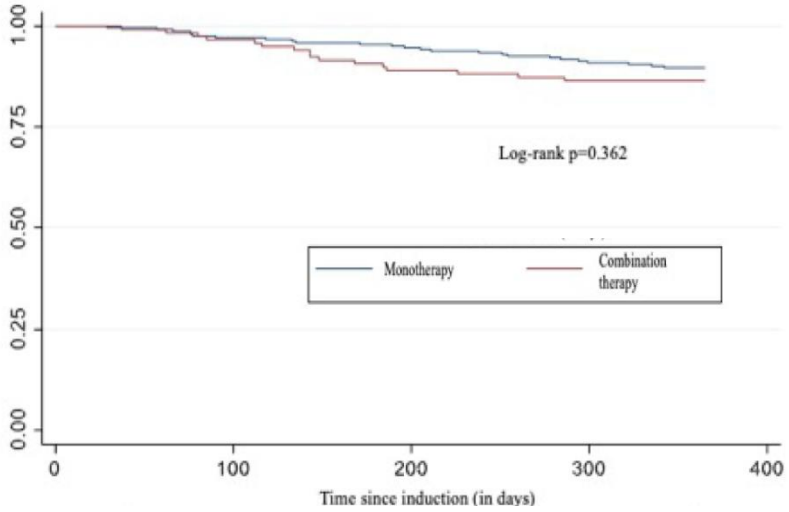


1. Colombel JF, et al. *N Engl J Med*. 2010;362(15):1383-95.
2. Panaccione R, et al. *Gastroenterol*. 2014;146(2):392-400.

Combination Therapy NOT Always Necessary

- SONIC post-hoc: infliximab levels more important than combination therapy[1,2]
- Ustekinumab does NOT benefit from combination therapy[3,7]
- Vedolizumab does NOT benefit from combination therapy[4-7]
- 5-ASA not helpful when escalating to advanced therapies[8-9] (nor cost-effective)[10]

Persistence of Ustekinumab with and without IMMs[7]



Recommended:

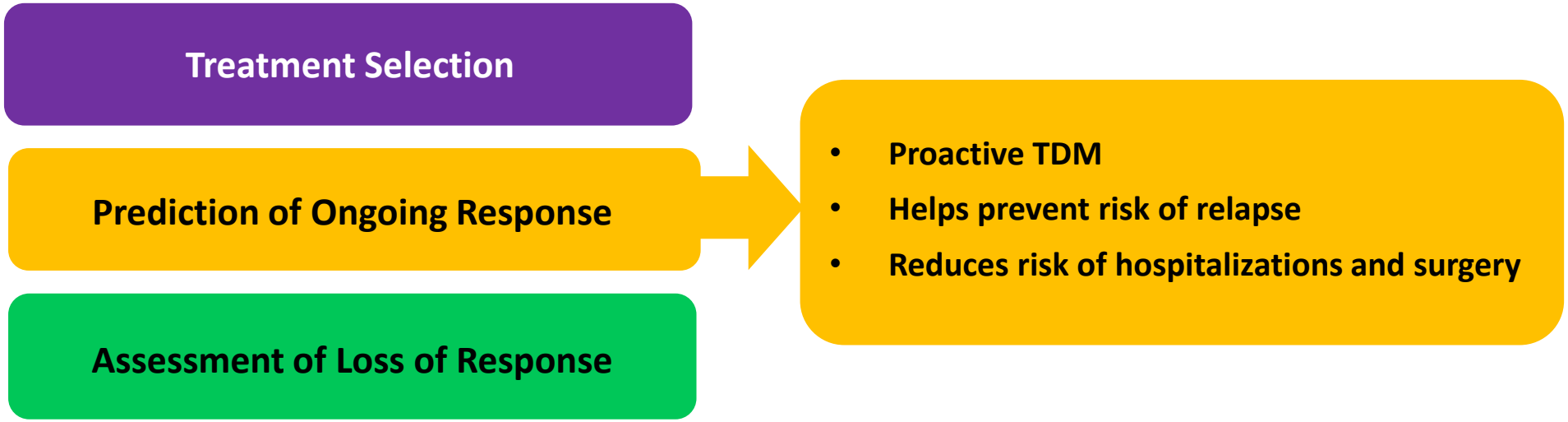
- Monotherapy of vedolizumab and ustekinumab
- Stopping 5-ASA after treatment escalation in UC (and CD)

Possible in the future:

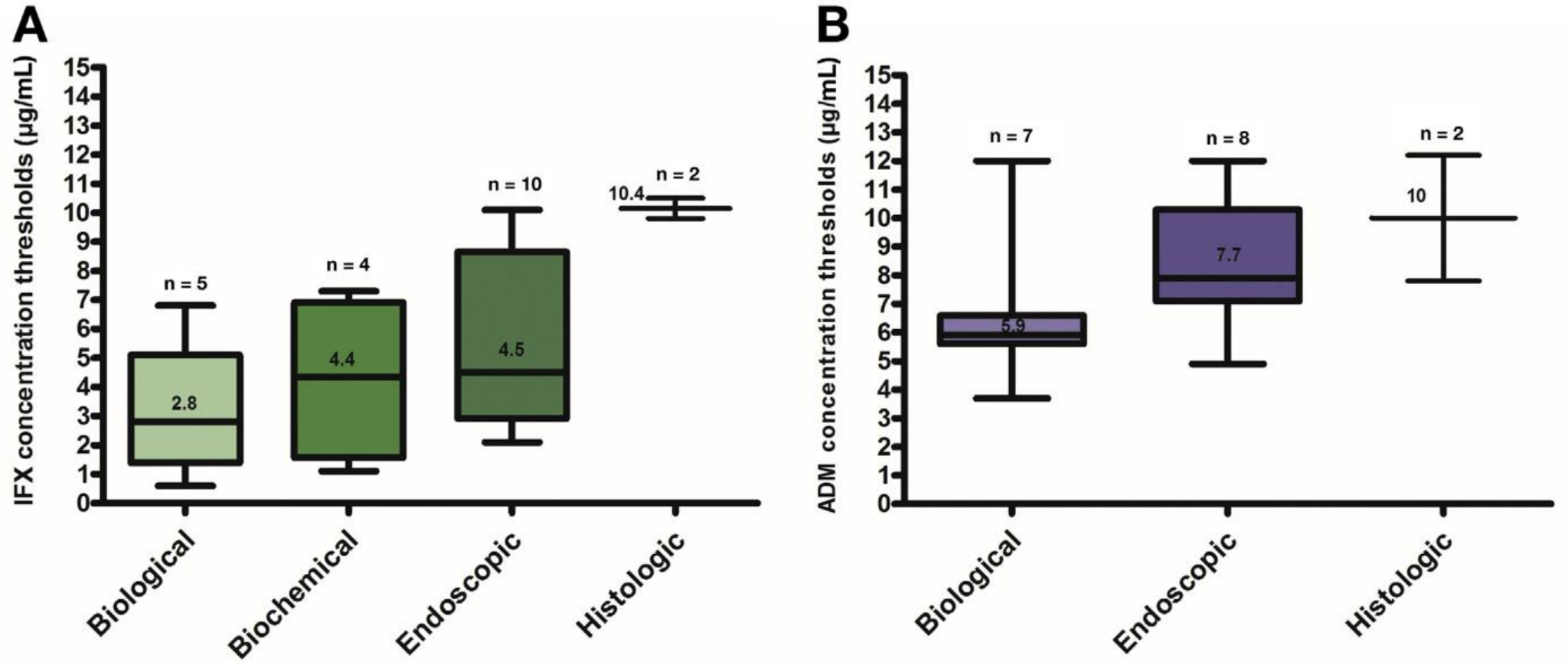
- Optimized monotherapy of anti-TNF to avoid IMM use

1. Colombel JF, et al. *N Engl J Med*. 2010;362(15):1383-95.
2. Colombel JF, et al. *Gastroenterol*. 2017;152(5):S37-38.
3. Sands BE, et al. *Am J Gasteroenterol*. 2018;113:S330.
4. Colombel JF, et al. *Gastroenterol*. 2015;148(4):S277-8.
5. Koylov U, et al. *Inflamm Bowel Dis*. 2017;23:404-408.
6. Amiot A, et al. *Aliment Pharmacol Ther*. 2017;46:310-321.
7. Hu A, et al. *Clin Gastroenterol Hepatol.* 2020. [epub ahead of print].
8. Singh S, et al. *Am J Gastroenterol*. 2018;113(8):1197-1205.
9. Ungaro RC, et al. *Gut*. 2019;68:977-84.
10. Shaffer S, et al. *Am J Gastroenterol.* 2021; 116:125-133.

Phases of Therapeutic Drug Monitoring

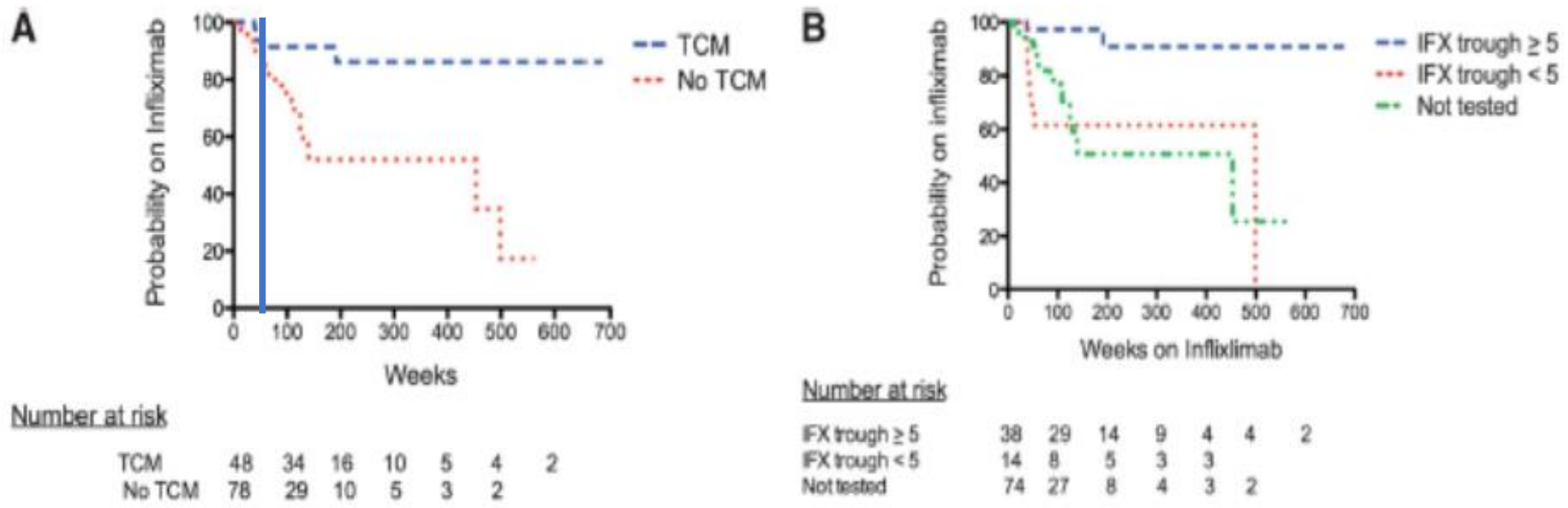


Infliximab Levels Associated with Specific Outcomes of Interest



Papamichael K, et al. *Clin Gastroenterol Hepatol*. 2019;17:1655–1668.

Proactive Monitoring to Optimize IFX Maintenance and Durability



- Single physician, retrospective cohort study of pts in clinical remission
- Optimized IFX dose to trough (5-10µg/mL) n=48
- No dose optimization n=78
- Conclusion: Dose optimization ↑ probability to remain on IFX in 5 years

Vaughn BP et al. Inflamm Bowel Dis 2014

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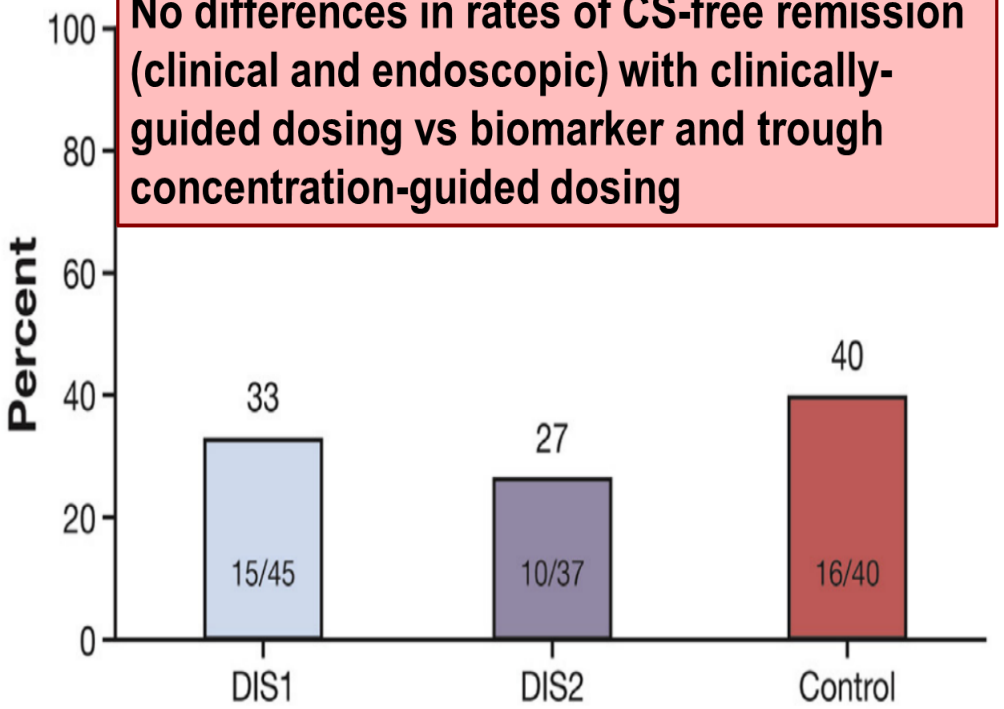
Randomized Prospective Trials of TDM Infliximab in IBD

TAILORIX[1]

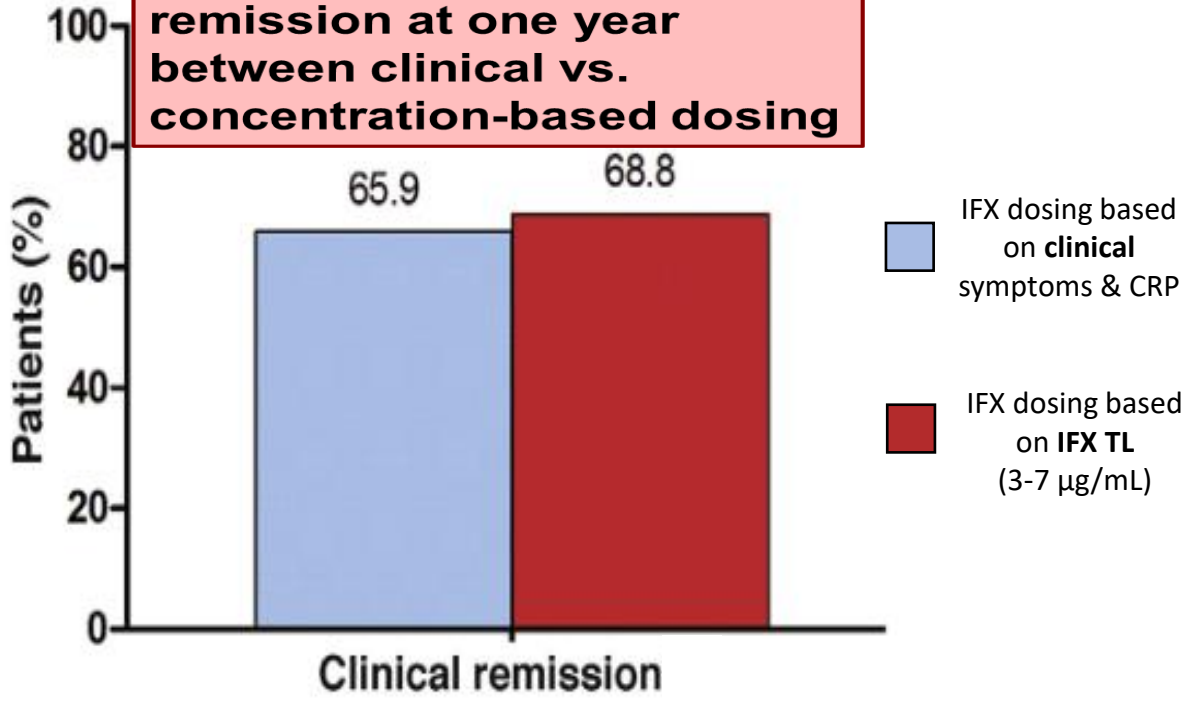
No differences in rates of CS-free remission (clinical and endoscopic) with clinically-guided dosing vs biomarker and trough concentration-guided dosing



DIS1: dose increases (2 maximum) in steps of 2.5 mg/kg based on clinical symptoms and biomarker analysis and/or serum infliximab concentrations
DIS2: dose increase from 5 to 10 mg/kg based on the same criteria;
CONTROL: dose increase to 10 mg/kg based on clinical symptoms alone

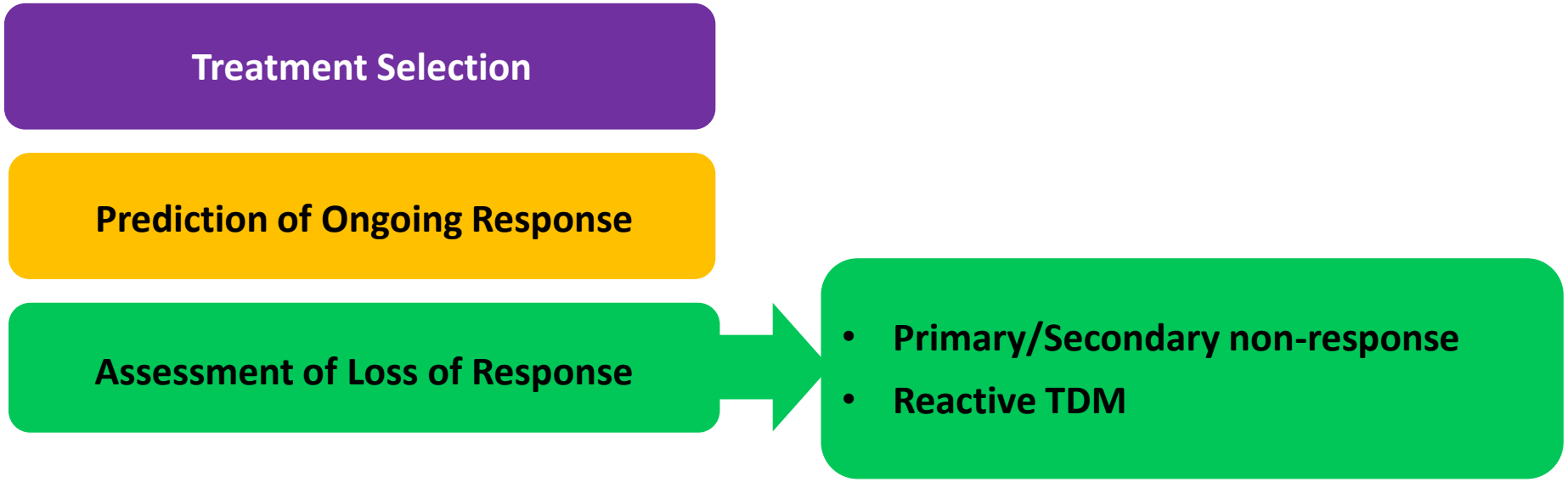
TAXIT[2]

No difference in clinical remission at one year between clinical vs. concentration-based dosing



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

Evolution of Therapeutic Drug Monitoring for Anti-TNF Therapies



Proposed Approach to Therapeutic Drug Monitoring with Anti-TNFs

Anti-TNF therapy

Losing Response?

- Reassess disease activity
- Assess adherence to maintenance schedule
- Appropriate dosing relative to disease activity/patient factors (i.e. perianal disease)

Assess drug level/antibodies (if available)

No or low levels & ADAs (+)

- **High titers** → **Switch anti-TNF ***
- **Low titers** → **TNF dose escalation or switch ***

Anti-TNF level (if available)

(+) levels & ADA (-)

- **Low levels** → **Dose escalation**
- **Therapeutic*** → **Confirm disease activity, if present, then switch to a different drug mechanism #**

*** Consider adding or optimizing immunomodulators**

 # Consider SURGERY if appropriate including exams under anesthesia for perianal disease

Slides courtesy of Tina Ha MD

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Suggested Target Trough Concentrations Reactive TDM

Drug	Suggested Trough Concentration, µg/ml	Publications of Interest
		4;
		3;
Ce		
Ustekinumab	Post-induction (w8) Maintenance ≥0.8-4.5	Restellini, 2018; Adedokun OJ, 2018; Battat R, 2017; Papamichael 2019
Vedolizumab	Induction (w6) ≥18.5-35.2 Post-induction (w14) ≥12.6-17 Maintenance ≥ 12-13.6	Restellini, 2018; Dressen E, 2018; Yacoub W, 2018; Williet N, 2017; Papamichael, 2019

Interpretation:

- **The most informative level is 0!**
- **Remember that trough levels are interpreted in the context of disease activity**
- **Generally, a level ≥ 10 means there is drug present, but this may not be enough!**
- **What is "high enough" depends on whether you can dose escalate**

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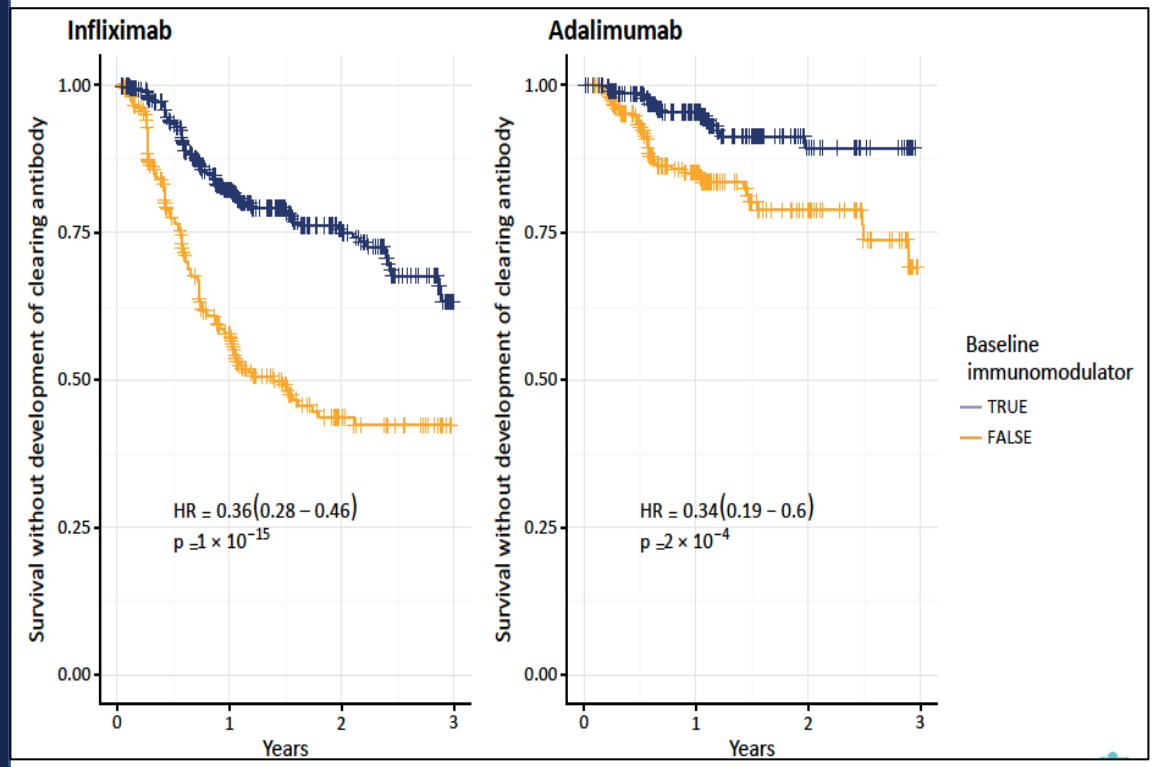
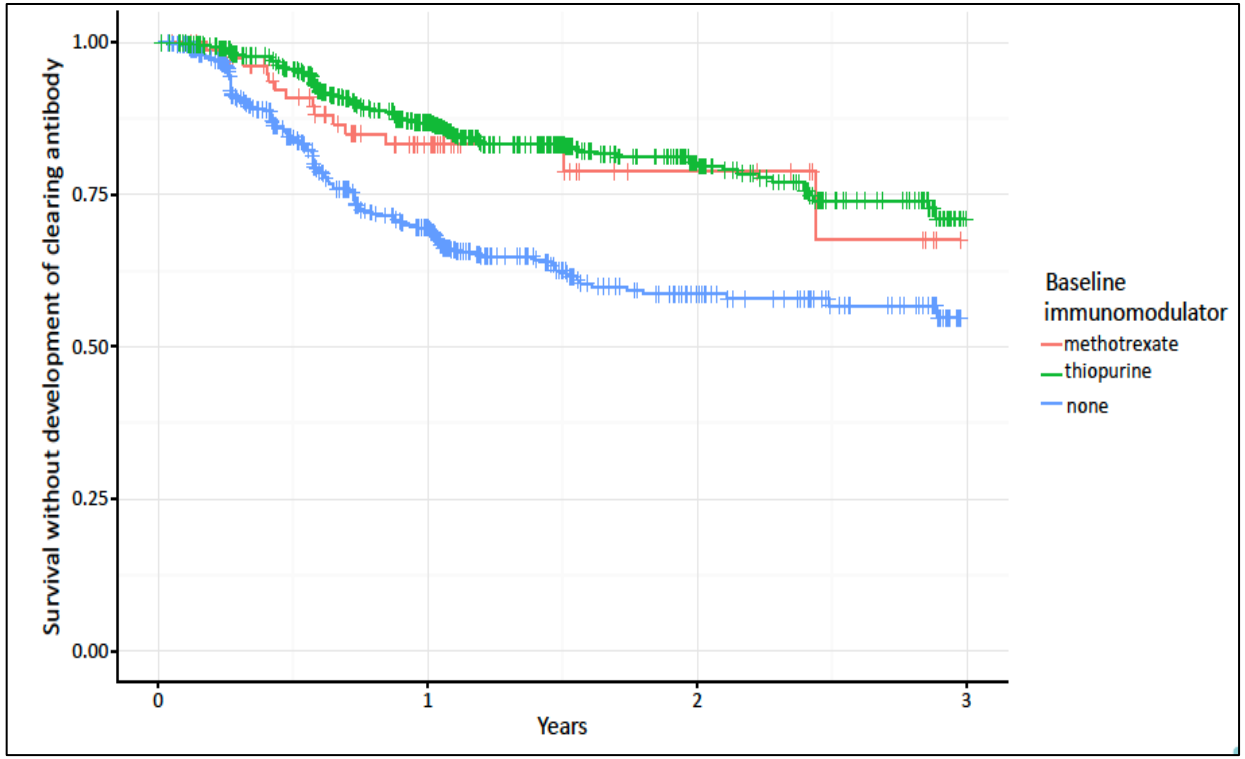
Immunogenicity and Combination Therapy





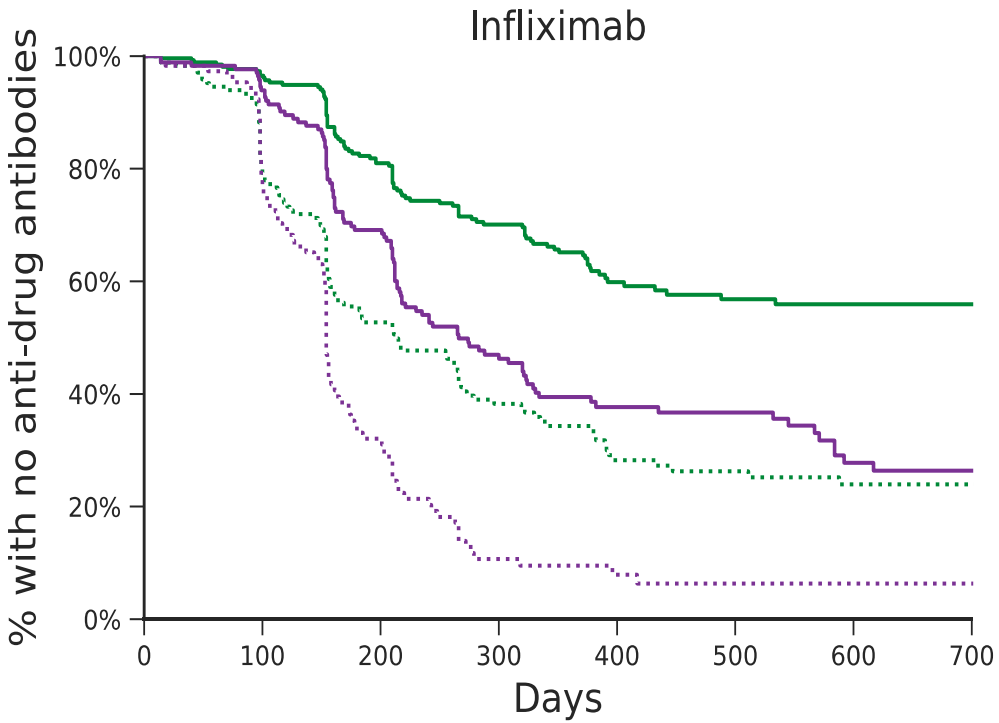
Immunomodulators Decrease Risk of immunogenicity: IFX or ADL

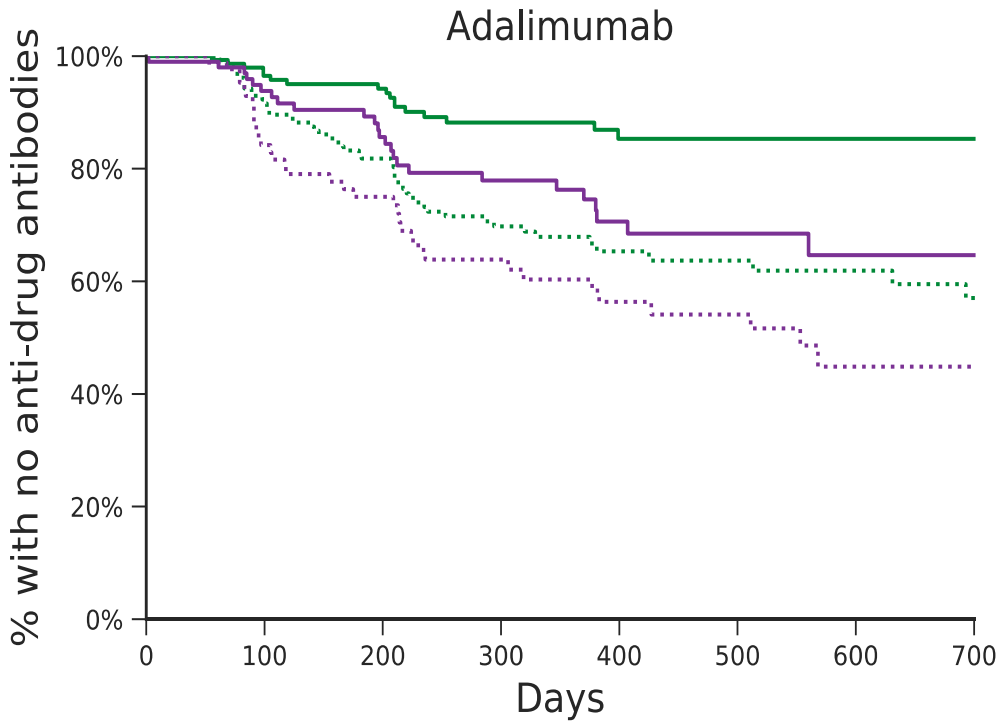
Thiopurines or Methotrexate both work well

Kennedy et al Lancet Gastro 2019.

Evolution of ADAs by HLA DQA1*05 Genotype & IMM Use

(ADA titre ≥10AU/ml at any time)





0 copies of DQA1*05, immunosuppressants on Visit 1
0 copies of DQA1*05, no immunosuppressants on Visit 1
≥1 copy of DQA1*05, immunosuppressants on Visit 1
≥1 copy of DQA1*05, no immunosuppressants on Visit 1

Sarkoz et al Gastro 2019.

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Patients at Risk for Anti-Drug Antibodies and Role for Combination IMM

- Patient receiving episodic therapy
  - Intentional
  - Unintentional: break in therapy due to coverage issues or complication
- "Pseudo-episodic therapy"
  - Sub-therapeutic serum drug levels
  - Patient with high drug clearance between doses
- Patient who developed anti-drug antibodies previously
- High BMI, Smoking
- HLA DQA1*05

Recommendation:

- **For anti-TNF only**
- **This is not helpful if there is no drug detectable!**
- **Remember to follow-up with additional levels to show that your approach worked**

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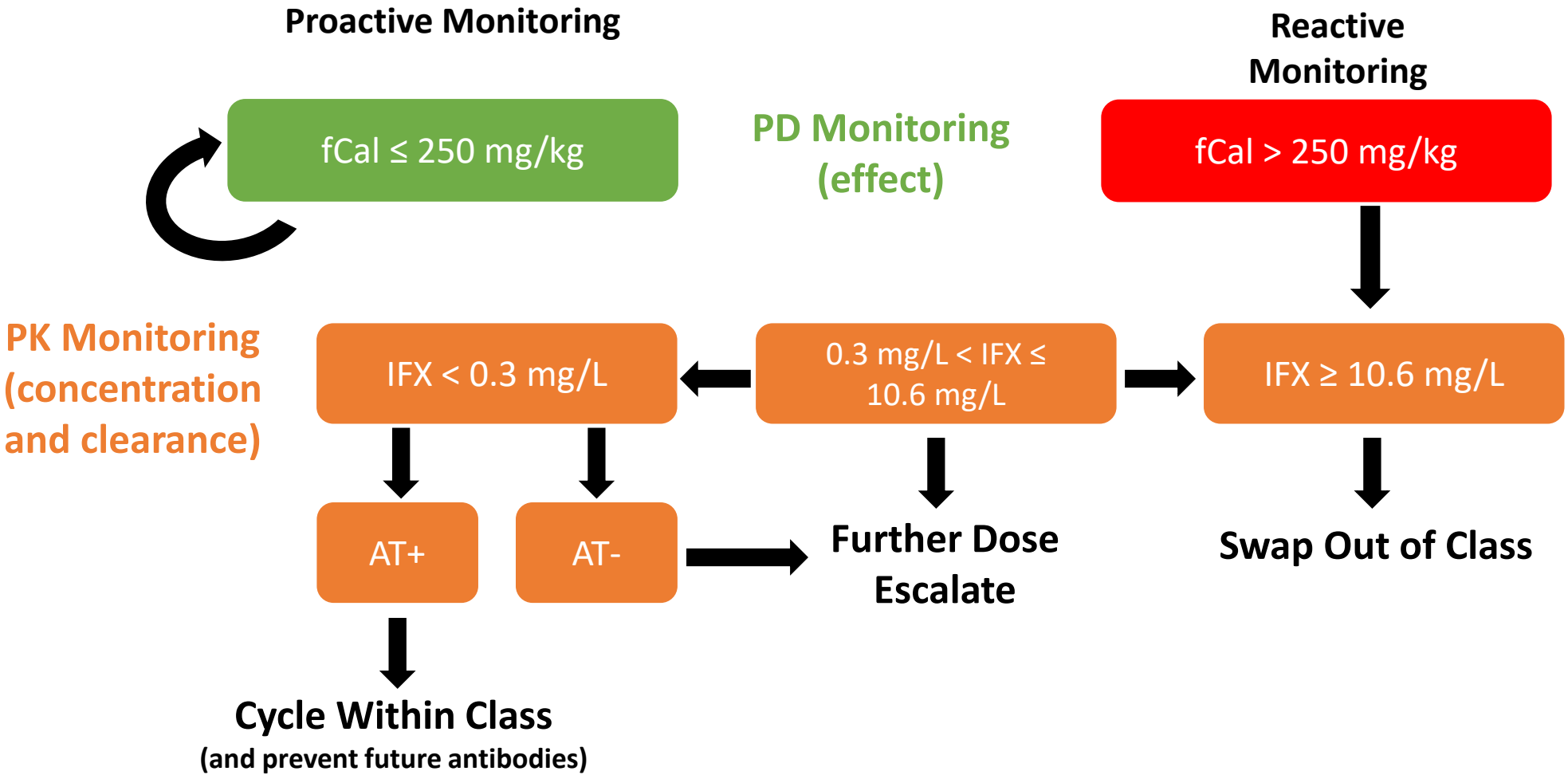
Vermeire S et al. *Gut*. 2007;56(9);1226.; Rubin DT et al. ACG 2013; Kennedy et al Lancet Gastro 2019.

Proactively Monitor Disease and Reactively TDM

Subclinical Relapse (the asymptomatic patient) and Inform TDM



Modified from Dreesen E, et al. *Clin Gastroenterol Hepatol*. 2020;18(3):637-646.e11.

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Summary: Drug and Disease Monitoring

- TPMT, NUDT15 prior to thiopurines
- Role of HLA DQ1*05 evolving
- REactive drug monitoring is helpful with anti-TNF, the downside is waiting until the drug has failed the patient and patient is symptomatic
- PROactive drug monitoring, prospective randomized data for anti-TNF overall do not support this approach, but makes sense for some high-risk patients
- Vedolizumab and ustekinumab have low immunogenicity and no proven benefit of combination therapy or established need for serum concentration measurements
- Monitor disease Proactively, test drug levels Reactively for TDM
  - Can detect subclinical relapse or lack of response and then consider reactive TDM and dose optimization

Panel Discussion

Moderator: Anita Afzali, MD

Gary Lichtenstein, M.D.

Bincy Abraham, MD

Brian Feagan, MD

Casey Chapman, M.D.

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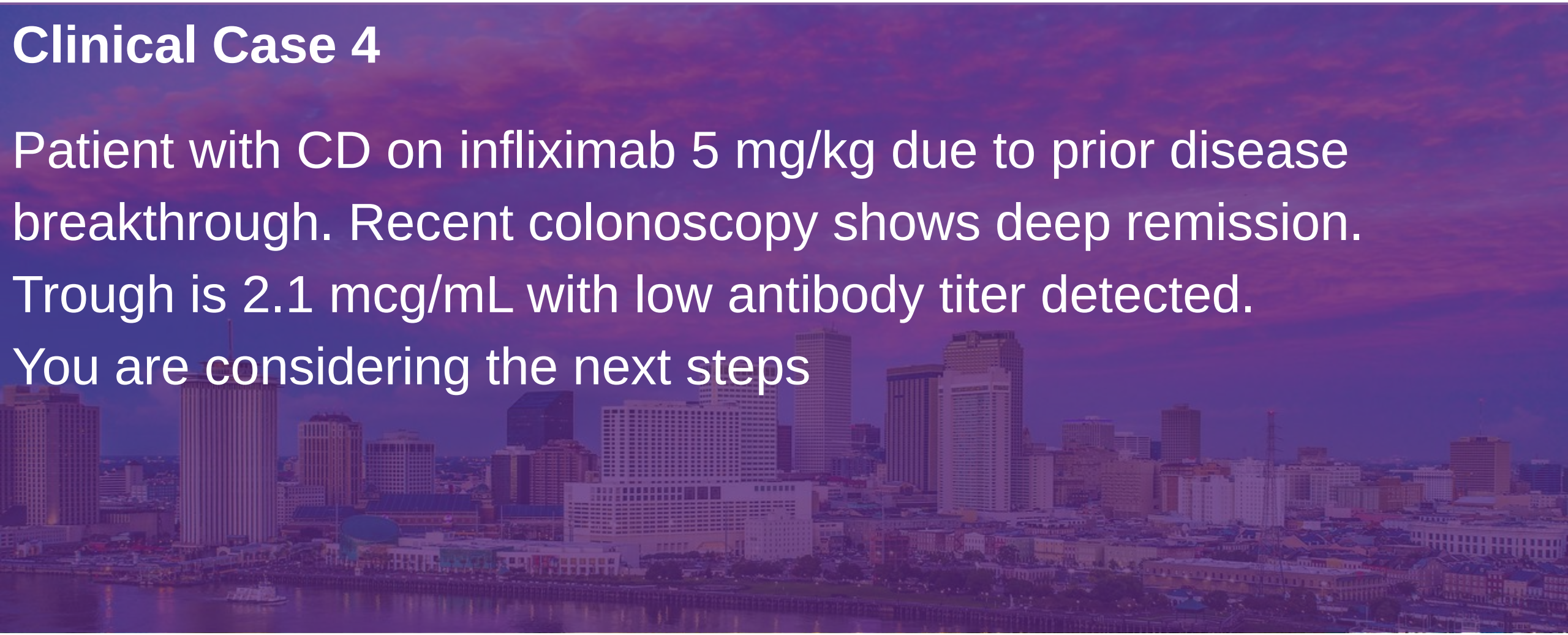

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