Treat to Target or Treat to Drug Level

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Disclosures

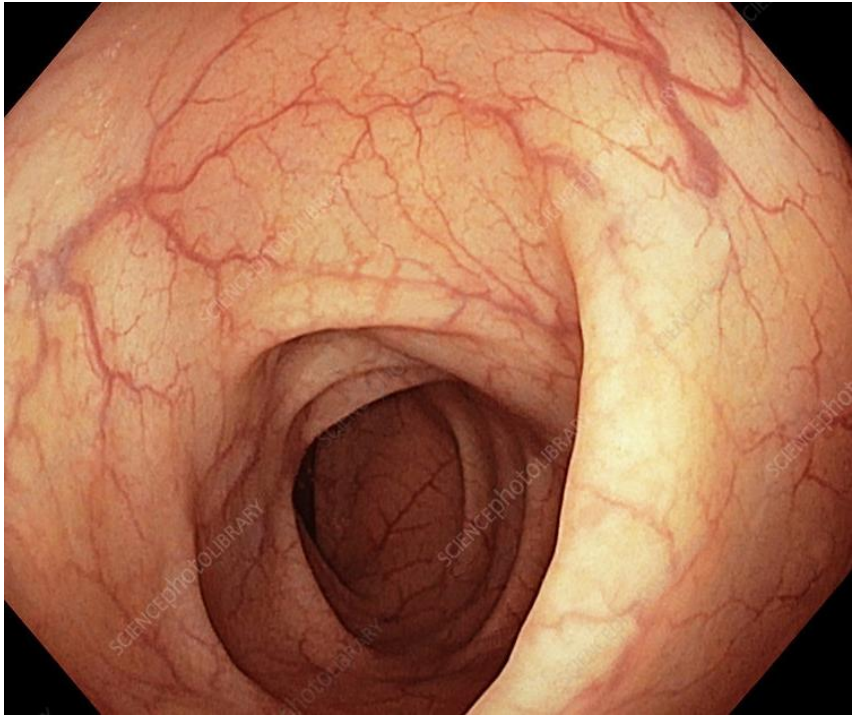
- Consulting and participation in advisory boards for Abbvie, BMS, Fresenius Kabi, Fzata, Janssen, Magellan Health, Pfizer, Samsung Bioepis, Sebela, and Takeda
- Participation in DSMB: Adiso
- Executive Committee Member of the IBD Education Group and Scientific Co-Director CorEvitas Registry
- Grant support from Janssen*

What does T2T mean in UC?

- Resolution of rectal bleeding and abdominal pain and normalization of BM frequency and bowel urgency
- Normalization of serum and/or fecal biomarkers
- Resolution of mucosal ulceration and friability or achieving normal mucosa (MES 0)
- Resolution of histologic activity (acute and chronic)

T2T

- Concept of T2T suggests treating beyond symptoms to achieve a deeper remission
  - Resolution of inflammation
  - Healing of mucosa
  - Histologic healing (aspirational)



AGA clinical practice guidelines on the role of biomarkers for the management of UC

- **Recommendation 1**: *In patients with UC in symptomatic remission, the AGA suggests a monitoring strategy that combines biomarkers and symptoms, rather than symptoms alone (Conditional recommendation, moderate certainty of evidence)*
  - 6–12-month interval
  - Fecal biomarkers may be optimal (but inconvenient)
  - Consider downstream consequences of testing and associated costs

Singh, S, et al. Gastroenterology. 2023; 164(3): 344-372

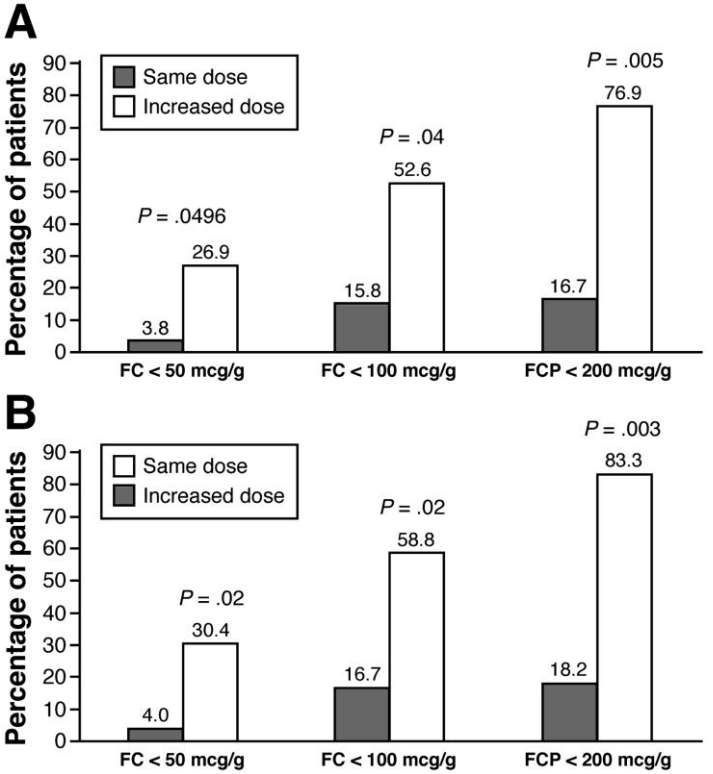
AGA clinical practice guidelines on the role of biomarkers for the management of UC

- **Recommendation 2**: In patients with UC in symptomatic remission, the AGA suggests using fecal calprotectin <150 mcg/g, normal fecal lactoferrin, or normal CRP to r/o active inflammation and avoid routine endoscopic assessment of disease activity (Conditional recommendation, very low to low certainty of evidence)

Singh, S, et al. Gastroenterology. 2023; 164(3): 344-372

What is the evidence for T2T in UC?

- RCT (n=119) UC patients based on SCCAI, FCP >50 mcg/g, and no more than 3 g/day mesalamine
- 1:1 to continue dose or increase dose by 2.4 g/day
- **Primary outcome**: continued remission with FCP <50 mcg/g
  - 4% controls vs. 27% dose escalation group
  - No difference in relapse rate



Osterman, MT, et al. Clin Gastroenterol Hepatol. 2014;12(11):1887-93 e3

What is the risk of relapse in patients with UC in symptomatic remission with elevated vs. normal FCP during routine follow up?

Outcome/# of participants (studies)	Relative effect, RR (95% CI)	Anticipated absolute effects (95% CI)			Certainty of evidence
		Normal FCP	Elevated FCP	Difference	
		Pooled Relapse Rate			
Risk of relapse at 12 mo./1286 (17 cohorts)	4.4 (3.5-5.5)	15	65 (52-82)	50 (37-67 more)	Moderate

Singh, S, et al. Gastroenterology. 2023; 164(3): 344-372

Why do we need TDM in clinical practice?

Response rates

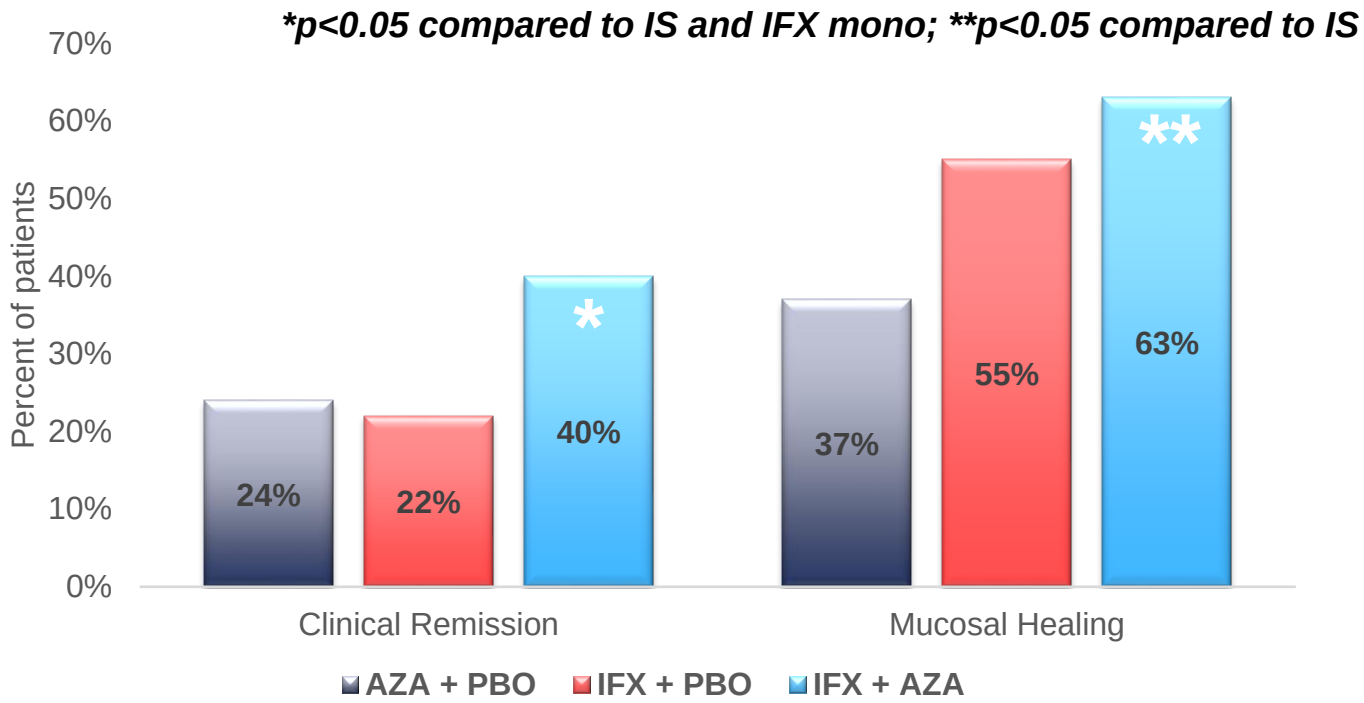
- 10-30% of IBD patients are primary non-responders
- Annual risk for loss of response to infliximab or adalimumab was calculated to be 13 and 24%, respectively (secondary non-responders)
  - Immunogenicity
  - **Suboptimal dosing**

Loss of response

- Dose escalation (increase the dose or decrease the interval)
- Switch within class (anti-TNF 1 ⟷ anti-TNF 2 ⟷ ???)
- Switch out of class (other mechanism of action)

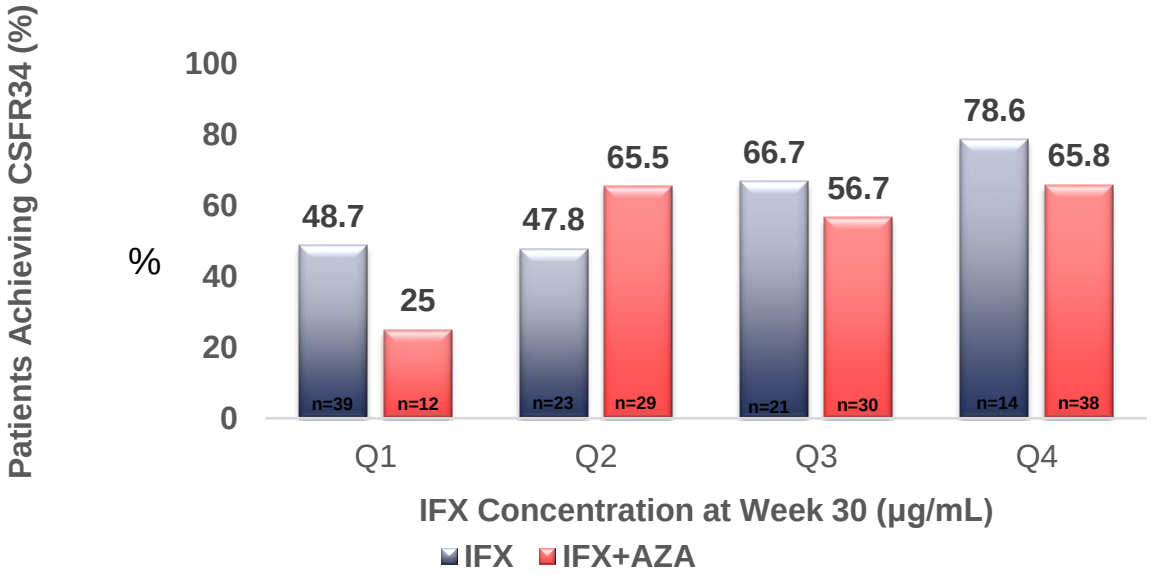
1.Allez M, et al. J Crohns Colitis 2010;4:355–66
2.D'Haens G, et al. Am J Gastroenterol 2011;106:199–212
3.Gisbert J, et al. Am J Gastroenterol 2009;104(3):760-7
4.Billioud V, et al. Am J Gastroenterol 2011; 106(4):674-84

UC SUCCESS: Corticosteroid-free clinical remission and mucosal healing at week 16



Panaccione, R, et al. Gastroenterology. 2014; 146(2): 392-400 e3

Proportions of patients achieving SF remission at wk 34 by serum trough IFX concentration at wk 30



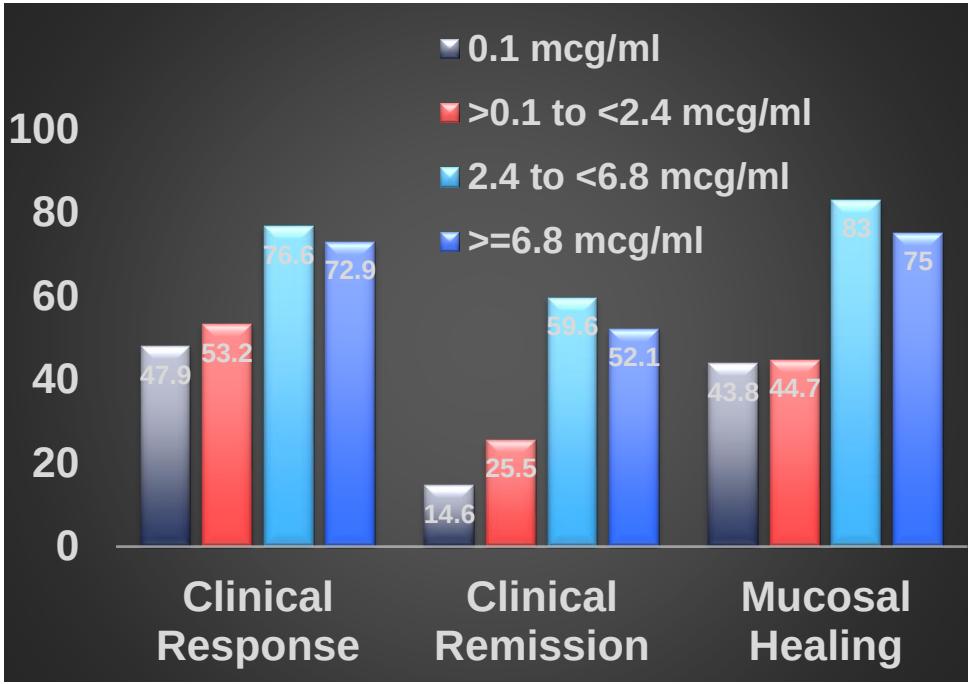
Q1: <0.84 µg/mL; Q2: 0.84 µg/mL to <2.36 µg/mL; Q3: 2.36 µg/mL to <5.02 µg/mL; Q4: ≥5.02 µg/mL

Association of IFX concentrations with clinical 0utcomes in UC

Post hoc analysis ACT 1 & 2

- 242 patients with UC
- IFX 5 mg/kg at weeks 0-2-6
  - 5 mg/kg q8 w
- IFX trough concentration quartile analysis at week 8, 30 and 54

Maintenance Week 30



Adedokun OJ, et al. Gastroenterology 2014;147(6):1296-1307

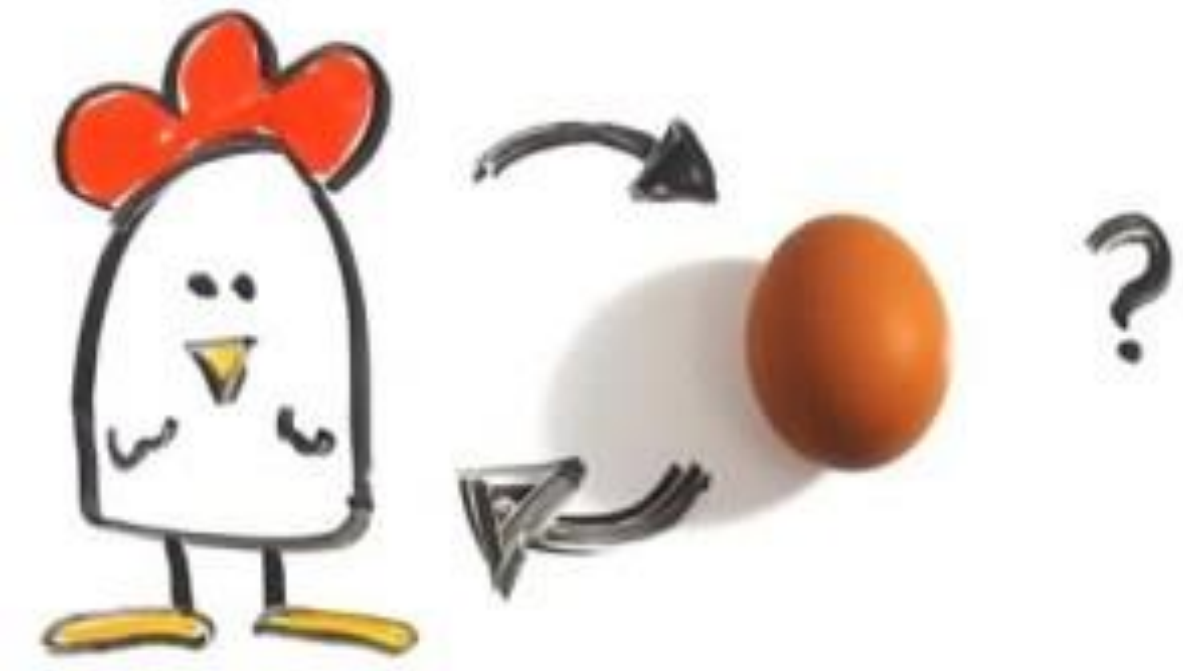
Different endoscopic outcomes may require different thresholds in patients with UC

Post hoc analysis ACT 1 & 2

- Endoscopic improvement at Week 30 (MES ≤1)
  - Week 14 ≥5.1 µg/mL
  - Week 30 ≥2.3 µg/mL
- Endoscopic remission at Week 30 (MES =0)
  - Week 14 ≥6.7 µg/mL
  - Week 30 ≥3.8 µg/mL

Vande Casteele, N, et al. Clin Gastroenterol Hepatol. 2019;17(9): 1814-1821 e1811.

Argument against proactive TDM is that therapeutic drug levels are a marker of response not a target to achieve



AGA Guidelines: Proactive vs reactive therapeutic drug monitoring

AGA SECTION

American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease

Joseph D. Feuerstein,[1] Geoffrey C. Nguyen,[2] Sonia S. Kupfer,[3] Yngve Falck-Ytter,[4] and Siddharth Singh[5]; on behalf of American Gastroenterological Association Institute Clinical Guidelines Committee

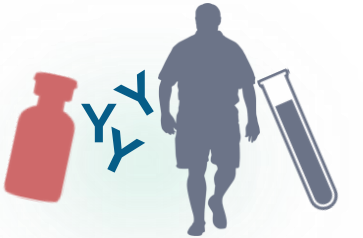
"The current evidence supports the use of reactive TDM to guide treatment changes in patients with active IBD who are being treated with anti-TNF agents or thiopurines. However, there is insufficient evidence to inform on the use of routine proactive TDM with anti-TNF agents in patients with quiescent disease."

Feuerstein, JD et al. Clin Gastroenterol Hepatol. 2017;153:827-834.

What factors influence the pharmacokinetics of biologics (anti-TNF)?

Decreases drug clearance

Concomitant immunosuppressives

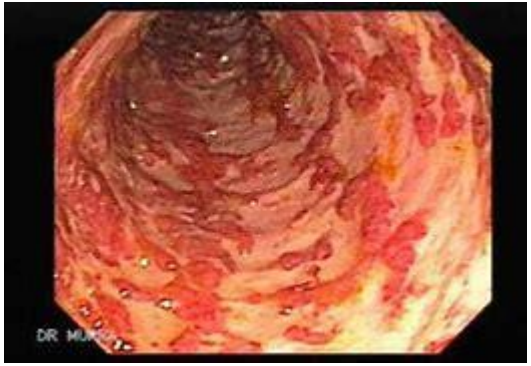


Increases drug clearance

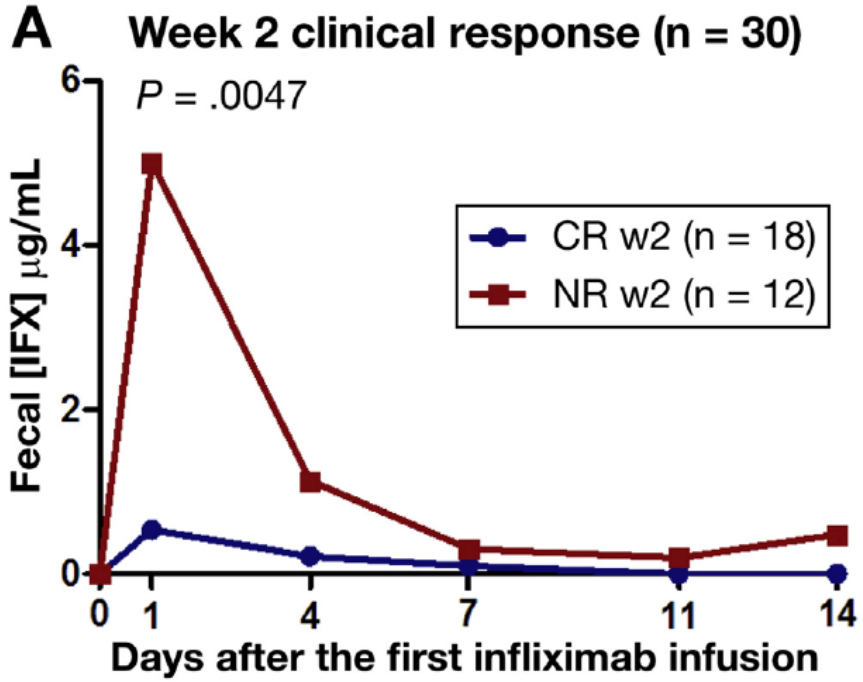
Anti-drug antibodies
Low serum albumin
High baseline CRP
High baseline TNF concentration
High body mass index
Male sex

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

“The Shark, the Sieve, and the Sponge”

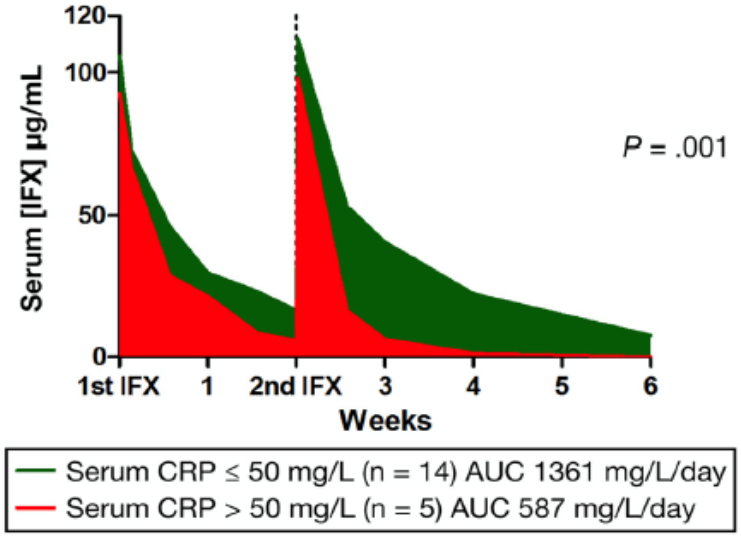


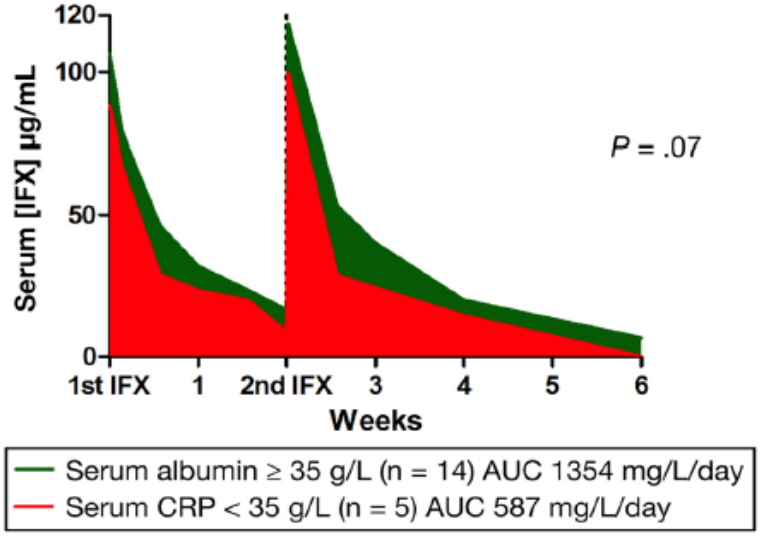
Fecal loss of IFX predicts clinical response



Brandse JF, et al. Gastroenterology. 2015;149(2):350-355.e2.

Low albumin and high CRP associated with decreased IFX exposure in UC





Brandse JF, et al. Gastroenterology. 2015;149(2):350-355.e2.

JAMA Network™

QUESTION Among patients with immune-mediated inflammatory diseases undergoing maintenance therapy with infliximab, is proactive therapeutic drug monitoring more effective than standard therapy to sustain disease control without disease worsening?

CONCLUSION Proactive therapeutic drug monitoring was more effective than standard therapy in sustaining disease control without disease worsening among patients with immune-mediated inflammatory diseases undergoing maintenance therapy with infliximab.

POPULATION

238 Men
216 Women

Adults with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn disease, or psoriasis undergoing infliximab maintenance therapy

Mean age: 45 years

LOCATIONS

20 Hospitals in Norway

INTERVENTION

458 Patients randomized
454 Patients analyzed

227
Therapeutic drug monitoring
Dose and interval adjustments based on scheduled monitoring of serum drug levels and antidrug antibodies

227
Standard therapy
Standard infliximab therapy without drug and antibody level monitoring

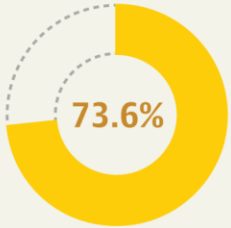
PRIMARY OUTCOME

Sustained disease control without disease worsening over 52 weeks, defined by disease-specific composite scores or patient-physician consensus on disease worsening leading to a major change in treatment

FINDINGS

52-Week sustained disease control

Therapeutic drug monitoring
167 of 227 patients



Standard therapy
127 of 227 patients

The adjusted between-group difference was significant:

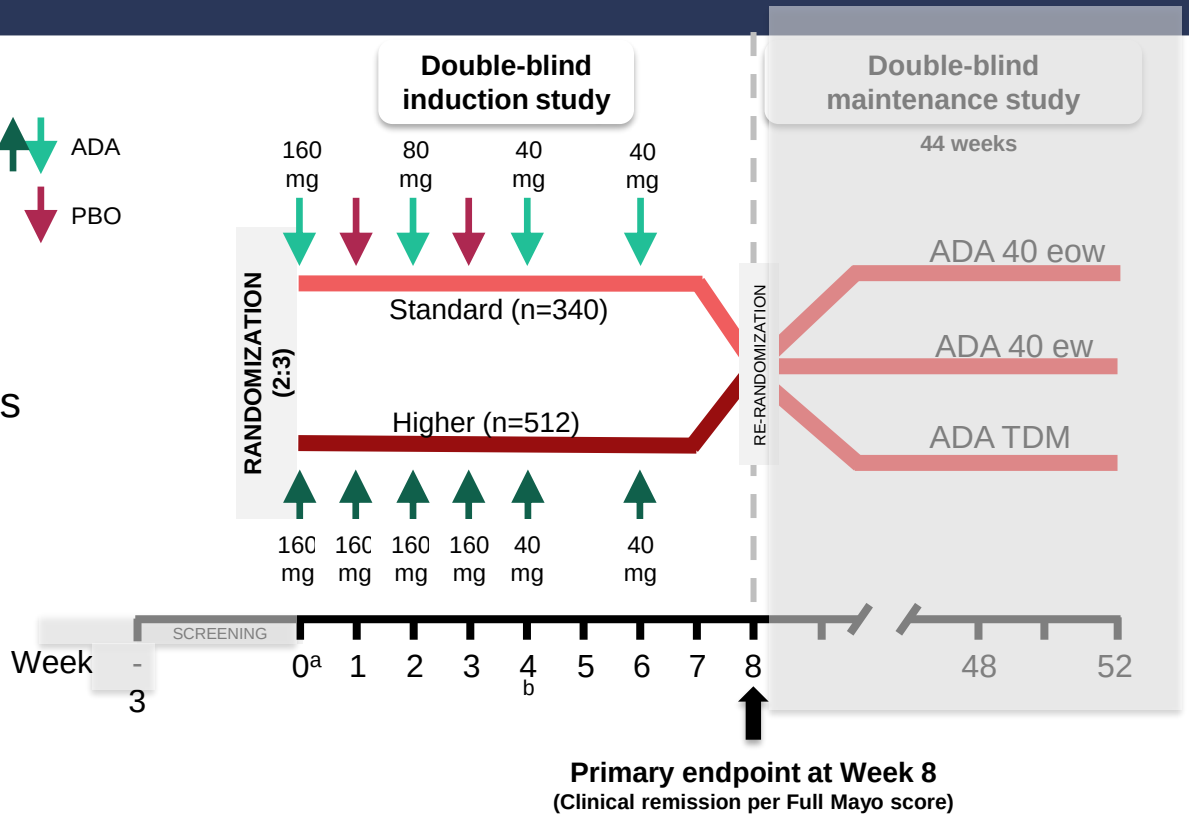
17.6% (95% CI, 9.0%-26.2%); $P < .001$

Syversen SW, Jørgensen KK, Goll GL, et al. Effect of therapeutic drug monitoring vs standard therapy during maintenance infliximab therapy on disease control in patients with immune-mediated inflammatory diseases: a randomized clinical trial. *JAMA*. Published December 21, 2021. doi:10.1001/jama.2021.21316

When is enough enough?: SERENE-UC study design

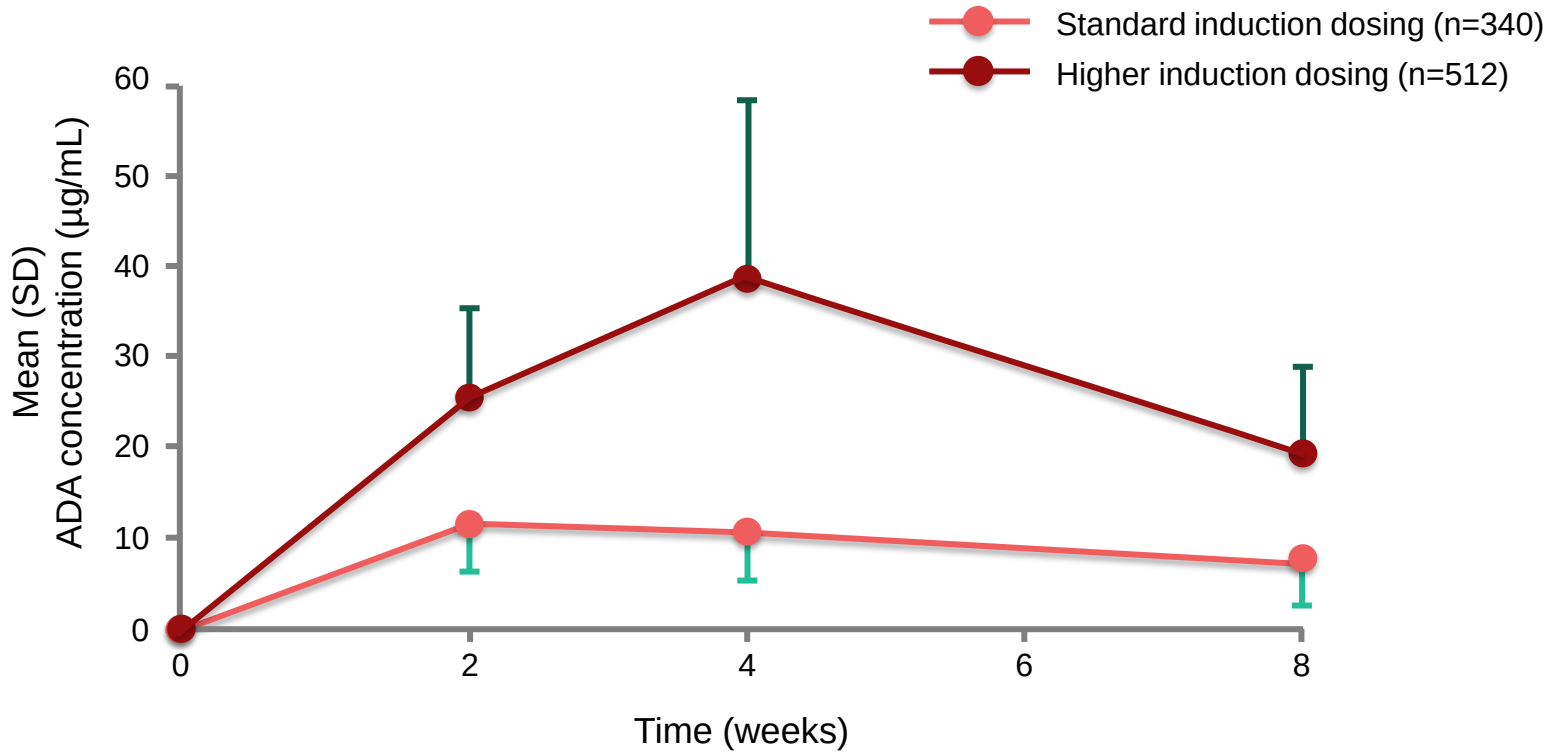
Main Inclusion Criteria:

- **Adult patients:** 18–75 years
  - **Moderate to severe UC**
    - Mayo Score of 6 to 12 points and
    - **Centrally read** endoscopy subscore of 2 to 3
  - **Bio-naïve, or IFX failure/intolerant (≤25%)**



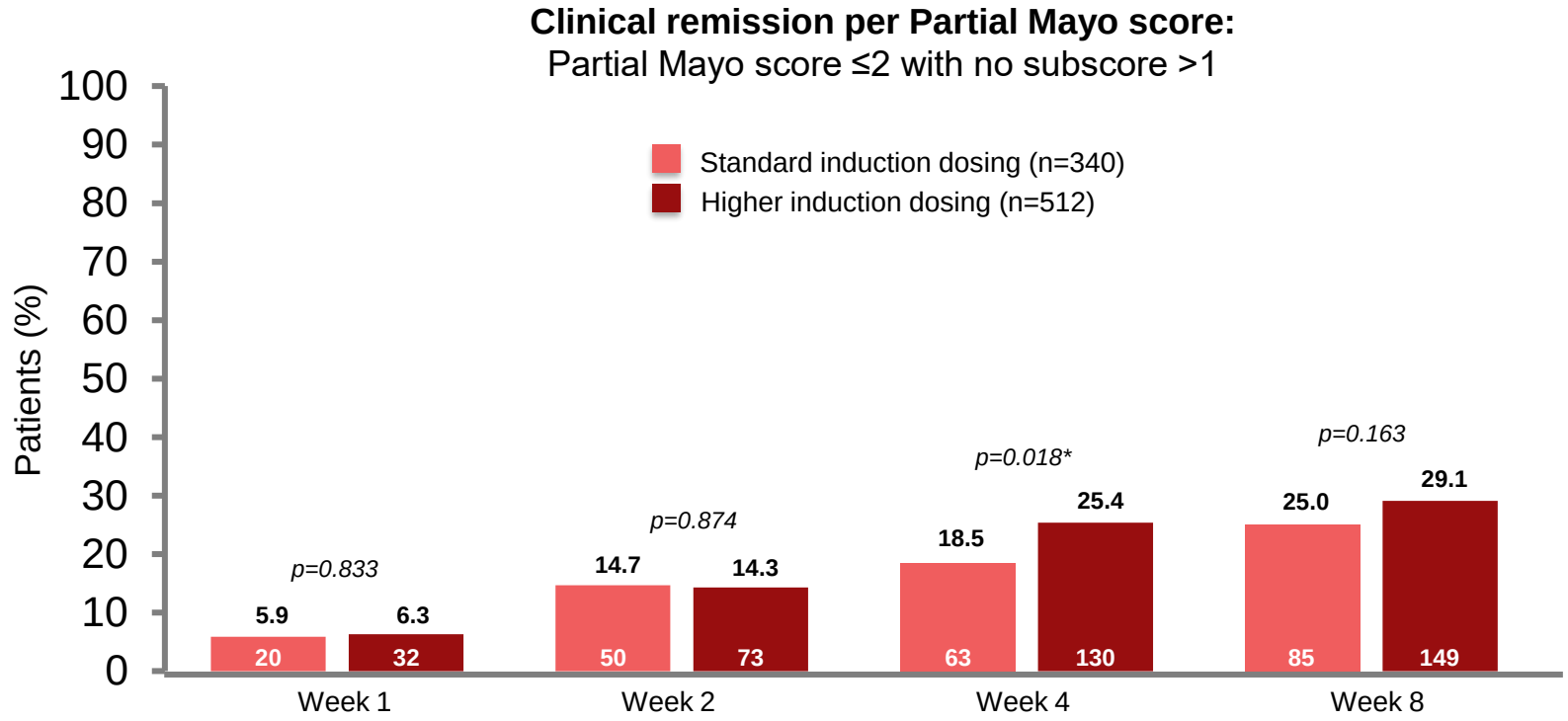
Panes, J, et al. Gastroenterology. 2022

Adalimumab trough serum concentrations: Standard vs higher induction dosing regimen



Panes, J, et al. Gastroenterology. 2022

Clinical remission per Partial Mayo score over time



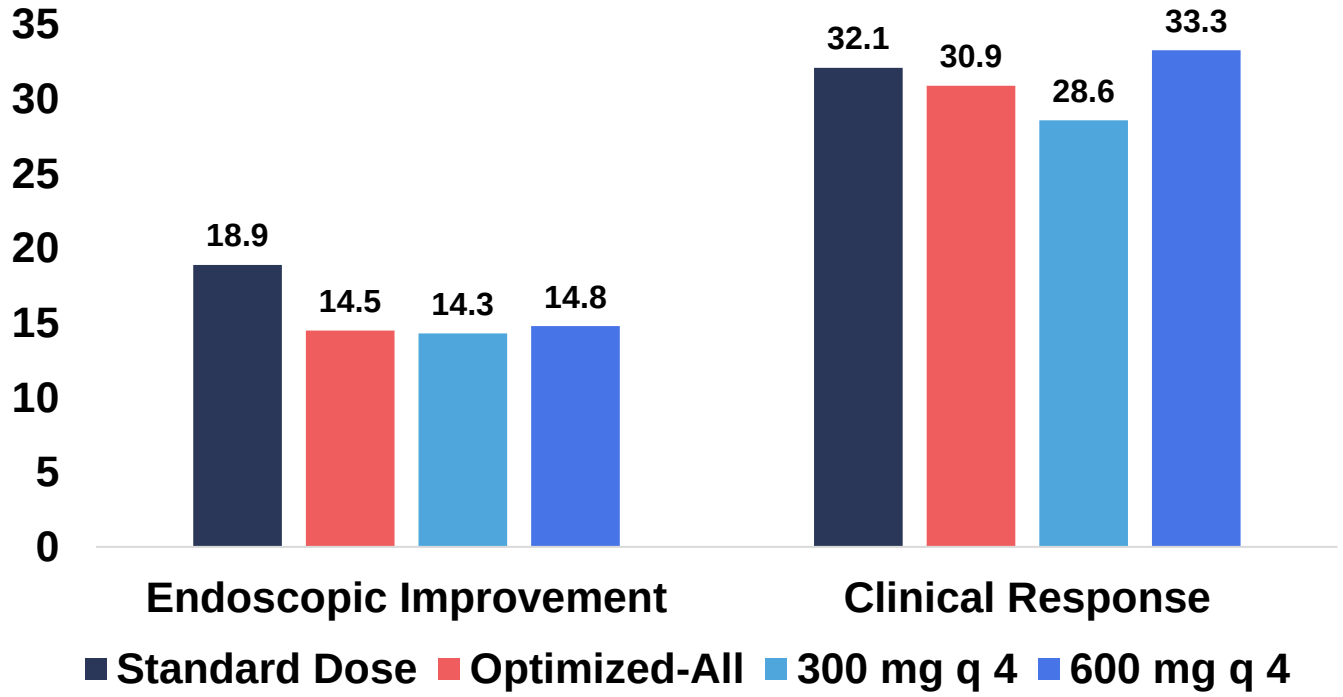
Panes, J, et al. Gastroenterology. 2022

A randomized trial of vedolizumab dose optimization in patients with moderate to severe UC who have early nonresponse and high drug clearance: the Enterpret trial

- Phase 4, open label study to assess the efficacy and safety of VDZ dose optimization versus standard dosing in moderate to severe UC patients who had primary non-response to VDZ at week 6 and had high drug clearance
- Patients received VDZ 300 mg at week 0 and 2
- All patients had a VDZ level at week 5
- 108 nonresponders at week 6 randomized 1:1 to standard dosing at week 6, 14, and 22 vs. optimized dosing
  - If week 5 VDZ level 30-49, 600 mg at week 6 then 300 mg q 4 weeks
  - If week 5 VDZ level <30, 600 mg at week 6 then monthly
- **Primary outcome**: Endoscopic improvement at week 30 (MES 0 or 1)

Osterman M, et al. DDW 2022:791

Endoscopic improvement and clinical response at week 30



Osterman M, et al. DDW 2022:791

Suggested biologic trough levels in clinical practice

Biologic	Target Trough Level
Infliximab	5-10
Adalimumab	8-12
Certolizumab pegol	>20
Vedolizumab	>11, >15?
Ustekinumab	>1 >4.5?

Cheifetz, AS, et al. (2021). Am J Gastroenterol; 116(10):2014-25.

Summary and recommendations

- Recommendation for T2T approach in UC based on data demonstrating higher risk of relapse if FCP elevated
  - Decision to dose optimize or change therapy depends on **ability to optimize existing therapy**, **severity of inflammation**, and treatment history
  - **Perfect is the evil of good, symptoms still important!**
- TDM most (only) relevant for anti-TNFs
  - To achieve optimal outcomes, **either use anti-TNF with concurrent IS or utilize proactive TDM**
  - Minimum IFX and ADA level 3 and 5 respectively
  - Do not need to increase drug levels into “therapeutic range” if clinical endpoints are met
  - Very high drug levels are not needed
- Treat the whole patient not the diagnostic test