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Modern Use of Therapeutic Drug Monitoring (TDM) Across Agents

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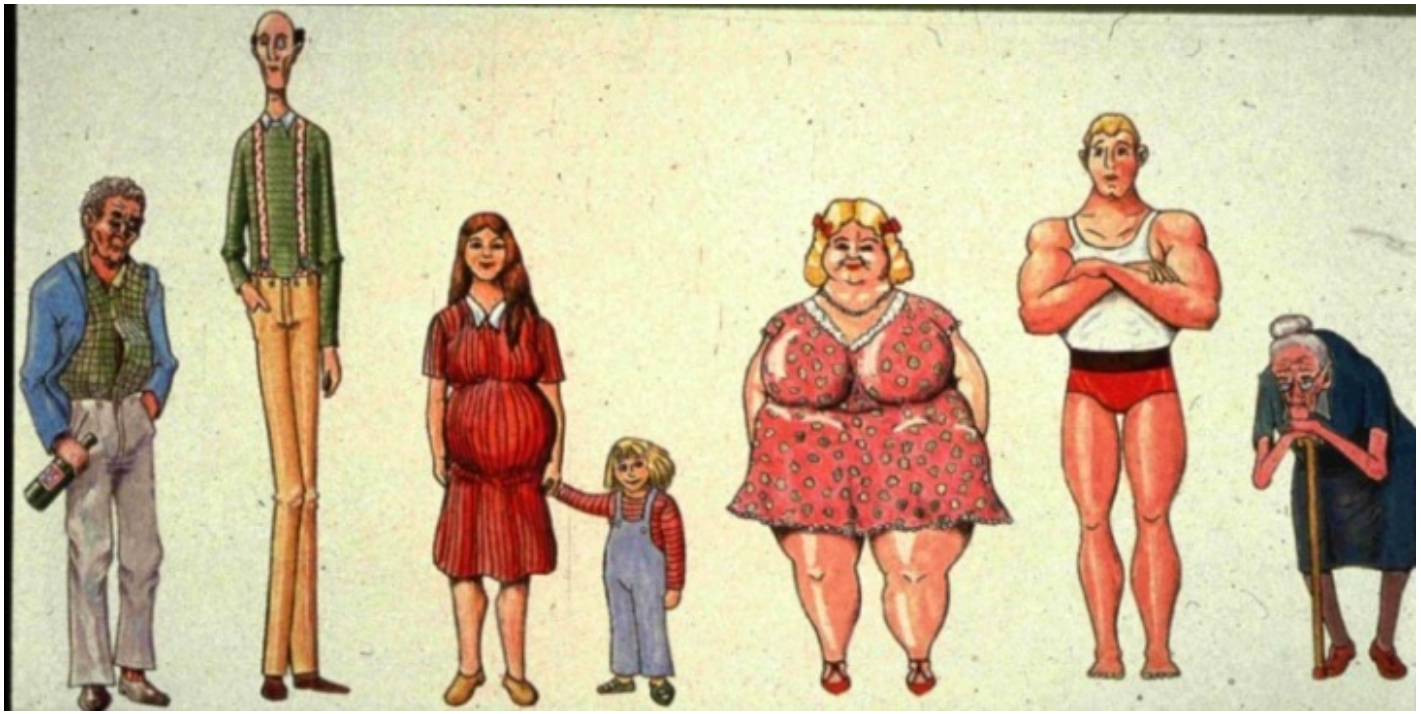
Conflicts of interest

- Investigator Initiated Research
  - R-Biopharm, Takeda, UCB
- Consulting & Speaker Fees
  - Alimentiv, Celltrion, Prometheus, R-Biopharm, Takeda, UCB

Why do we perform TDM?



Inter- & intra-individual variability in pharmacokinetics

PK Covariates Explaining Variability

Factors	Influence on mAbs targeting		
	Tumor necrosis factor-α	Integrins	Interleukins
Dosing regimen			
Dosing interval	Infliximab [136], adalimumab [146]: decreased serum concentrations with increased dosing interval	Vedolizumab: increased serum concentrations with decreased dosing interval [62, 98]	Ustekinumab: increased serum concentrations with decreased dosing interval [28, 147]
Route of administration	Golimumab: no difference in serum concentration at steady state between subcutaneous and intravenous administration [90]	Vedolizumab: increased drug concentrations in serum when administered subcutaneously [148]	Unknown
Patient-related factors			
Gender	Infliximab [79], adalimumab: increased clearance in men [105] Certolizumab pegol: increased clearance in women [88]	Vedolizumab: no effect [48]	Ustekinumab: increased clearance in men [149]
High body weight	Infliximab, certolizumab pegol, golimumab: increased clearance [150] [86, 105] [87, 88] [89, 90, 113]	Vedolizumab: increased clearance [48, 97, 115]	Ustekinumab, risankizumab: increased clearance [114] [100]
Low albumin	Infliximab, certolizumab pegol, golimumab: increased clearance [58] [87, 88] [89, 90, 113]	Vedolizumab: increased clearance [48, 115]	Ustekinumab, risankizumab: increased clearance[114] [100]
Inflammatory burden[a]	Infliximab, adalimumab, certolizumab pegol, golimumab: increased clearance [150] [86] [87, 88] [113]	Vedolizumab: increased clearance in patients with UC [48, 115]	Ustekinumab: decreased trough concentrations [147]
Immunogenicity	Infliximab, adalimumab, certolizumab pegol, golimumab: increased clearance [57, 58] [83, 84, 151] [87, 88] [89, 113]	Vedolizumab, natalizumab: increased clearance [97, 116, 134], [152]	Unknown
Concomitant medication/combination therapy	Infliximab: reduced anti-drug antibody formation and decreased mAb clearance with concurrent thiopurine or methotrexate [57]	Vedolizumab: no effect [48]	Ustekinumab: no effect [114]
Genetic variation (FcRn)	Infliximab, adalimumab: increased clearance with genetic variant of the FcRn [49]	Unknown	Unknown

CRP, FC, endoscopy

Lefevre PLC, Shackelton LM, Vande Casteele N. *BioDrugs* 2019;33:453-468

Factors contributing to immunogenicity

- Product-related factors
  - Sequence variation
  - Glycosylation
  - Host cells
  - Contaminants and process-related impurities
  - Formulation
  - Handling and storage
- Patient factors
  - Route of administration
  - Dose and treatment duration
  - Genetic factors
  - Concomitant diseases and/or medication
- Unknown factors

Schellekens H. *Nat Rev Drug Discov* 2002;1:457-62.

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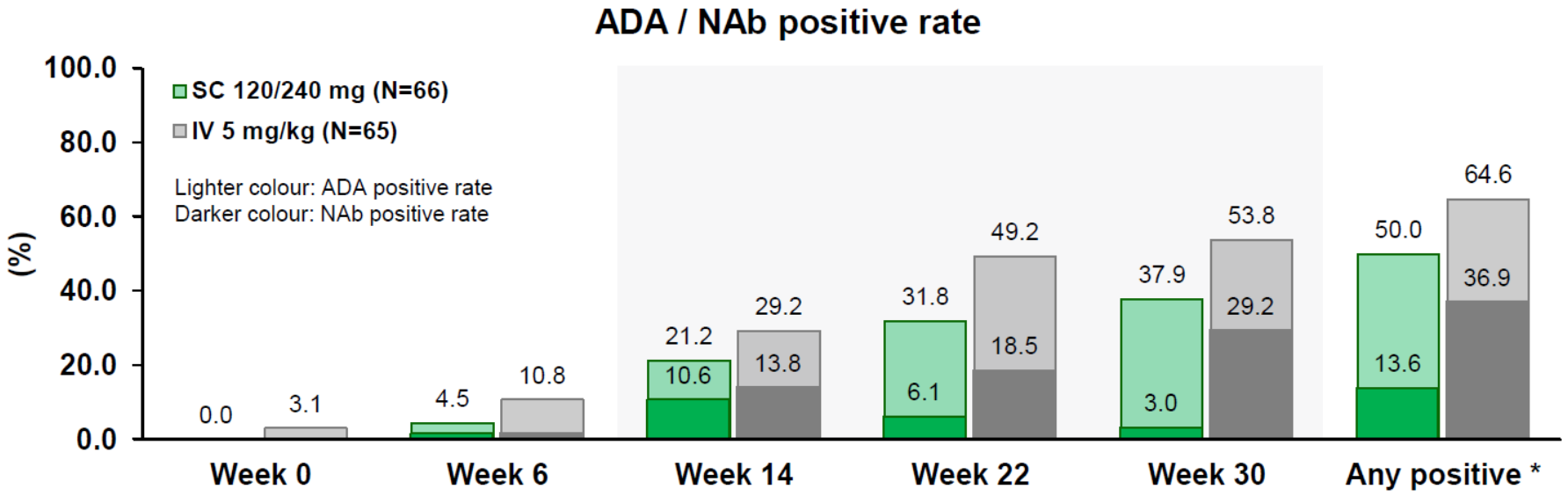
Subcutaneous vs. intravenous infliximab

- Proportions of patients with positive ADA were slightly lower in SC throughout the treatment period.



Immune response against CT-P13 SC in human serum was detected using an electrochemiluminescence (ECL) platform with an Affinity Capture Elution (ACE) step. More than 25 ng/mL of ADA can be detected in the presence of 120 µg/mL of CT-P13 in CD and UC serum.
* All immunogenicity results (including EOS and unscheduled visit) after study drug administration at Week 0 were considered.

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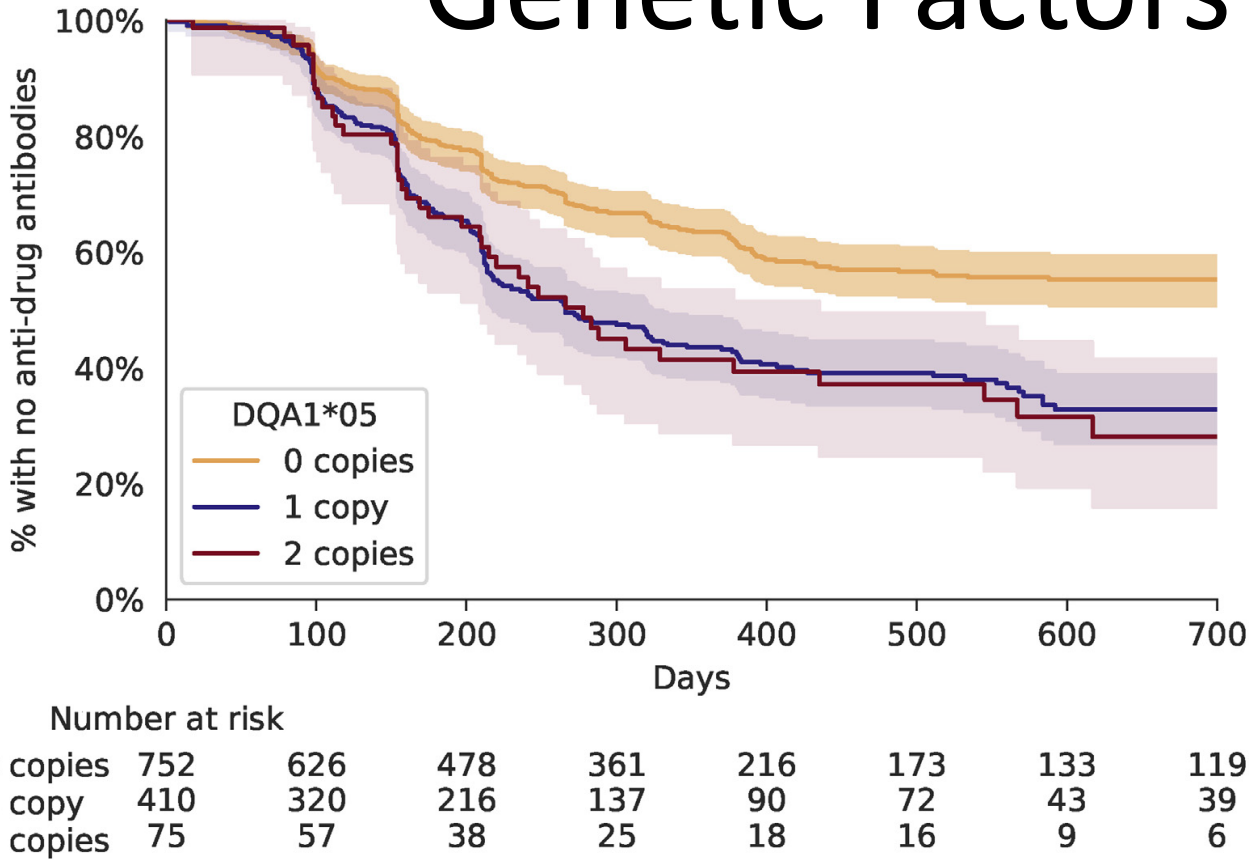
Schreiber S *et al., United Eur Gastroent* 2019;7(10):1412-1413

Genetic Factors

HLA-DQA1*05 Carriage Associated with ADAb to infliximab and adalimumab in CD

GWAS in 1240 patients with Crohn's disease treated with IFX/ADM ± immunomodulator



Number at risk

0 copies	752	626	478	361	216	173	133	119
1 copy	410	320	216	137	90	72	43	39
2 copies	75	57	38	25	18	16	9	6

Sazonovs A, *et al. Gastroenterology* 2020;158:189-199

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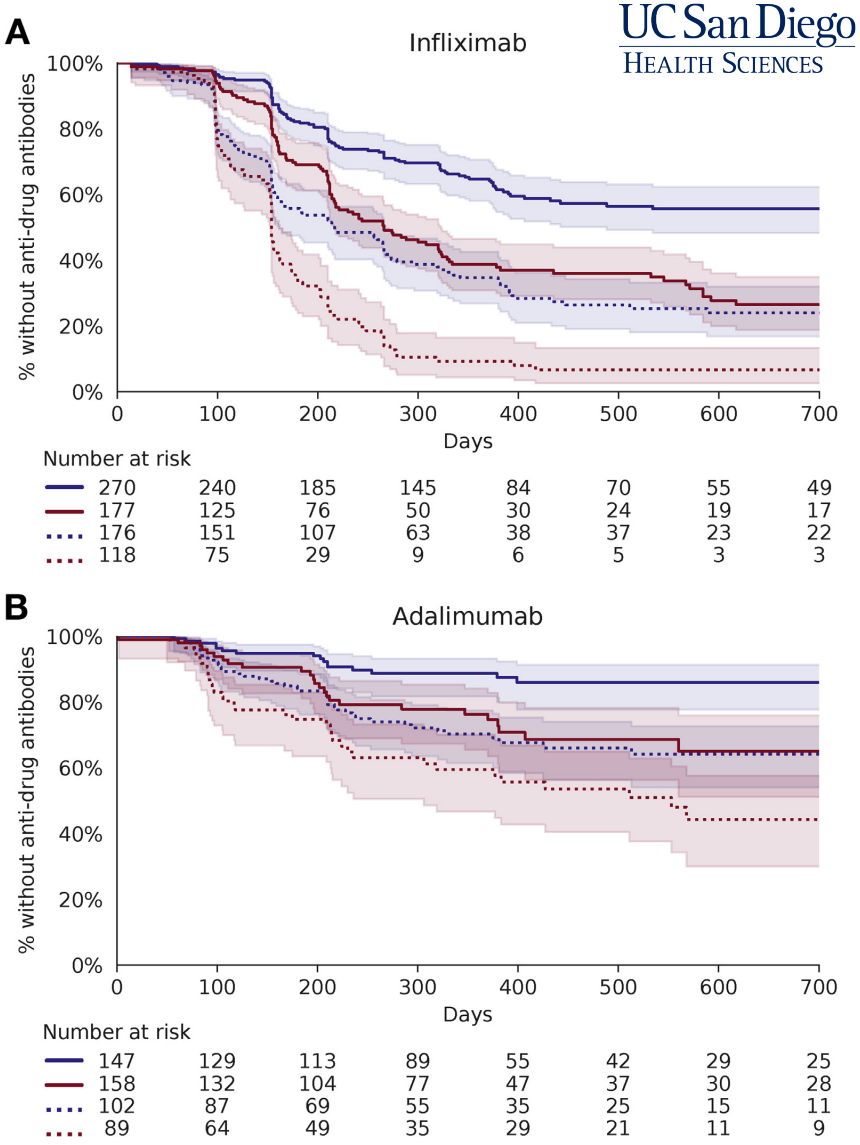
Protective effect of immunomodulators

- HLA-DQA1*05 allele, carried by approximately 40% of Europeans, significantly increased the rate of immunogenicity (hazard ratio, 1.90; 95% confidence interval, 1.60–2.25)
- Highest rates of immunogenicity, 92% at 1 year, were observed in patients treated with infliximab monotherapy who carried HLA-DQA1*05
- Lowest rates of immunogenicity, 10% at 1 year, were observed in patients treated with adalimumab combination therapy who did not carry HLA-DQA1*05

- Figure legend dotted: monotherapy; solid: combotherapy; red: carrier of HLA-DQA1*05 allele; blue: noncarriers

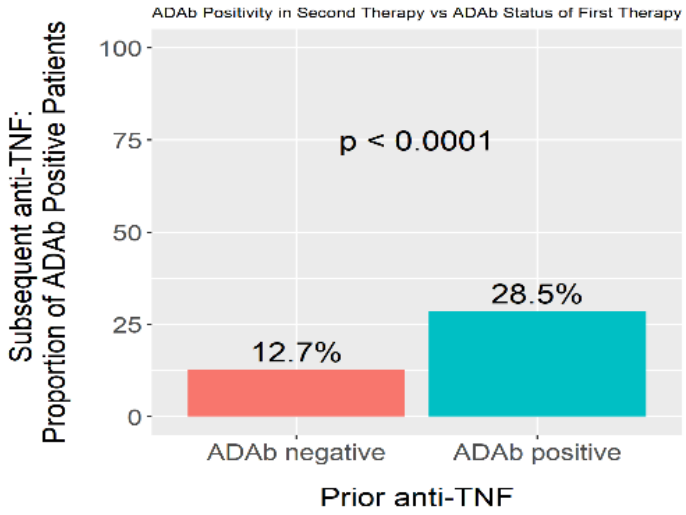
Sazonovs A, *et al. Gastroenterology* 2020;158:189-199



Patients with Antibodies to a Prior Anti-TNF Are More Likely to Develop Antibodies to a Subsequent Anti-TNF

IFX to ADM switch

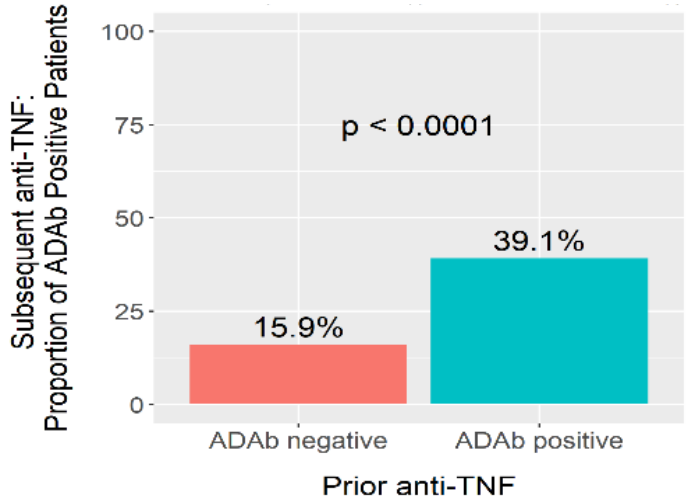
N = 1506 2171



Hazards ratio, 2.82 (95%CI 2.35-3.38)

ADM to IFX switch

N = 1427 803



Hazards ratio, 3.34 (95%CI 2.81-4.20)

Vande Casteele N, *et al. Under Review*

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Overall immunogenicity rates

Table 1. Range of rates (%) of ADAbs formation to biologics in patients with IBD[a,b].

Biologic agent	All studies (*n*)	CD (*n*)	UC (*n*)	CD or UC (*n*)
Infliximab[c]	0.0–65.3 (73)	2.9–60.8 (22)	6.1–41.0 (8)	0.0–65.3 (43)
Adalimumab	0.3–38.0 (22)	0.3–35.0 (11)	2.9–5.3 (3)	14.0–38.0 (8)
Certolizumab pegol	3.3–25.3 (4)	3.3–25.3 (4)	–	–
Vedolizumab	1.0–4.1 (4)	1.0–4.1 (2)	3.7 (1)	4.0 (1)
Golimumab	0.4–2.9 (2)	–	0.4–2.9 (2)	–
Ustekinumab	0.7 (1)	0.7 (1)	–	–

[a]Only studies reporting rates of ADAbs were included (eight studies did not report specific proportions of patients developing ADAbs).
[b]Immunogenicity analyses are product- and assay-specific.
[c]One selected study was excluded from analysis as this had a small sample size ($n = 28$) and a high rate of immunogenicity (79%).
–, no publications available; ADAbs, anti-drug antibodies; CD, Crohn's disease; *n*, number of studies; UC, ulcerative colitis.

Vermeire S, *et al. Ther Adv Gastroenterol* 2018;11:1-13

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TDM at Secondary Loss of Response

Drug Concentration / Anti-drug Abs	Subtherapeutic drug trough concentration	Therapeutic drug trough concentration
Undetectable ADAb	**Nonimmune-mediated pharmacokinetic failure** **51%** ↓ Dose escalate by either increasing the dose or decreasing the interval between drug administrations	**Mechanistic or pharmacodynamic failure** **25%** ↓ Switch to drug out of class
Detectable ADAb	**Immune-mediated pharmacokinetic failure** **19%** ↓ Switch to drug in class and consider adding an immunomodulator	**Mechanistic or pharmacodynamic failure** **5%** ↓ Switch to drug out of class and consider adding an immunomodulator

FIRST, look at trough concentration – if optimal, then ADAbs are probably inconsequential.

SECOND, if trough low/un-detectable, then examine ADAbs

Vande Casteele N, *et al. Gastroenterology* 2017;153(3):835-857.e6.

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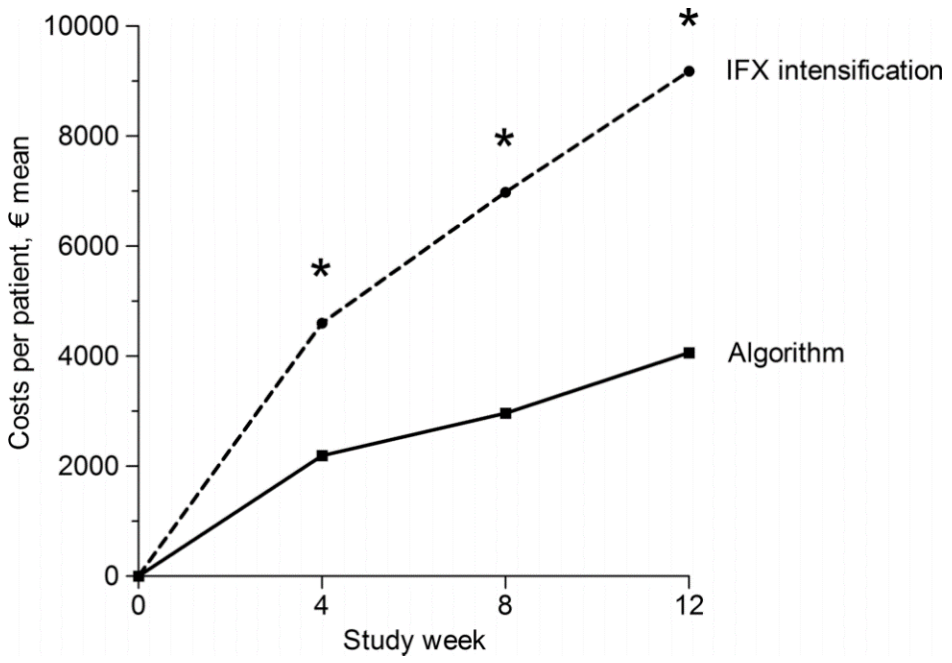
Reactive TDM: Prospective Evidence

RCT in CD (N=69)

- ✓ Confirmed secondary loss of response
- ✓ Dose escalation vs. Reactive TDM
- ✓ Response rates at week 12
  - Control group 53%
  - Algorithm group 58%

  P=0.81
- ✓ Cumulative cost at week 12
  - Control group € 9,178
  - Algorithm group € 6,038

  P<0.001



Steenholdt C, *et al. Gut* 2014 Jun;63(6):919-27

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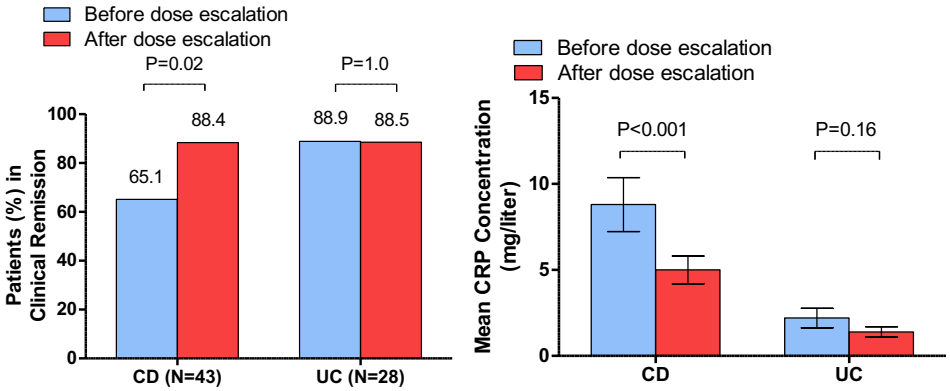
Proactive TDM: TAXIT

<u>Optimization Phase</u> (N=148)



- ✓ Dose escalation led to better clinical and biochemical outcomes
- ✓ Dose de-escalation didn't affect disease activity and reduced drug cost by 28%

<u>Randomized (1:1) Maintenance Phase</u> (N=251)

Concentration- vs. clinically-based dosing

- 69% vs 66% achieved combined clinical and biochemical remission 1 year after optimization (p = 0.686)
- 7% vs 17% required rescue therapy [RR, 2.4 (1.2-5.1), p = 0.018]
- 74% vs 57 % stayed in IFX target range (p = 0.001)
- Clinically based dosing at risk for undetectable trough concentrations [RR, 3.7 (1.7-8.0), p = 0.001]

Vande Casteele N, *et al. Gastroenterology* 2015;148(7):1320-1329.e3.

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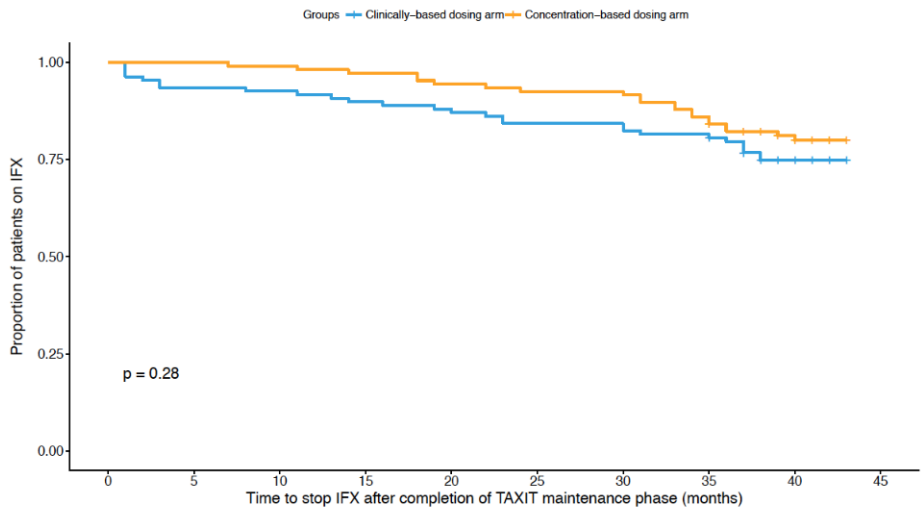
TDM During Maintenance Therapy

TAXIT Long-Term Follow-up

- At the end of the study, 91% of patients in clinically-based vs. 90% of patients in the concentration-based dosing group had mucosal healing.
- During follow-up, the rate of hospitalization, surgery and steroid use was <15% in both groups.
- **<u>Proactive TDM continued 1x/ year</u>**

Infliximab Continuation



Pouillon L, *et al. Clin Gastroenterol Hepatol* 2018;16(8):1276-1283.e1.

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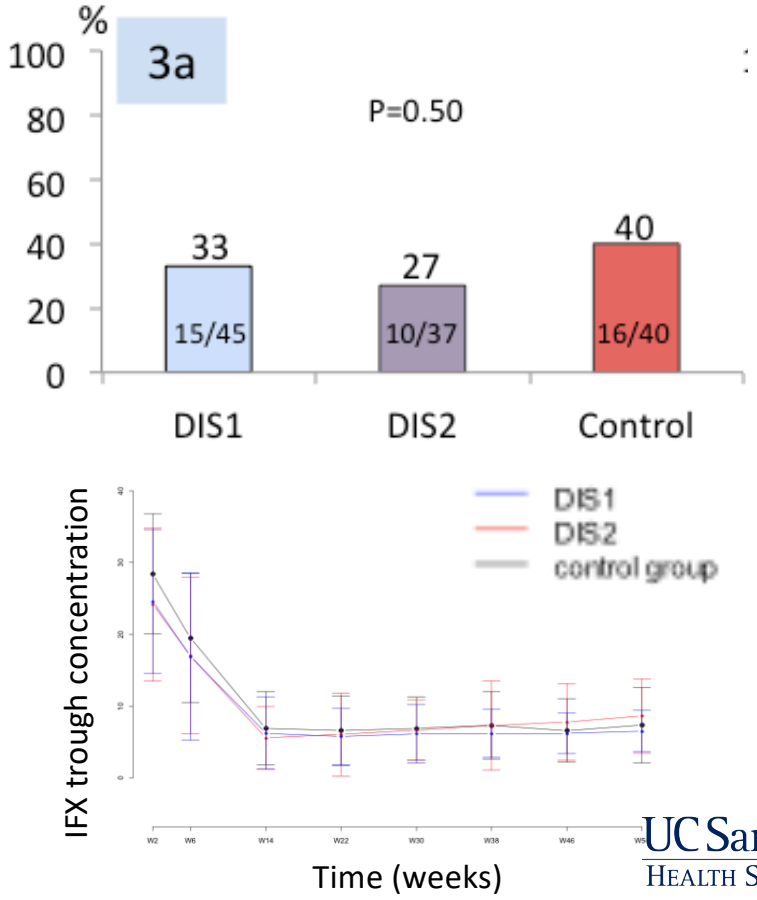
Symptoms vs. Symptoms, biomarkers and TDM in biologic-naïve CD patients: TAILORIX

Week 14 1:1:1 randomization

- CG (n=40) 5→10 mg/kg
  1. CDAI >220
  2. 150< CDAI <220 for 2 weeks
- DIS1 (n=45) 5→7.5→10 mg/kg increments
  1. CDAI >220 **AND** CRP/FC
  2. 150< CDAI <220 for 2 weeks **AND** CRP/FC
  3. IFX <1 µg/mL*
  4. IFX between 1-3 µg/mL
  5. IFX between 3-10 µg/mL with 50% drop from W14
- DIS2 (n=37) 5→10 mg/kg increments
  1. CDAI >220 **AND** CRP/FC
  2. 150< CDAI <220 for 2 weeks **AND** CRP/FC
  3. IFX <1 µg/mL*
  4. IFX between 1-3 µg/mL
  5. IFX between 3-10 µg/mL with 50% drop from W14

*patients received extra 4-week interval infusion



D'Haens G, *et al. Gastroenterology* 2018; 154(5):1343-1351

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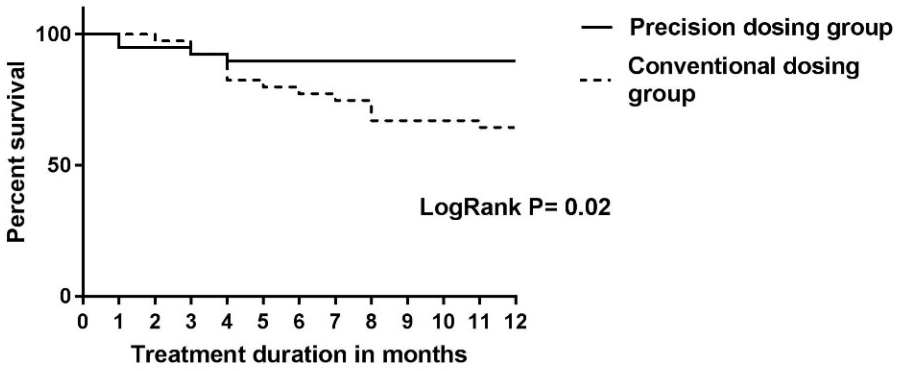
Precision Trial (Proactive TDM)



Multicenter RCT in CD&UC (N=80)

- Infliximab maintenance therapy
  - Control: no change in therapy allowed
  - Active: individualized dosing using iDose (1-10mg/4-12W)
- Target of 3 µg/mL was used
- Loss of clinical response
  - Control : 36% (14/39)
  - Active: 13% (4/32)

Strik A, et al. *DDW* 2019

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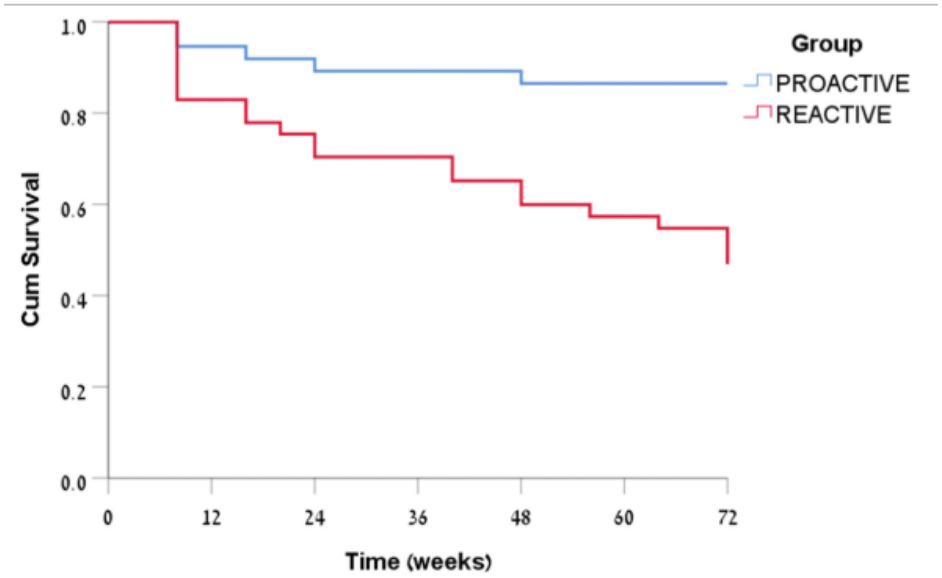
Proactive vs. Reactive TDM: PAILOT

RCT in Pediatric Luminal CD (N=78)

- Multi-center non-blinded RCT
- Adalimumab maintenance therapy, week 4 onwards
  - Proactive: 5 µg/mL threshold
  - Reactive: Symptoms/CRP/FeCal
- Corticosteroid-free clinical remission PCDAI <10 (W8-72)
  - Proactive: 34/39 (82%)
  - Reactive: 19/41 (46%)

Time to disease exacerbation



Assa A, *et al. Gastroenterology* 2019;157:985-996.e2

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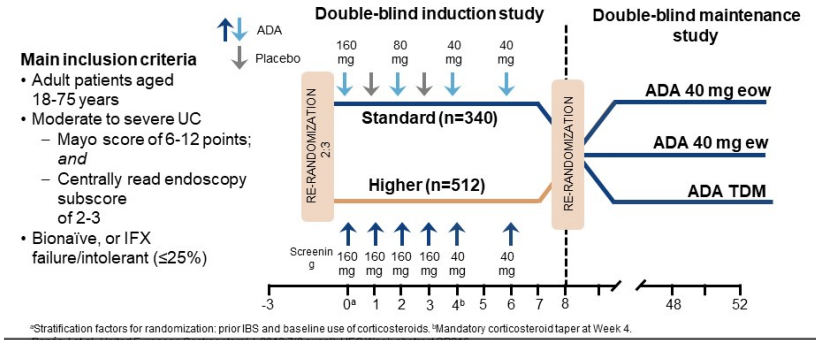
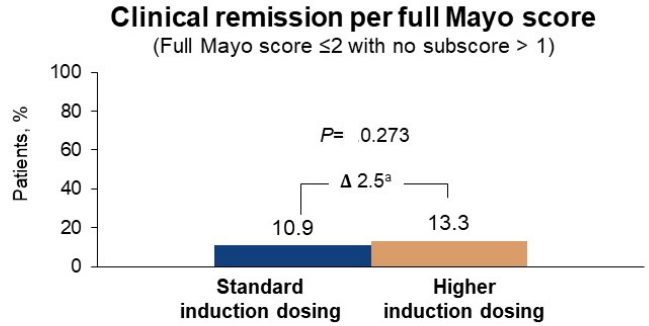
SERENE-UC (induction): Similar outcomes observed for standard and higher induction dosing of adalimumab

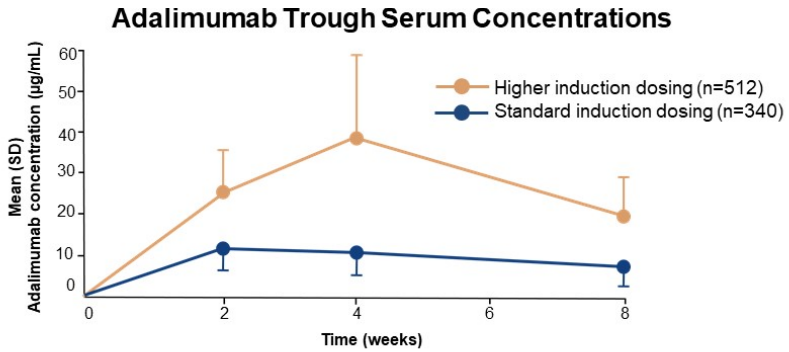
Study Design



Primary Efficacy Endpoint at Week 8



ITT analysis set. [a]Adjusted by stratification factors. Central reviewer scoring of endoscopy results was used for all efficacy assessments. Rectal bleeding subscore and stool frequency subscore components of Mayo were based on entries into a patient's diary on the 5 days prior to each study visit and averaged.



ITT analysis set. [a]Adjusted by stratification factors. Central reviewer scoring of endoscopy results was used for all efficacy assessments. Rectal bleeding subscore and

Panes J, *et al. UEG* 2019

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SERENE-UC (maintenance): Clinical remission at Week 52 was numerically but not statistically higher in patients receiving ADA 40 EW vs. 40 EOW during maintenance

Primary Endpoint

	ADA 40 mg EW N=152 n (%)	ADA 40 mg EOW N=145 n (%)	ADA TDM regimen N=74 n (%)
Primary Endpoint[a] (ITT-RP)			
Clinical Remission[b] among Wk 8 responders[c]	60 (39.5)	42 (29.0)	27 (36.5)
Treatment Difference (40 mg EW − 40 mg EOW)	10.5%		
95% CI	(−0.8%, 20.6%)		
p-value[d]	0.069		

Secondary Endpoints

Ranked Secondary Efficacy Endpoints	ADA 40 mg EW n/N (%) *p*-value[d]	ADA 40 mg EOW n/N (%)	ADA TDM regimen n/N (%)
1. Wk 8 responders[c] achieving endoscopic improvement[e]	78/152 (51.3) 0.098	60/145 (41.4)	34/74 (45.9)
2. Wk 8 responders[c] taking steroids at BL who are steroid-free for ≥90 days	71/95 (74.7) 0.002*	49/92 (53.3)	34/47 (72.3)
3. Wk 8 responders[c] taking steroids at BL who are steroid-free for ≥90 days and in clinical remission[b]	37/95 (38.9) 0.093	25/92 (27.2)	19/47 (40.4)
4. Wk 8 remitters[b] achieving clinical remission[b]	24/42 (57.1) 0.161	15/37 (40.5)	12/24 (50.0)
5. Wk 8 remitters[b] achieving endoscopic improvement[e]	27/42 (64.3) 0.272	19/37 (51.4)	13/24 (54.2)
6. Wk 8 remitters[b] taking steroids at BL who are steroid-free for ≥90 days	21/27 (77.8) 0.074	14/26 (53.8)	12/16 (75.0)
7. Wk 8 remitters[b] taking steroids at BL who are steroid-free for ≥90 days and in clinical remission[b]	15/27 (55.6) 0.151	9/26 (34.6)	10/16 (62.5)
8. Wk 8 responders[c] with IBDQ response[f]	101/152 (66.4) 0.422	90/145 (62.1)	51/74 (68.9)

Colombel JF, *et al. ECCO* 2020

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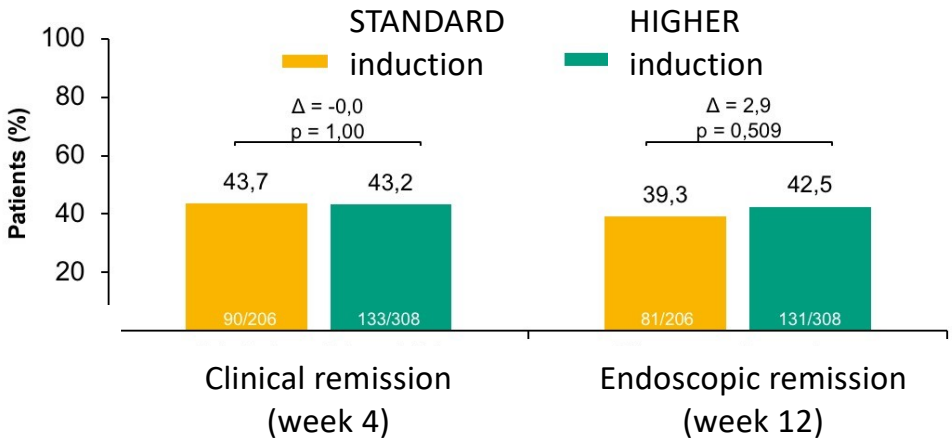
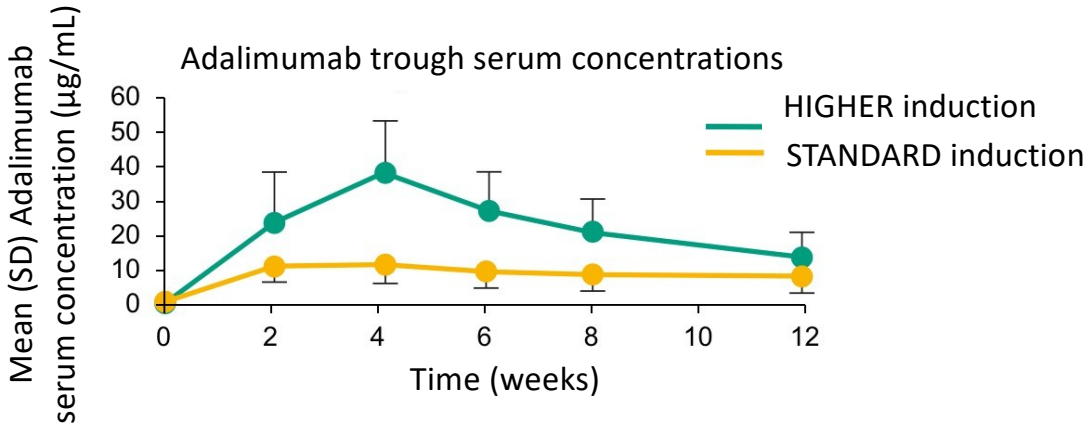
SERENE-CD (induction): Similar outcomes observed for standard and higher induction dosing of adalimumab





D'Haens G, *et al. UEG* 2019

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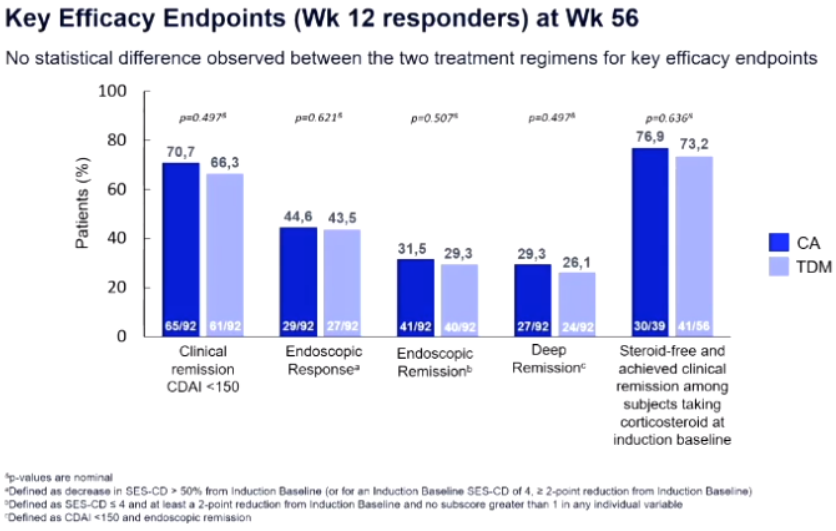
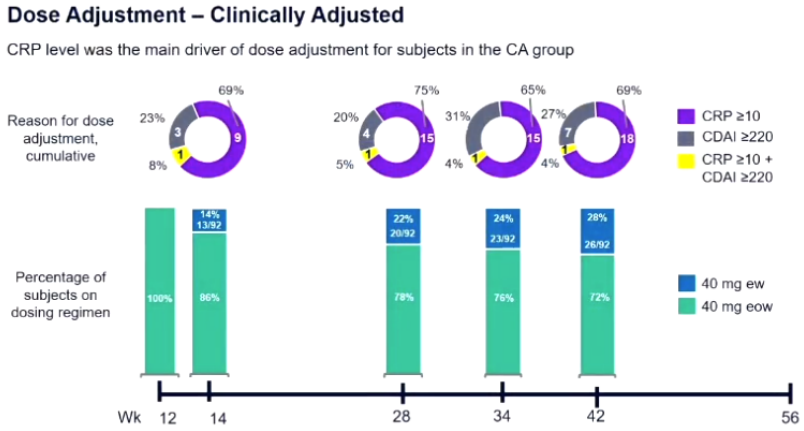
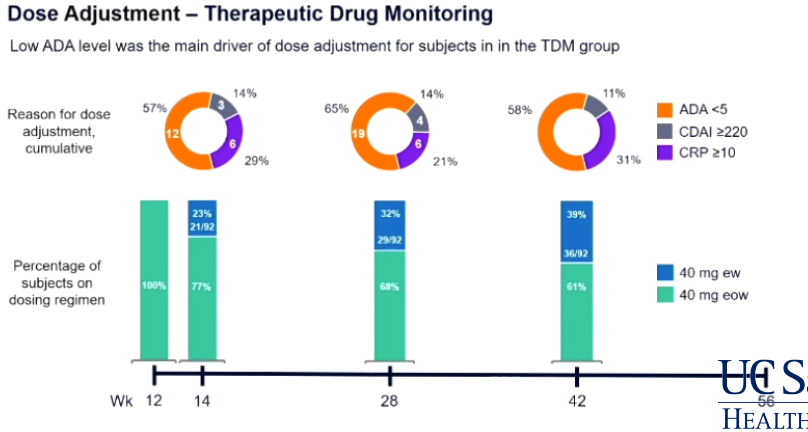
SERENE-CD (maintenance): Proactive TDM in addition to clinical symptoms and biomarkers to guide dose adjustment did not provide additional benefit







Danese S, *et al. UEG* 2020

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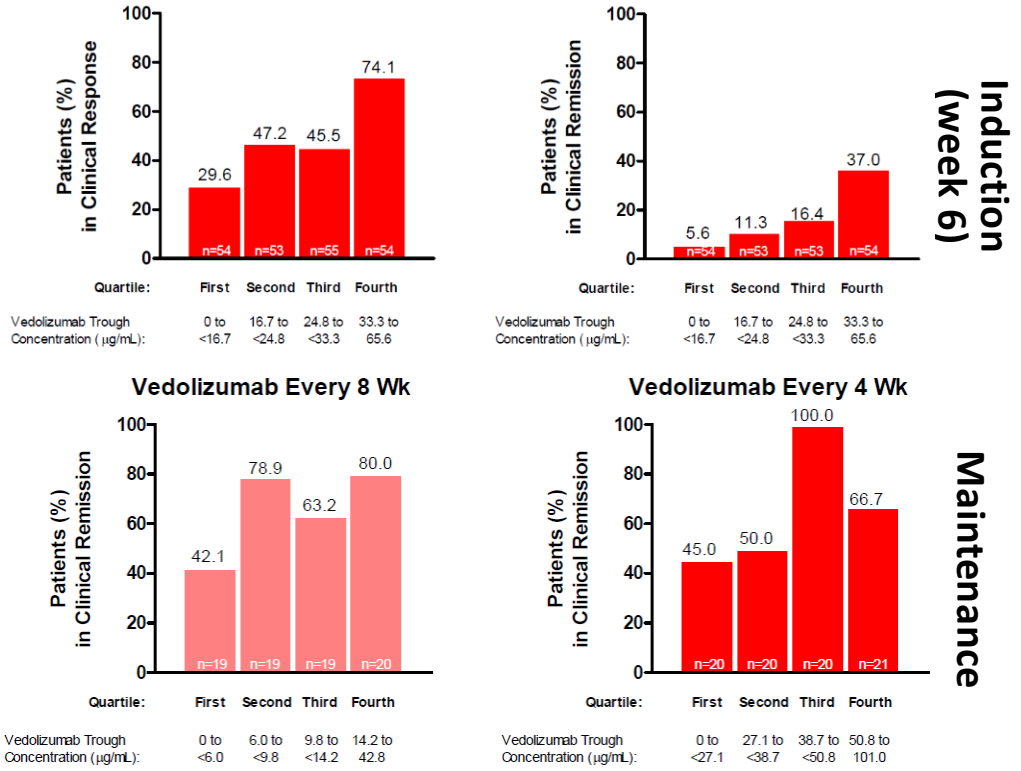
Therapeutic drug monitoring for vedolizumab

- Apparent exposure-response relationship in GEMINI trials
- 95% saturation of $\alpha_4\beta_7$ at 1 µg/mL vedolizumab
- Thresholds associated with better outcomes (N=179 IBD):
  - Week 2 >30 µg/mL
  - Week 6 >24 µg/mL
  - Maintenance >14 µg/mL



Feagan BG, *et al. N Engl J Med* 2013;369(8):699-710
Dreesen E, *et al*. *Clin Gastroenterol Hepatol* 2018 [Epub ahead of print]

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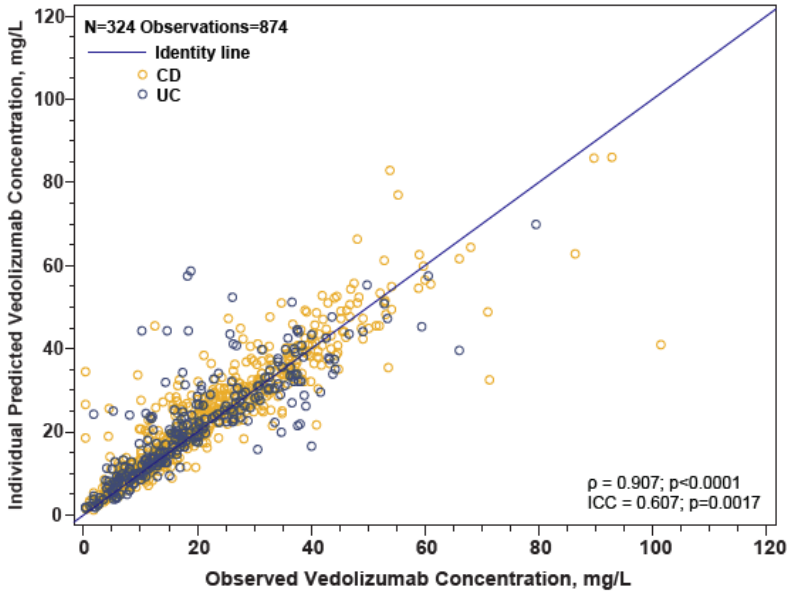
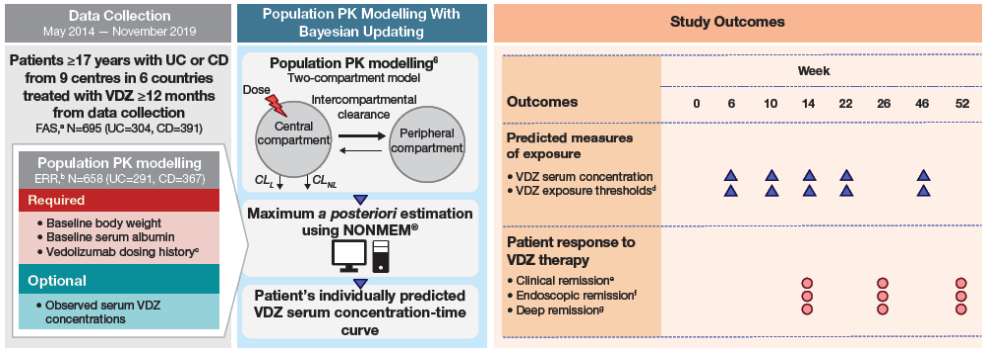
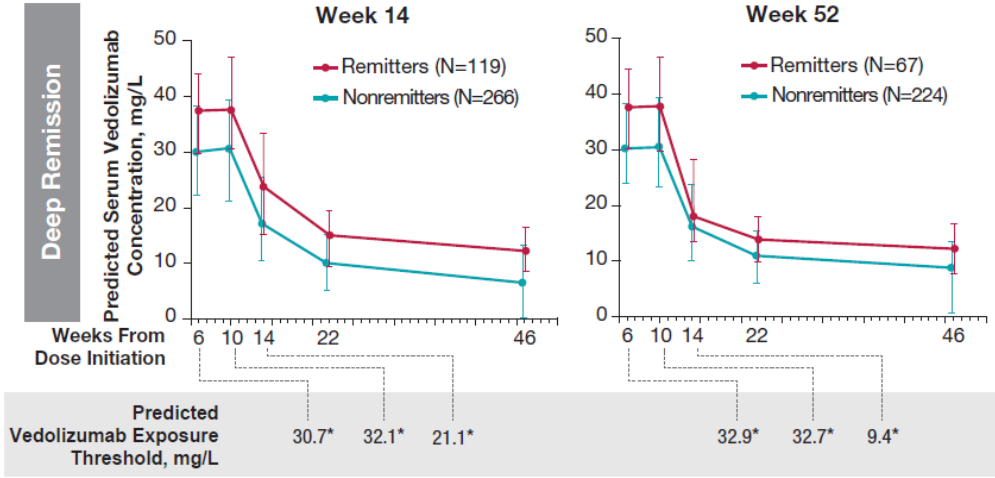
Real world exposure-response relationship of vedolizumab in IBD using Bayesian population PK modeling (ERELATE)



Design

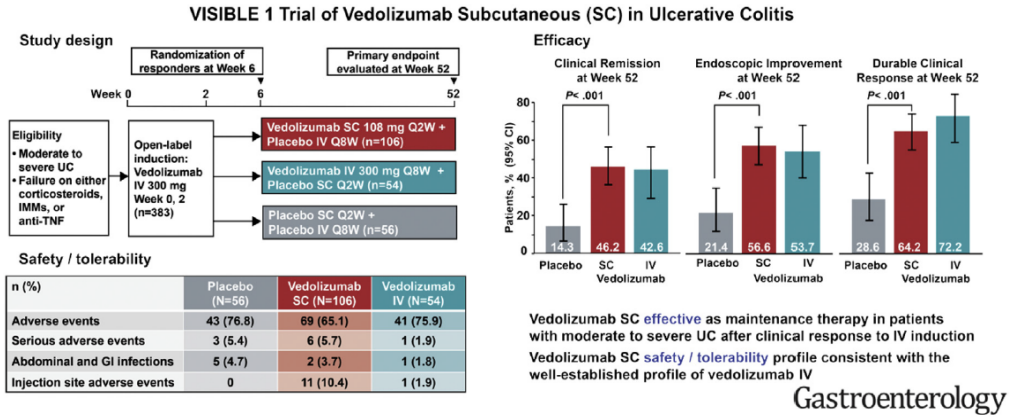


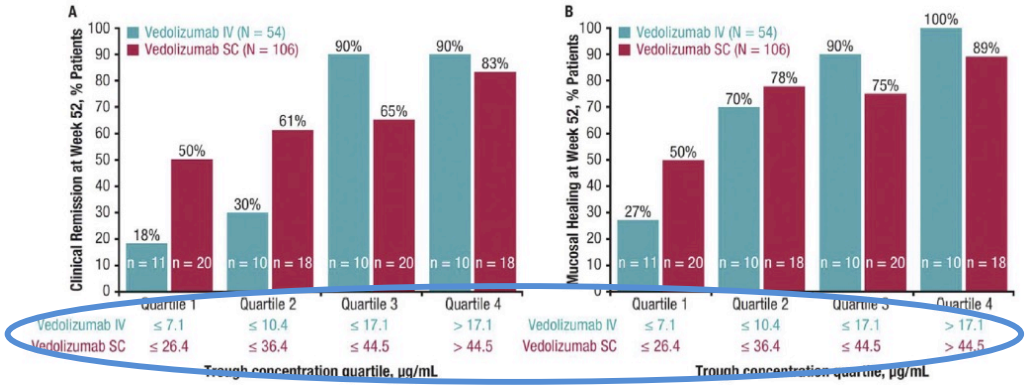
Results



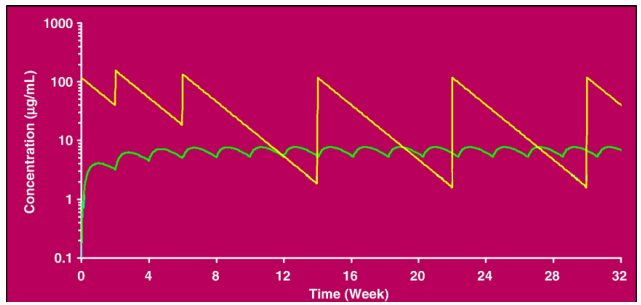
Vande Casteele N, *et al. UEG* 2020

VISIBLE: Vedolizumab SC following IV induction



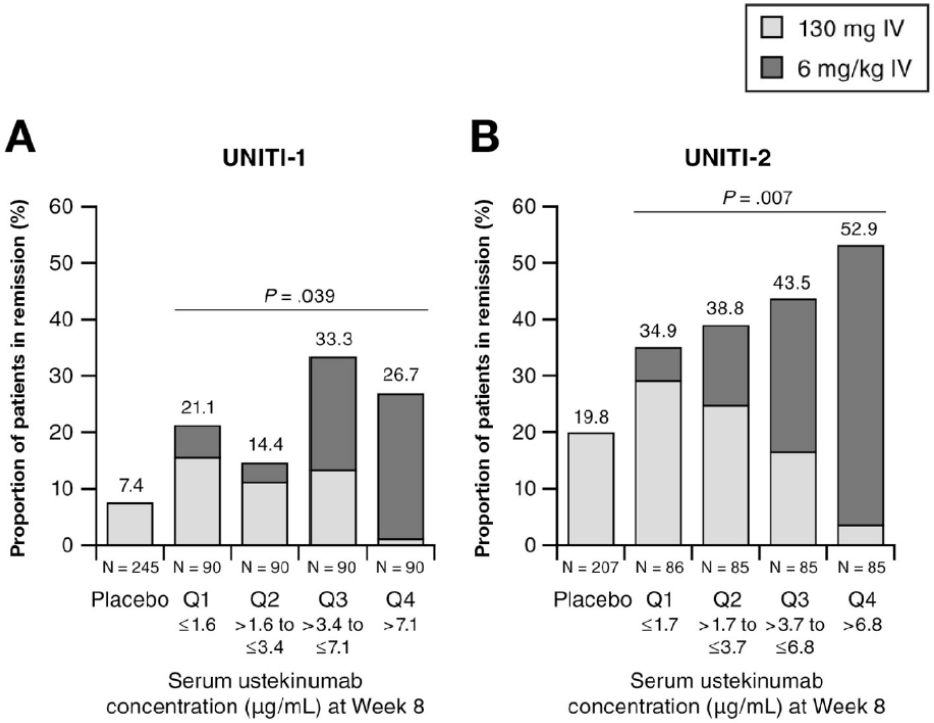


Caverage instead of Ctrough will be exposure measure to compare SC and IV exposure



Sandborn WJ, *et al. Gastroenterology* 2020;158:562-572

Therapeutic drug monitoring for ustekinumab



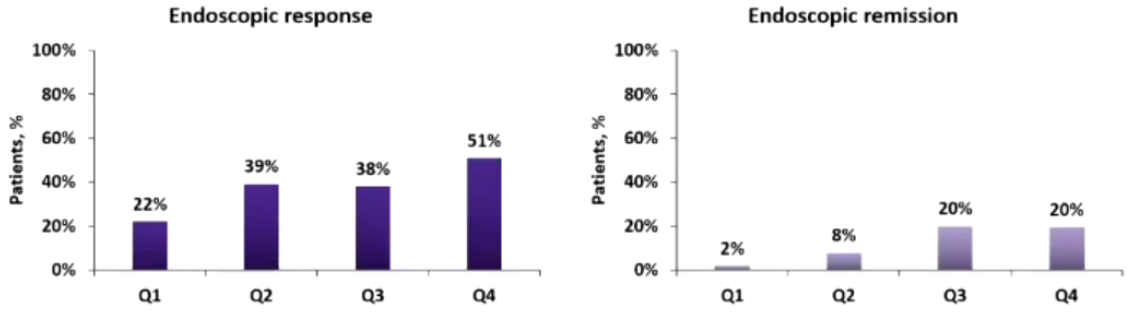
- Apparent exposure-response relationship in UNITI trials
- Thresholds associated with better outcomes
  - Maintenance >0.8 – 1.35 µg/mL (Clinical remission)
  - Maintenance >4.5 µg/mL (Endoscopic response)
- Maintenance <0.5 µg/mL associated with worse outcomes

Adedokun OJ, *et al. Gastroenterology* 2018;154:1660-1671
Battat R, *et al*. *Clin Gastroenterol Hepatol* 2017;15:1427-1434.e2

STARDUST: Ustekinumab exposure-response for endoscopic outcomes

Results: Exposure–response (endoscopic measures)

- At Week 16, ustekinumab concentrations were positively associated with proportions of patients achieving endoscopic response (SES-CD ≥50%) and endoscopic remission (SES-CD <3)



Week 16 concentration (µg/mL) quartiles			
Q1	Q2	Q3	Q4
<1.3	1.3 to <2.6	2.6 to <4.8	≥4.8

SES-CD, Simple Endoscopic Score for Crohn's Disease; Q, quarter

D'Haens G, *et al. UEG* 2020

Summary

- Genetic testing may identify risk factors associated with immunogenicity
- New formulations may improve PK (e.g. infliximab, vedolizumab)
- Besides trough concentrations, other exposure measures may be important (e.g. clearance, average concentration)
- Reactive TDM will continue to be an important tool at time of loss of response
- Pharmacokinetics with use of TDM can be used to identify patients most likely to benefit from proactive TDM
  - Join our workshop tomorrow on how to identify patients at risk for accelerated drug clearance *prior* to initiating therapy (Canada Future Directions: “New Era, New Science, New Antibodies”)

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Key Take Aways

Why: inter- and intra-individual variability in PK and PK-PD relationship

How: validated assays with evolution towards rapid measurements (PoC)

Who: patients at risk for accelerated drug clearance and/or poor outcomes

When: during induction and/or at time of loss of response

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