COMBINING "BEDSIDE" AND CLINICAL RESEARCH DATA TO INFORM DISEASE PROGRESSION AND OUTCOMES/BIOMARKER SELECTION

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DISCLOSURES

- Diane Mould is president of Projections Research Inc, a consulting company for the pharmaceutical industry
- Dashboards recommend doses and dose intervals that are not consistent with the labeled dose

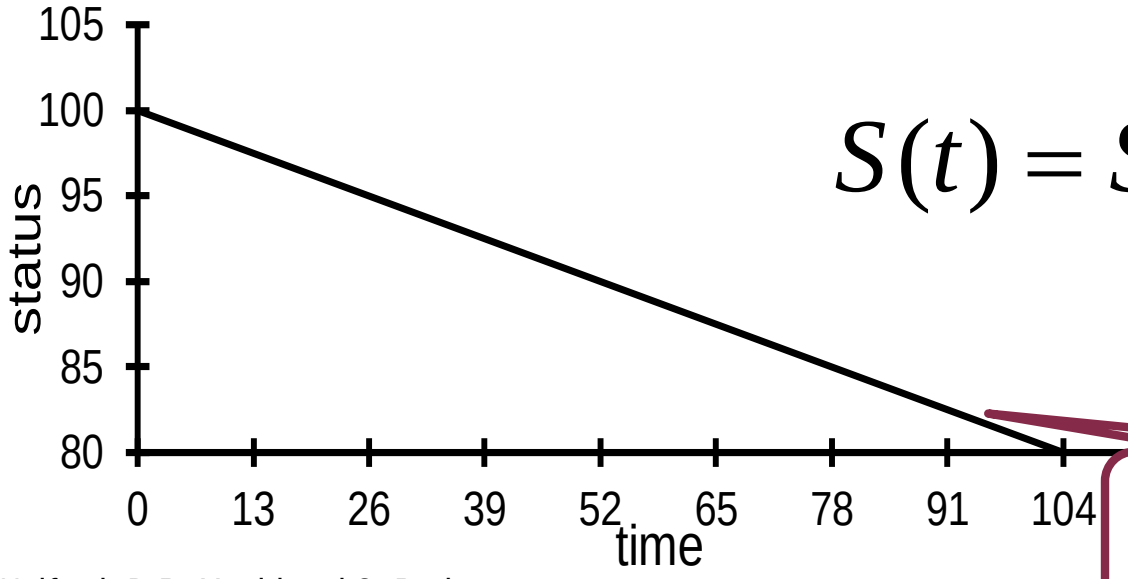
SOME ISSUES TO CONSIDER

- Some diseases are inherently different in adults and pediatrics
  - Some cancers occur predominantly in pediatrics, others predominantly in adults
    - Pediatric cancers often different than tumors in adults. Unlike many adult cancers, childhood cancers not strongly linked to lifestyle or environmental risk factors.
  - Pediatric and adult patients can react differently to treatments
    - Pediatric cancers often respond better to chemotherapy.
    - Children tend to tolerate chemotherapy better than adults.
    - Cancer chemotherapy and radiation therapy can have long-term side effects, so pediatric survivors need careful attention for the rest of their lives.

http://www.cancer.org/acs/groups/cid/documents/webcontent/003125-pdf.pdf

MORE ISSUES TO CONSIDER

- Disease progression models can require a lot of data to develop
  - Metrics of disease progression often inherently variable (especially if assessment is subjective)
- Need data collected over sufficient period of time to develop a function
- Often don't have "natural history" in untreated patients
- Standard of care changes over time, so the expected progression in active control arm needs to be updated periodically



$$S(t) = S_0 + \alpha \cdot t$$

Observations need to be available over sufficient time to assess progression rate

N.H.G. Holford, D.R. Mould and C. Peck
"Disease Progression Models" in Principles of Clinical Pharmacology 3rd Edition,
Editor: A. Atkinson Academic Press New York NY 2012

WAYS TO ADDRESS SOME OF THESE ISSUES

- Use (pool) data from multiple previous studies to build models
  - can sometimes work with major academic centers for long term data
- Utilize published summary data (meta-analyses)
  - Need to ensure that the summary metrics (e.g. mean response, median response etc.) allow combining meta data
- Find a published model and use as an informative prior
- Collect "bedside" data to refine models
  - Need to verify the quality of the data
  - Can be combined with meta-analysis

J French, When and how should I combine patient-level data and literature data in a meta-analysis? PAGE 19 (2010) Abstr 1944 [www.page-meeting.org/?abstract=1944]

DISEASE PROGRESSION MODELS

- Disease progression models are a good platform to understand drug action and to extrapolate to pediatrics
- Models of disease progression developed for many diseases
  - Rheumatoid arthritis, HIV, diabetes, Alzheimer's Disease, Parkinson's Disease, several cancers, osteoporosis
- Other than probability models, there are no longitudinal models of IBD progression
  - Probability of achieving remission or of therapeutic failure
- Why is there no disease progression model for IBD?
  - No well accepted marker of IBD progression
- The etiology of IBD is unclear.
  - IBD is multifactorial. It is a complex interaction of environmental, genetic, and immune factors.

DISEASE ACTIVITY VS DISEASE SEVERITY

Activity

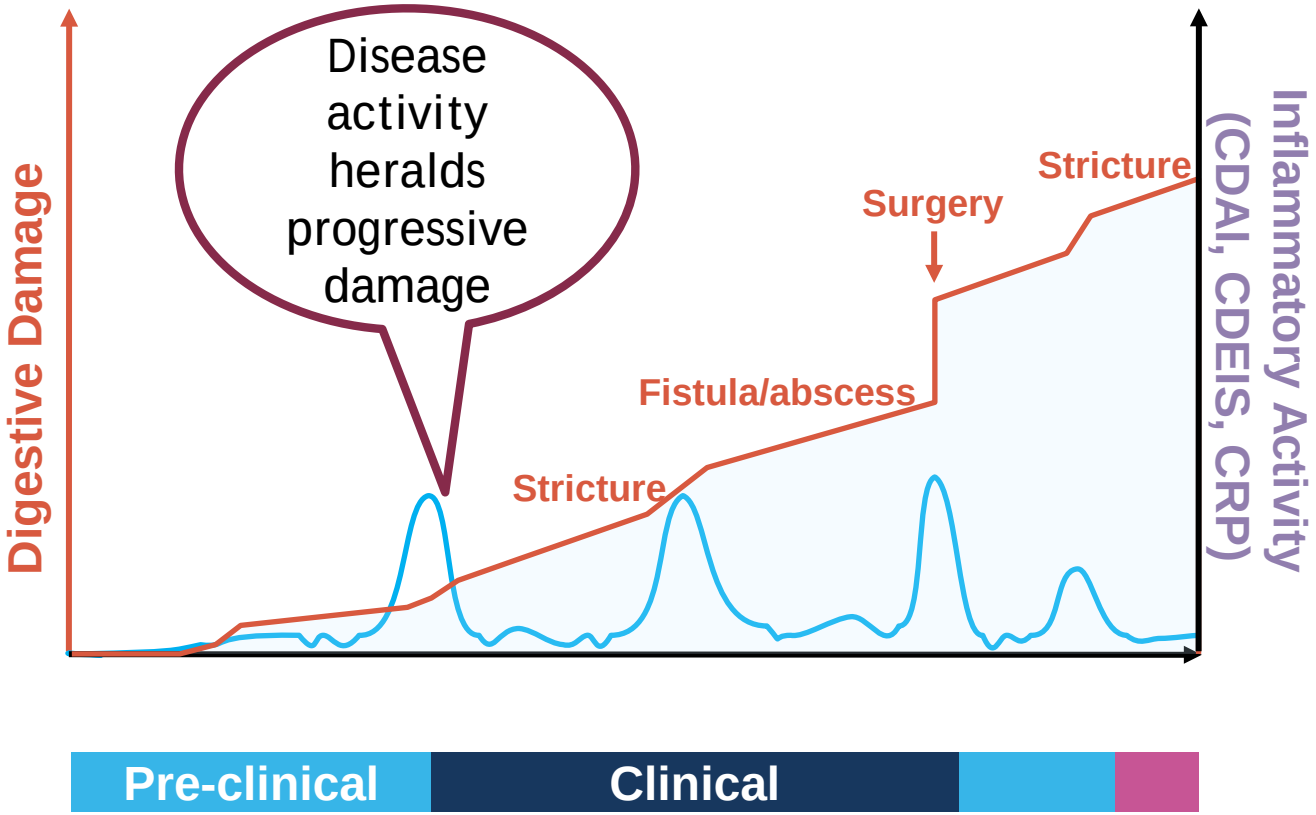
Reflects cross sectional assessment of biological (inflammatory) impact on symptoms, signs, endoscopic, (histologic), and biomarkers

Severity

Includes longitudinal (disease course) and historical factors that provide a more complete picture of the prognosis and overall "burden" of disease

This is what we have available to model but doesn't really relate to progressive damage

PROGRESSION OF DIGESTIVE DISEASE DAMAGE AND INFLAMMATORY ACTIVITY



CDAI = Crohn's disease activity index; CDEIS = Crohn's disease endoscopic index of severity; CRP = C-reactive protein

Pariente B, et al. *Inflamm Bowel Dis.* 2011;17(6):1415-1422.

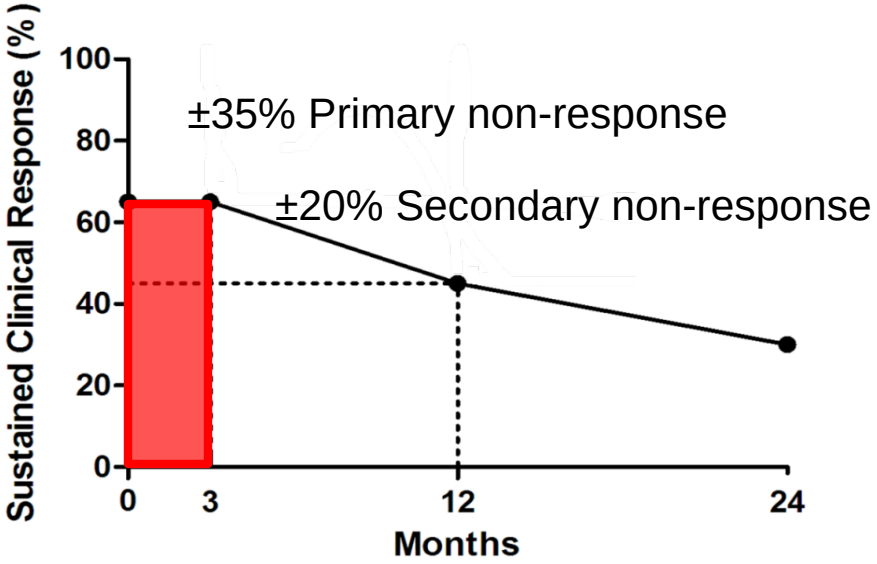
PEDIATRIC IBD

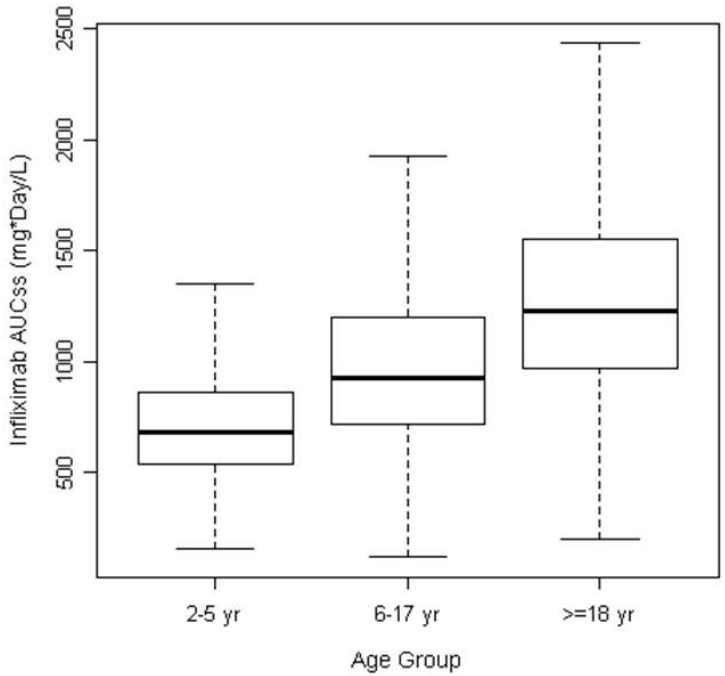
- The incidence of pediatric inflammatory bowel disease is increasing
  - IBD first presents in childhood and adolescence in approximately 20% of all cases
- Unlike adults, growth failure is an important sign in pediatric onset IBD, most commonly in CD patients.
- Childhood-onset IBD is characterized by extensive intestinal involvement and rapid early progression

Dubinsky M. World J Gastroenterol. 2008 21;14(3):413-20.
Van Limbergent, J, Russell, RK, Drummond, et al. Gastroenterology, 135(4):1114-1122.

OTHER PROBLEMS

- Many of the agents used to treat IBD are MAbs
- Complex pharmacokinetics
  - Many factors impact MAb PK
  - High interpatient variability
  - PD affects PK
- Currently high treatment failure rate in adult
  - More than 33% of patients show no response to induction therapy (primary non-responders)
  - Up to 50% of responders lose response over time (secondary non-responders)
- Frequently lower exposure in pediatrics than adults
  - Higher failure rate in pediatrics





I Ordás, DR Mould, BG Feagan, WJ Sandborn Clin. Pharmacol. Ther. 91(4):635-46 2012
Z Xu, DR Mould, C Hu, et al "A Population-Based Pharmacokinetic Pooled Analysis of Infliximab in Pediatrics" ACCP National Meeting 2012 San Diego CA.

ROUTES OF CLEARANCE FOR MABS

Antibody salvage	• FcRn protects IgG
Metabolism	• Breakdown by proteolysis

Target binding	• Nearly irreversible binding to antigen
	• IgG TNF inhibitors bind FcγRs
	  • May partly regulate clearance through RES
	  • Elicits CDC or ADCC
	• Usually relates to clearance, not volume of distribution

Cellular uptake	• Phagocytosis • Pinocytosis (not receptor mediated)
ADAs	• Extent of "humanization" • Route of administration • Dose regimen and duration
Atypical clearance mechanisms	• Disorders of endogenous catabolic pathways • Excessive loss of Igs into urinary/gastrointestinal tracts (disease) • Increased intestinal clearance of IgG related to lesion severity reported

FcγR = Fcγ receptor; RES = reticular endothelial system; CDC = complement-dependent cytotoxicity; ADCC = antibody-dependent cell-mediated cytotoxicity.

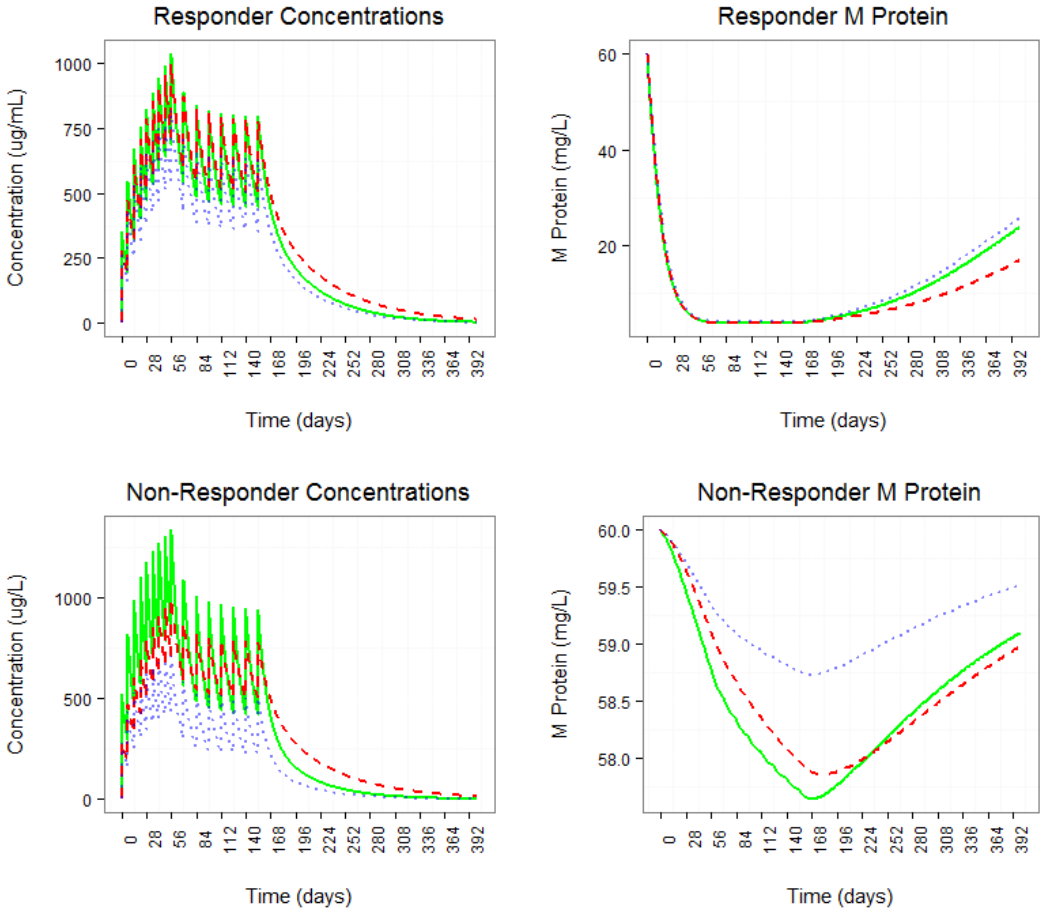
http://www.fda.gov/downloads/Drugs/.../Guidances/UCM192750.pdf. Accessed February 26, 2016. Kapel N, et al. *Eur J Clin Chem Clin Biochem.* 1992;30(4):197-202; Beeken WL, et al. *Gastroenterology*. 1972;62(2):207-215.

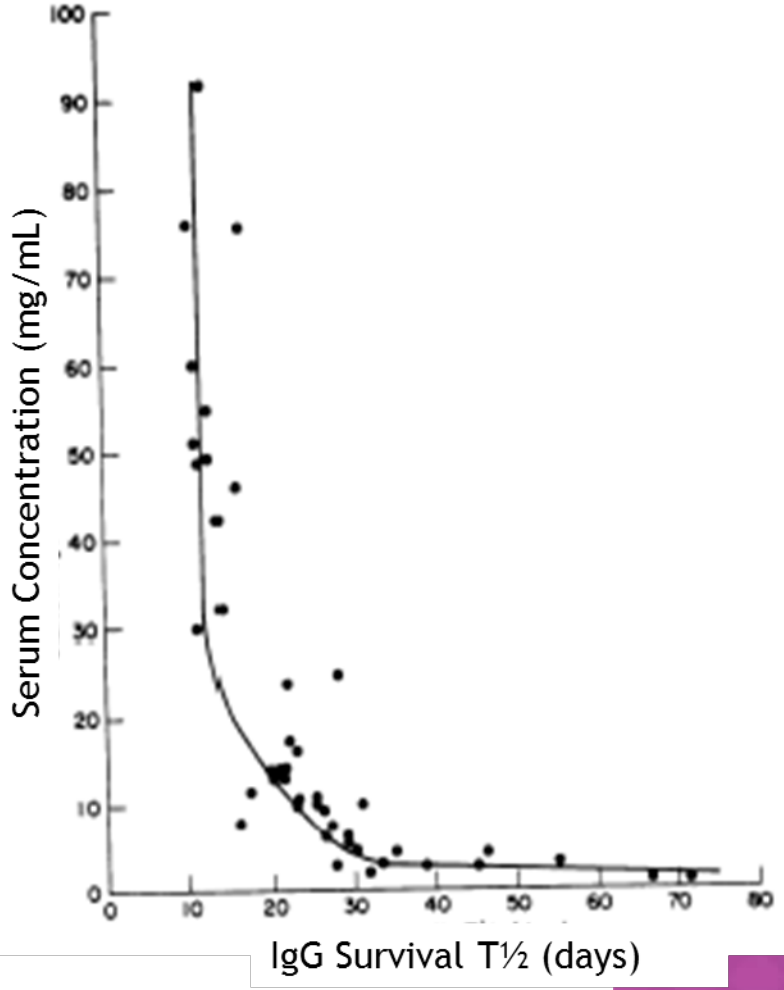
COMPARING PK OF SMALL MOLECULES TO MABS

Chemical Entities	Therapeutic Biologics
PK usually independent of PD	PK often dependent on PD
Usually linear PK (half-life independent of dose)	Often non-linear PK (half-life dependent on dose)
Metabolic breakdown	Proteolytic breakdown
Renal clearance often important	Renal clearance uncommon if molecular weight higher than 20 kD
Free concentrations useful ("coverage")	Free concentrations MAY cause problems (immunogenicity)
Binding implies distribution	Binding implies clearance
Tissue penetration often good	Usually poor tissue penetration

Mould DR. Using Pharmacometrics in the Development of Biological Therapeutic Biological Agents. In: ***Pharmacometrics: The Science of Quantitative Pharmacology.***

DARATUMUMAB – FCRN SATURATION POTENTIAL

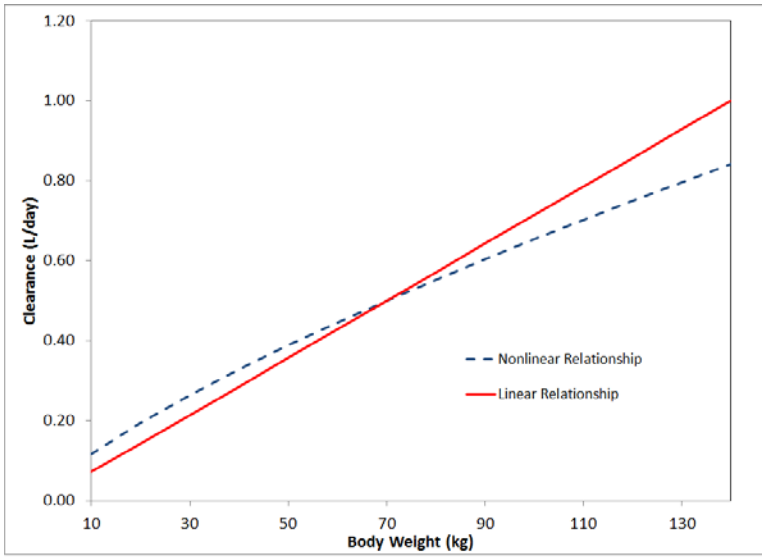


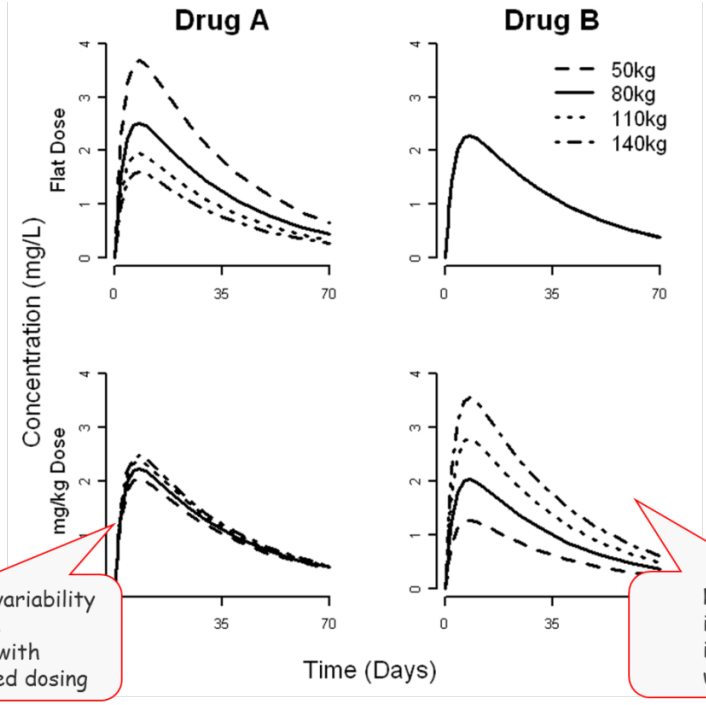


Jacobs FMJ, Mould DR. Clin. Pharmacol. Ther. 2017;102(6):903-904. *Immunoglobulins: Biological Aspects and Clinical Uses*. Washington, DC: National Academy of Sciences; 1970.

PROTEOLYTIC BREAKDOWN

- Often a prevalent route of clearance for mAbs
- Usually weight dependent
  - Greater weight → faster clearance (shorter half-life)
  - Non-linear
- Weight-based dosing does not fix things!





Mould DR, et al. *BioDrugs*. 2010;24(1):23-39.

OBESITY AS A SPECIAL CONSIDERATION FOR TNF INHIBITORS

Obesity

- Similar to a low-grade systemic inflammation
- Involves other cell types (outside of adipocytes) residing in adipose tissue

Adipose tissue

- Endocrine organ that synthesizes peptide and nonpeptide compounds
- TNF, IL-6 (30% from adipose tissue) and CRP related to body mass index

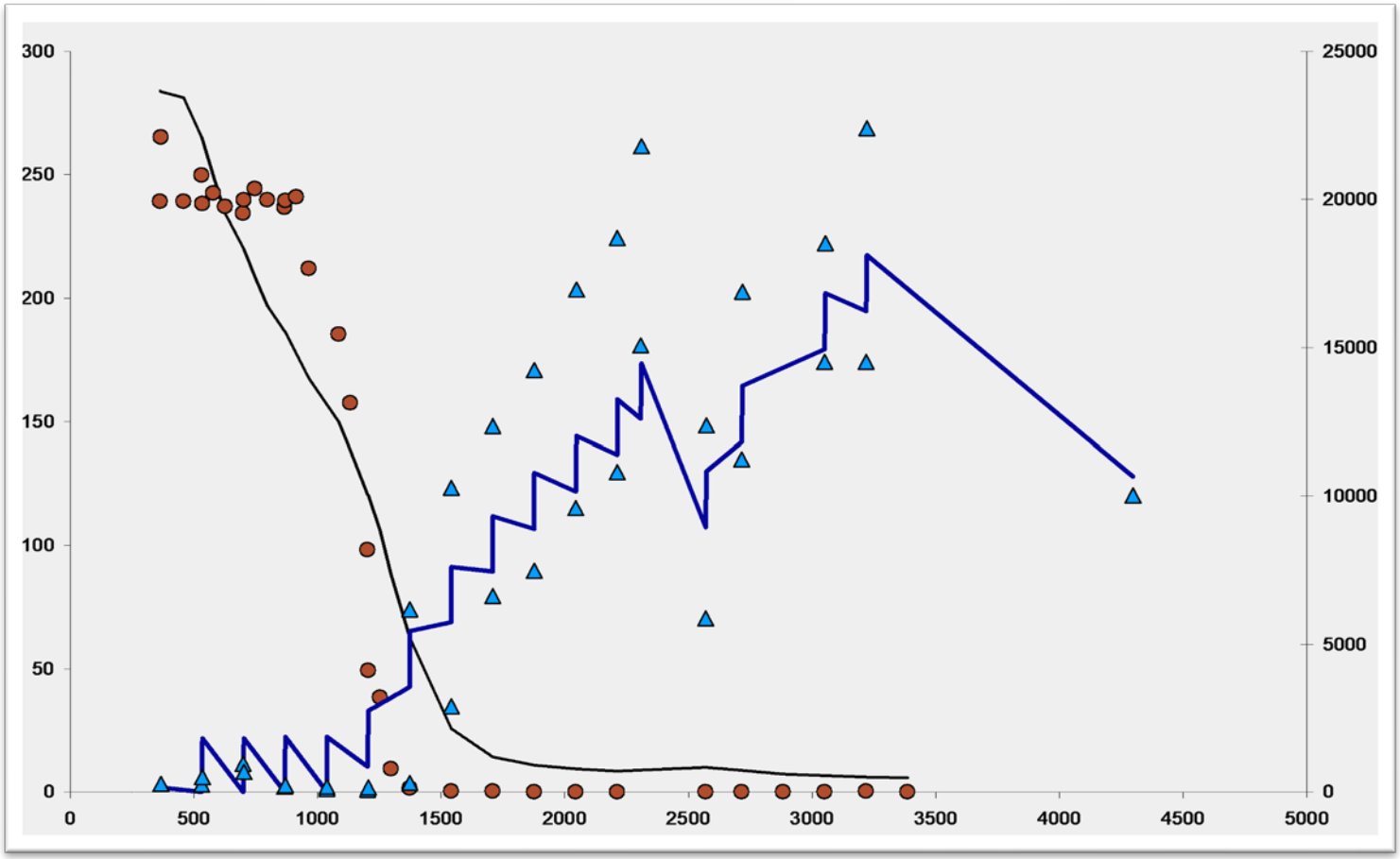
May predict need for dose escalation or shorter intervals

- High circulating TNF means higher antigen burden
  - Bioavailability of mAbs compromised with SC administration
- Increased inflammatory cytokines in patients who are obese may lead to more ADA

IL = interleukin; sc = subcutaneous.

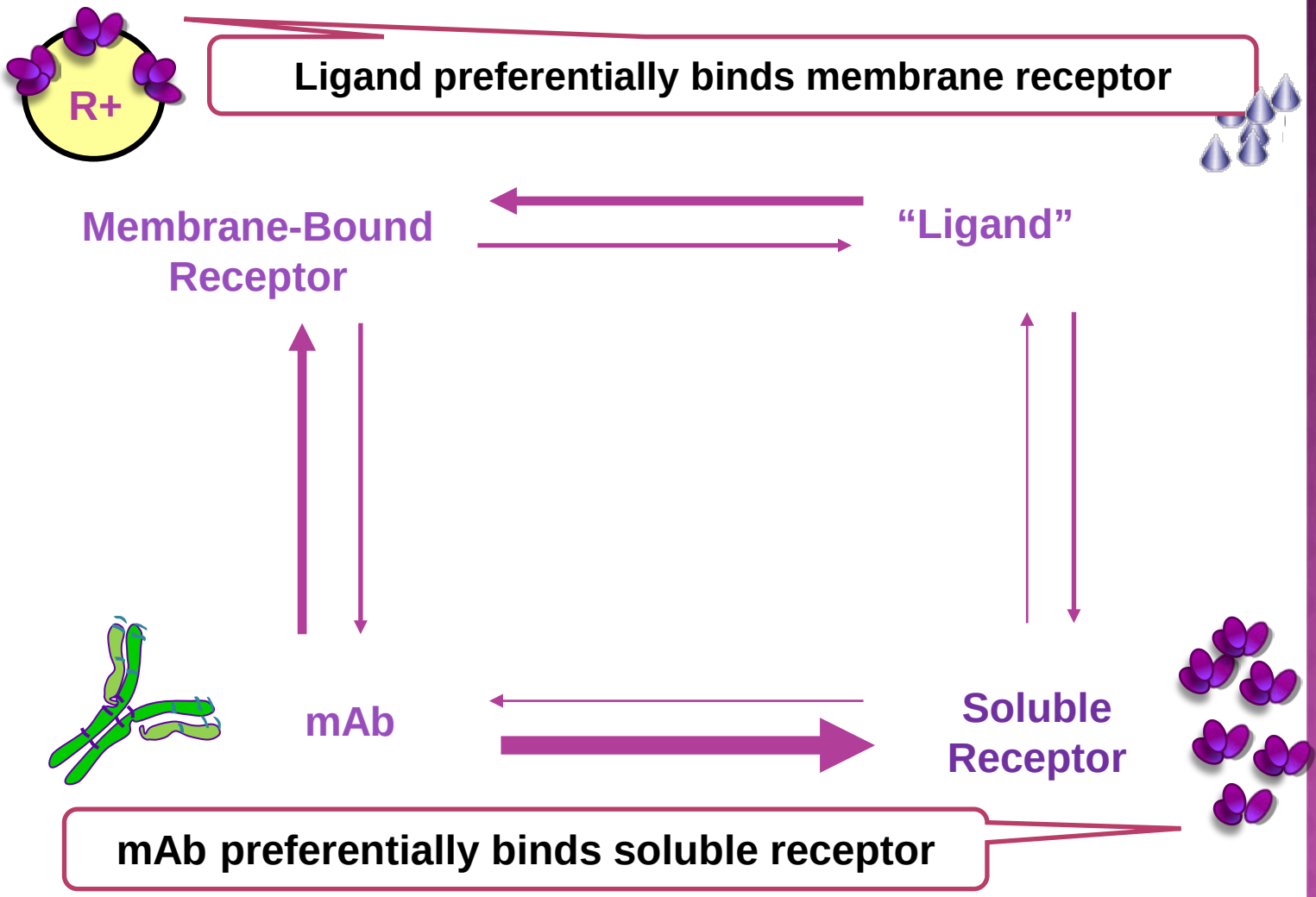
Gremese E, et al. *Arthritis Care Res (Hoboken)*. 2013;65(1):94-100.

RECEPTOR-MEDIATED CLEARANCE



Mould DR, et al. *Br J Clin Pharmacol*. 2007;64(3):278-291.

COMPETITIVE BINDING



Mould DR. Using Pharmacometrics in the Development of Biological Therapeutic Biological Agents. In: *Pharmacometrics: The Science of Quantitative Pharmacology .*

IMPACT OF DISEASE ON IFX CLEARANCE

Population	Mean IFX Clearance (L/d)	Reference
RA	0.264	Kavanaugh A, et al. *J Rheumatol*. 2000;27(4):841-850.
AS	0.273	Xu Z, et al. *J Clin Pharmacol*. 2008;48(6):681-695.
UC	0.407	Fasanmade AA, et al. *Eur J Clin Pharmacol*. 2009;65(12):1211-1228.
CD	0.383	Fasanmade AA, et al. *Clin Ther*. 2011;33(7):946-964.

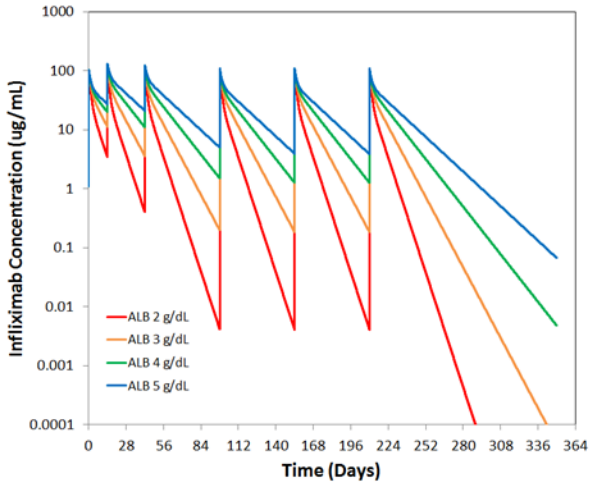
- Estimated IFX clearance in IBD is **40% to 50%** higher than other inflammatory diseases
- Is this caused by diseases or other factors?
  - Inter-study or assay variability, concomitant medications, etc

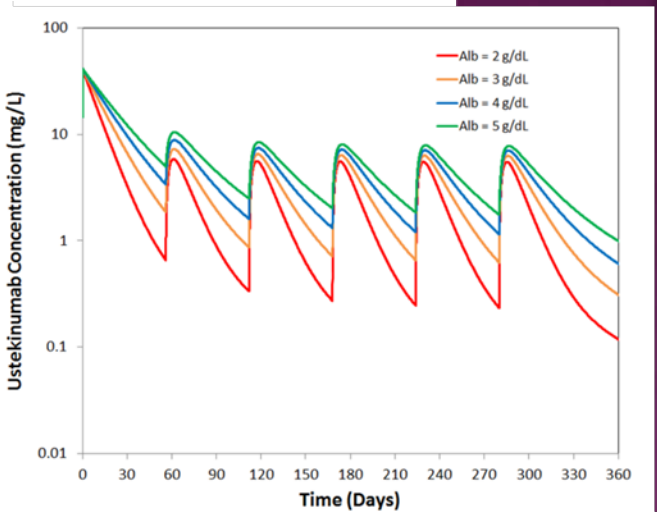
IFX = infliximab; RA = rheumatoid arthritis; AS = ankylosing spondylitis; UC = ulcerative colitis; CD = Crohn's disease; IBD = inflmmatory bowel disease.

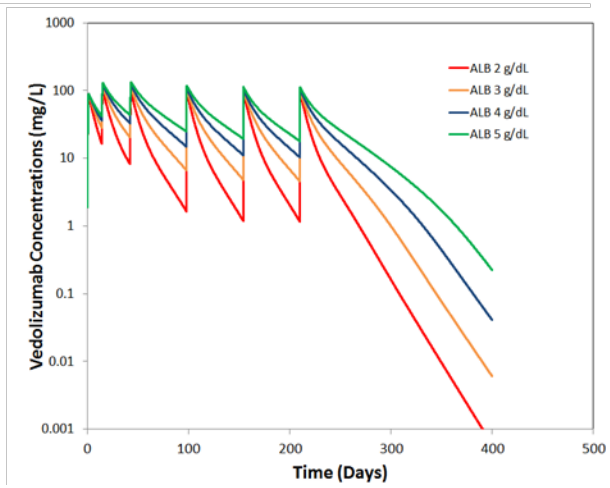
Kavanaugh A, et al. J Rheumatol. 2000;27(4):841-850. Xu Z, et al. J Clin Pharmacol. 2008;48(6):681-695. Fasanmade AA, et al. *Eur J Clin Pharmacol*. 2009;65(12):1211-1228. Fasanmade AA, et al. *Clin Ther*. 2011;33(7):946-964.

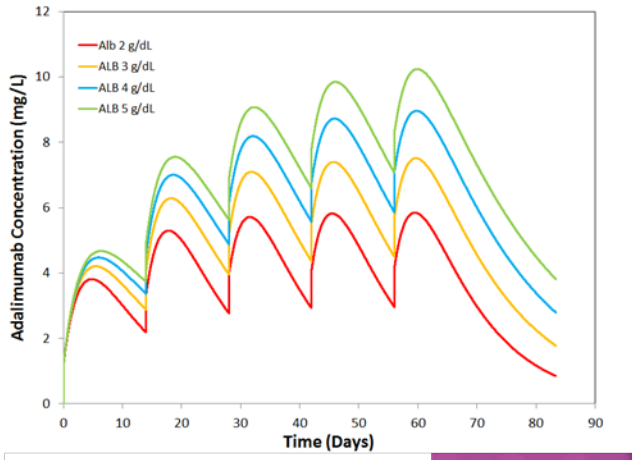
IMPACT OF ALBUMIN ON MAB CLEARANCE

- Albumin doesn't cause changes in MAb clearance but is predictive
  - Same recycling through FcRn etc
  - Low Albumin associated with worse disease









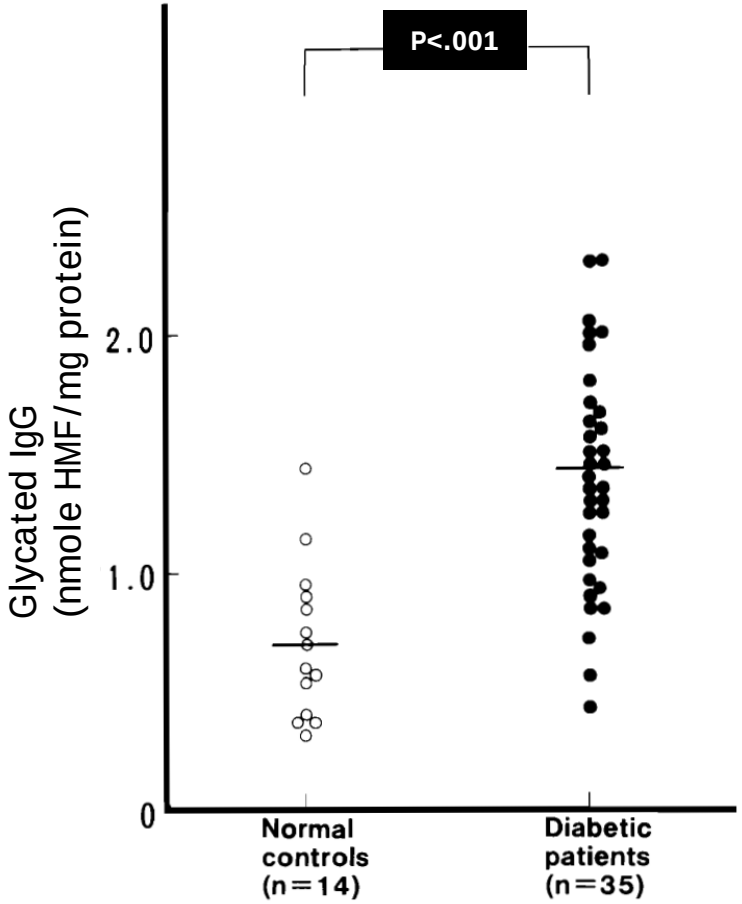
ATYPICAL CLEARANCE: FECAL LOSS OF IFX IN SEVERE IBD

- **In severe IBD, mAbs may be lost in feces through ulcerated and denuded mucosa (protein losing enteropathy), forming an alternate route of clearance and contributing to primary non-response**

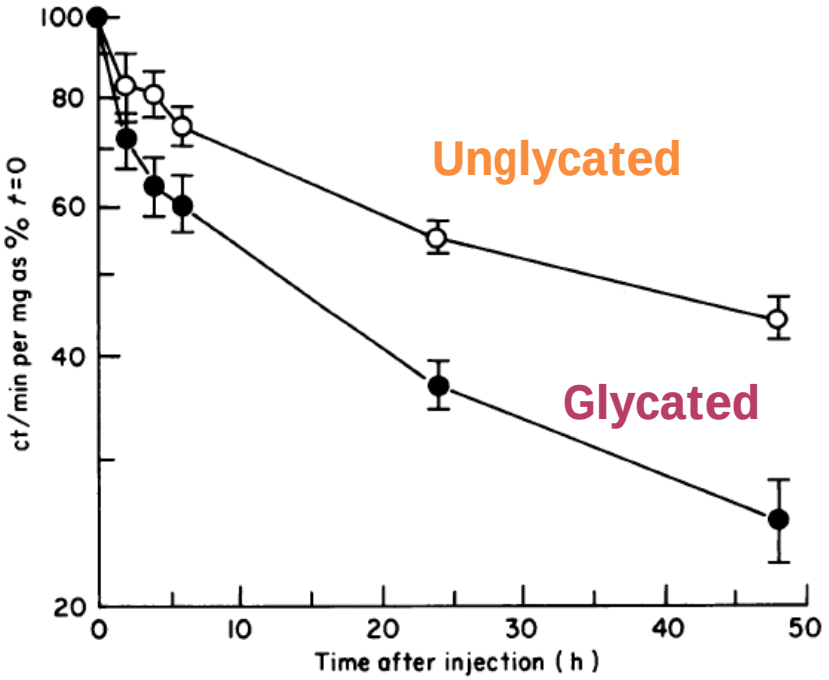
- Patients with IBD colitis starting on IFX 5 mg/kg
- 7 serial fecal samples in first 14 days after first infusion
- IFX can be detected in feces of patients with IBD with colonic disease
  - Peak in fecal IFX occurs in the first few days after infusion
- Non-responders to IFX induction have lower serum IFX concentration (day 14) compared with responders
  - These non-responders have significantly higher fecal IFX concentration on day 1 (*P*=.024)

Brandse JF, *et al. Gastroenterology* 2013;144(5):S7763.

INCREASED GLYCATION MAY ACCOUNT FOR ENHANCED CLEARANCE IN DIABETIC PATIENTS



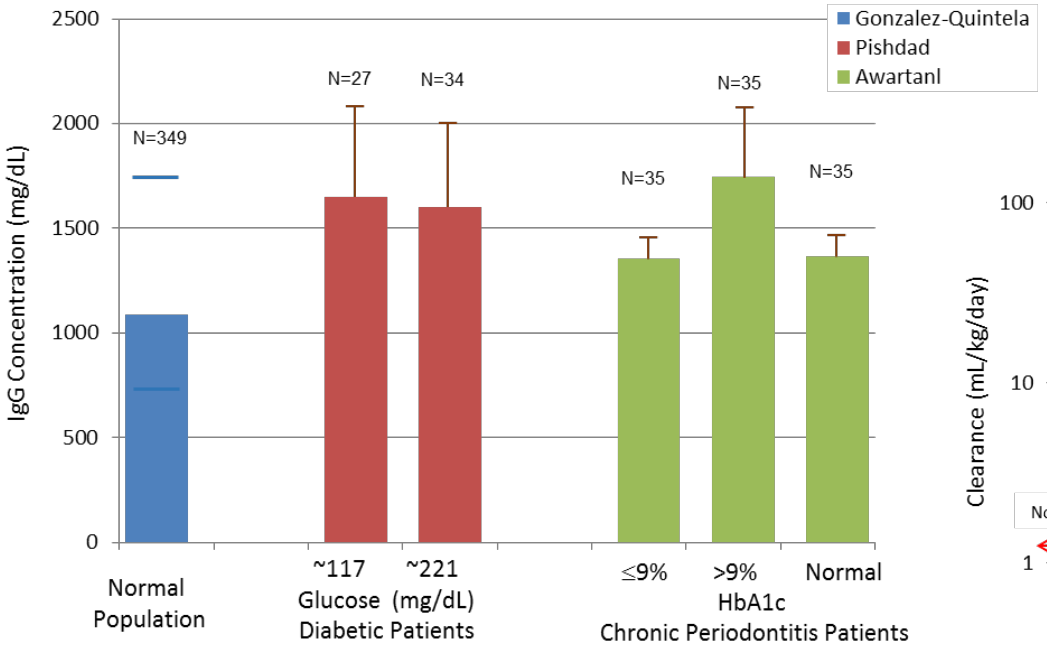
Glycated IgG levels in normal controls and patients with diabetes mellitus determined by colorimetric assay. *Horizontal lines* show mean values.

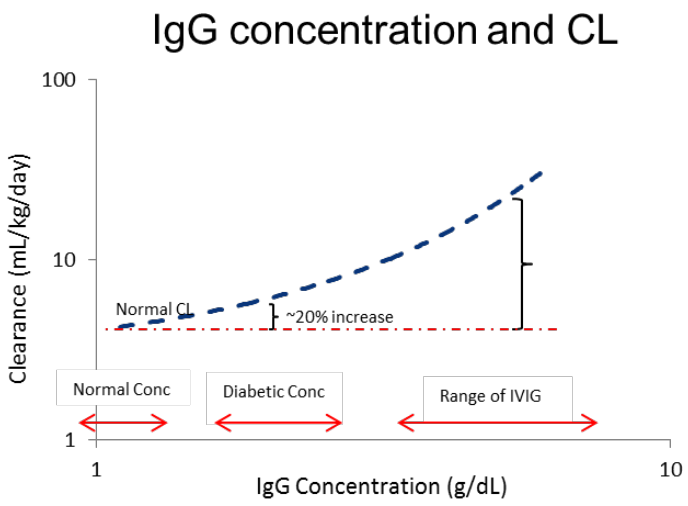


The amount of radioactivity per mg of whole blood over time, up to 48 hours after injection. The values are expressed as a percentage of the t=0 values for both glycated (•) and unglycated IgG (o). Points shown are obtained from the mean of six animals and bars show ±1 SEM.

Kaneshige H. *Diabetes*. 1987;36(7):822-828. Kennedy DM, et al. *Clin Exp Immunol*. 1993;94(3):447-451.

ANOTHER POSSIBLE FACTOR WITH DIABETES





A ~20% increase in CL would be expected for diabetics due to elevated circulating IgG concentrations, but note also periodontal disease!

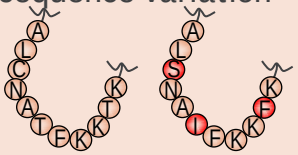
Gonzalez-Quintela, et al. *Clin Exp Immunol*. 2008;151(1):42-50. Pishdad GR, et al. *Med J Islam Repub Iran*. 1995;9(2):123-125. Awartani F, et al. *J Contemp Dent Pract*. 2010;11(2):33-40. Tam, et al. PEGS. 2014

FACTORS AFFECTING ADA

Structural properties

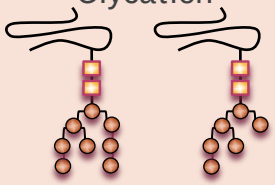
Sequence variation

Human



Bacterial

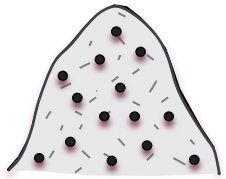
Glycation



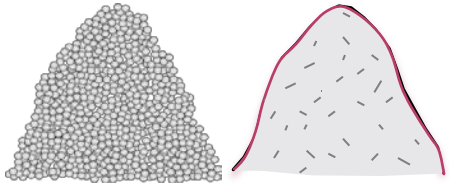
Immunogenicity

Other factors

Contaminants and impurities (from initial production or downstream processing)



Formulation

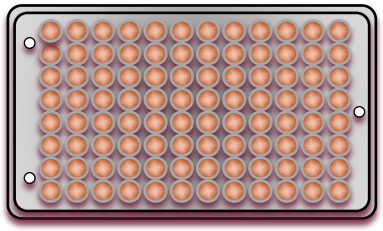


Route of application

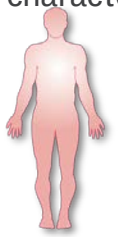
Dose

Episodic exposure

Assay technologies



Patient characteristics

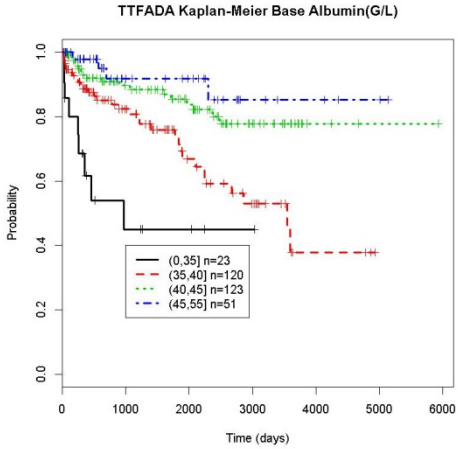


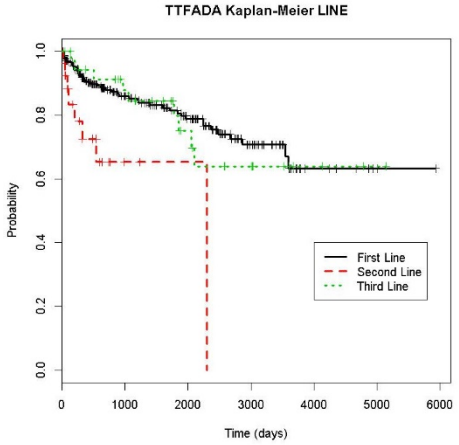
Unknown factors

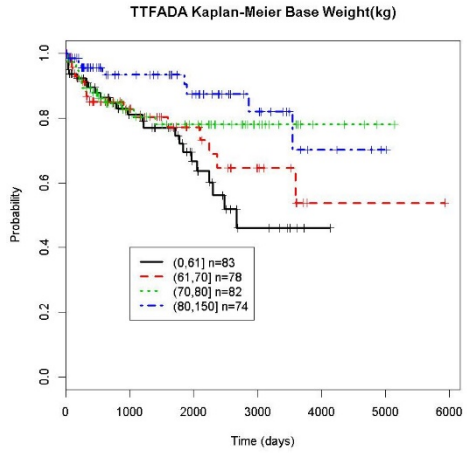
?

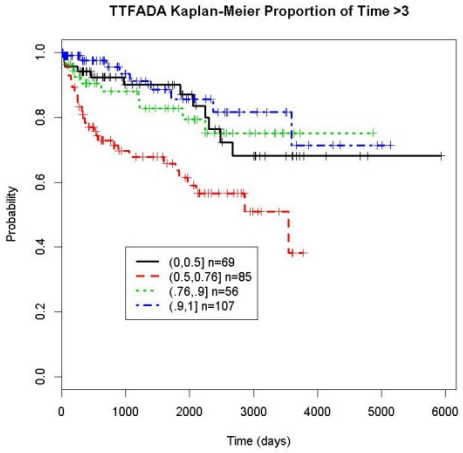
Brinks V, et al. *Pharm Res*. 2011;28(10):2379-2385. Schellekens H. *Nat Rev Drug Discov*. 2002;1(6):457-462. Brinks V, et al. *Pharm Res*. 2011;28(10):2379-2385. Ordás I, et al. *Clin Pharmacol Ther*. 2012;91(4):635-646. Vincent FB, et al. *Ann Rheum Dis*. 2013;72(2):165-178. van Schouwenburg PA, et al. *Nat Rev Rheumatol*. 2013;9(3):164-172.

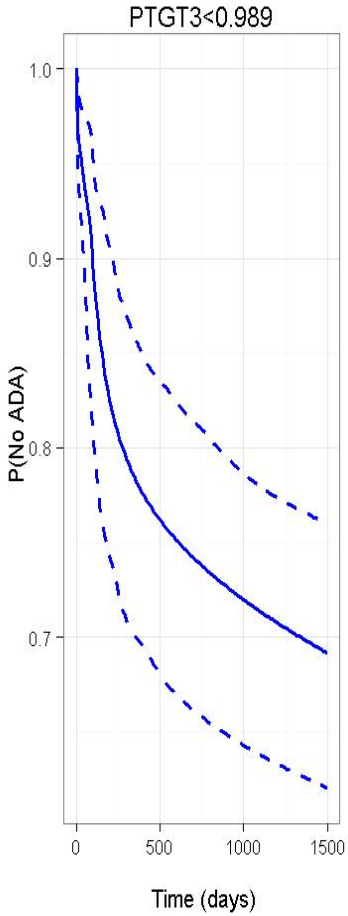
MAINTAINING MEASURABLE CONCENTRATIONS IS IMPORTANT

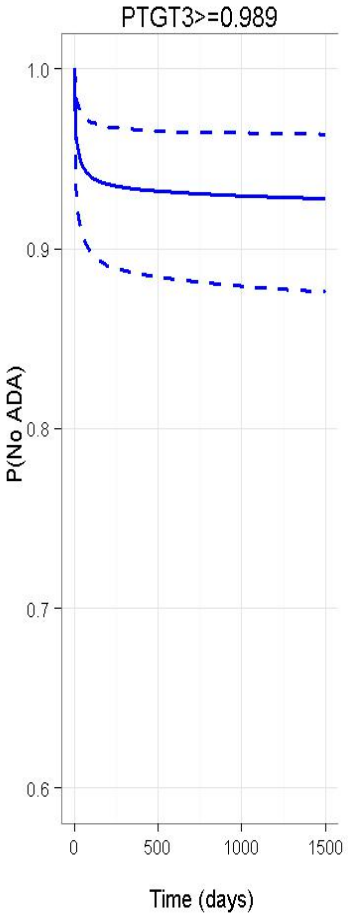






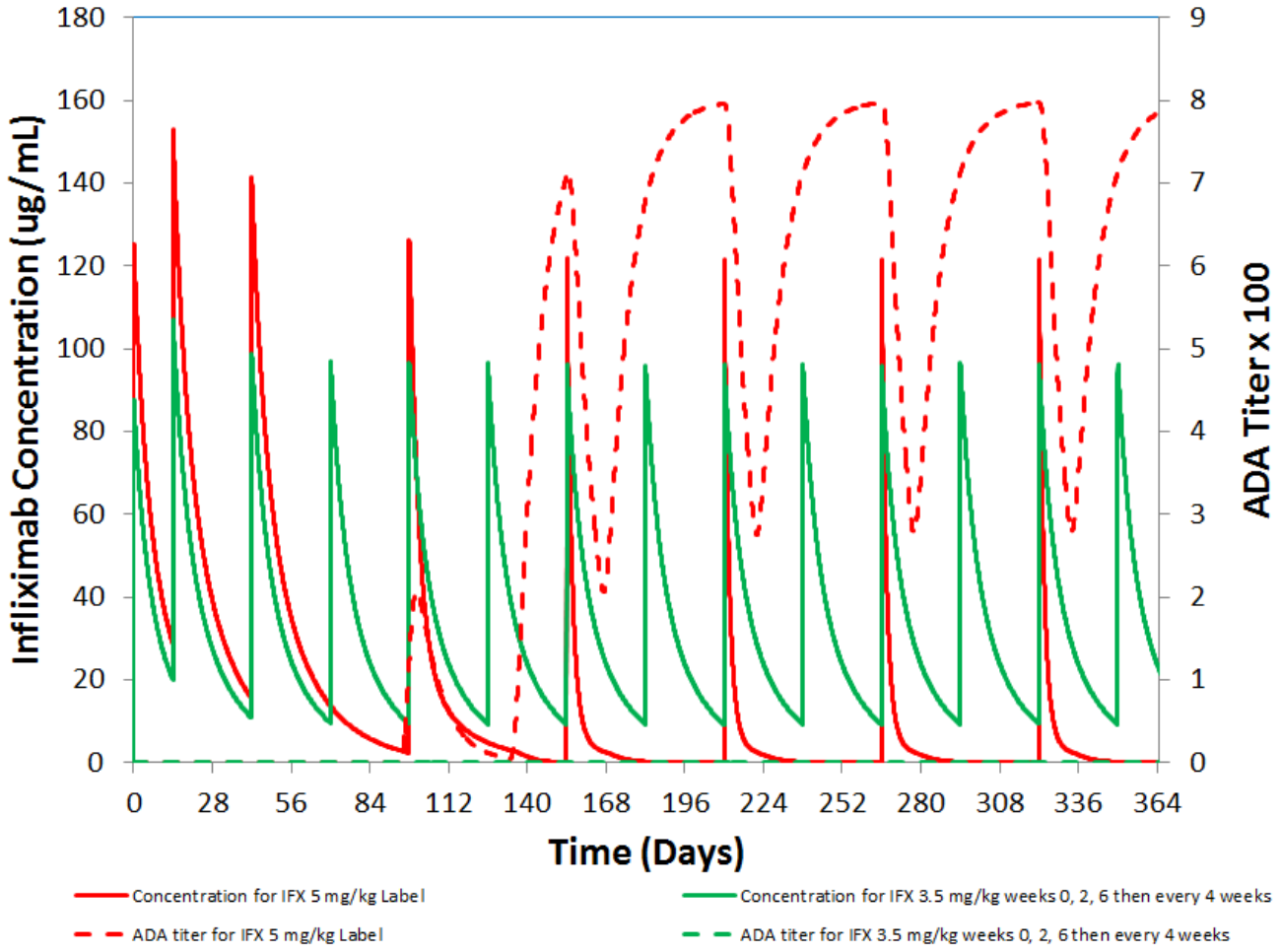




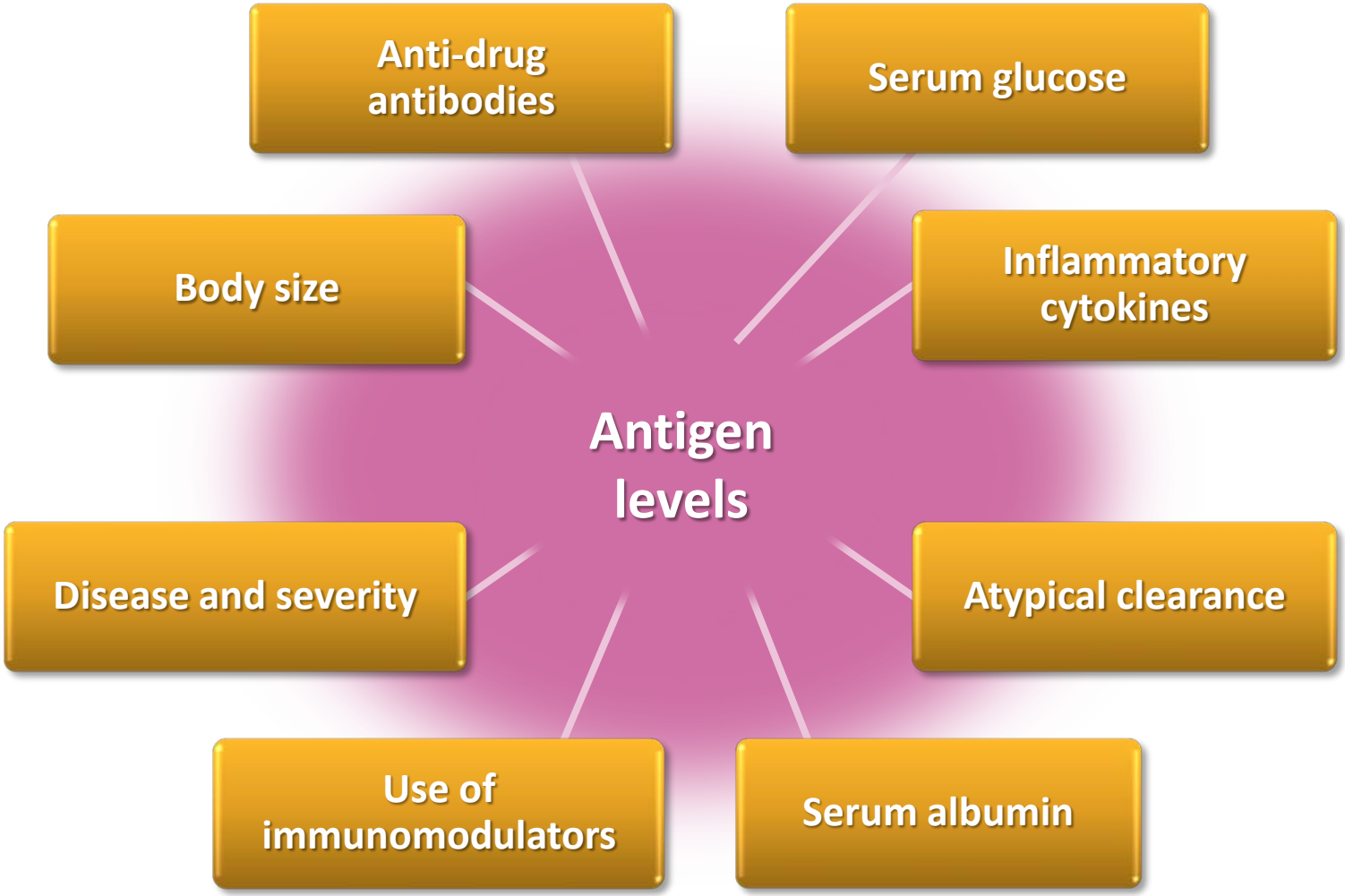


ECCO = European Crohn's and Colitis Organisation.
Brandse JF, et al. Presented at 11th Congress of ECCO; March 18, 2016; Amsterdam, The Netherlands. Abstract DOP068.

EARLY AND APPROPRIATE DOSE ADJUSTMENT MAY REVERSE ADA



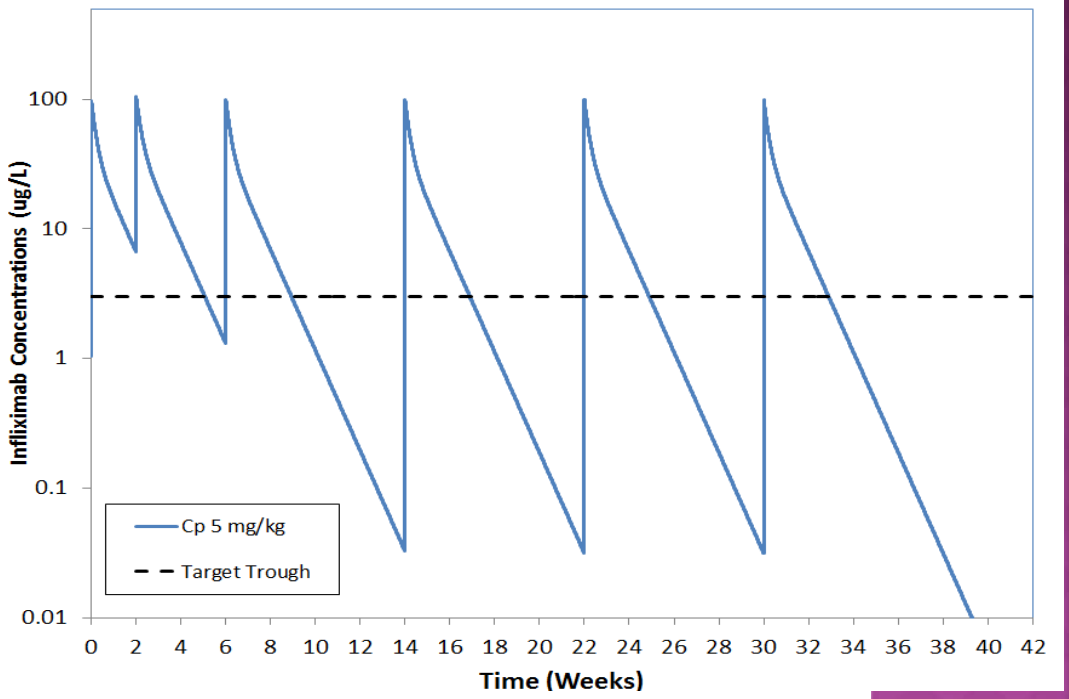
PATIENT FACTOR EFFECTS ON IFX PK



Deyhim T, Cheifetz AS, Papamichael K. Drug Clearance in Patients with Inflammatory Bowel Disease Treated with Biologics. J Clin Med. 2023;12(22):7132.

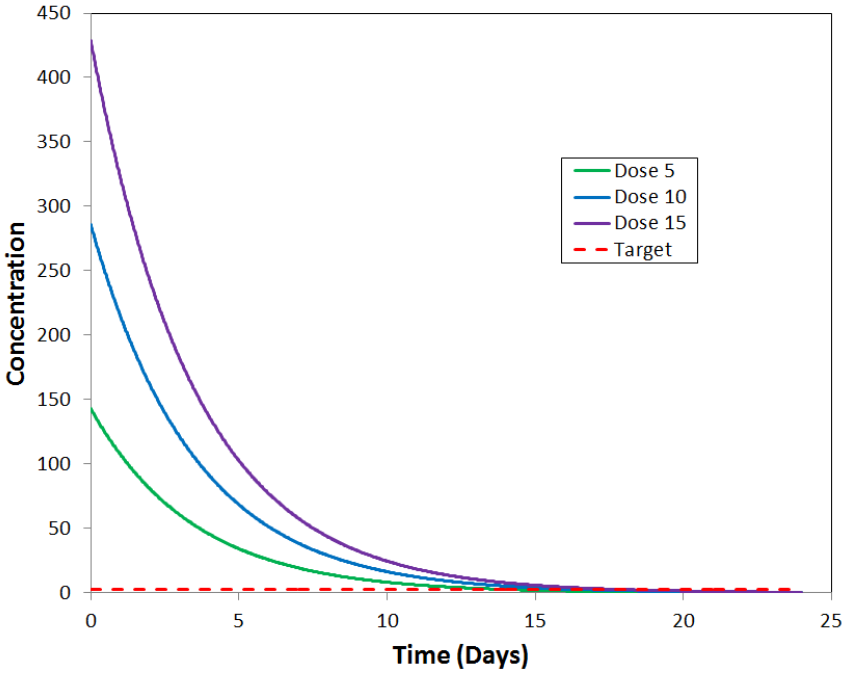
CLINICAL SCENARIO

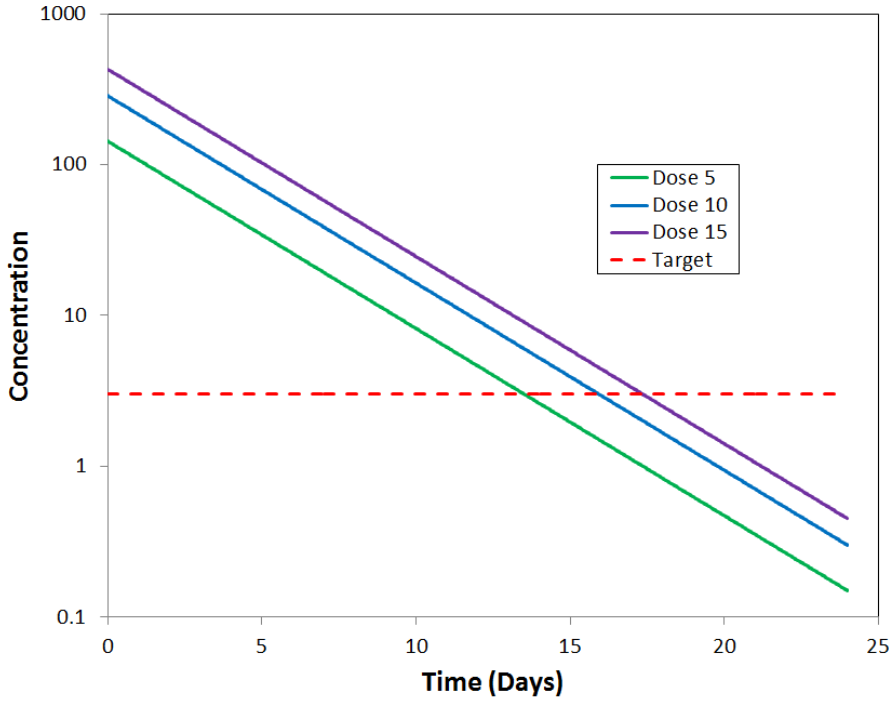
- Treating a patient with severe UC
  - Male, 25 years of age, weight 65 kg, albumin 2.5 g/dL, elevated CRP (100 mg/L)
- Administer infliximab 5 mg/kg at 0, 2, and 6 weeks
  - Initial symptom improvement; CRP appears to decrease initially (CRP 30 mg/L)
  - Then see a loss of response. Symptoms return, CRP begins to increase
- What happened?



UC = ulcerative colitis; CRP = C-reactive protein.

INCREASE DOSE OR SHORTEN INTERVAL?

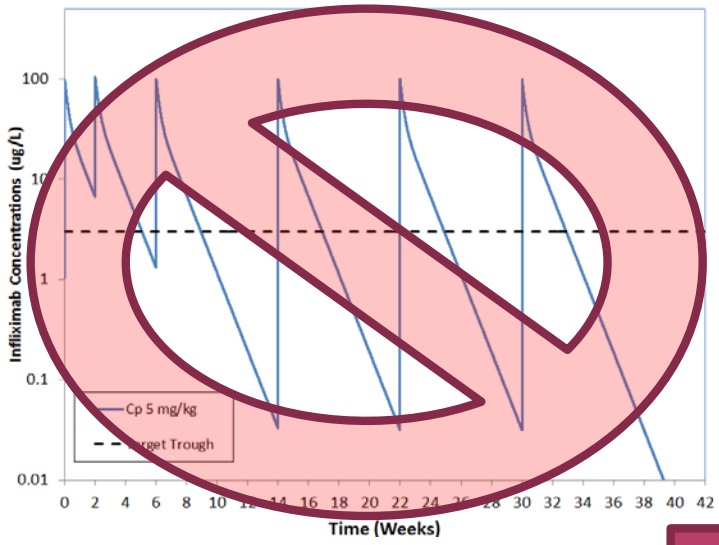


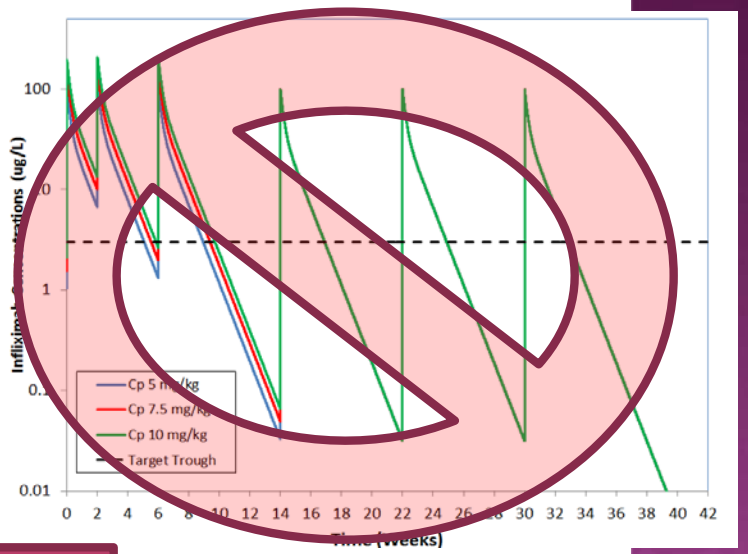


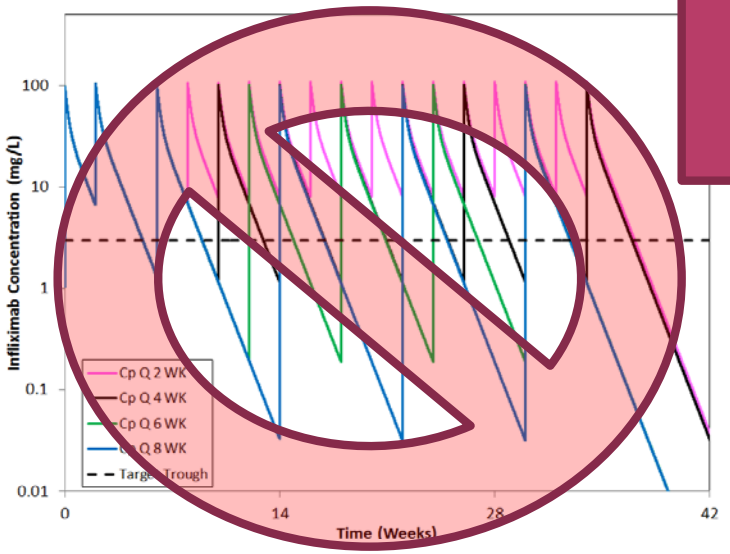
- Increasing the dose 3-fold yielded an increase in time (over the target of 1 week)
- Shortening interval is often a better option!

Note: Example generated for this presentation.

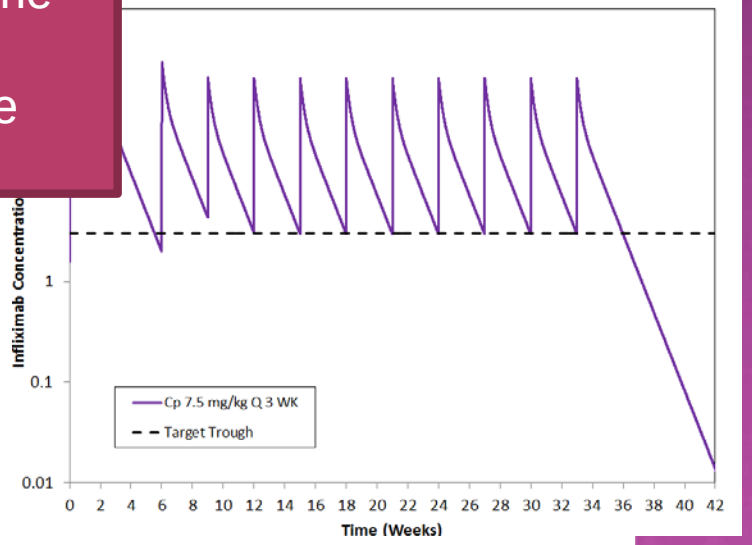
EXAMPLE SCENARIO - WHAT SHOULD WE DO?





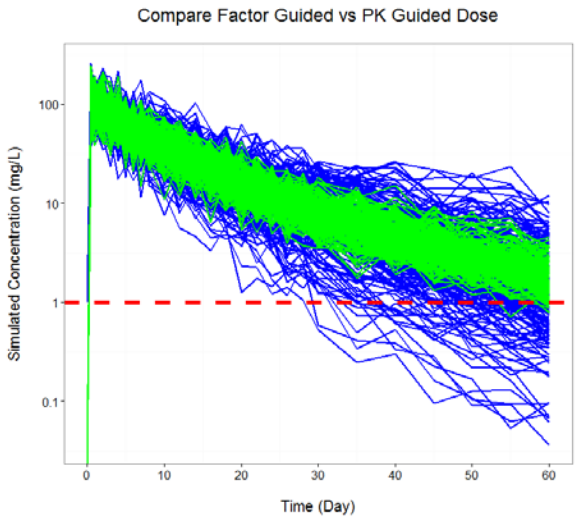


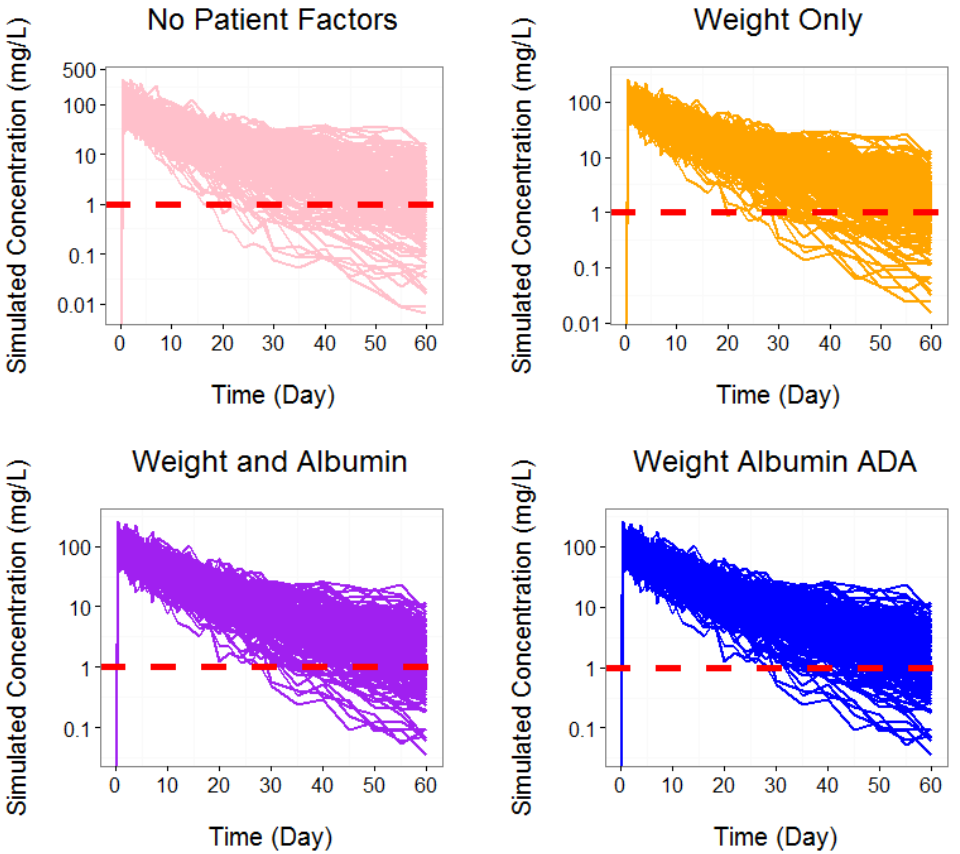
It's not just the dose;
it's the dose interval



STRATEGIES TO MAINTAIN EFFECTIVE EXPOSURE

- Consider shortening the dose interval for patients with low albumin
- Consider increasing dose for patients with low weight
- Therapeutic drug monitoring is useful, consider PK-guided dosing





- Blue is dosing based on weight albumin ADA
- Green is PK guided

Dotan I, et al. *Inflamm Bowel Dis*. 2014;20(12):2247-2259.

PATIENT FACTORS ACCOUNTED FOR WITH BAYESIAN DOSING VS DRUG LABEL

	Weight	Albumin	ADA	Glucose	CRP	Sex	IMM
Accounted for in Dashboards	✓	✓	✓	✓	✓	✓	✓
Accounted for in Labeled Dose regimen	?		?				?

? Not always included, no specific recommendations

- By accounting for all patient factors, patient exposure can be better controlled

WHAT IS A DASHBOARD?

- Helps manage information
  - In a car, provides information on speed, gas, oil pressure
  - Here, includes GPS + computer that can forecast lap speed, performance issues
- Similar to dashboards in clinical practice
  - Links to EMR to utilize “bedside data”
  - Makes use of population PK model as a prior (“big data”)
  - Tracks response to treatment, prognostic factors
  - Forecast exposure - helps determine appropriate doses

DASHBOARD PROCESS

ENTER PATIENT → **UPDATE INFORMATION** → **PREDICT TROUGH OUTCOMES** → **CHOOSE DOSE AND INTERVAL**

iDose Projections Research Dashboard Entries About Log Out
Logged in as Diane Mould

Dose dev Site

Help

Patient 956683036

When to Dose | Find a Dose | Refine the Dose | History

Find the dose for the next trough concentration

Dose interval mode

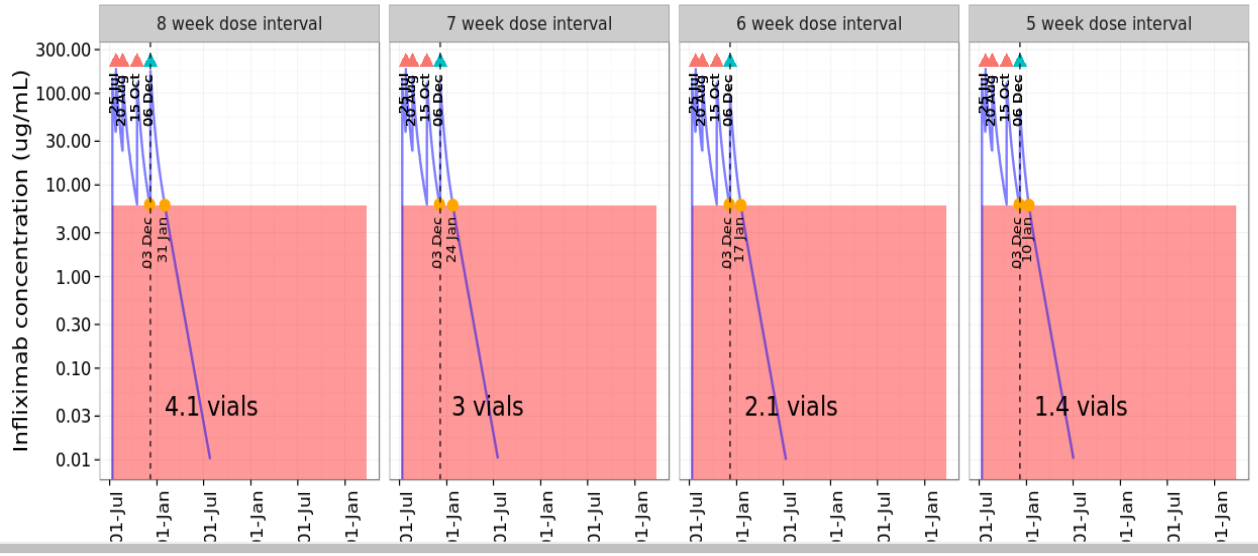
- Automatic
- Manual

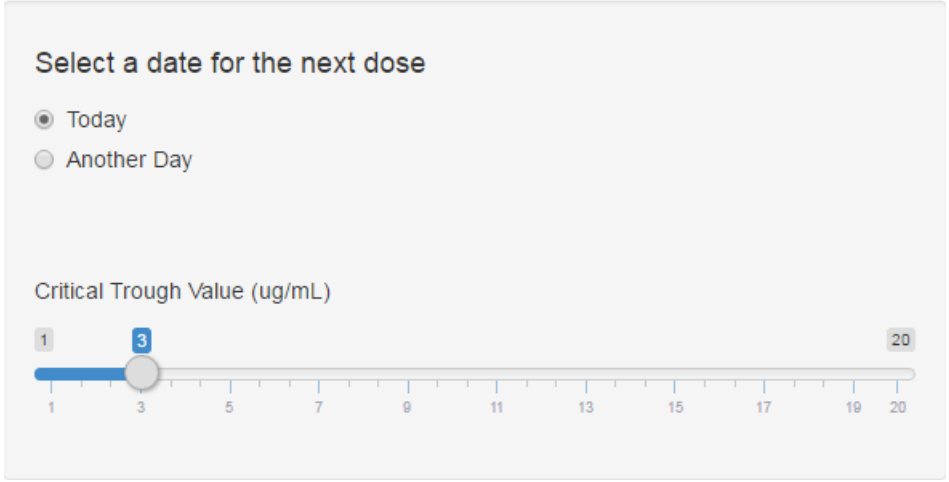
Plot options

Concentration

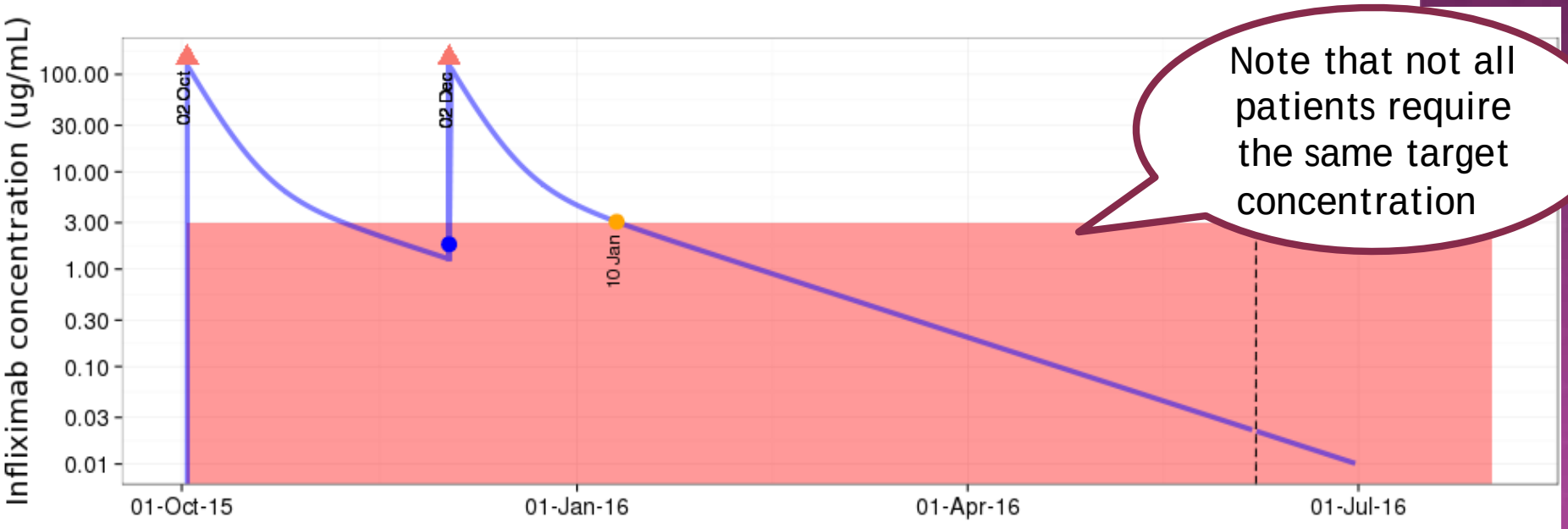
Save Doses

Plot | Table



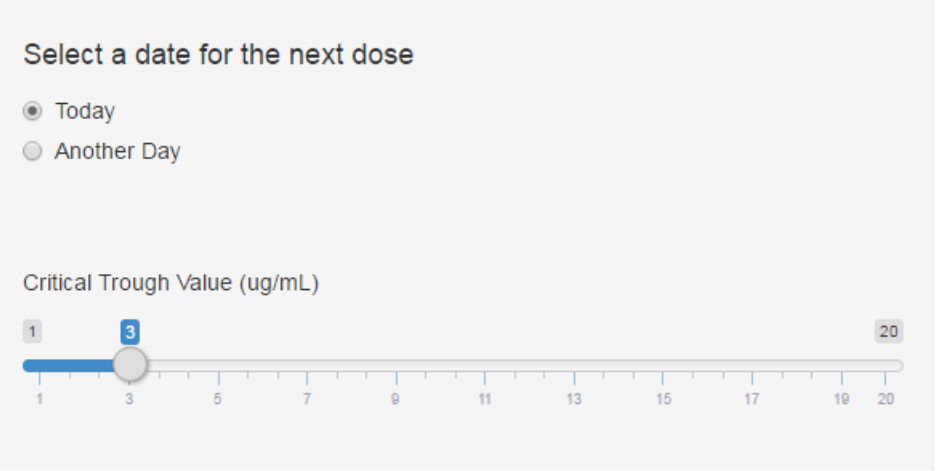


48 kg, 250 mg
5.2 mg/kg every 8 weeks
CRP = 150
Albumin = 3.2

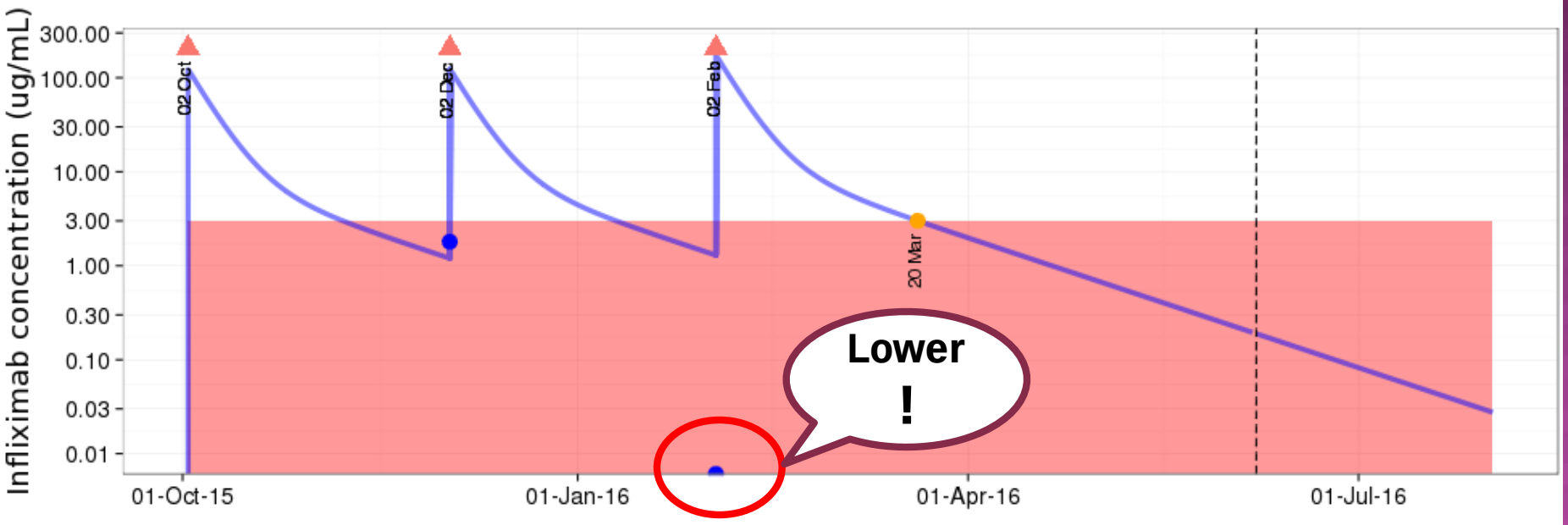


- Shorten interval or increase dose?
  - Increase dose → 350 mg

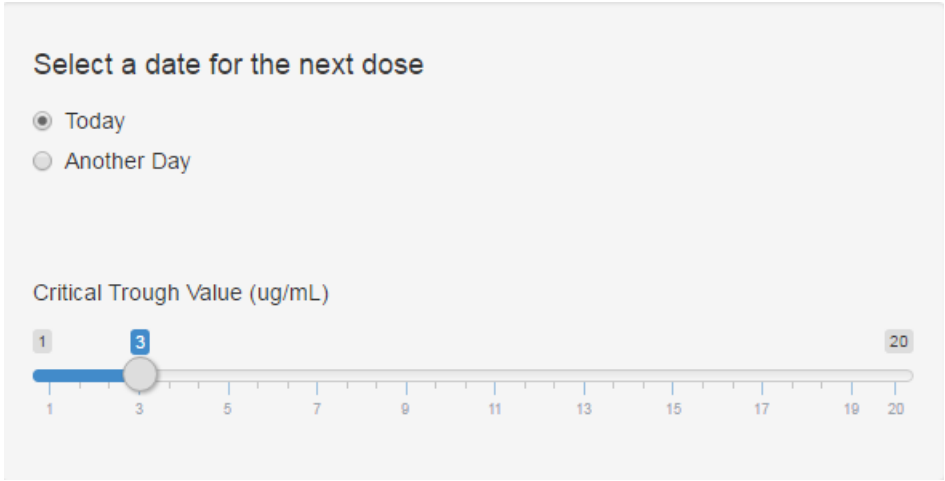
'Because I do not dare to give it every 4 weeks…'



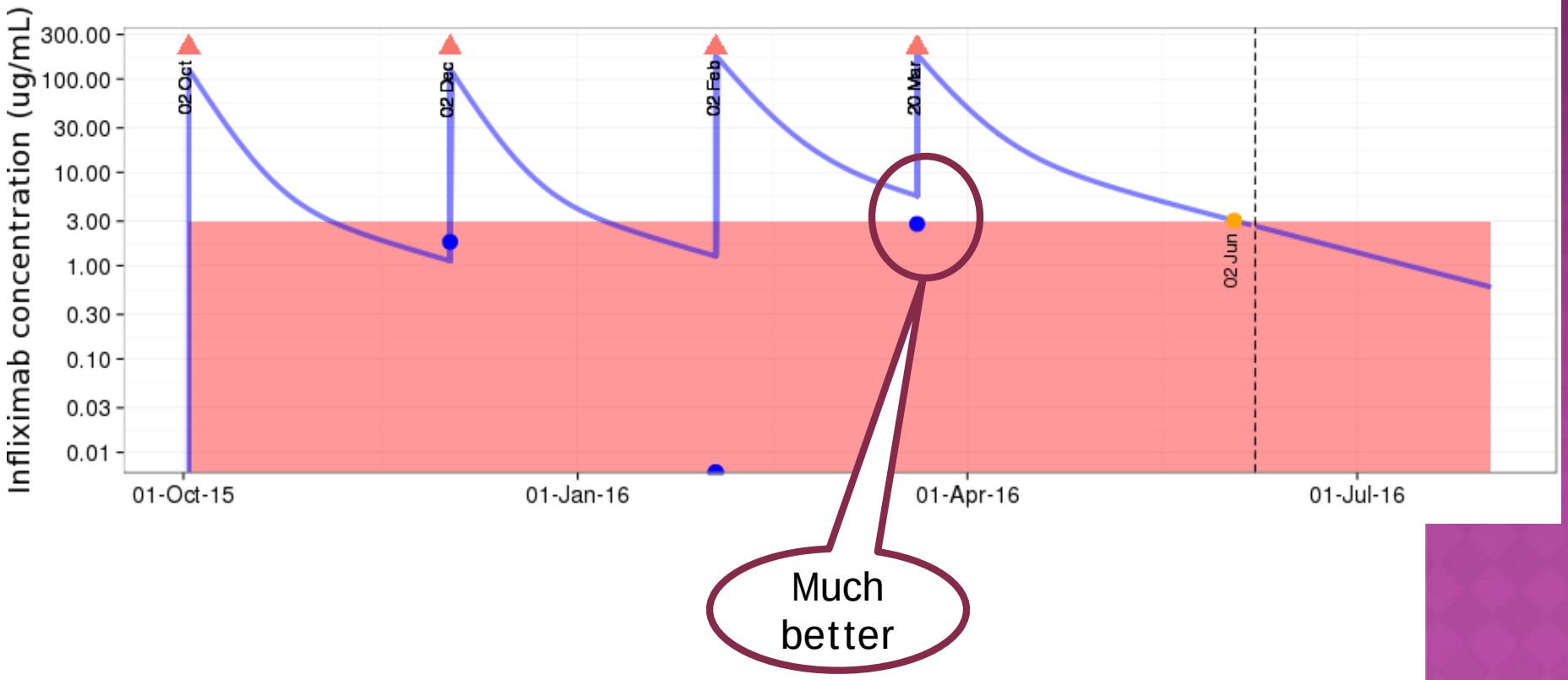
48 kg, 350 mg
7.3 mg/kg every 8 weeks
CRP = 150
Albumin = 3.2

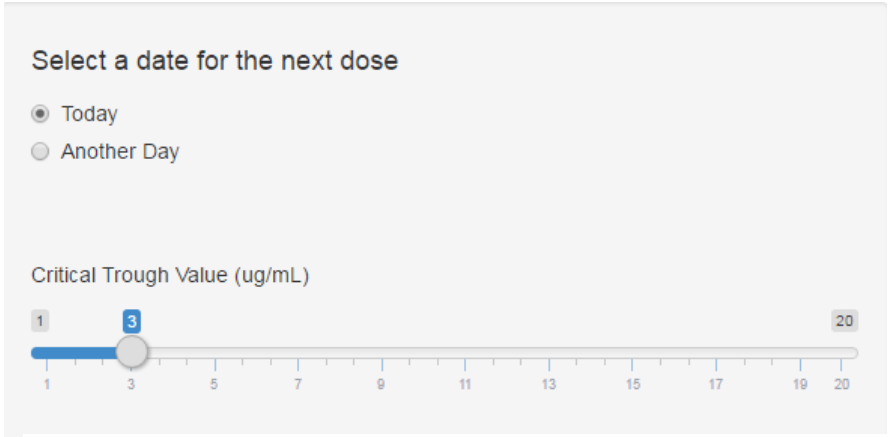


- Shorten interval or increase dose?
  - Shorten interval → 4 weeks

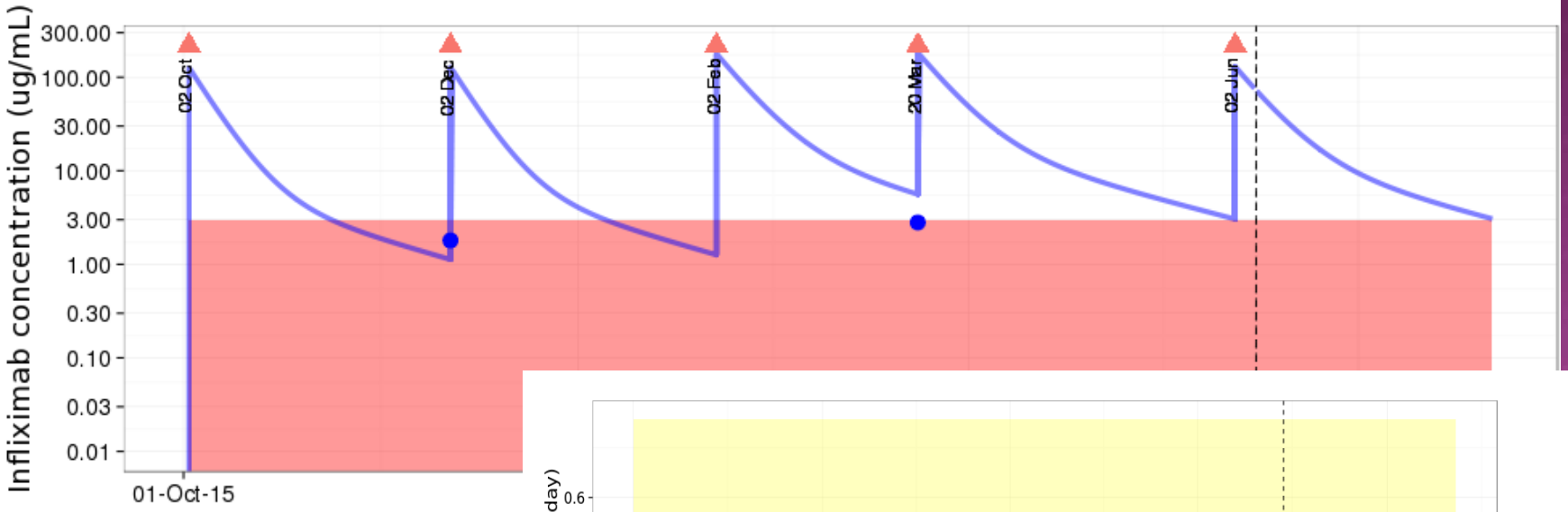


48 kg, 350 mg
7.3 mg/kg every 6 weeks
CRP = 40
Albumin = 3.5

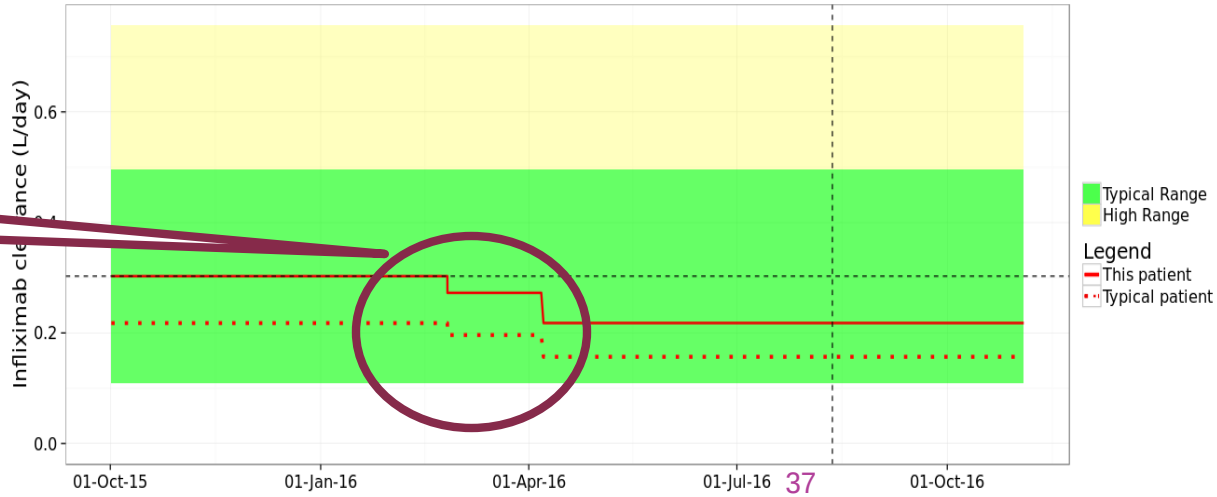




48 kg, 320 mg
5.2 mg/kg every 6 weeks
CRP = 5.0
Albumin = 3.8

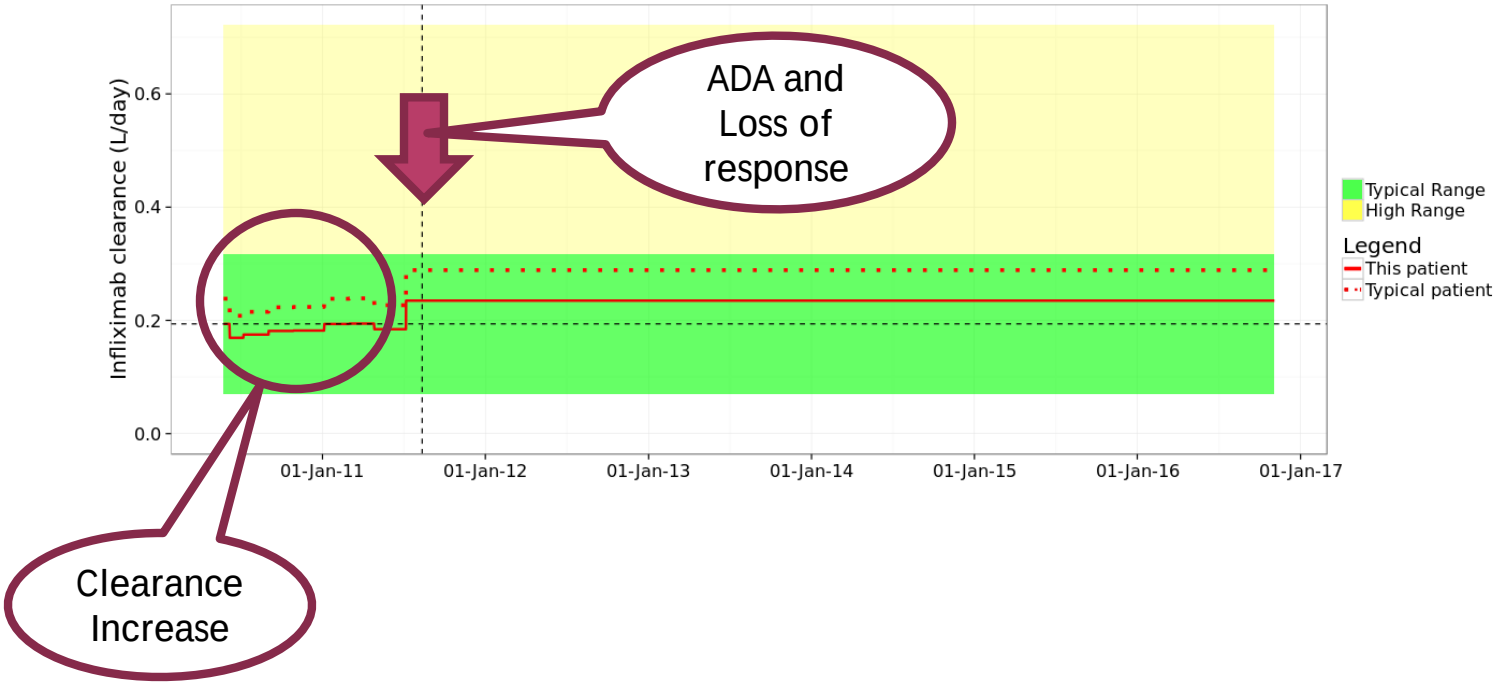


Clearance Slowing



USING BEDSIDE DATA TO SELECT BIOMARKERS

- What we are learning: MAb clearance is often a good indicator of impending flare and loss of response!

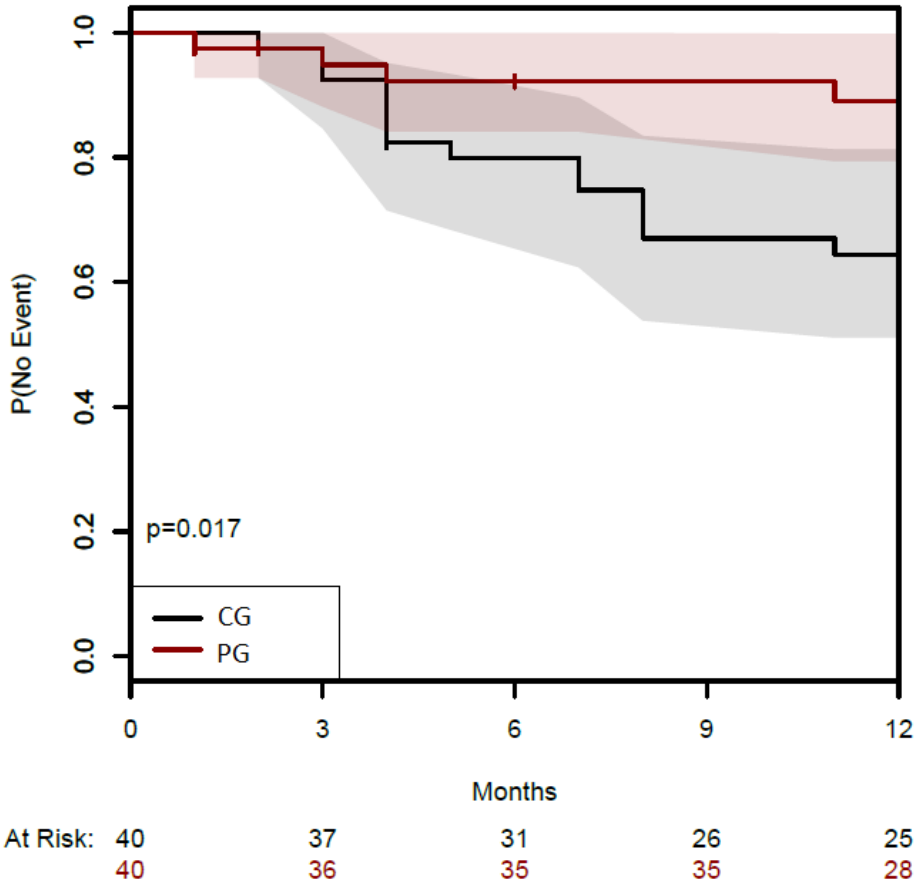


- An additional benefit of dashboards is that all relevant data on treatment and response brought together, resulting in better data for modeling or updating models

FIRST TEST OF DASHBOARD DOSING

- Conducted at Academic Medical Center Amsterdam
- Adult IBD patients in maintenance
- 40 patients on Clinician Guided (CG) dosing
- 40 patients on Precision Guided (PG) dosing

ACADEMIC MEDICAL CENTER RESULTS

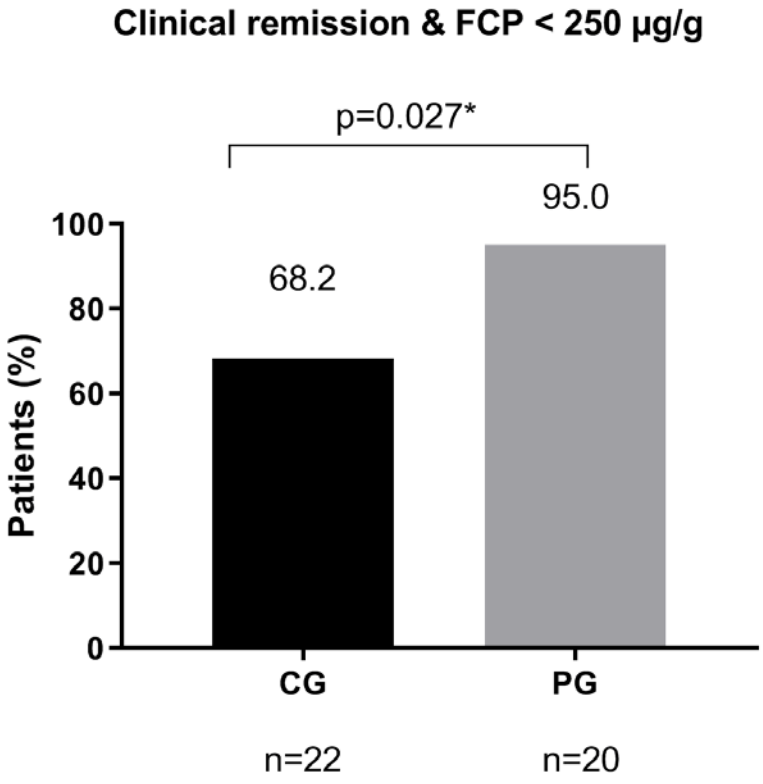


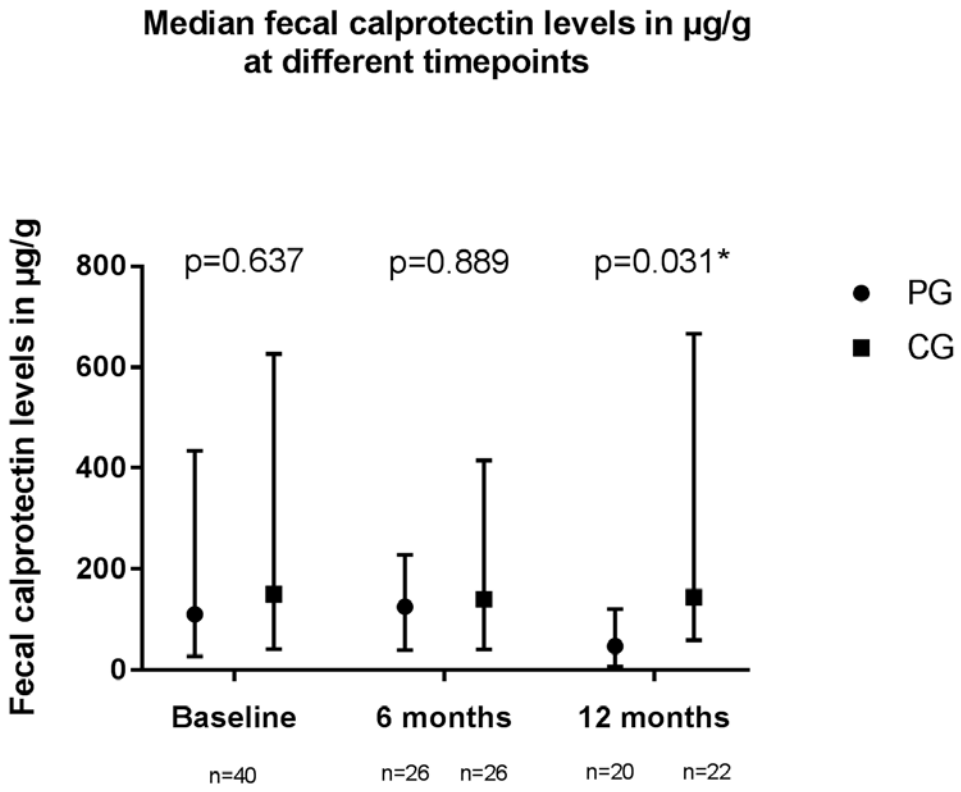
- **PG (12/40,30%):**
  - N=1 lost to follow-up
  - N=4 clinical LOR
  - N=4 stop IFX
  - N=3 opening old fistula tract

- **CG (15/40, 37.5%):**
  - N=1 lost to follow-up
  - N=14 clinical LOR

PG – precision guided CG – clinician guided

ACADEMIC MEDICAL CENTER RESULTS



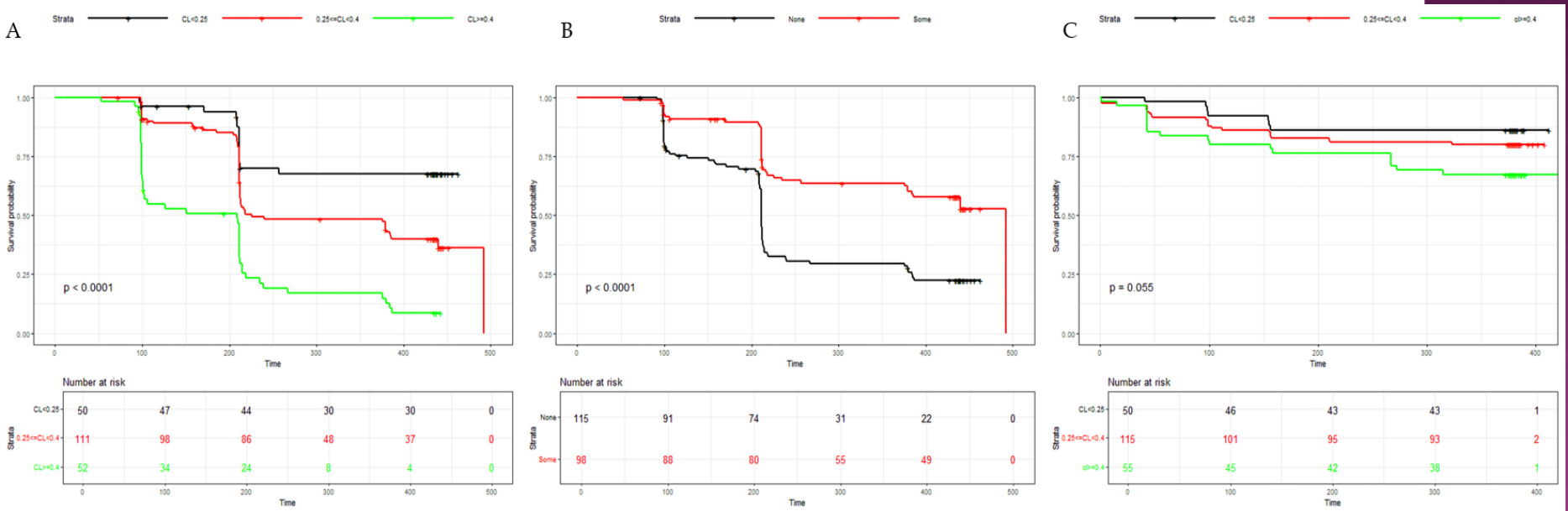


PG – precision guided CG – clinician guided

CELLTRION STUDY

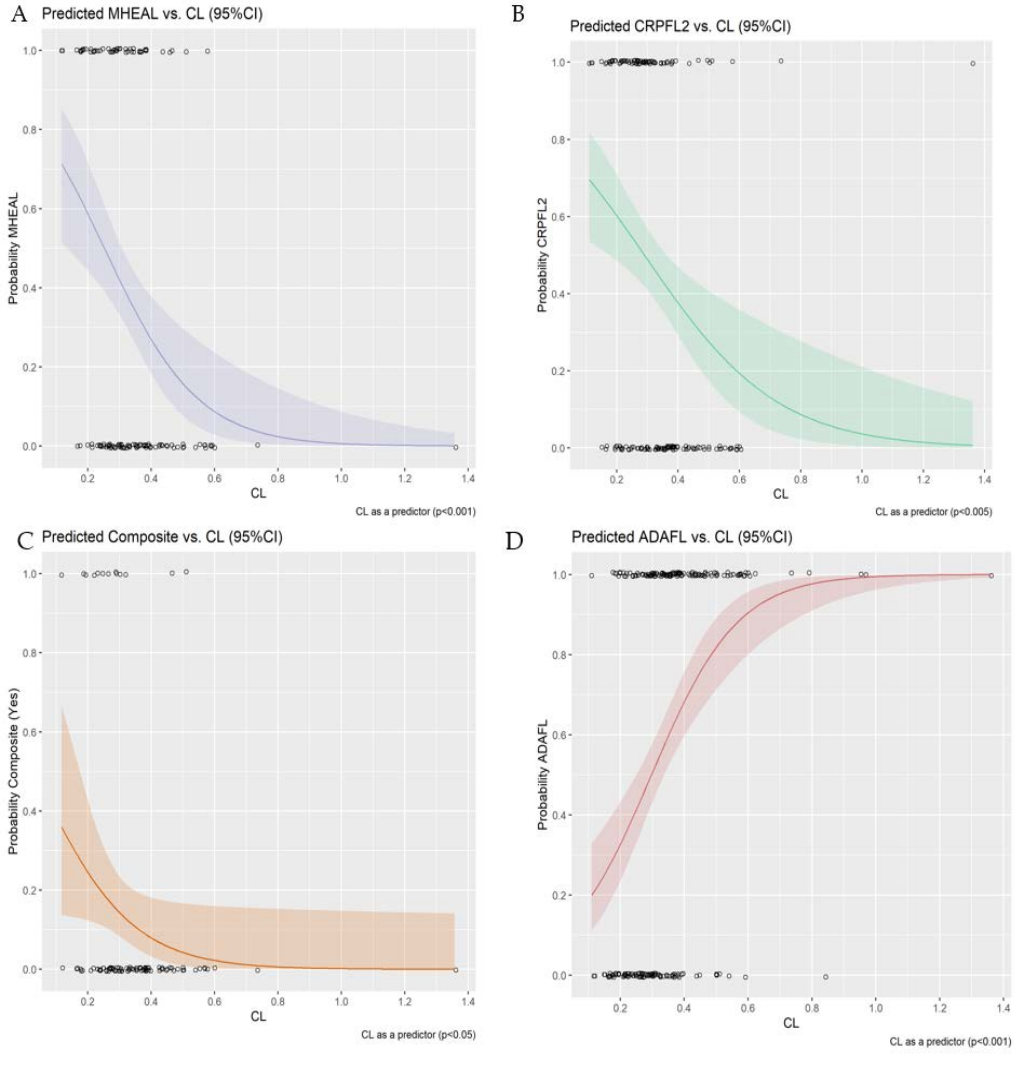
- Data from the CT-P13 3.4 randomized, phase 3 trial comparing biosimilar and originator IFX in patients with active CD (ClinicalTrials.gov No. NCT02096861), were obtained with permission from Celltrion, Inc. (Incheon, South Korea).
- Data were used to determine initial clearance and correlate with clinical outcomes

TIME TO FIRST INCIDENCE OF ADA



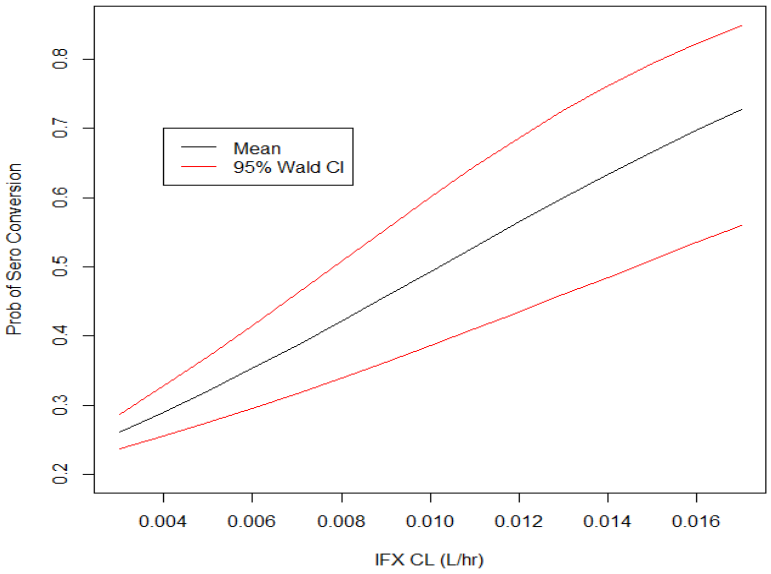
- Large study of IFX in Adult CD patients
- Patient age, sex, and disease duration not influential to early ADA
- Initial clearance and use of immunosuppressants are predictive of early ADA
- Fast initial clearance predicts early discontinuation of IFX

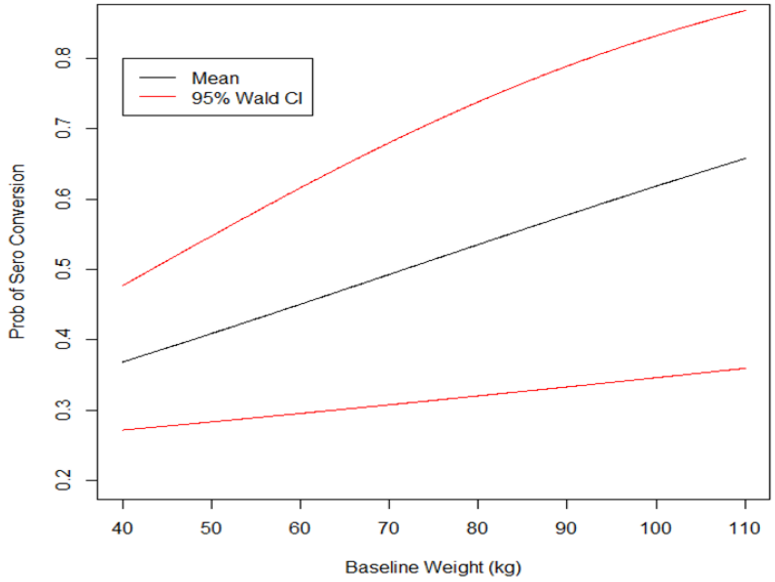
PROBABILITY OF RESPONSE AND ADA IN IBD PATIENTS



A: Mucosal healing; B: CRP normalization at 54 weeks; C: Composite endpoint; D: Development of ADA.
Solid line is median probability.
Shaded areas are 95% confidence intervals, open symbols are individual clearance values.
CI: Confidence interval; MHEAL: Mucosal healing; CL: Clearance; CRPFL2: CRP(less than 10 mg/L) at week 54; Composite: A composite endpoint for MHEAL, CRP normalization (less than 10 mg/L), CDAI and fecal calprotectin at week 54; ADAFL: Positive for ADA

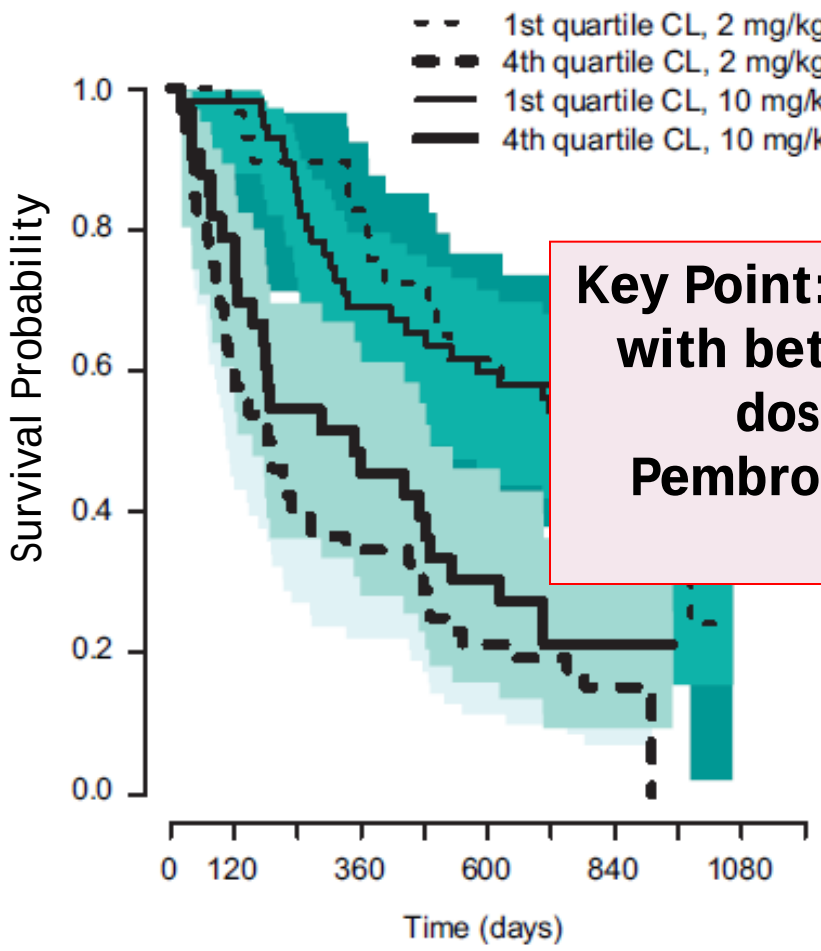
IMPACT OF IFX CLEARANCE AND WEIGHT ON ADA FORMATION IN RA PATIENTS



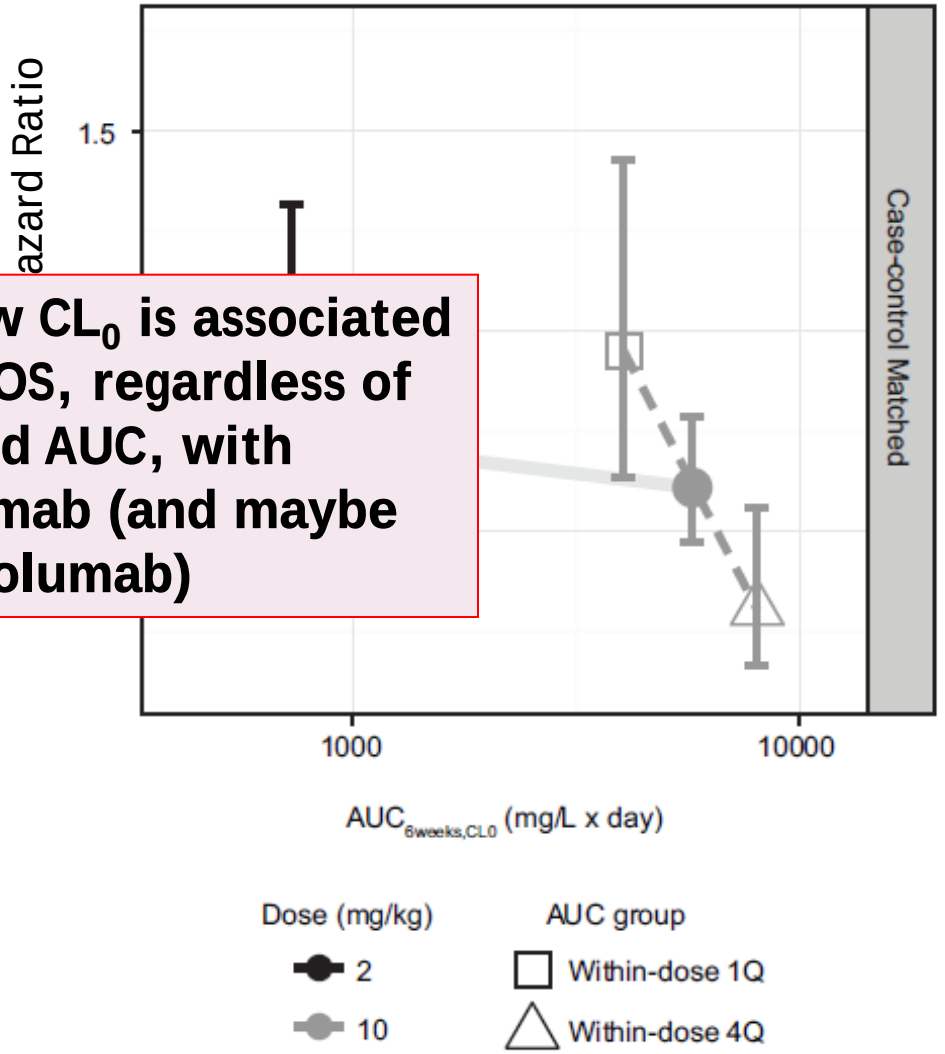


Factor	Odds Ratio	95% Wald based confidence intervals (CI)
0.1 L/day increase in CL	1.78	(1.50, 2.12)
10kg increases in WT	1.19	(1.06, 1.33)

NOT LIMITED TO MABS FOR INFLAMMATORY DISEASE



Key Point: Low CL_0 is associated with better OS, regardless of dose and AUC, with Pembrolizumab (and maybe Nivolumab)

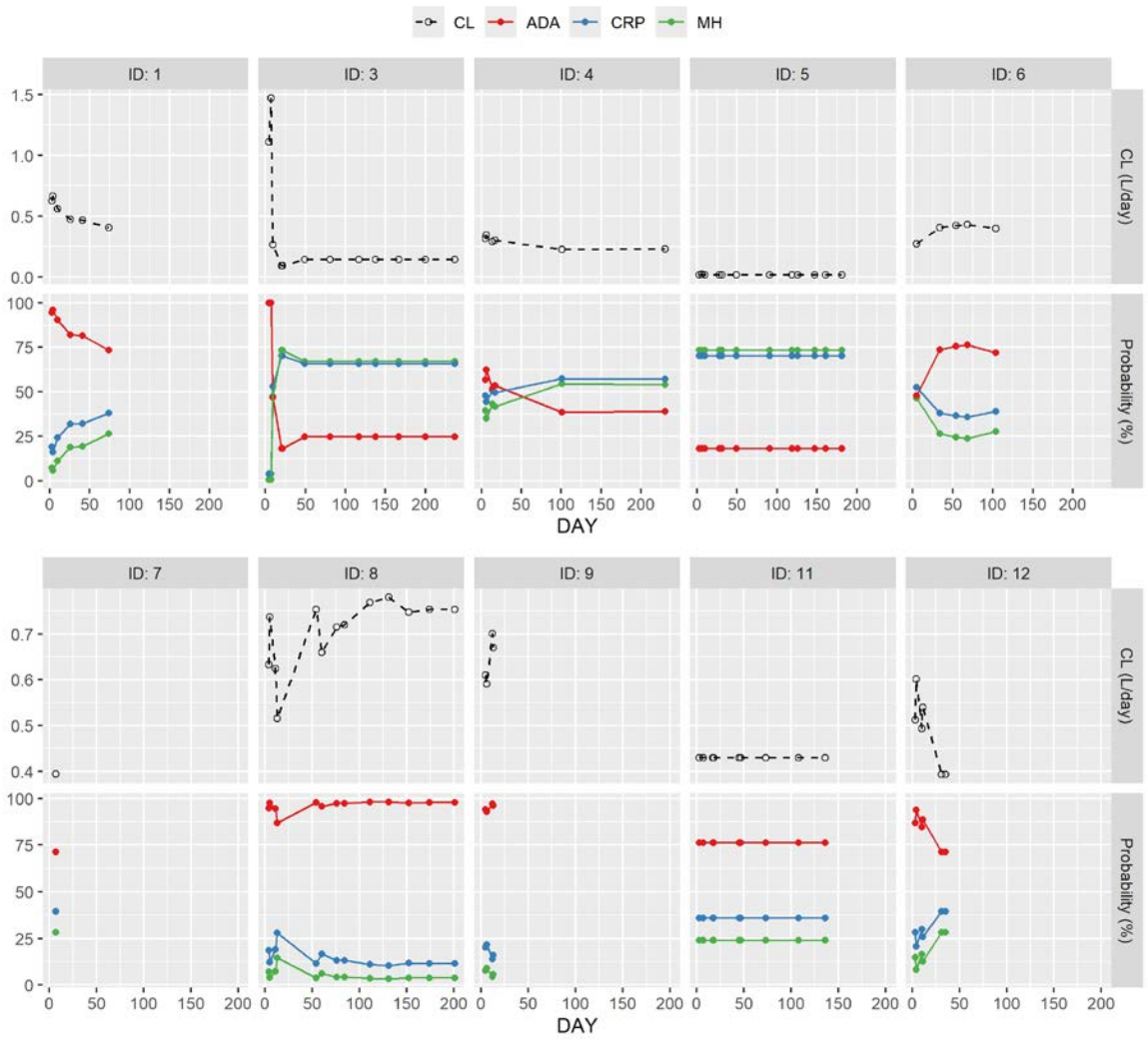


Turner, et al. Clin Cancer Res. 2018 Dec 1;24(23):5841-5849

ACUTE SEVERE ULCERATIVE COLITIS

- Small proof of concept study
  - 10 patients
- Usually colectomy is required in 20-40% of patients in induction
  - Accelerated induction (more frequent dosing in the first 2 weeks) has been reported to reduce colectomy rate
- 8 of 10 Patients treated using dashboard all completed induction
  - 2 patients developed ADA one had been previously treated with IFX

TRACKING INDIVIDUAL CL VS

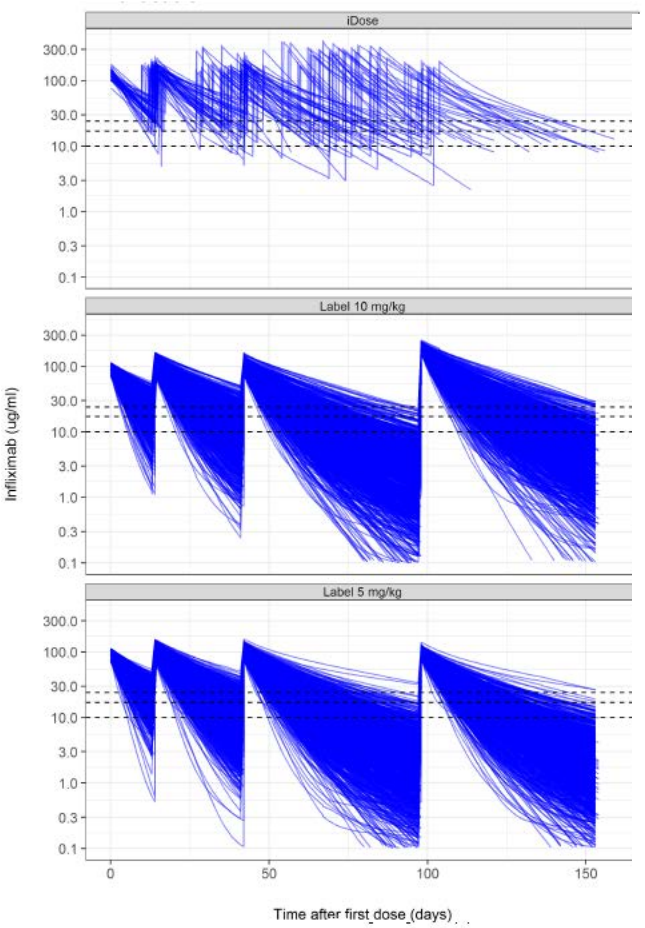


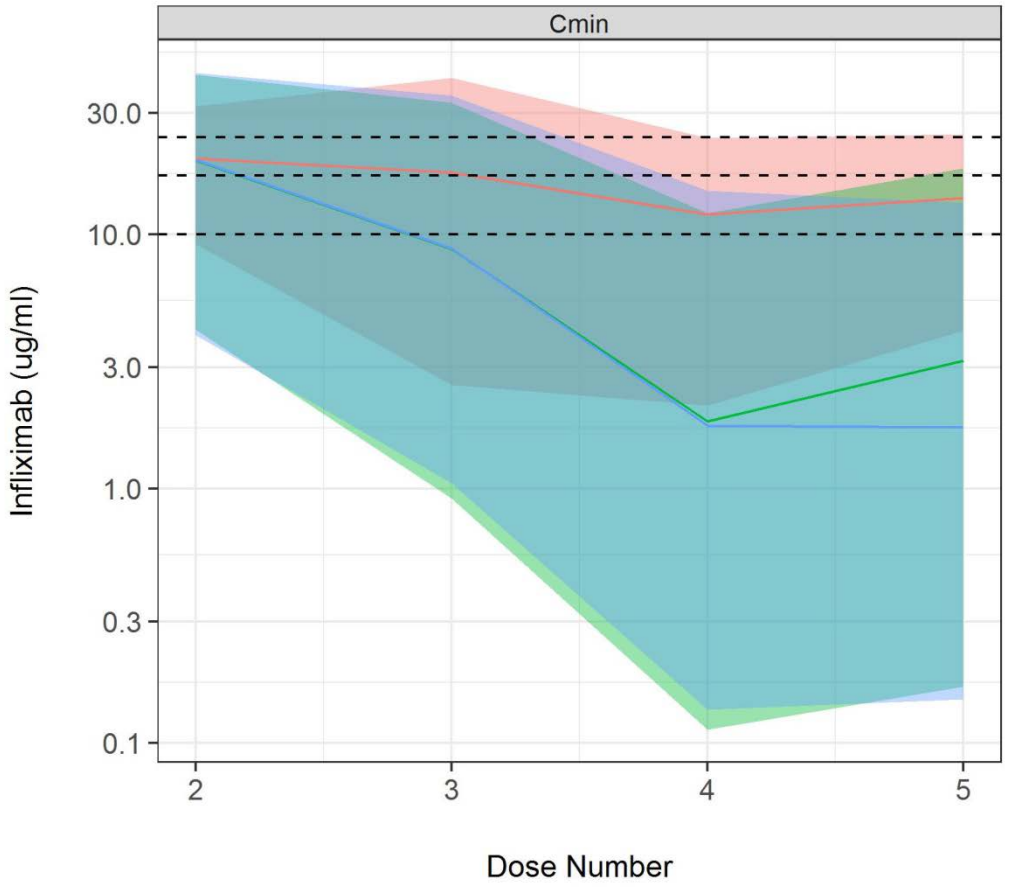
- As CL trends down, the other outcome probabilities change
- Baseline CL is not the final story

MT SINAI STUDY IN PEDIATRIC AND ADULT IBD

- This was a one-arm open label study evaluating the effectiveness of individualized dashboard based dosing.
- Predominantly pediatric patients, but there were some adult patients
- First dose was at the treating physicians' discretion
  - After which iDose was used.

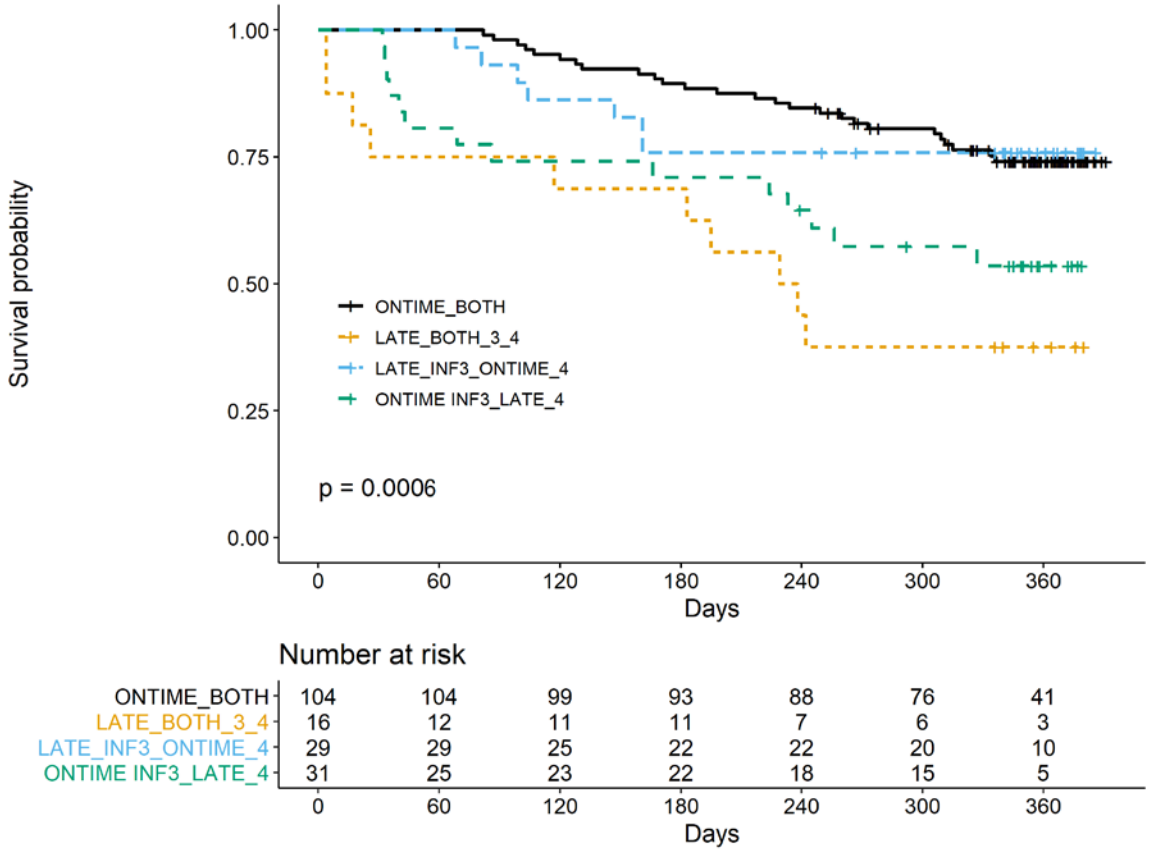
BAYESIAN SYSTEMS ALLOW BETTER CONTROL OF PATIENT EXPOSURE





Mould DR, et al. AAPS J. 2018;20(4):76 epub

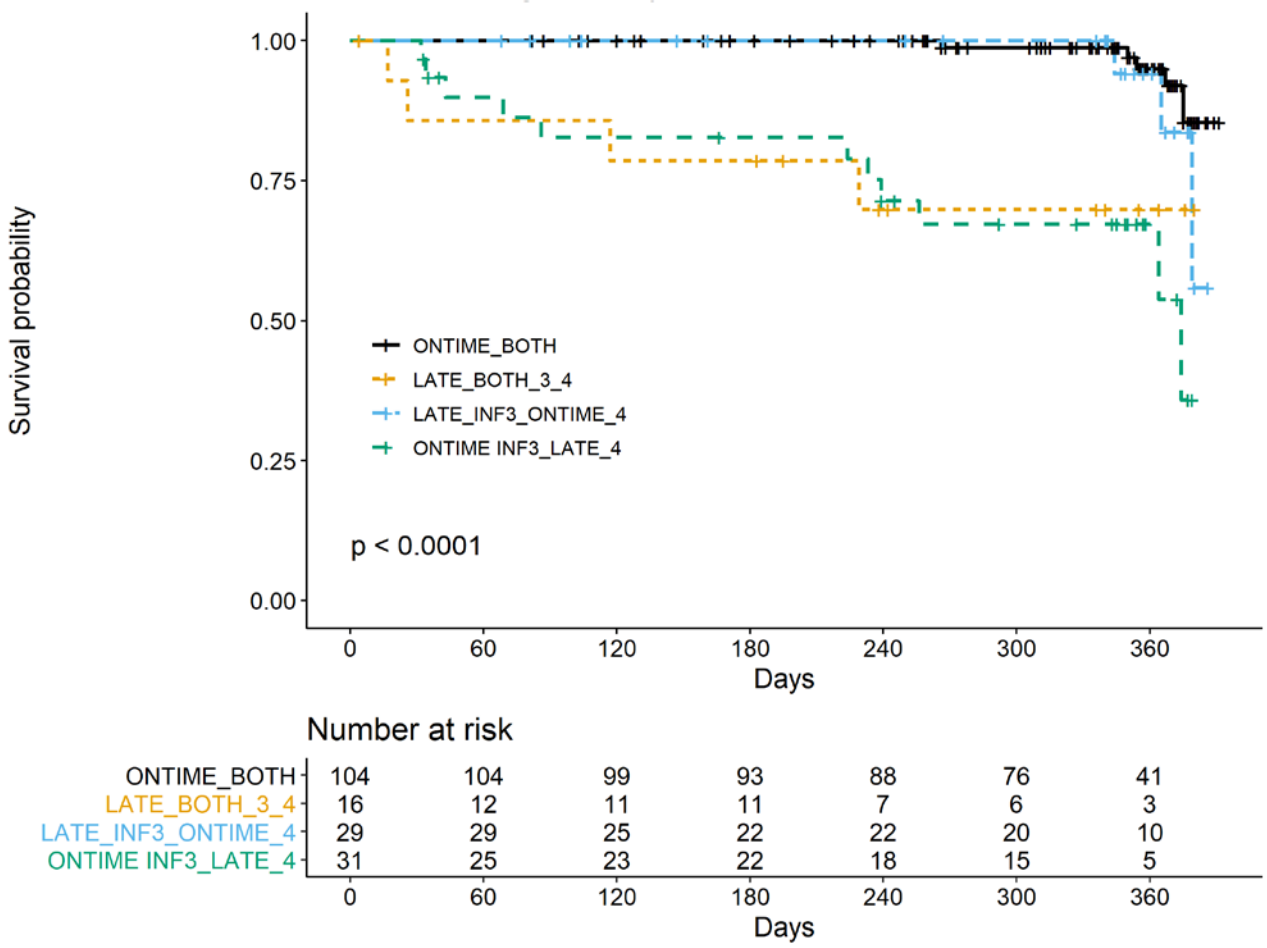
MT SINAI RESULTS



Total Number Compliant Patients	Total Number Enrolled
114 (63.3% enrolled)	180 enrolled
17 (14.9%) early terminations LOR	
6 (5.3%) Lost to follow up	
50 (43.9%) still in follow up (less than 1 year) at time of publication	

- This plot shows the impact of compliance on the benefit of model informed precision dosing

MT SINAI RESULTS



APPROVAL OF ANTI-INFLAMMATORY MABS IN PEDIATRICS

- Only Infliximab and adalimumab approved for pediatric use in IBD
  - This compromises the ability to conduct an adequate well-controlled study in pediatrics
- Certolizumab approved for adult use in CD in 2008
- Vedolizumab approved for adult use in 2014
- Ustekinumab approved for adult use in CD 2016 and UC 2019
- Golimumab approved for adult use in UC in 2013

REGULATORY EVALUATIONS OF DRUGS FOR PEDIATRIC IBD PATIENTS

- FDA pediatric extrapolation uses adult drug trial data for children, with "full extrapolation" meaning efficacy is entirely assumed from adult studies.
- Only requires safety/PK data in pediatrics;
  - supported by similar disease, drug action, and blood levels (PK)
- Reduces need for pediatric efficacy trials
  - Uses ICH E11A to offer a nuanced continuum (full, partial, none) and modern tools like modeling to bridge data from adults to pediatrics
  - Promotes faster access to safe meds for children.

REVIEW OF PREVIOUSLY PUBLISHED STUDIES OF VEDOLIZUMAB IN PEDIATRIC IBD PATIENTS

- A 2025 article reviewed 14 papers in this evaluation of the effectiveness and safety of vedolizumab.
  - 36% of all patients with UC/IBD-U experienced clinical remission at 6 weeks, 50% of the patients at 14 weeks, and 48% and 53% of patients at 22 weeks
  - 45% of patients maintained clinical remission after 1 year.
  - Less than 8% of UC/IBD-U patients experienced serious side effects
  - 15%–34% of patients experienced mucosal healing.

Abu Hammour K, Abu Hamour A, Abu-Farha RK et al. A systematic review of vedolizumab in treating pediatric ulcerative colitis: efficacy and safety insights. Therap Adv Gastroenterol. 2025;18:17562848251356063.

VEDOKIDS STUDY

- Data from 129 children
  - PK data were evaluated assisted by a published adult model as a Bayesian prior.
  - The PK model was used for exposure-response evaluation and investigating doses in pediatric patients to match the adult exposure at the labelled dose.
- At Week 30, 104/129 (81%) children remained on vedolizumab
  - 39 (31%) in the exposure-response evaluation were in deep biochemical remission.
  - Increased baseline clearance associated with lower deep biochemical remission rates at Week 30
    - Higher weight and lower serum albumin were associated with increased clearance ($p < 0.001$)

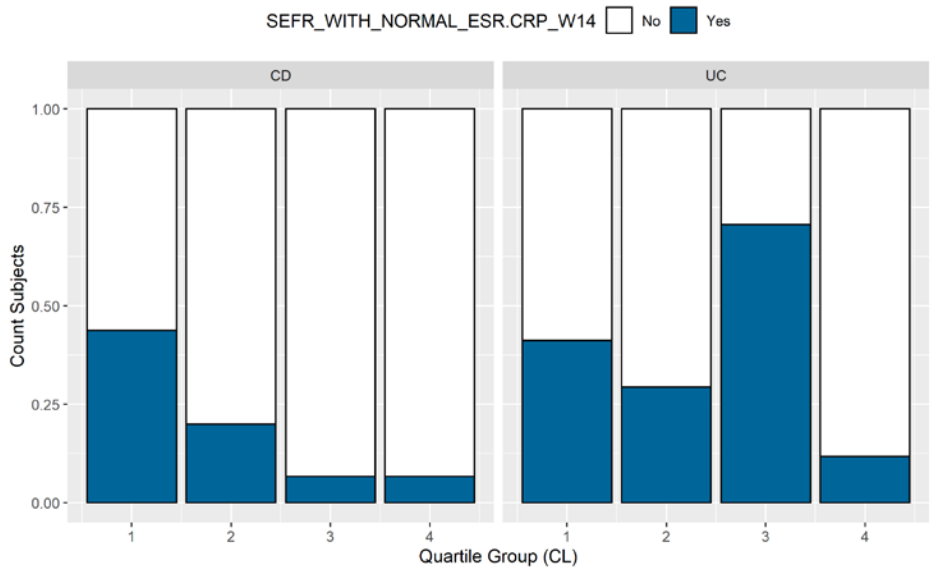
COMPARISON OF ADULT AND PEDIATRIC VEDOLIZUMAB PK

Parameter	Pediatric Estimate (units)	Adult Estimate
Clearance (CL)	0.160 L/day	0.159 L/day
Central compartment volume of distribution (Vc)	2.046 L	3.19 L
Peripheral compartment volume of distribution (Vp)	2.340 L	1.65 L
Intercompartmental clearance (Q)	0.120 L/day	0.12 L/day
Maximum nonlinear clearance (Vmax)	0.273 mg/Day	0.265 mg/day
Concentration at half-maximum nonlinear clearance (K_M)	1.107 mg/L	0.964 µg/mL
Effect of weight on Clearance	0.374	0.362
Effect of Albumin on Clearance	-1.18	-1.18
Effect of weight on Vc	0.464	0.467
Effect of weight on Vp	NE	1 FIX
Effect of Weight on Vmax	NE	0.75 FIX
Effect of Weight on Q	NE	0.75 FIX
Effect of Prior Biologics on Clearance	0.165	NE
Residual error (%Coefficient of Variation)	50.4	23.5
IIVCL	33.2	57.36
IIVV1	19	39.5
IIVVmax	108.6	73.6

Stein R, Turner D, Hussey S, et al. Baseline Drug Clearance Predicts Outcomes in Children With Inflammatory Bowel Disease Treated With Vedolizumab: Results From the VedoKids Prospective Multicentre Study. Aliment Pharmacol Ther. 2025;61(6):1000-1010.

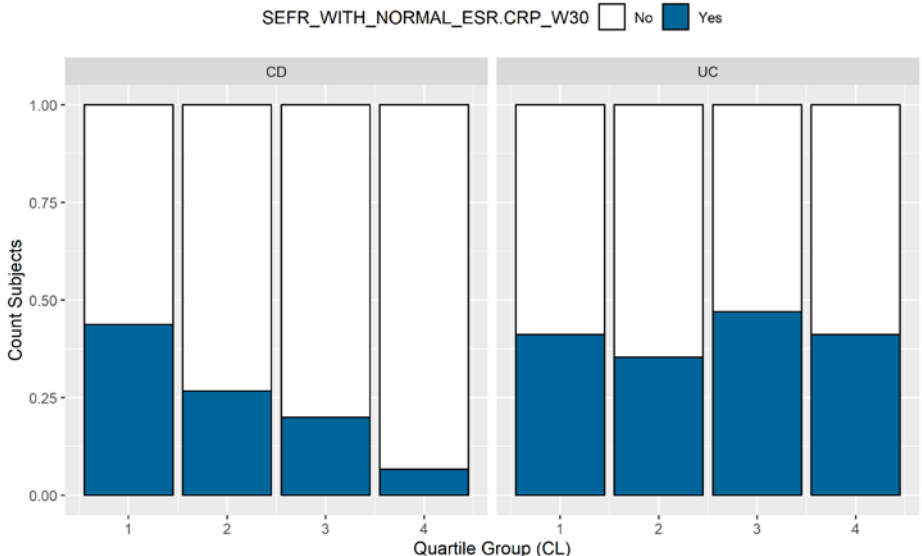
Rosario M, Dirks NL, Gastonguay MR, et al. Population pharmacokinetics-pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn's disease. Aliment Pharmacol Ther. 2015;42(2):188-202.

PEDIATRIC DRUG CLEARANCE DRIVES RESPONSE



Characteristic	OR[1]	95% CI[1]	p-value
log2(CL)	0.32	0.12, 0.76	0.014
DIAG			
CD	—	—	
UC	2.18	0.94, 5.29	0.076
BIOP			
BIOP.L	0.46	0.17, 1.10	0.094
BIOP.Q	1.28	0.61, 2.65	0.5

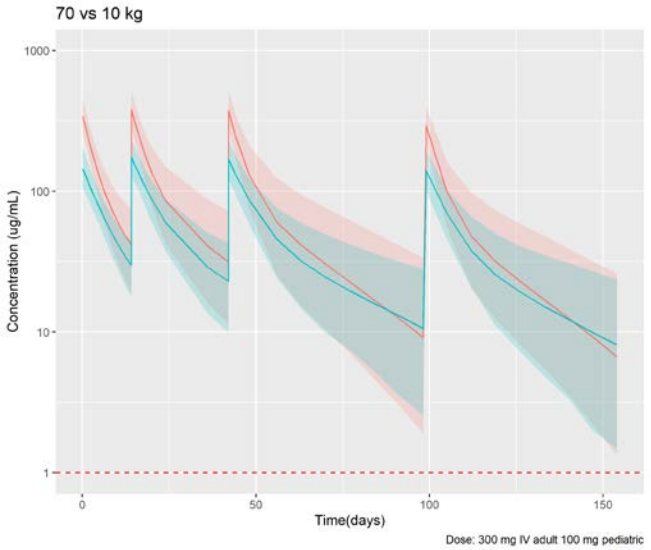
[1] OR = Odds Ratio, CI = Confidence Interval

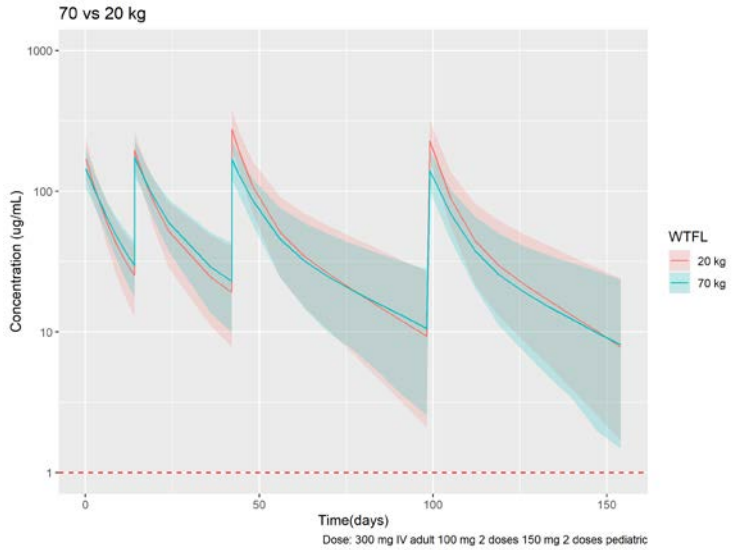


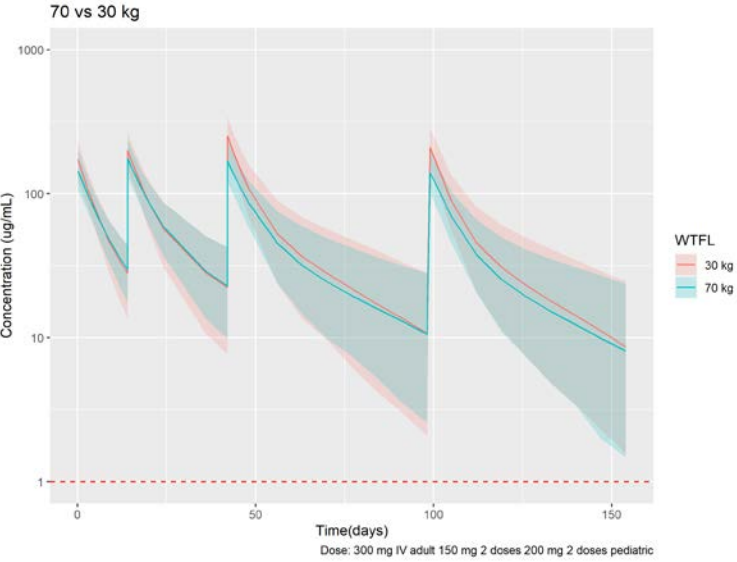
Characteristic	OR[1]	95% CI[1]	p-value
log2(CL)	0.48	0.20, 1.06	0.077
BIOP			
BIOP.L	0.28	0.09, 0.68	0.009
BIOP.Q	0.80	0.38, 1.61	0.5

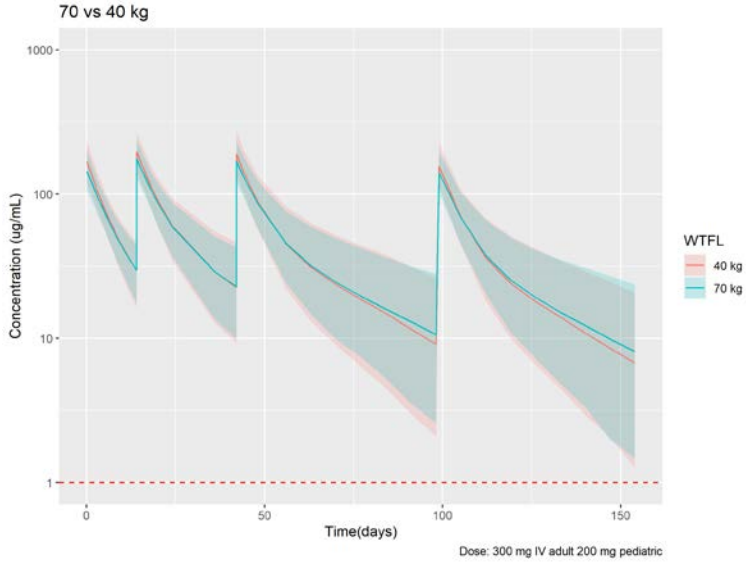
[1] OR = Odds Ratio, CI = Confidence Interval

SIMULATED EXPOSURE FOR PEDIATRIC PATIENTS (10-40 KG) VS ADULT(70 KG) EXPOSURE AT LABELED DOSE





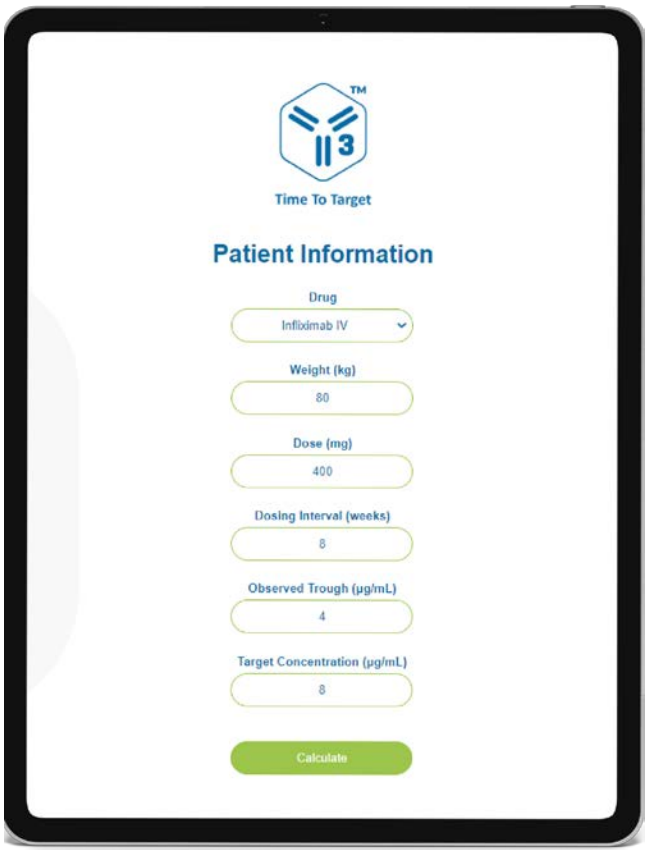


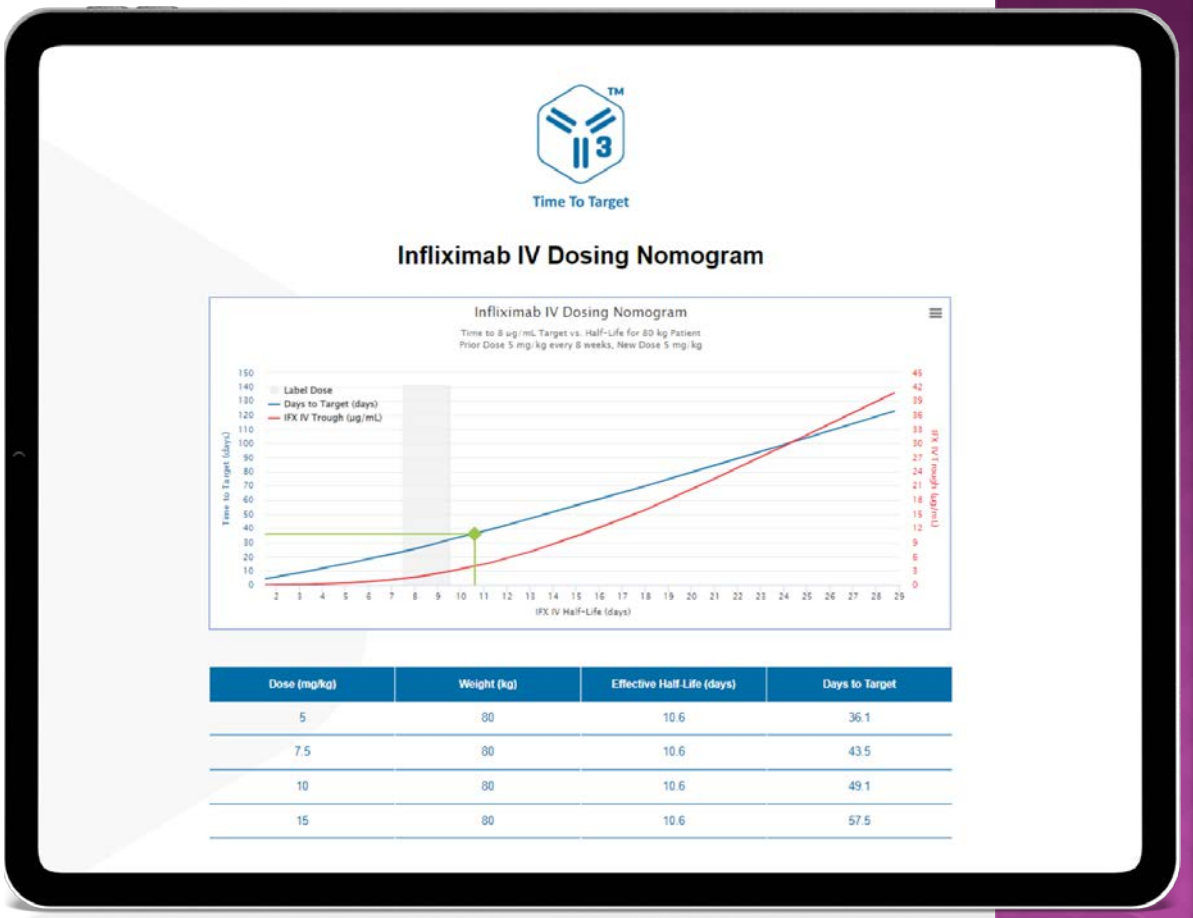


IMPROVING UPTAKE BY HEALTH CARE PROVIDERS

- Using a Dashboard takes time to learn
- Taking smaller steps! MIPD systems require training and resources
  - Most physicians have fundamental training in PK and PD
  - Most MIPD systems use specialized Bayesian statistical approaches
- Physicians are familiar with apps
  - Apps for dosing warfarin are quite common for example
  - Making the application of MIPD more familiar and simpler may facilitate uptake in the medical community
    - Slight hit to precision, major improvement in speed and ease of use

MAKE MIPD MORE LIKE AN APP





Dose (mg/kg)	Weight (kg)	Effective Half-Life (days)	Days to Target
5	80	10.6	36.1
7.5	80	10.6	43.5
10	80	10.6	49.1
15	80	10.6	57.5

DISEASE PROGRESSION

- There is a difference between indicators of disease activity and disease progression
  - CRP and other indicators of IBD activity don't align well with progression but often herald impending progression of disease
  - MAb clearance may be more sensitive than CRP in indicating response or impending flare/ADA
- Pharmacokinetics of MAb is dependent on pharmacodynamics
  - If disease severity improves, clearance will slow
  - If disease severity is worsening clearance will increase
- If the objective of therapy is to halt or at least slow progression then markers such as individual clearance may be useful to measure success

THANK YOU!

My thanks to Dr Anne Strik, Dr Walter Reinisch, Dr Stephen Hanauer and Dr Marla Dubinsky for their input

Questions? Send to DRMould@PRI-Home.net

BACK UP SLIDES

SO WHAT IS "BAYESIAN" ?

- Bayesian statistics is a theory in which the evidence about the true state of the world is expressed in terms of degrees of belief ("Bayesian probabilities" or Likelihood)
- Bayesians believe that the data are true but the model may be wrong. Frequentists believe the model is true and the data may be wrong
- One of the key ideas of Bayesian statistics is that probability is orderly opinion, and that inference from data is nothing other than the revision of such opinion in the light of relevant new information

Note that this is probably not Bayes

AND BAYES SAID

$$"Posterior \propto Prior \times Likelihood"$$

- Mathematical functions make up the Posterior, the Prior and the Likelihood
  - Prior represents what is known
  - Likelihood is based on observed data

DID SOMEBODY SAY "TELL ME MORE?"

- An example of a Prior: "All cab drivers in NYC are crazy"
  - Everybody has a prior on all sorts of things. This is a common one. It can be based on experience or too much TV but there is often some form of information behind it

INFLIXIMAB PRIOR

$$CL = \left(\theta_1 \bullet \left(\frac{Weight(kg)}{70} \right)^{\theta_6} \bullet \left(\frac{ALB\left(\frac{g}{dL} \right)}{4} \right)^{\theta_{10}} \bullet (1 + \theta_{12} \bullet IRP) \right) \bullet \exp(\eta_1)$$

$$Vc = \theta_2 \bullet \left(\frac{Weight(kg)}{70} \right)^{\theta_7} \bullet \exp(\eta_2)$$

$$Q = \left(\theta_3 \bullet \left(\frac{Weight(kg)}{70} \right)^{\theta_8} \right) \bullet \exp(\eta_3)$$

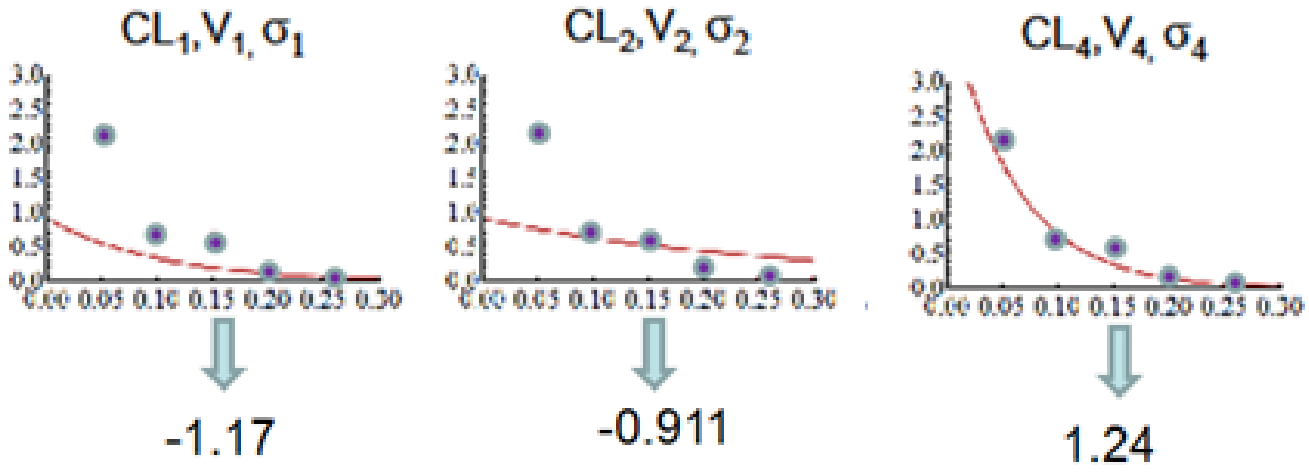
$$Vp = \theta_4 \bullet \left(\frac{Weight(kg)}{70} \right)^{\theta_9} \bullet \exp(\eta_4)$$

- Published values and equations define the Prior
- Eta (η) values define how much the individual patient deviates from the average patient with those covariates
- Taken across many patients, eta values are a distribution reflecting expected parameter range
- Goal of Bayesian statistics is to find the individual etas

Xu Z, et al. A Population-based Pharmacokinetic Pooled Analysis of Infliximab in Pediatrics. Presented at 41st Annual Meeting of the ACCP; September 23-35, 2012; San Diego, CA. Abstract.

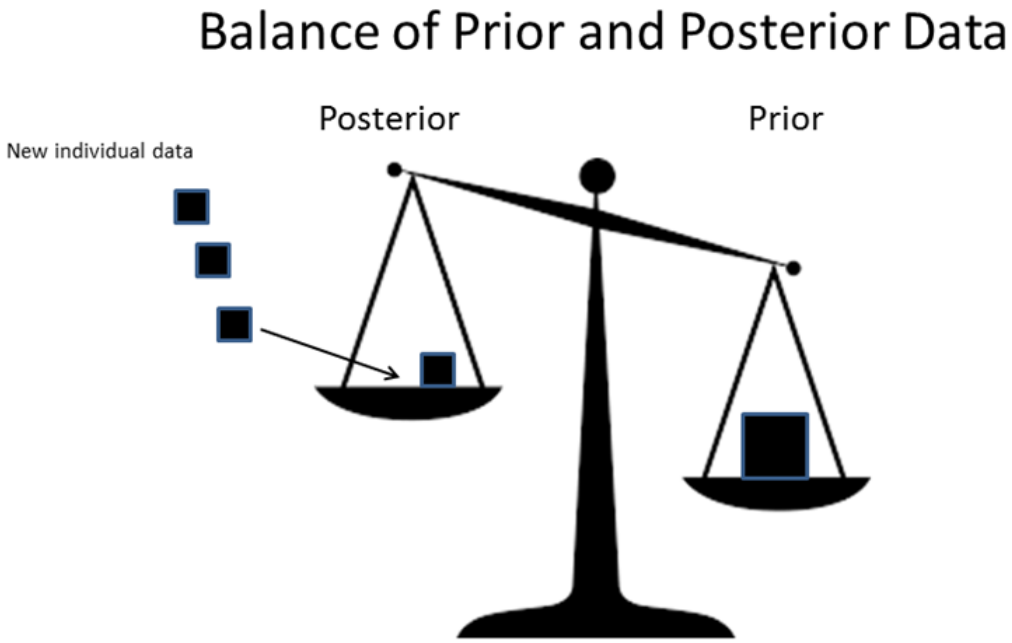
LIKELIHOOD

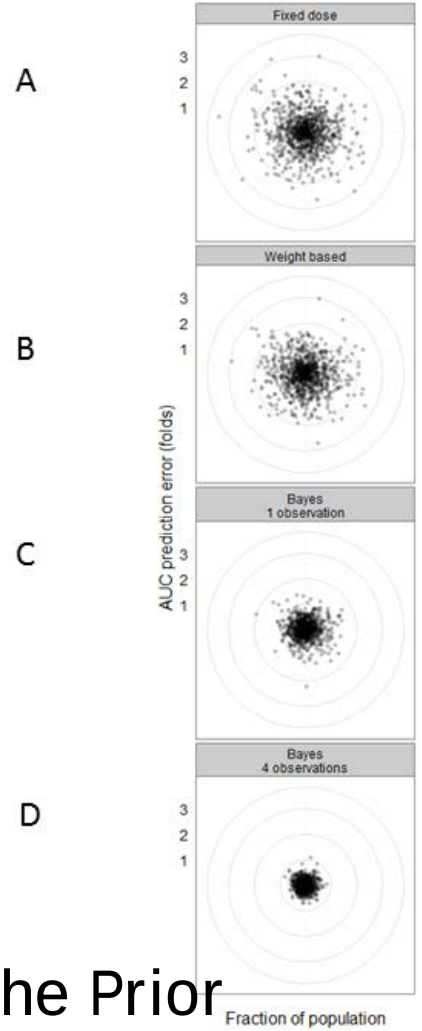
- Various etas from the Prior tested and Likelihood is determined for each set of sampled parameters. Likelihood is a metric comparing observed and calculated (Bayesian probability).
- Parameters with maximal Likelihood determines Posterior (as the product of the Prior and the Likelihood)
- Individual's values of eta are calculated from the Posterior



Likelihood

BAYESIAN LEARNING





- Initially with no data, forecasts reflect the Prior
- As data are added, forecast moves from prior
  - Bayesian Learning

Mould DR, D'Haens G, Upton RN. Clin Pharmacol Ther. 2016;99(4):405-18

LETS GO BACK TO NYC

- Remember our Prior "All cab drivers in NYC are crazy"
- If we stand at near the curb and watch drivers for a few minutes we see some cab drivers are indeed nuts but there are a few that appear ok
  - Now we have data, and a likelihood
  - However we are not willing initially to move entirely away from our prior yet
  - We might say "Cab drivers in NYC are mostly crazy"
- Now we stand at the curb for an hour and see that half the cab drivers are not crazy
  - We can move further from the prior because we have more data

AND THEN THERE WAS RESPONSE

- Once an individual's set of etas is determined the individual's parameters (i.e. the Posterior) are used to calculate a range of regimens that meets the specified criteria (such as a trough concentration of 3 mg/L) for that patient
  - There are often several dose regimens that will achieve a target criteria
- All recommended dose regimens use the same Posterior (eta values)

PATIENTS CHANGE OVER TIME

- Following the first dose, we collect another trough and update patient factors
  - Bayesian systems "learn" more about the patient so data entry errors become less problematic
- During treatment patients gain weight, ALB levels normalize and their PK changes
  - Until the patient is really stable, there will be some error in the forecast troughs
- Dose adjustments are then calculated based all available observations which is reflected in an updated posterior
- As the system gets more information about patient, eta values approach their true eta values and dose recommendations improve