# Regulatory Perspectives of Implementing TDM – Challenges and Opportunities

*2017 ASCPT Symposium "Clinical Practice, Hurdles and Expectations in the Individualized Treatment Route to Optimizing Therapy for Biologics" (3/17/17)*


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TDM: Therapeutic Drug Monitoring

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- The presentation today should not be considered, in whole or in part as being statements of policy or recommendation by the United States Food and Drug Administration.

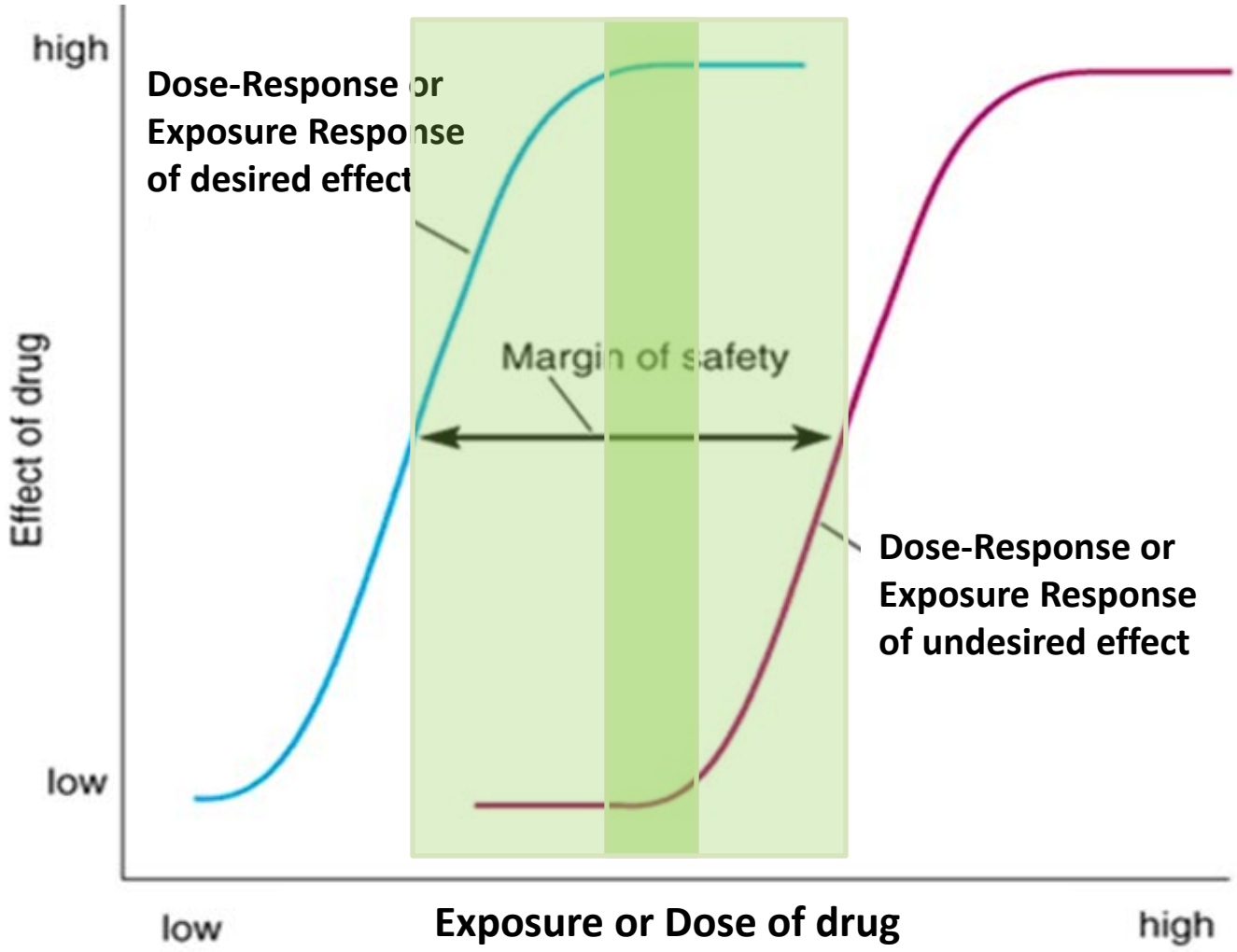
- Throughout the talk, representative examples of commercial products may be given to illustrate a methodology or approach to problem solving. No commercial endorsement is implied or intended.

# Overview

- Introduction – essential elements of TDM
- Challenges on the path toward individualized therapy
  - What's the target therapeutic range?
  - Managing secondary treatment failures
  - From retrospective/observational studies to prospective studies
  - Evolution of knowledge and additional considerations
- Considerations regarding technical tools
  - Assays for drug concentration and for antidrug antibodies (ADA)
  - Response measures (will not be covered)
- Summary

# Therapeutic Drug Monitoring Essentials

(a textbook example)




**Elements:**

**1. Concentration**

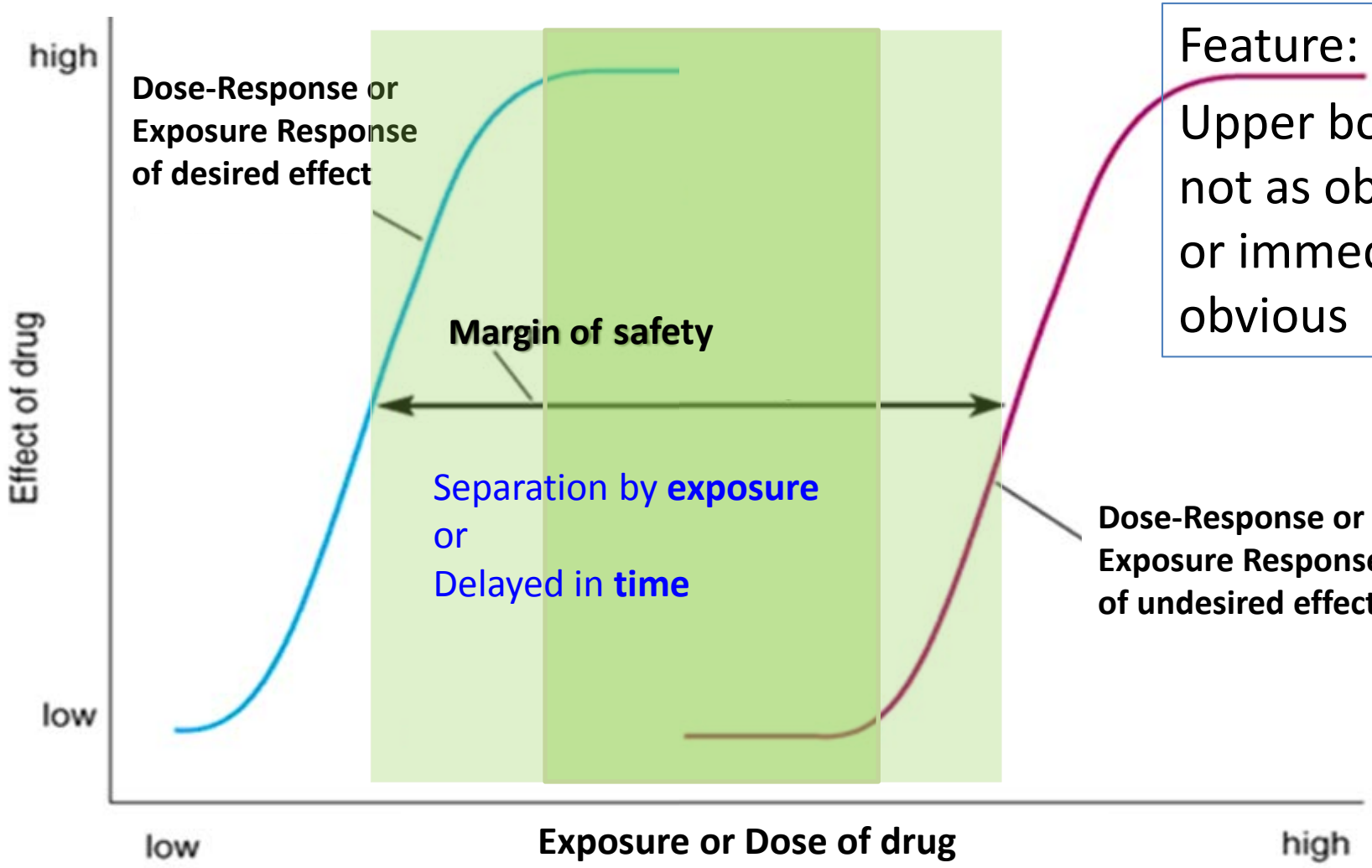
- Upper bound
- Lower bound

**2. Response**

- Toxicity
- Clinical effects

# Therapeutic Drug Monitoring Essentials

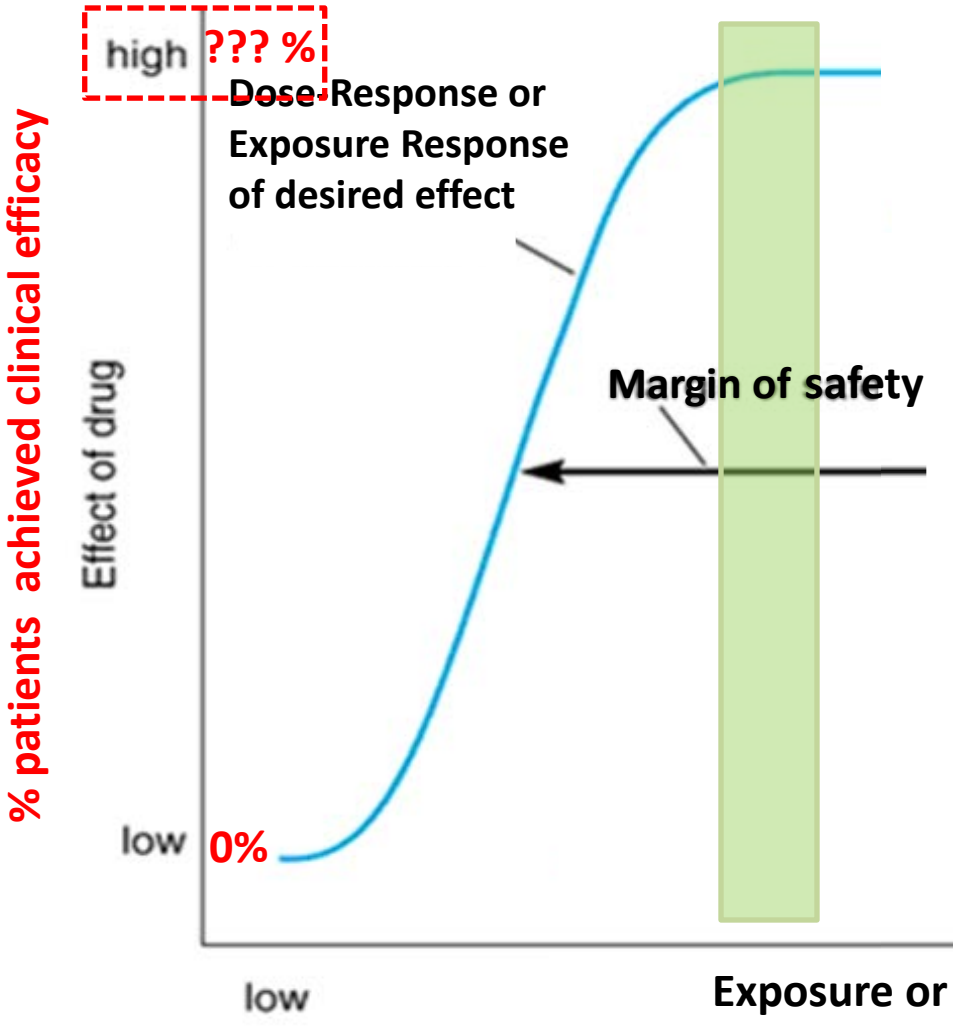
(example - extension to biologics)




Feature:

Upper bound not as obvious or immediately obvious

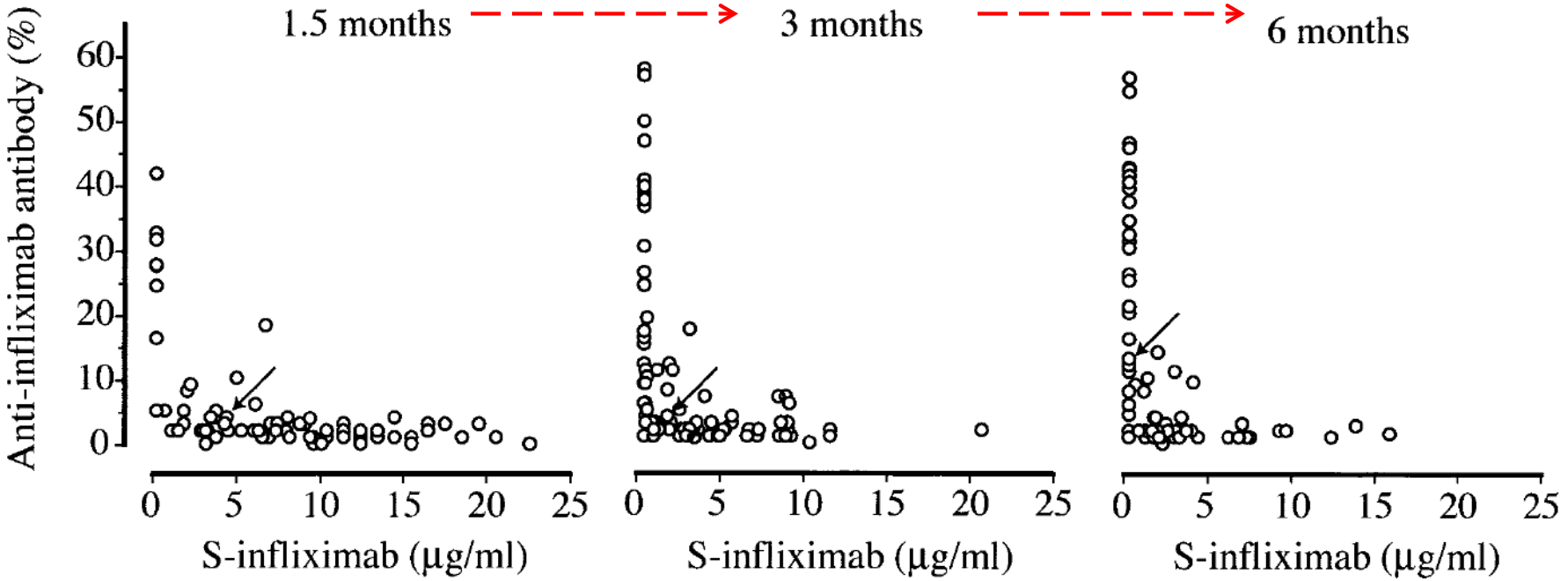
# The 3rd Element: Non-responders at Population Emax




- **If High = 100% …**
  - Dosing to achieve E-R plateau will benefit all (100%)
  - Maximum dose (exposure) **not** required for all; lower may be adequate for some.
- **If High < 100% (say, 50%)**
  - Dosing to achieve E-R plateau will benefit only 50% subjects
  - Ineffective in the other 50%
  - Dose individualization can avoid ineffective treatment
- **Who will benefit? How to tell?**

# The 4th Element - Immunogenicity
## (May result in secondary treatment failure)

- **% of infliximab bound to anti-drug antibody (ADA) ↑ over time**
- **Infliximab (S-), active drug, concentration ↓ with ↑ of ADA**




Bendtzen *et al.* Arthritis Rheumatism 2006

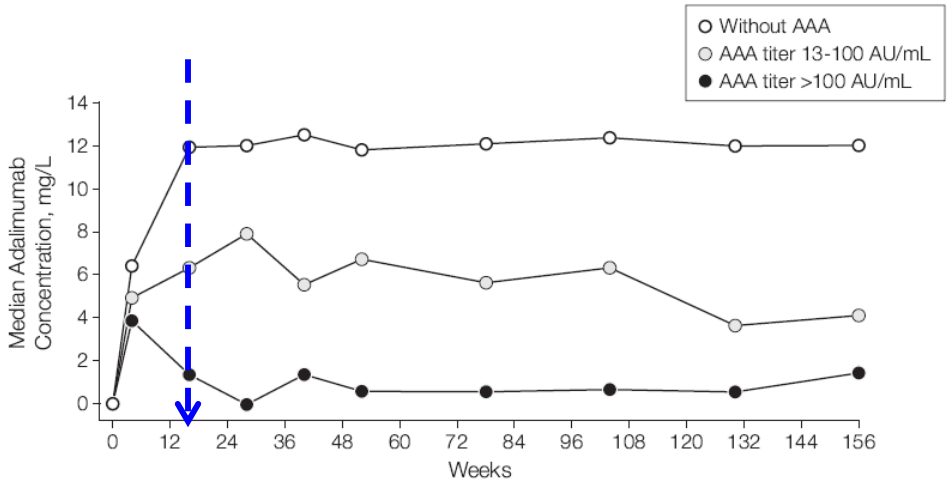
# 4th Element - Immunogenicity

## (May result in secondary treatment failure)

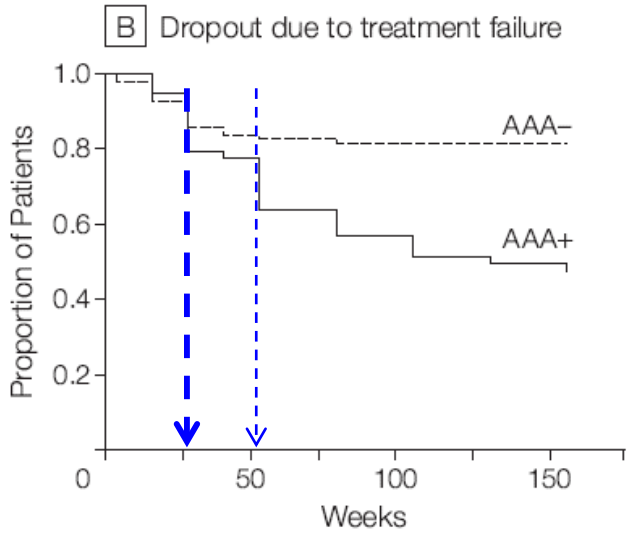
- Antibody+ patients - lower adalimumab concentration & higher dropout rate
- PK negatively affected before efficacy, PK is a more sensitive endpoint
- Monitoring concentrations may be useful. **How about ADA monitoring?**

**Figure 4.** Overall Patient Dropout and Dropout Due to Treatment Failure

**Figure 2.** Median Adalimumab Concentrations Over Time




| Week | 0 | 4 | 16 | 28 | 40 | 52 | 78 | 104 | 130 | 156 |
|---|---|---|---|---|---|---|---|---|---|---|
| No. of patients | | | | | | | | | | |
| Without AAA | 196 | 187 | 177 | 164 | 145 | 139 | 131 | 118 | 107 | 93 |
| AAA 13-100 AU/ml | 45 | 43 | 42 | 37 | 34 | 34 | 28 | 24 | 19 | 17 |
| AAA >100 AU/ml | 31 | 31 | 28 | 27 | 22 | 19 | 16 | 14 | 11 | 8 |




| No. at risk | | | | |
|---|---|---|---|---|
| AAA– | 196 | 151 | 135 | 118 |
| AAA+ | 76 | 59 | 43 | 29 |

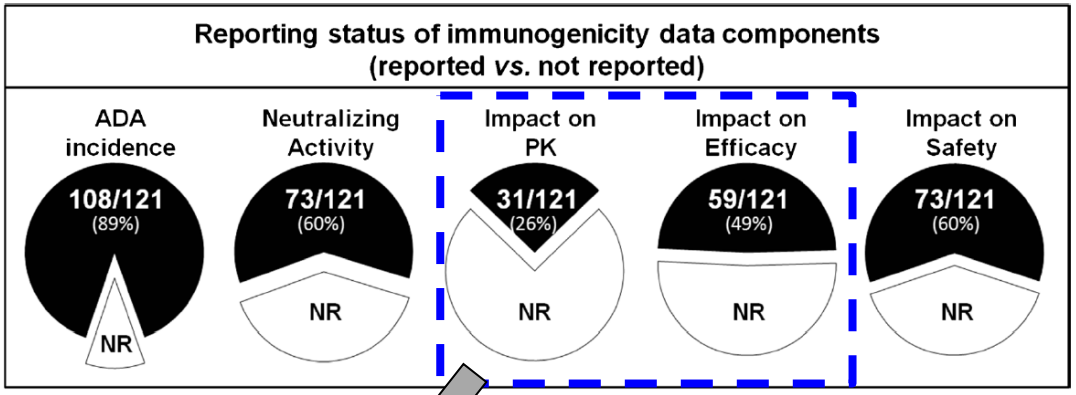


Bartelds *et al.* JAMA 2011

## Evaluating and Reporting the Immunogenicity Impacts for Biological Products—a Clinical Pharmacology Perspective

*(AAPS J, 2016)*

Yow-Ming C. Wang,[1,2] Jie Wang,[1] Yuen Yi Hon,[1] Lin Zhou,[1] Lanyan Fang,[1] and Hae Young Ahn[1]




NR: not reported; ADA: binding, anti-drug antibodies; PK: pharmacokinetics

**Fig. 2.** Summary of immunogenicity impact reporting in the prescribing information

**Reported Impact on PK + Efficacy**

N = 16

**Concordance PK + Efficacy**

N = 14

**8* w/ negative impact**

**6 w/ no impact**

* 5 mAbs, 3 enzymes

Concordance definition:

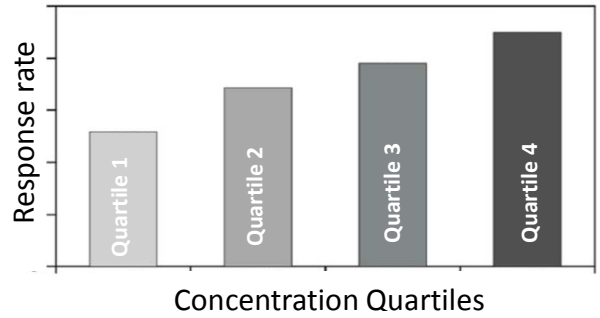
- ADA+ → higher clearance (lower exposure) & reduced efficacy
- ADA+ → no effect on clearance & no effect on efficacy

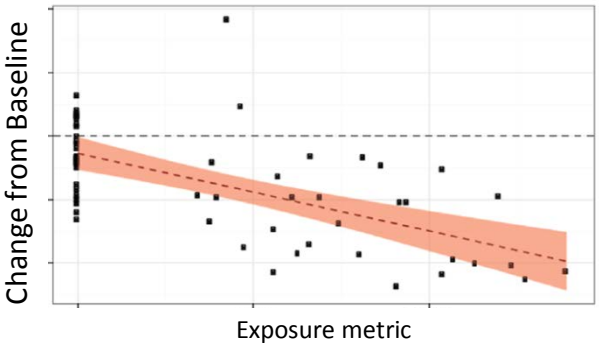
# Challenge #1 - Target Concentration Range?

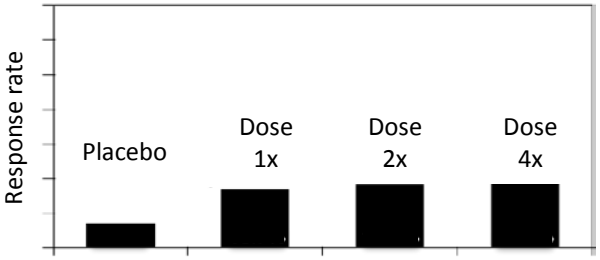
- Retrospective analysis of clinical trial data is often the basis for literature reports

- Available trough concentration data (often a subset)
  → find the upper quartile range
  → defined as target range

- Some cases are not so easy…
  E-R & dose range in efficacy trials,
  - Limited dose range with efficacy & PK data
  - E-R shown from a single dose level
  - No dose-response, but data show E-R



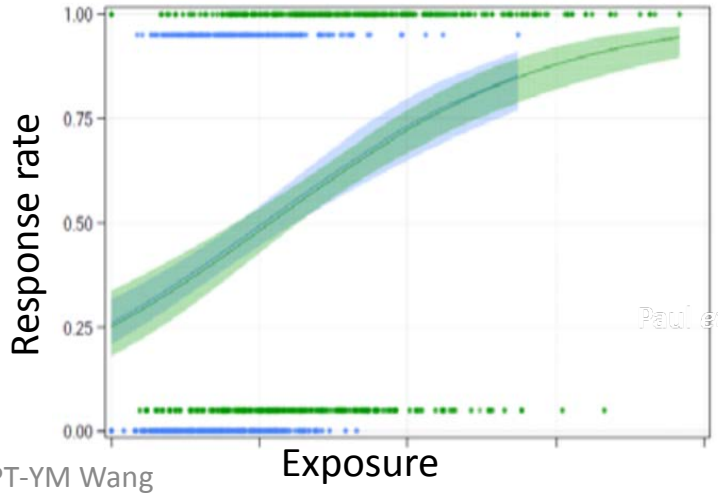



# Challenge #1 - Target Concentration Range?

- Is the target concentration range from population E-R suitable for all subjects?
- Considering PK and PD variability,

  * same dose ≠ same exposure

  * same exposure ≠ same response
- Desired exposure may be lower in some subjects.
- Will the benefit/risk profile at higher exposure be favorable for these subjects?



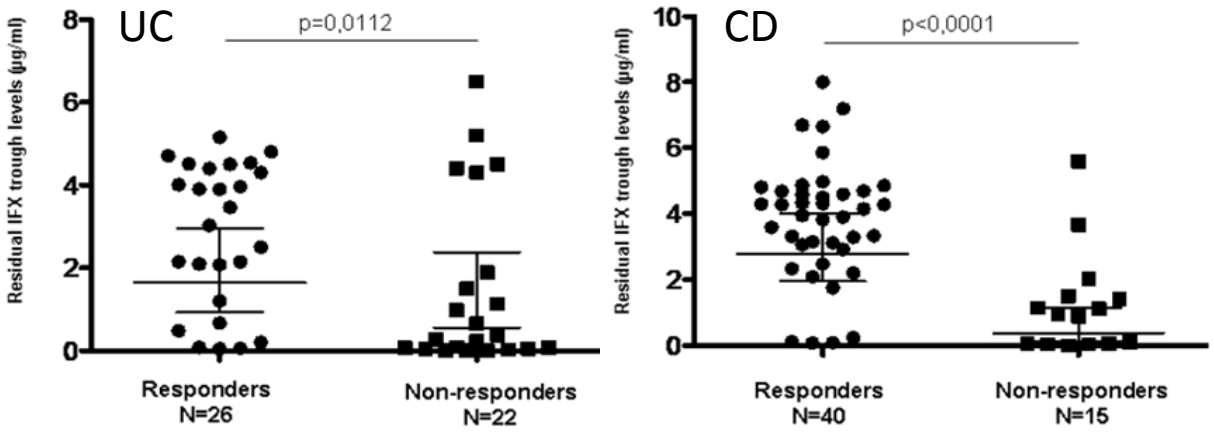

Paul et al. 2013 IBD

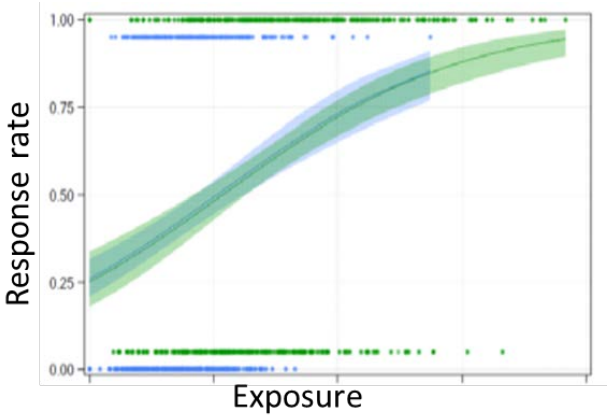
# Challenge #2 – Addressing Non-Responders

- Non-responders may exist despite achieving high exposure.
- Will pushing the concentration into E-R plateau (or high) range have favorable benefit/risk for these subjects?

➢ When to stop the dose increase or stop the treatment?

➢ Availability of response marker/metric for decision-making?




Paul *et al.* IBD 2013

# Challenge #3 - Addressing Secondary Treatment Failure with ADA Monitoring?

**What We Know…**

- Drug levels are important
- ADA+ → lower drug levels, in many cases
- ADA+ → may lose efficacy
- Not all ADA+ are equal… but, some have higher titers
- ADA+ after repeat dosing

**We May Not Know for Sure …**

- The target levels or range?
- Overcome by increase dose?
  - When is it not likely to work?
- What's a bad level of ADA?
- Clinical meaning of ADA titer?
- Time course?
  e.g., onset of occurrence, duration of persistence

# Substantial Research on Dose Optimization (TDM) in Secondary Treatment Failure of IBD

| | ADA- (or ADA low, ±) | ADA+ (or ADA high) |
|---|---|---|
| **Drug level HIGH** | Switch drug | Switch drug (or add immunomodulators) |
| **Drug level LOW** | ↑ Dose | Switch drug (or add immunomodulators) |

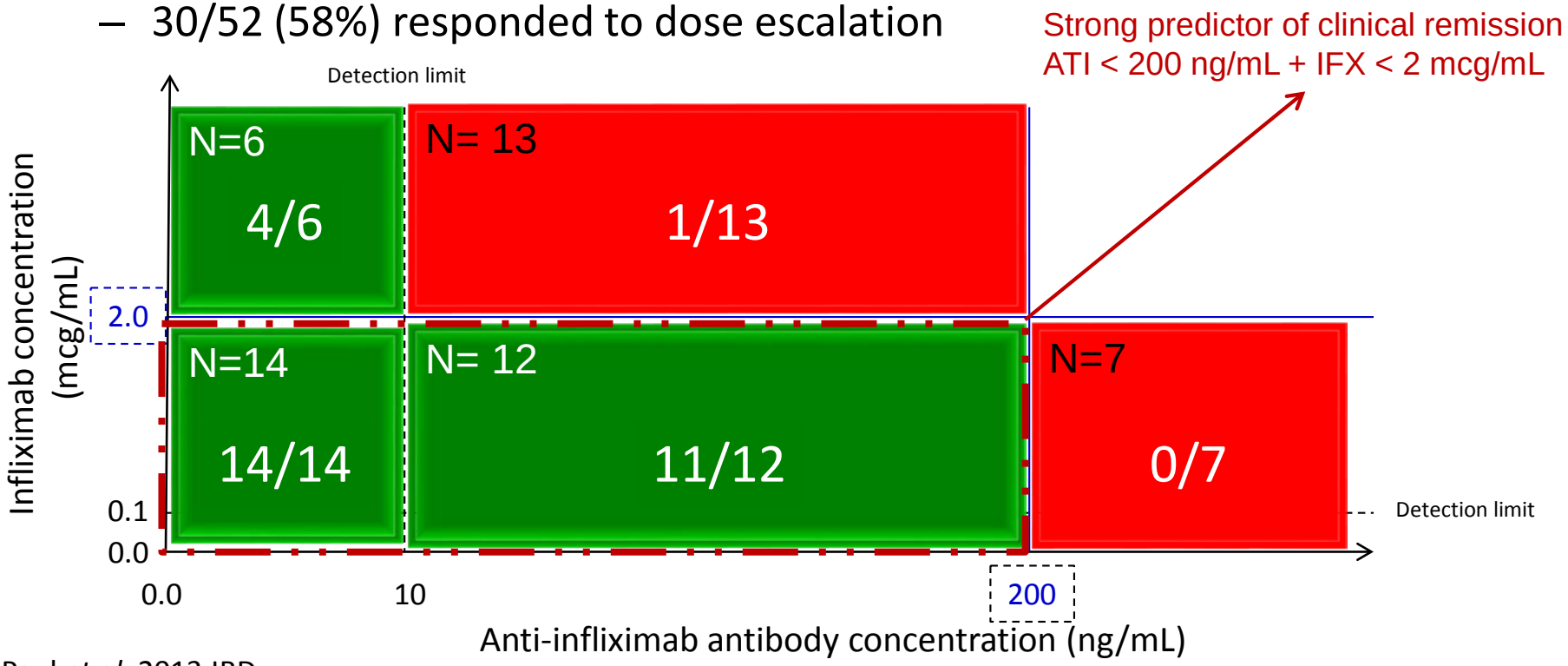
↑ Dose in some reports

- Generally monitor drug level & ADA, in addition to disease status.
- The goal post for each parameter differed across reports, generally based on institutional experience.
- Definitions of loss of response also differed across reports.

➢ Present challenges to future large scale implementation

# An Observational Study Evaluating Association of Clinical Outcomes with Trough & ADA Levels

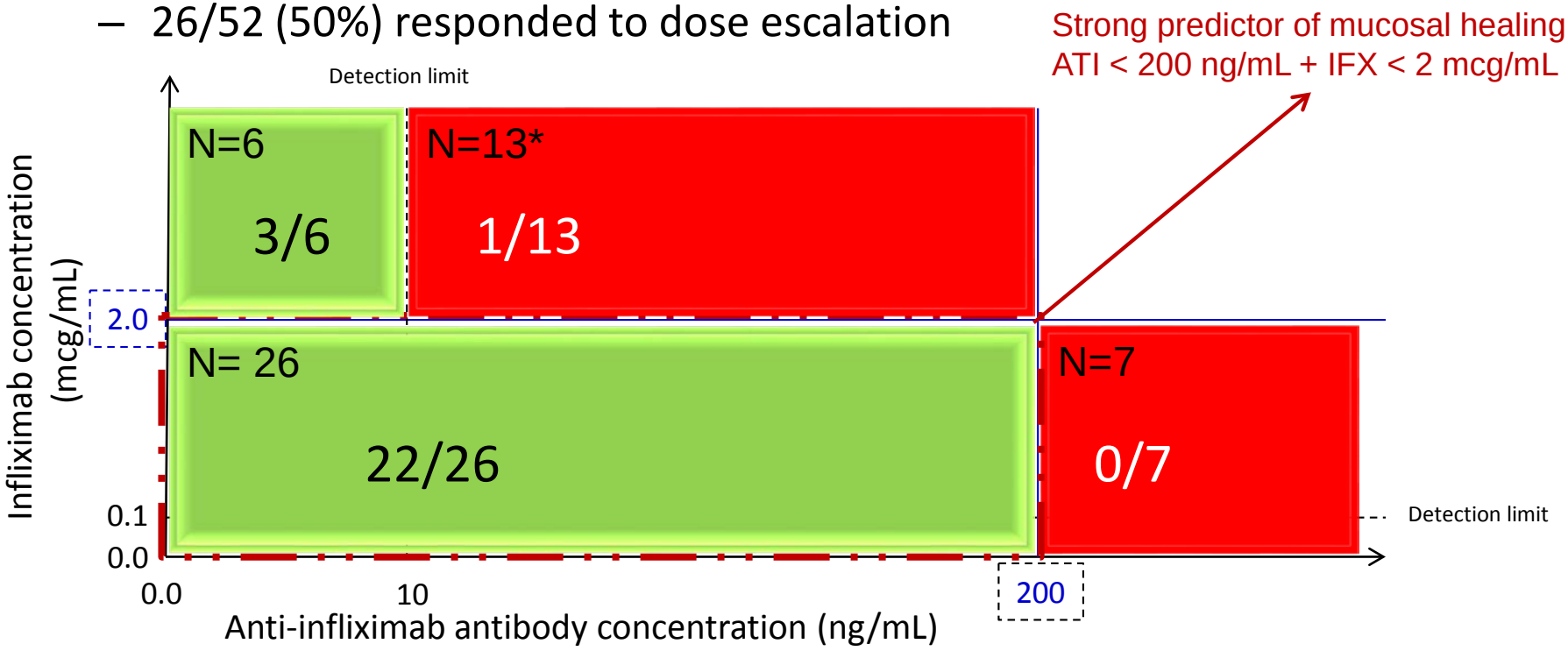
- UC/CD patients (N=52), infliximab dose escalated by physicians
- Drug level and ADA level collected prior to dose change
- **Clinical remission** vs. levels of drug & ADA before dose change
  - 30/52 (58%) responded to dose escalation




Paul *et al.* 2013 IBD

# An Observational Study Evaluating Association of Clinical Outcomes with Trough & ADA Levels

- UC/CD patients (N=52), infliximab dose escalated by physicians
- Drug level and ADA level collected prior to dose change
- **Mucosal healing** vs. levels of drug & ADA before dose change
  - 26/52 (50%) responded to dose escalation



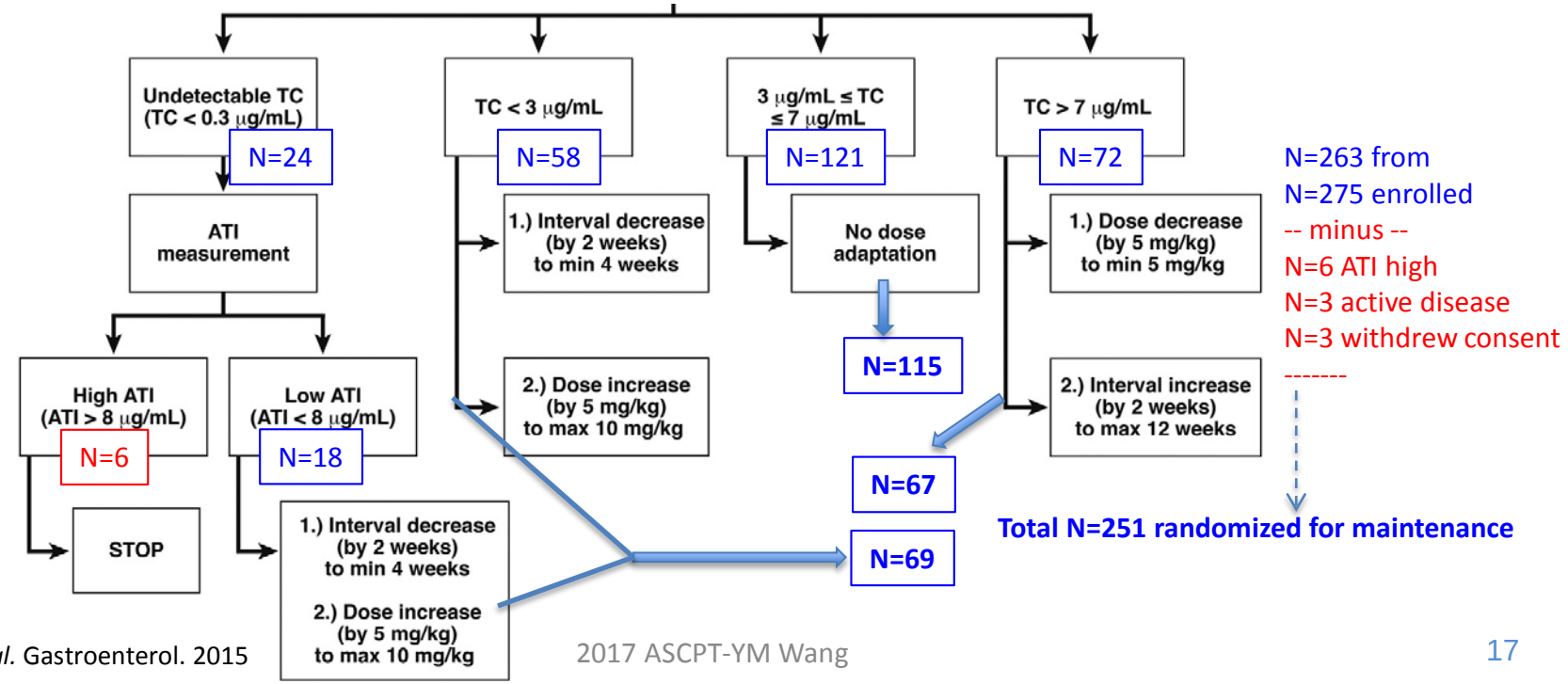

Paul *et al.* 2013 IBD

* Assumed 13 (instead of 12) same as clinical remission data since text in paper was inconsistent.

# Prospective Study (TAXIT trial)

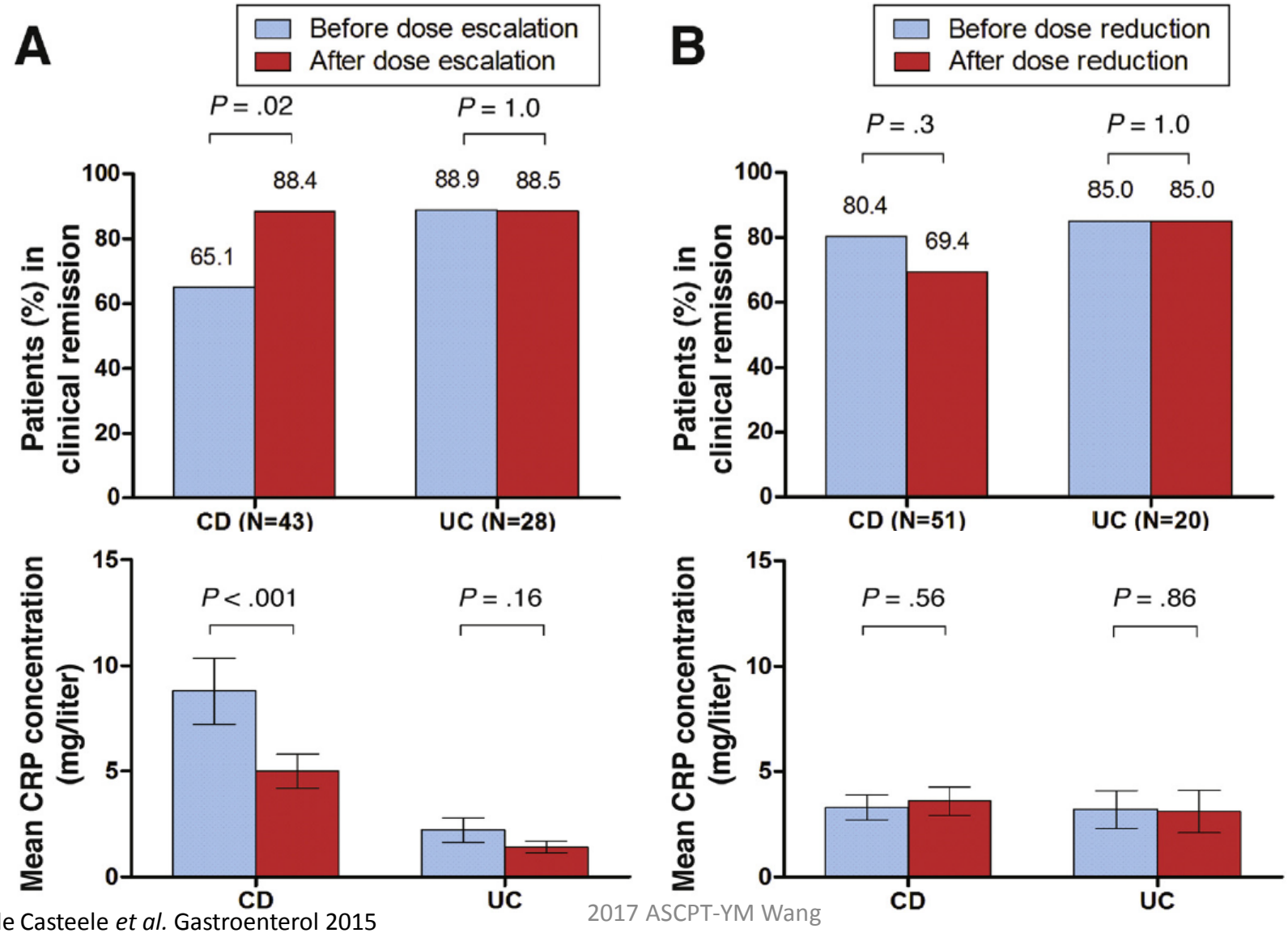
## infliximab maintenance therapy in UC/CD patients

- Aim: to compare the efficacy, cost-effectiveness, and safety of (1) concentration-based dosing vs. (2) clinically based dosing
- On infliximab for ≥ 14 weeks, in stable clinical response (n=263)
- Dose optimization to reach trough concentration = 3-7 mcg/mL




Vande Casteele *et al.* Gastroenterol. 2015

# TAXIT Trial – Dose Optimization Outcome



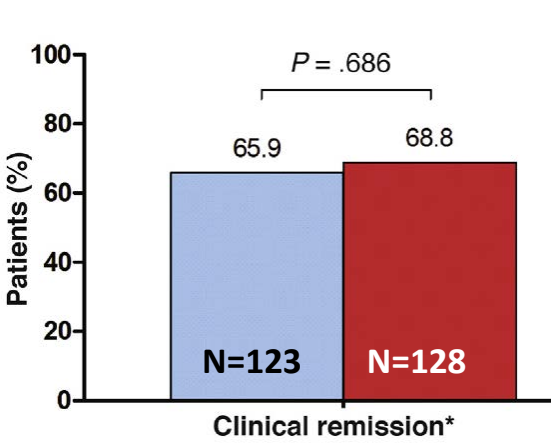

Vande Casteele *et al.* Gastroenterol 2015

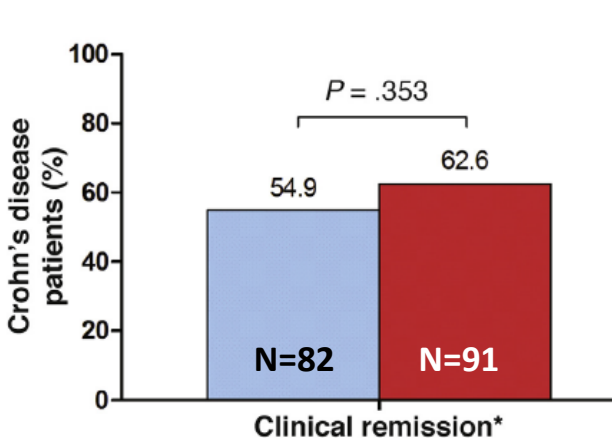
# Prospective Study (TAXIT trial)

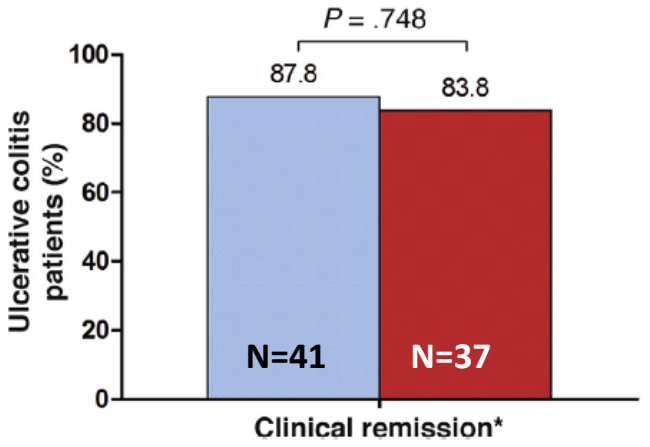
- N=251 successfully dose optimized with trough level = 3-7 mcg/mL
- Randomized (1:1) to maintenance dose adjustment
  - By clinical features – Clinically based dosing group
  - By trough concentrations – Concentration-guided dosing group
- Treatment for 1 year

Clinically based dosing
Concentration-based dosing

**Conclusions:** Continued concentration-based dosing was not superior to clinically based dosing for achieving remission, but was associated with fewer flares during the course of treatment.




Vande Casteele *et al.* Gastroenterol 2015

# Emerging Knowledge May Require Additional Considerations for TDM

- Advancing from managing secondary treatment failures to preventing it with aggressive initial treatment (top-down approach)
  - Aim to reach a target concentration range early
  - When to measure? What's the target concentration range?
- Further granularity of immunogenicity, e.g., transient ADA, persistent ADA, neutralizing activity
  - What's the characteristics of ADA?
  - How do they affect the therapeutic management?
- Many drugs for chronic indications are available in fixed dose pre-filled syringes or auto-injectors
  - How much flexibility for dose individualization?

# Considerations Regarding Technical Tools

- An increasing number of suppliers for drug assay and ADA assay using various technologies; e.g., laboratory developed test (LDT)
- ➢ Will results from all assays lead physicians to the same dosing decision?

| Test provider | Methodology | Infliximab levels | Anti-infliximab antibody levels | Adalimumab levels | Anti-adalimumab levels |
|---|---|---|---|---|---|
| A | Reporter gene luminometry | Yes | Yes | Yes | Yes |
| B | ECLIA | Yes | Yes | Yes | Yes |
| C | LC-MS/MS | Yes | Yes | N/A | N/A |
| D | HMSA | Yes | Yes | Yes | Yes |
| E | ELISA | Yes | Yes | Yes | Yes |

ECLIA, electrochemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; HMSA, homogenous mobility shift assay; LC-MS/MS, liquid chromatography, tandem mass spectrometry; N/A, test not available.

Sofia et al., Ther Adv Gastroenterl 2016

# Consideration for ADA Monitoring

- Drug interference in ADA assay – a prevalent issue in approved BLAs (2005-2011)
- ADA assay drug tolerance < Trough Css in 13 of 22 products
  - In some cases, drug tolerance < PK assay LLOQ (Lower Limit of Quantification)

* A simplified view for illustrative purposes: single fixed value for drug tolerance

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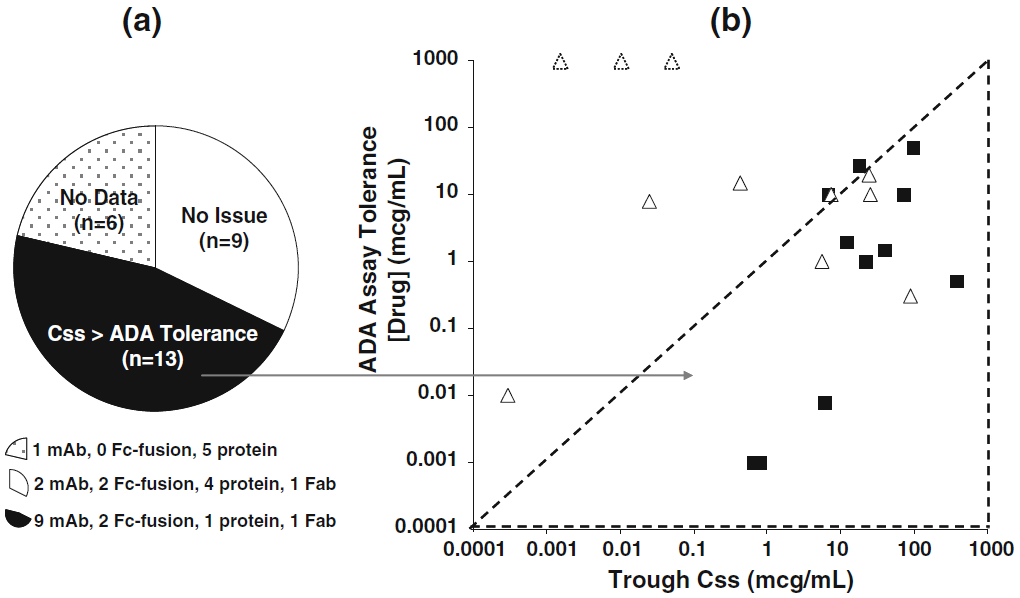
**A Survey of Applications of Biological Products for Drug Interference of Immunogenicity Assays**

*Wang et al., Pharm Res (2012) 29:3384–3392*



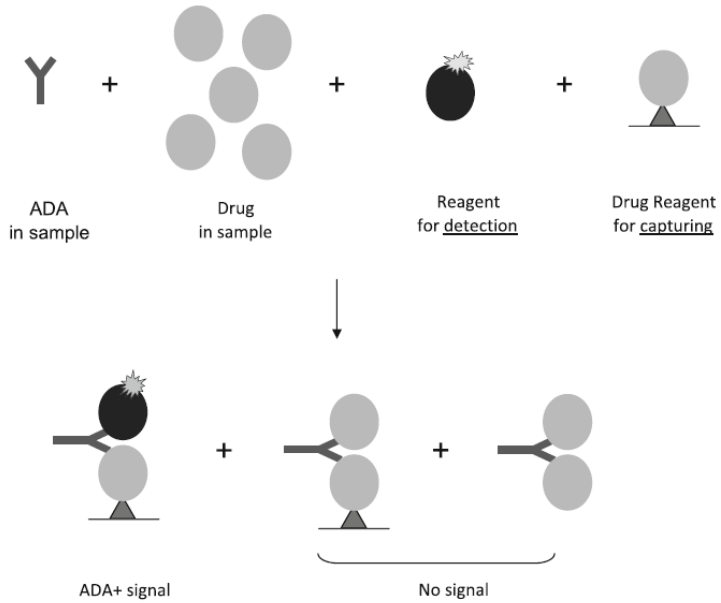
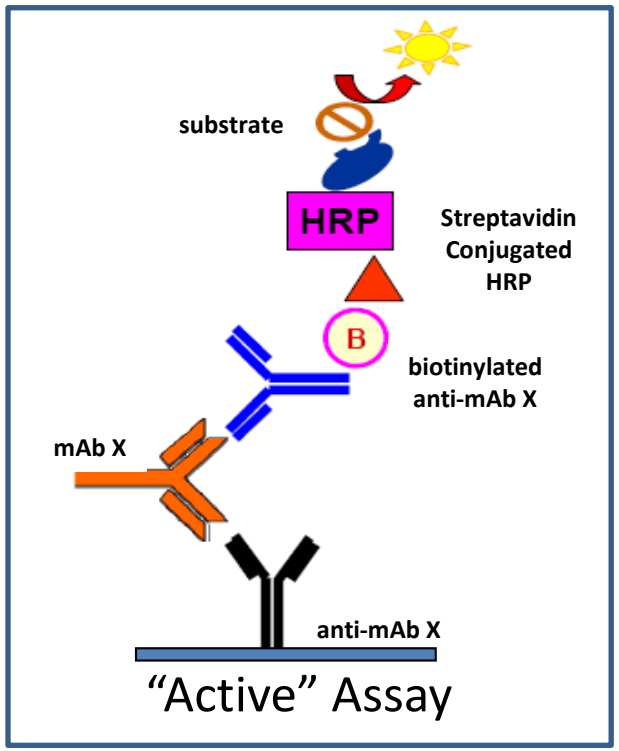
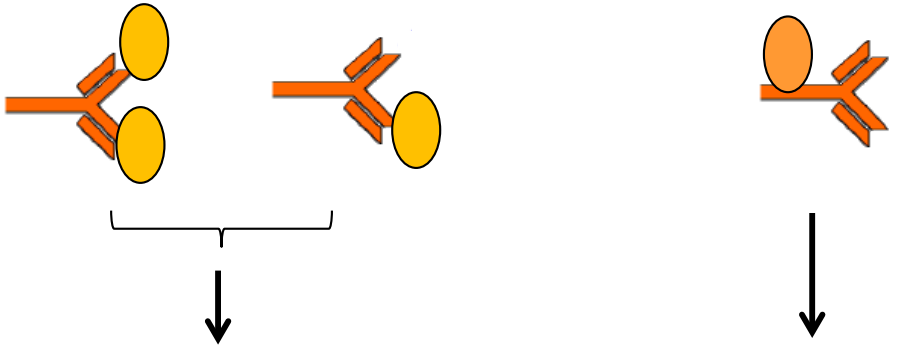




**Fig. 1** A schematic example of immunogenicity assay. (ADA: anti-drug antibody).

# Considerations for Drug Level Assay (1)

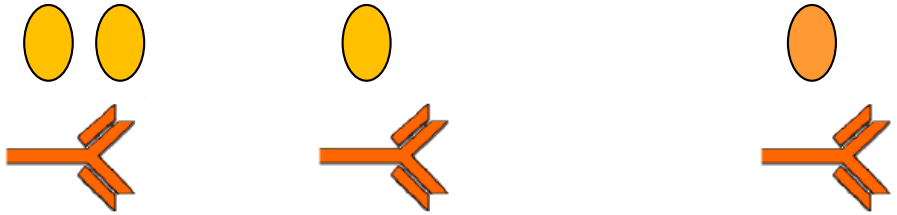




- PK assay in the presence of ADA (e.g., mAbs)
- With active drug assay for mAbs




**What if the assay measures total mAb concentration?**

- **e.g., the assay has an acid dissociation step…**

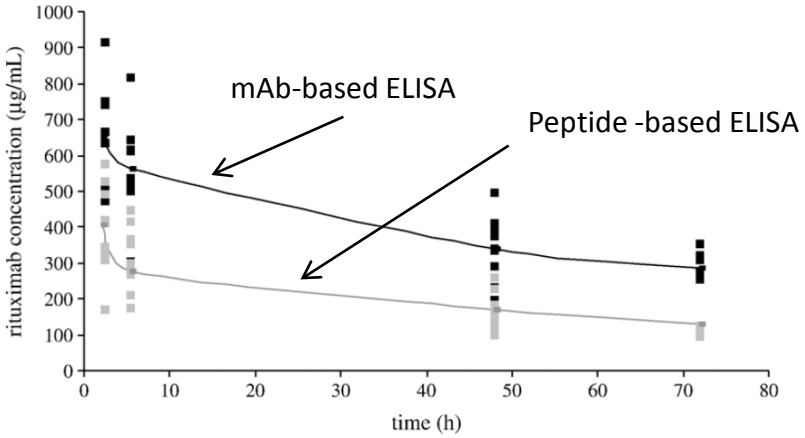


- **Will the effects of ADA on PK be detectable?**

# Considerations for Drug Level Assay (2)

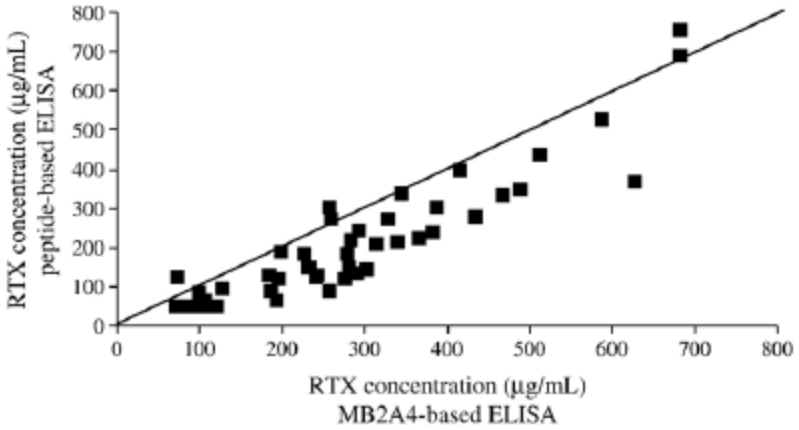
Example: ELISA for rituximab – assay reagents matter

Mouse data




Human data

Y = Peptide-based ; X = mAb-based




- Systematic differences in PK data from two assays
- Multiple possible reasons: differences in affinity, target interference, … etc.
  - Reagent-drug binding affinity differ by $10^4$ (mAb > peptide)
  - mAb can disrupt drug-target complex, detecting the target bound drug (i.e., total drug).
  - Peptide based assay detects the 'free' drug.

| | Capture reagent | Detection reagent |
|---|---|---|
| mAb | Anti-CDR mAb | Anti-h-IgG |
| Peptide | Target CD20 fragment | Anti-h-IgG |

Blasco 2007 J Immunol Methods

# Summary – Considerations for TDM (1)

- For dose individualization of biological treatment,
  - Adverse effects often are not a useful guide due to the nature of delayed manifestation.
  - PK (drug concentration level) may not be a reliable guide when treatments have response rates <100%.
  - It may be feasible by monitoring PK + response (PD/clinical).
- For management of loss of efficacy,
  - So far, research focused on monitoring PK + immunogenicity + response (PD/clinical)
- Emerging knowledge may require additional considerations
  - Impact of enhanced granularity of immunogenicity data
  - Drug product presentations & dosing flexibility

# Summary – Considerations for TDM (2)

- Fit-for-purpose assay tools
  - For institutional use, or national/international use
  - Suitability for use in TDM, e.g., turnaround time
- Fit-for-purpose studies
  - To guide institutional use of TDM, or
  - To support regulatory claim/labeling
- Soundness of TDM strategy from hypothesis generating studies, including how to address non-responders
- Robustness of prospective confirmatory evaluations of effectiveness & safety of TDM

# Acknowledgments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