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
Disclaimer

• 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

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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)

Dose-Response or Exposure Response of desired effect

Margin of safety

Separation by exposure or Delayed in time

Dose-Response or Exposure Response of undesired effect

Feature:
Upper bound not as obvious or immediately obvious

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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 4\textsuperscript{th} Element - Immunogenicity
(May result in secondary treatment failure)

- % of infliximab bound to anti-drug antibody (ADA) \(\uparrow\) over time
- Infliximab (S-), active drug, concentration \(\downarrow\) with \(\uparrow\) of ADA

Bendtzen \textit{et al.} Arthritis Rheumatism 2006

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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

<table>
<thead>
<tr>
<th>Week</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>196</td>
</tr>
<tr>
<td>4</td>
<td>187</td>
</tr>
<tr>
<td>12</td>
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<td>252</td>
<td>11</td>
</tr>
<tr>
<td>254</td>
<td>8</td>
</tr>
</tbody>
</table>

Weeks: 0 4 12 24 36 48 60 72 84 96 108 120 132 144 156

No. at risk
AAA− 196 151 135 118
AAA+ 76 59 43 29
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 Ahn1

- Reported Impact on PK + Efficacy
  - N = 16

- Concordance
  - PK + Efficacy
  - N = 14

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

8* w/ negative impact
6 w/ no impact

* 5 mAbs, 3 enzymes

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

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

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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?
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

- 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

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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

![Graph showing response to dose escalation](graph)

Strong predictor of mucosal healing

\[ \text{ATI} < 200 \text{ ng/mL} + \text{IFX} < 2 \text{ mcg/mL} \]

**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 $\geq 14$ weeks, in stable clinical response (n=263)
• Dose optimization to reach trough concentration = 3-7 mcg/mL
TAXIT Trial – Dose Optimization Outcome

A

- **Before dose escalation**
  - CD (N=43): 65.1%
  - UC (N=28): 88.4%

- **After dose escalation**
  - CD (N=43): 88.9%
  - UC (N=28): 88.5%

**Significance:**
- CD: \( P = 0.02 \)
- UC: \( P = 1.0 \)

B

- **Before dose reduction**
  - CD (N=51): 80.4%
  - UC (N=20): 69.4%

- **After dose reduction**
  - CD (N=51): 85.0%
  - UC (N=20): 85.0%

**Significance:**
- CD: \( P = 0.3 \)
- UC: \( P = 1.0 \)

- **Mean CRP concentration (mg/liter)**
  - CD: \( P < 0.001 \)
  - UC: \( P = 0.16 \)

  - CD: \( P = 0.56 \)
  - UC: \( P = 0.86 \)

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Vande Casteele *et al.* Gastroenterol 2015

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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

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.
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?

<table>
<thead>
<tr>
<th>Test provider</th>
<th>Methodology</th>
<th>Infliximab levels</th>
<th>Anti-infliximab antibody levels</th>
<th>Adalimumab levels</th>
<th>Anti-adalimumab levels</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>Reporter gene luminometry</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>B</td>
<td>ECLIA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>C</td>
<td>LC-MS/MS</td>
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<td>Yes</td>
<td>N/A</td>
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<td>HMSA</td>
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<tr>
<td>E</td>
<td>ELISA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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.
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

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

<table>
<thead>
<tr>
<th>Capture reagent</th>
<th>Detection reagent</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAb</td>
<td>Anti-CDR mAb</td>
</tr>
<tr>
<td>Peptide</td>
<td>Target CD20 fragment</td>
</tr>
</tbody>
</table>

• 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.

Y = Peptide-based ; X = mAb-based

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
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