THERAPEUTIC DRUG MONITORING: OVERCOMING THE HURDLES

Diane R Mould PhD FCP FAAPS
Projections Research Inc.
Diane Mould is president of Projections Research Inc., a consulting company working with the pharmaceutical industry.
GLOBAL PREVALENCE OF IBD

GLOBAL PREVALENCE OF RA

Age-standardized disability-adjusted life year (DALY) rates from Rheumatoid arthritis by country (per 100,000 inhabitants)
GLOBAL PREVALENCE OF PSORIASIS
## Comorbidity with RA

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (HTN)</td>
<td>122 (35.9)</td>
</tr>
<tr>
<td>Diabetes mellitus (DM)</td>
<td>105 (30.9)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>88 (25.8)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>66 (19.4)</td>
</tr>
<tr>
<td>Peptic ulcer disease (PUD)</td>
<td>35 (10.3)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>29 (8.5)</td>
</tr>
<tr>
<td>Chronic liver disease (CLD)</td>
<td>26 (7.6)</td>
</tr>
<tr>
<td>Ischemic heart disease (IHD)</td>
<td>25 (7.4)</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>23 (6.8)</td>
</tr>
<tr>
<td>Tuberculosis (TB)</td>
<td>15 (4.4)</td>
</tr>
<tr>
<td>Cardiovascular accidents (CVA)</td>
<td>13 (3.3)</td>
</tr>
<tr>
<td>Interstitial lung fibrosis (ILF)</td>
<td>9 (2.7)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>9 (2.7)</td>
</tr>
<tr>
<td>Chronic renal failure (CRF)</td>
<td>8 (2.4)</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>7 (2.1)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>Inflammatory bowel disease (IBD)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Other</td>
<td>36 (0.0)</td>
</tr>
<tr>
<td>Extraintestinal manifestations</td>
<td>Adverse effects of treatments</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Peripheral and axial arthritis</td>
<td>Steroids: cataracts, glaucoma, mood changes, osteoporosis...</td>
</tr>
<tr>
<td>Erythema nodosum, pyoderma gangrenosum, oral aphtae</td>
<td>Immunosuppressors: infections, neoplasia, liver toxicity, myelosuppression...</td>
</tr>
<tr>
<td>Uveitis, episcleritis, blepharitis</td>
<td>Biologics: infections, neoplasia, demyelinating disease, infusion</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>Reactions, drug-induced lupus</td>
</tr>
</tbody>
</table>

Many of the agents used to treat inflammatory diseases are MAbs

Complex pharmacokinetics
- Many factors impact MAb PK
- High interpatient variability
- PD affects PK

Currently high treatment failure rate in adult
- Many patients show no response to induction therapy (primary non-responders)
- Responders can lose response over time (secondary non-responders)

Frequently lower exposure in pediatrics than adults
- Higher failure rate in pediatrics

Some of the loss of response is due to ADA but in other patients, low trough levels were associated with poor outcomes

Association of low troughs with therapeutic failure
- Published studies of MAb PK don’t point to high variability but covariate impacts are large
  - Data from severe patients often not included in these assessments

Association of high clearance with therapeutic failures

M. Silverberg et al. Alimen Pharmacol Ther submitted 2017
Impact of low ALB and high ADA titer very large
- Low ALB or high ADA implies fast clearance

Impact of weight minor
- High weight, high clearance

Other factors
- Diabetes/hyperglycemia can increase clearance > 20%
- Concomitant immunosuppressants can decrease clearance by 20%
- Disease severity
- Route of administration can impact ADA
- FcRn saturation

MAINTAINING MEASURABLE CONCENTRATIONS IS IMPORTANT


ECCO = European Crohn’s and Colitis Organisation.
Unlike TDM for small molecules, MAbs generally don’t have narrow therapeutic window

- TDM application here is not to avoid adverse events, but potentially to improve efficacy

No prospective correlation between exposure (troughs) and response for many marketed MAbs

- What trough is appropriate?

Expect between subject variability for PD to be higher than PK

TNF antagonists have shown benefits in randomized controlled trials for inducing and maintaining clinical remission in inflammatory diseases.

Owing to the high variability in drug exposure, the use of therapeutic drug monitoring (TDM) has become common in clinical practice.
- Common in EU, Asia, middle east, Canada
- Less common in US

The use of TDM and individualized dose adjustments retrospectively shown to improve outcomes, and often reduce therapy costs.

Many US insurance companies do not reimburse for this expense
- TDM is not in the prescribing instructions for marketed MAbs
- No prospective trials showing clear benefit
  - While there are publications suggesting clinical benefit and cost reduction, most are retrospective
  - Need to test all MAbs? All indications?

Assay costs in US can be quite high ($250 to $2500 per assay)

Turnaround time long (5-7 days for contract labs) so information comes in after dose was administered.
  - Point of care assays needed

Difficulty in interpreting results (complex PK, increasing dose doesn’t always result in higher troughs)
Patients treated with therapeutic anti-TNF MAbs often dose adjusted to maintain concentrations above a therapeutic trough

- Panel A - shorten interval
- Panel B - Increase dose

Owing to the impact of multiple factors on PK, dose adjustment not intuitive
Incorporating TDM and Dashboards into Disease Management

- Are therapeutic failures due to insufficient drug exposure?
  - Can loss of response be reversed with appropriate dosing?
  - Can ADA be managed with dashboards?
- Can TDM combined with dashboard guided dosing reduce failure rate
  - Integration into workflow
  - How often to monitor
  - How to find the “right trough” for each patient
  - Many unanswered questions
- MAbs have complex PK but it’s a simple PK problem.
  - However underlying computations are complex
CDAI = Crohn’s disease activity index; CDEIS = Crohn’s disease endoscopic index of severity; CRP = C-reactive protein

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

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 and response - helps determine appropriate doses
48 kg, 250 mg
5.2 mg/kg every 8 weeks
CRP = 150
Albumin = 3.2

Note that not all patients require the same target concentration

- 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 4 weeks
CRP = 40
Albumin = 3.5

Much better
48 kg, 320 mg
5.2 mg/kg every 6 weeks
CRP = 5.0
Albumin = 3.8
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.
Correlations between low MAb exposure and loss of response or therapeutic failure
- Primarily retrospective

MAb PK quite different than small molecules
- Many possible routes for clearance
- MAb PK (and thus exposure) is influenced by multiple factors
  - Weight, albumin, concomitant administration of immune suppressants, ADA, disease type, and severity
  - High weight, low albumin, presence of ADA lack of concomitant immune suppressants and more severe disease usually indicates clearance is fast (and half-life is short)

Incidence of ADA associated with many factors
- Low dose, SC route of administration, manufacturing considerations, intermittent exposure
- Similar predictive factors regarding PK

Therapeutic drug monitoring potential
- Difficult to interpret
- Primarily retrospective evaluations

Dashboards being investigated to answer questions!
My thanks to Dr Stephen Hanauer and Dr Marla Dubinsky for their input

Questions? Send to DRMould@PRI-Home.net