Therapeutic Drug Monitoring in IBD

Lecture Objectives

• Definition and premises of therapeutic drug monitoring (TDM)

• Review data on TDM of biologics in IBD
  – Drug levels
  – Anti-drug antibody levels

Therapeutic Drug Monitoring

• Individualization of drug dosage by maintaining plasma or blood drug concentrations within a targeted therapeutic range

• Predicated on the assumptions that a definable relationship exists between dose and drug concentration, and between the drug concentration and pharmacodynamic effects

↑Dose  ➞  ↑Concentration  ➞  ↑Effectiveness

The premise of Therapeutic Drug Monitoring

Loss of Response (LOR)

• Objective evidence of recrudescent inflammation after successful induction and maintenance

• Occurs in up to 40% of patients

• Rule out other causes of treatment failure
  – Strictureing disease
  – Infection
  – Small intestinal bacterial overgrowth
  – Bile acid diarrhea
  – Irritable bowel syndrome
  – Chronic pain syndrome

Infliximab concentrations and outcomes in Crohn’s disease (CD)

Higher infliximab concentrations correlate with:

1. Higher rates of clinical remission and response
2. Lower values of C-reactive protein
3. Higher rates of endoscopic improvement

References:
Baert NEJM 2003; Maser CGH 2006; Colombel NEJM 2010; Steenholdt Scand J Gastro 2011; Cornillie Gut 2014; Imaeda J Gastroenterol 2014; Colombel Aliment Pharmacol Ther 2015

Trough levels of infliximab correlate with outcomes

Baer EA, Clin Gastroenterol Hepatol 2006
What is the optimal infliximab trough level?
- 1487 serum samples from 483 CD patients on maintenance IFX
  - Prometheus assay
  - Tls correlated with remission, defined as CRP <5.0 mg/L
  - A TL >2.79 μg/mL had a 77.6% specificity and 52.5% sensitivity for remission (AUC=0.681; 95% CI 0.632-0.731)

What is the optimal infliximab trough level?
- 53 with CD and 25 with UC
  - ELISA
  - Tls were correlated with mucosal healing (SES ≤3 or Mayo ≤1)
  - TL >5 μg/mL had 85% specificity and 39% sensitivity for mucosal healing

Defining the upper limit of the target infliximab trough levels
- Incremental gain in rates of mucosal healing in relation to infliximab trough level

Meta-analysis of studies of adalimumab TDM
- Of 13 studies that analyzed outcomes according to trough adalimumab level, only 1 study reported no correlation between high trough levels and clinical response
- Patients with therapeutic trough levels were more likely to be in clinical remission (OR 2.6; 95% CI: 1.79-3.77)
Factors that influence the PK of anti-TNF

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti Drug Antibodies (ADA)</td>
<td>Increased drug clearance</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>Reduced formation of ADA</td>
</tr>
<tr>
<td>Low albumin</td>
<td>Increased drug clearance</td>
</tr>
<tr>
<td>High baseline CRP</td>
<td>Increased drug clearance</td>
</tr>
<tr>
<td>Male sex</td>
<td>Increased drug clearance</td>
</tr>
<tr>
<td>High body size</td>
<td>Increased drug clearance</td>
</tr>
<tr>
<td>High TNF</td>
<td>Increased drug clearance</td>
</tr>
<tr>
<td>Loss of drug in the lumen</td>
<td>Increased drug clearance*</td>
</tr>
<tr>
<td>Genetic Variation of Fc-Receptor (FcRn)</td>
<td>Increased drug clearance**</td>
</tr>
</tbody>
</table>

*Bradnse Gastroenterology 2015
**Billiet Am J Gastroenterol 2016

Can immunomodulators reverse ADA and LOR?

- 23 patients (21 CD and 2 UC) on adalimumab monotherapy developed ADA and LOR
- Prescribed thiopurine (n = 14) or methotrexate (n = 9)
- 11 (48%) lost the ADA and had an increase in trough levels and restoration of response
- Median time to seroreversal 5 months

FDA Guidance on ADA

“SPONSORS SHOULD DEVELOP AND IMPLEMENT SENSITIVE (ADA) IMMUNOASSAYS COMMENSURATE WITH THE OVERALL PRODUCT DEVELOPMENT PROGRAM.

Concomitant assessment of levels of therapeutic protein product in the sample is recommended to assess the potential for the presence of the product to interfere with detection of antibody in the assay”

Anti-drug antibodies (ADA)

- Neutralizing ADA:
  - Bind to distinct functional domains of the therapeutic protein product and inhibit their activity
  - Increase clearance by forming immune complexes

SONIC: AZA decreased the formation of ADA

<table>
<thead>
<tr>
<th></th>
<th>Infliximab</th>
<th>Combination</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ADA at 30 wks</td>
<td>14.6%</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>Median trough 30 wks</td>
<td>1.6</td>
<td>3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median trough 46 wks</td>
<td>1.0</td>
<td>3.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Anti-drug antibodies (ADA)

- Non-neutralizing ADA:
  - Bind to areas of the therapeutic protein product other than specific functional domains
  - May exhibit a range of effects on safety and efficacy
  - Enhanced or delayed clearance of the protein
  - Induction of anaphylaxis
  - Diminished efficacy of the protein by causing uptake by FcR-expressing cells
  - Facilitation of epitope spreading, allowing the emergence of neutralizing antibodies
**Clinical significance of antibodies to adalimumab**

- 536 samples analyzed by HUMSA
- Effects of week 4 adalimumab concentration and immunomodulators on ADA formation

**Results:**
- ADA detected in 20% of patients after median of 34 (12.4-60.5) weeks
- ADA+ status correlated with lower drug concentration (p=0.001)
- Week 4 drug concentration <5 µg/mL associated with increased risk of development of ADA (HR=25.1; 95% CI 5.6 - 111.9)
- IMM co-treatment prevented ADA (HR=0.23; 95% CI 0.06 - 0.86)
- Both lower serum drug concentration (p=0.0213) and ADA (p=0.013) were independently associated with future CRP
- ADA+ status associated with LOR (OR=3.04; 95% CI 1.04 - 9.09)

**Managing patients with ADA – The early experience**

<table>
<thead>
<tr>
<th>Action</th>
<th>Response (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detectable ADA</td>
<td>Increase IFX</td>
<td>1/6 (17)</td>
</tr>
<tr>
<td>(n=18)</td>
<td>Change anti-TNF</td>
<td>11/12 (92)</td>
</tr>
</tbody>
</table>

**Transient vs. sustained ADA**

- 53 patients with ADA
  - Sustained ADA, 26/38 (68%)
  - Transient ADA, 15

- Transient ADA 2/15 (13%) discontinued IFX
Recapture of response with dose intensification

- No/Low ADA titer
- Higher ADA titers correlated with unsuccessful dose intensification

Recapture of response in patients with high ADA

- Patients with high ADA should be switched to an alternate anti-TNF

Recapture of response in patients with no ADA or low titer ADA

- Patients with no/low ADA should have dose escalation

Anti-TNF and ADA in secondary loss of response: Interpretation and course of action

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Drug, No/low ADA</td>
<td>Increased non-ADA-mediated clearance or insufficient bioavailability caused by ADA</td>
</tr>
<tr>
<td>Low Drug, High ADA</td>
<td>Low bioavailability caused by ADA</td>
</tr>
<tr>
<td>High Drug, No/low ADA</td>
<td>Pharmacodynamic issue (non-TNF-driven disease) or low drug concentration in inflamed bowel</td>
</tr>
<tr>
<td>High Drug, High ADA</td>
<td>False positive ADA</td>
</tr>
<tr>
<td>High Drug, Non-functional ADA</td>
<td></td>
</tr>
</tbody>
</table>

Potential roles of TDM of biologics

1) Management of loss of response ✓
2) Optimizing induction of response Limited data
3) Optimizing maintenance of response TAXIT
TAXIT

- 1-year randomized controlled trial
- 263 adults (178 with CD and 85 with UC)
- Full or partial responders on maintenance infliximab
- Optimization: Dose adjusted to target trough levels of 3–7 µg/mL
- Maintenance: Clinical (n=123) vs. trough-based (n=128) dosing
- Primary end point: Remission (clinical remission and CRP≤5) at 1 year after optimization phase

Optimization Phase

- 69 (91%) achieved level of 3–7 after dose escalation
- Decrease in median CRP (3.2 vs 4.3, p<0.001)
- 8 of 12 with detectable ATI were escalated successfully

- 67 (83%) achieved level of 3–7 after dose reduction
- 28% reduction in drug cost (P<0.001)

Dose escalation:
Effects on remission and CRP

Dose reduction:
Effects on remission and CRP
Maintenance Phase

- 133 Patients assigned to dosing of infliximab based on symptoms and EIM disease activity.
- 136 Patients assigned to dosing of infliximab based on infliximab trough concentration.
- 12 Patients discontinued the study due to adverse events.
- 4 Patients discontinued due to disease control.
- 1 Patient developed adverse drug reaction.
- 3 Patients lost to follow-up.
- 1 Patient was non-compliant.
- 2 Patients not evaluable.

111 Completed 52-week trial
103 Completed 52-week trial

Clinical response and clinical remission at week 6 by vedolizumab trough quartiles at week 6

- Patients (%) in Clinical Response:
  - Quartile 1: 20.6
  - Quartile 2: 47.3
  - Quartile 3: 65.5
  - Quartile 4: 74.1

- Patients (%) in Clinical Remission:
  - Quartile 1: 5.6
  - Quartile 2: 11.5
  - Quartile 3: 10.4
  - Quartile 4: 37.0

Percentage of patients in remission at 1 year after the optimization phase

- Clinical-based dosing: 65.9%
- Trough-level-based dosing: 90.8%

Endoscopic remission at week 10 by certolizumab trough quartiles at week 8

- AUC = 0.094

Clinical remission at week 52 by vedolizumab trough quartiles at week 46

Assays available in the United States

<table>
<thead>
<tr>
<th>Assay Provider</th>
<th>Type of assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prometheus</td>
<td>Liquid-phase mobility shift assay</td>
</tr>
<tr>
<td>Esoterix</td>
<td>Electro-chemi-luminescence immunoassay</td>
</tr>
<tr>
<td>ARUP</td>
<td>Cell Culture/Quantitative Chemiluminescent Immunoassay</td>
</tr>
<tr>
<td>Mayo</td>
<td>Liquid-chromatography tandem mass spectrometry (infliximab) ELISA (vedolizumab)</td>
</tr>
<tr>
<td>Miraca</td>
<td>ELISA</td>
</tr>
</tbody>
</table>
### Prometheus

<table>
<thead>
<tr>
<th>Drug</th>
<th>Limit of detection</th>
<th>ADA</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>1.0 μg/ml</td>
<td>&lt;3.1 U/ml</td>
<td>Trough &gt;3 μg/ml predicts CRP&lt;5.0*</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1.6 μg/ml</td>
<td>&lt;1.7 U/ml</td>
<td>Trough &gt;5 μg/ml predicts lower CRP†</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>1.6 μg/ml</td>
<td>1.6 U/ml</td>
<td></td>
</tr>
</tbody>
</table>

**Target ranges for drug trough levels not defined**  
**ADA low and high titers not defined**

*Vande Casteele, Gut 2015; †Marz DDW 2013; ‡Marz DDW 2013*

### Mayo

<table>
<thead>
<tr>
<th>Drug</th>
<th>Limit of detection</th>
<th>ADA</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>1.0 μg/ml</td>
<td>&lt;3.1 U/ml</td>
<td>If trough ≤ 5.0 μg/mL, reflex testing for ADA</td>
</tr>
<tr>
<td>Infliximab-dyyb</td>
<td>1.0 μg/ml</td>
<td>&lt;3.1 U/ml</td>
<td></td>
</tr>
</tbody>
</table>

**Target ranges for drug trough levels not defined**  
**ADA low and high titers not defined**

### Esoterix

<table>
<thead>
<tr>
<th>Drug</th>
<th>Limit of detection</th>
<th>ADA</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>0.4 μg/ml</td>
<td>&lt;22 ng/mL</td>
<td>ADA titers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low: 22-200</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interm: 201-1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High: &gt;100</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>0.6 μg/ml</td>
<td>&lt;25 ng/mL</td>
<td>ADA titers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low: 25-100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interm: 101-300</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High: &gt;300</td>
</tr>
</tbody>
</table>

**Target ranges for drug trough levels not defined**

### Miraca

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug range</th>
<th>ADA range</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>0.3-16 μg/ml</td>
<td>10-200 ng/mL</td>
<td>Target 3.5 -10.0 μg/ml</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Target 6.0 -12.0 μg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>2-60 μg/ml</td>
<td>35-500 ng/mL</td>
<td>Target &gt;40 μg/ml</td>
</tr>
</tbody>
</table>

Miraca also has assays for golimumab and ustekinumab

### ARUP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Limit of detection</th>
<th>ADA</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>0.65 μg/ml</td>
<td>&lt;1:20</td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>0.65 μg/ml</td>
<td>&lt;1:20</td>
<td></td>
</tr>
</tbody>
</table>

**Target ranges for drug trough levels not defined**  
**ADA low and high titers not defined**

### Limitations of TDM

- Expensive
- No point-of-care testing
- Multiple assays
- Ranges for “low” vs. “high” ADA titers not defined for several assays
- Limited data on  
  - Induction of remission  
  - Maintenance of remission  
  - Perianal disease  
  - Postoperative recurrence
Conclusions

- TDM is necessary in patients who experience loss of response
  - Understanding the mechanism of LOR allows for rational treatment decisions
- TDM identifies patients in remission or stable response who are being under- and over-treated with anti-TNF
  - If under-treated, dose increase normalizes CRP (TAXIT) and may decrease ADA
  - If over-treated, dose decrease reduces costs (TAXIT) and may improve safety
- More data are needed on the role of TDM in other settings

Practical Advice

- Strongly consider an immunomodulator when starting a biologic
- Immunogenicity against one anti-TNF predicts immunogenicity against future anti-TNF
- The availability of TDM may influence the choice of biologic
- Use the same assay in each patient
- Familiarize yourself with at least 2 assays
- Anticipate cost and logistical issues