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10th Gastro Foundation Weekend for Fellows; Spier Resort Centre, Stellenbosch

Use of Anti-TNF Antibodies, Drug Levels, and Other Serological Markers in IBD

Gerhard Rogler, Department of Gastroenterology and Hepatology, University Hospital Zürich
When do we need diagnostic and therapeutic markers in IBD patients?

**Symptoms**
- IBD Diagnosis

**IBD Diagnosis**
- Prognosis?
- Risk for complications?
- Guidance for treatment options?

**Fluctuating disease activity**
- Assessment of disease activity?
- Optimization of drug safety & side effects

**Surgery**
- Risk for postop recurrence?

Markers:
- **Calprotectin**
- **CRP**
- **ASCA**, **ANCA**
- **Calprotectin**, **Trough levels**, **ADAs**; **CRP**, **TPMT activity**
Why do drug levels vary between patients?

• Antidrug antibodies causing clearance
• Immunosuppression decreasing clearance
• High concentrations of TNF causing clearance
• Drug loss through inflamed colonic mucosa
• Male gender – increased drug loss
• Body size – either high or low
Anti-TNF drug levels and anti-drug antibodies

Trough levels of anti-TNF
- Are significantly lower in patients losing response to this treatment
- Are significantly lower in patients without mucosal healing

Antibodies against anti-TNF
- Are more frequent in patients losing response to anti-TNF
- Are associated with low trough levels of anti-TNF
- Are associated with infusion reactions
- May fluctuate over time
Subgroup of patients with detectable HACA or subtherapeutic IFX concentrations in whom changes were instituted and outcome was assessable

<table>
<thead>
<tr>
<th></th>
<th>Response to test</th>
<th>Response</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Detectable HACA</strong></td>
<td>Increase IFX</td>
<td>1/6 (17%)</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td></td>
<td>Change anti TNF</td>
<td>11/12 (92%)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtherapeutic</strong></td>
<td>Increase IFX</td>
<td>25/29 (86%)</td>
<td>&lt;0.016</td>
</tr>
<tr>
<td></td>
<td>Change anti TNF</td>
<td>2/6 (33%)</td>
<td></td>
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*Afif Am J Gastro 2010;105:1133-39*
Hintergrund und Fragestellung

- ADAs- and Adalimumab serum levels were measured in 20 IBD-patients at different time points after s.c. injection (eow)
  - day 1 after injection, day 5, day 10–13, day 14 („trough level“).

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 5</th>
<th>Day 10–13</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab Concentration in Serum (µg/mL, Median)</td>
<td>3,7</td>
<td>3,95</td>
<td>4,4</td>
<td>4,25</td>
</tr>
<tr>
<td>Anti Drug Antibody Concentration in Serum (µg/mL, Median)</td>
<td>1,2</td>
<td>0,95</td>
<td>1,3</td>
<td>0,78</td>
</tr>
</tbody>
</table>

Only mild variation of serum levels. Under s.c. therapy time point of measurement seems to be less crucial.

Predictors of a “loss of response”

Prospective, monocentric study in Essen, 82 patients, 29 (35.4%) had a stable remission and 46 patients (56.1%) developed SLR (defined as dose escalation, interval shortening or change of therapy)

<table>
<thead>
<tr>
<th></th>
<th>Stable remission</th>
<th>SLR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>albumin</td>
<td>37,6 g/dL</td>
<td>34,4 g/dL</td>
<td>&lt;0,05</td>
</tr>
<tr>
<td>gamma-globulin</td>
<td>12,8 g/dL</td>
<td>17,4 g/dL</td>
<td>0,001</td>
</tr>
</tbody>
</table>

Low albumin levels and high gamma-globulin levels BEFORE therapy start are associated with a LoR

ECCO 2017  DOP035 Schoenefuss F., Hoffmann P.: High gammaglobulin and low albumin serum levels independently predict secondary loss of response to anti-TNFα therapy in IBD
Transient vs. Sustained ADAs

**Transient ADA (n=15)**

**Sustained ADA (n=38)**

How to interpret levels when loss of response?

Symptoms suggesting loss of response

Trough levels detectable

- Calprotectin/Endoscopy shows active inflammation
  - Switch to drug with different mode of action (non-anti-TNF)

- Endoscopy shows no inflammation
  - Rule out stenosis; consider treating IBS symptoms (mebeverine, otilonium,...)

Trough levels undetectable

- Antibodies high >8 mg/L equivalents
  - Switch within class

- No or low antibodies <8 mg/L equivalents
  - Optimize with same anti-TNF (decrease interval, increase dose, add immunomodulator)
Using trough levels to manage loss of response

1. Yes (i.e., LOR to a-TNF)
   - IBD-related inflammation?
     - Yes
       - Adequate drug trough level?
         - No (i.e., no LOR to a-TNF)
           - Fibrotic stricture?
             - Yes
               - Surgery, endoscopic dilation
             - No
               - IBS, BOG, BSD, cancer infection?
                 - No
                   - Switch anti-TNF or still intensify dose (?) + add immunomodulator (?) or corticosteroids?
                 - Yes
                   - Switch / add a different class
     - Yes
       - Anti-drug antibodies?
         - No
           - Intensify dose?
         - Yes
           - Switch anti-TNF or still intensify dose (?) + add immunomodulator (?) or corticosteroids?
   - No
     - Adequate drug trough level?
       - No
         - No
         - Yes
           - Switch / add a different class

Ben Horin APT 2011
Infliximab trough levels (TLI) and antibody to infliximab levels (ATI) were measured with the Leuven in-house developed direct ELISA and bridging ELISA, respectively.

**TAXIT algorithm**

- **TLI measurement**
  - **undetectable TLI** (TLI < 0.3 µg/ml)
    - **ATI measurement**
      - **high ATI level** (ATI > 8 µg/ml) → **STOP**
      - **low ATI level** (ATI < 8 µg/ml)
        - 1) interval decrease (by 2 weeks) to min 4 weeks
        - 2) dose increase (by 5 mg/kg) to max 10 mg/kg
  - **TLI < 3 µg/ml**
    - 1) interval decrease (by 2 weeks) to min 4 weeks
    - 2) dose increase (by 5 mg/kg) to max 10 mg/kg
  - **3 µg/ml ≤ TLI ≤ 7 µg/ml**
    - no dose adaptation
  - **TLI > 7 µg/ml**
    - interval increase (by 2 weeks)
Testing in patients who are responding to anti-TNF therapy: TAXIT study

- Undetectable TLI: 44%
- TLI < 3 μg/ml: 21%
- 3 μg/ml ≤ TLI ≤ 7 μg/ml: 9%
- TLI > 7 μg/ml: 26%
Results optimisation phase
Dose escalation (n=69)

CD: Harvey-Bradshaw ≤4 / UC: Partial MAYO ≤2

<table>
<thead>
<tr>
<th></th>
<th>Before optimisation</th>
<th>After optimisation</th>
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<tbody>
<tr>
<td>CD</td>
<td>64.3</td>
<td>88.1</td>
</tr>
<tr>
<td>UC</td>
<td>91.7</td>
<td>95.8</td>
</tr>
</tbody>
</table>

P=0.02 P=1.0

C-reactive protein (CRP) level

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<th></th>
<th>Before optimisation</th>
<th>After optimisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>6.4</td>
<td>3.0</td>
</tr>
<tr>
<td>UC</td>
<td>4.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

P<0.001 P=0.16

Dose escalation in Crohn’s disease patients with subtherapeutic levels results in a better disease control.
Results optimisation phase
Dose reduction (n=67)

CD: Harvey-Bradshaw ≤4 / UC: Partial MAYO ≤2

Before optimisation  After optimisation

CD (N=48)  UC (N=19)

P=0.60  P=1.0

81.4  94.4  74.4  88.9

C-reactive protein (CRP) level

Before optimisation  After optimisation

CD (N=48)  UC (N=19)

Mean CRP Concentration (mg/liter)

P=0.56  P=0.86

Successful dose de-escalation of patients with supra-therapeutic levels whilst retaining disease control
Biomarkers contribute to prediction of relapse in STORI

Predictive model for the time-to-relapse

Deleterious factors were:
- no previous surgery,
- steroid use within 12-6 months before infliximab withdrawal,
- male gender,
- haemoglobin $\leq 14.5$ g/dl,
- leukocyte count $> 6 \times 10^9$/l,
- hsCRP $\geq 5$ mg/l,
- faecal calprotectin $\geq 300$ µg/g,
- CDEIS $>0$,
- infliximab trough $\geq 2$ mg/l.
Conclusions

Anti TNF trough level and anti drug antibodies

- Show promise as a therapeutic guide
- Are particularly useful in patients losing response
- Require further work to define therapeutic ranges
Thank you for your attention