New Assay Generation for Antibodies Against Modified and Citrullinated Peptides Predicts Poor Response to TNF Inhibitor Therapy

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Disclosures

I have no relevant financial relationships to disclose

ACPAs delimit a subset of patients with a more severe RA disease

• Disease activity
  • Li H, et al. Clin Rheumatol. 2010

• Radiological progression

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• Radiological progression
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  • Shidara K, et al. Rheumatol Int. 2010

ACPAs delimit a subset of patients with a more severe RA disease

• Disease activity
• Radiological progression
• Disability
  • Predictor for restarting treatment

ACPAs delimit a subset of patients with a more severe RA disease

- Disease activity
- Radiological progression
- Disability
- Predictor for restarting treatment
- Therapy response

ACPAs and Therapy Response to TNF inhibitors

- Negative predictor:

- No association:

- Positive predictor:

AIMS

- To analyse several new ACPAs against antigens with additional post-translational modifications

- To analyse several new ACPAs against antigens with additional post-translational modifications

- To evaluate their predictive value for response to therapy using TNF inhibitors

Patient population

- Inflammatory polyarthritis, n=119
- Moderate or high disease activity (DAS28 ≥3.2)
- Diagnoses:
  - Rheumatoid arthritis (RA) (n=107, 89.9%)
  - Inflammatory polyarthritis (n=7, 5.9%)
  - Juvenile idiopathic arthritis (n=5, 4.2%)

Descriptives of patients at start of TNF-inhibitor treatment

| Inclusion age, mean ±SD | 53 ±14 |
| Female sex, n (%) | 96 (81) |
| Disease duration, mean ±SD, years | 14 ±11 |
| Current smokers, n (%) | 22 (19) |
| Ever smokers, n (%) | 58 (50) |
| Any concomitant DMARD, n (%) | 97 (82) |
| Concomitant MTX, n (%) | 80 (67) |
| Combination DMARD, n (%) | 22 (18) |
| Oral corticosteroids, n (%) | 32 (27) |
| DAS28, mean ±SD | 5.7 ±1.2 |
ACPA analyses

Commercial ELISAs
- Anti-cyclic citrullinated peptide (Medipan) anti-CCP
- Anti-mutated citrullinated vimentin (Orgentec) anti-MCV

Research ELISAs
- Anti-modified mutated citrullinated vimentin anti-modMCV
- Anti-modified vimentin anti-modvim

Research enzyme-linked lectin assay (ELLA)
- Sialylated anti-mutated citrullinated vimentin sial anti-MCV

Negative control
- Anti-vimentin (all patients negative)

Specific ACPAs at start of treatment with TNF-inhibitor (n=119)

<table>
<thead>
<tr>
<th></th>
<th>Positive n (%)</th>
<th>High* n (%)</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CCP abs</td>
<td>102 (85.7)</td>
<td>95 (79.8)</td>
<td>917 133-2000</td>
</tr>
<tr>
<td>Anti-MCV abs</td>
<td>103 (86.6)</td>
<td>76 (63.9)</td>
<td>142 43-585</td>
</tr>
<tr>
<td>Anti-modMCV abs</td>
<td>75 (63.0)</td>
<td>46 (38.7)</td>
<td>40 11-154</td>
</tr>
<tr>
<td>Anti-modvim abs</td>
<td>38 (31.9)</td>
<td>6 (5.0)</td>
<td>13 8-29</td>
</tr>
<tr>
<td>Sial anti-MCV abs</td>
<td>118 (99.2)</td>
<td>40 (33.6)</td>
<td>44 37-68</td>
</tr>
</tbody>
</table>

*High refers to concentrations that are >3 times the positive cut-off limit for the assay

DAS28 and ACPAs

<table>
<thead>
<tr>
<th></th>
<th>ACPA +</th>
<th>ACPA -</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CCP</td>
<td>5.78 (1.18)</td>
<td>5.34 (1.2)</td>
<td>0.157</td>
</tr>
<tr>
<td>Anti-MCV</td>
<td>5.82 (1.18)</td>
<td>5.06 (1.02)</td>
<td><strong>0.016</strong></td>
</tr>
<tr>
<td>Anti-modMCV</td>
<td>5.88 (1.21)</td>
<td>5.46 (1.11)</td>
<td>0.062</td>
</tr>
<tr>
<td>Anti-modvim</td>
<td>5.63 (1.22)</td>
<td>5.76 (1.18)</td>
<td>0.589</td>
</tr>
</tbody>
</table>

Concentrations of ACPAs in current smokers and non-smokers

<table>
<thead>
<tr>
<th></th>
<th>Smokers</th>
<th>Non-smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CCP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-MCV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-modMCV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-modvim</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Definition of response

Adequate response
- DAS28<3.2 after three months of treatment with the TNF inhibitor

Poor response
- DAS28≥3.2 after three months of treatment with the TNF inhibitor

DAS28 at 3 months follow-up

Adequate response
- DAS28<3.2 after three months of treatment with the TNF inhibitor

Poor response
- DAS28≥3.2 after three months of treatment with the TNF inhibitor
DAS28 at 3 months follow-up

Risk for poor response

Baseline variable | OR  | 95% CI  
--- | --- | ---  
Anti-CCP pos | 1.987 | 0.698-5.611  
Anti-MCV pos | 4.138 | 1.377-12.432  
Anti-modMCV pos | 3.294 | 1.477-7.349  
Anti-modvim pos | 2.293 | 0.930-5.656  
Sial anti-MCV pos | NA  

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--- | --- | ---  
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Current smoking | 4.000 | 1.104-14.490  
DAS28 (high vs moderate) | 8.400 | 3.512-20.089  
Female sex | 1.084 | 0.415-2.830  
Age | 1.031 | 0.999-1.063  
Disease duration | 1.030 | 0.990-1.071  

Relative risks of poor response to first TNF-inhibitor for positive ACPAs

Variabel | Adjusted for smoking | Adjusted for disease activity* | Fully adjusted model* 
--- | --- | --- | ---  
Anti-CCP | 1.52 | 0.53-4.40 | OR 95% CI  
Anti-MCV | 3.27 | 1.07-9.99 | 2.34 | 0.68-8.08 | 1.61 | 0.44-5.98  
Anti-modMCV | 2.79 | 1.23-6.33 | 3.26 | 1.31-8.11 | 2.67 | 1.04-6.87  
Anti-modvim | 2.12 | 0.84-5.35 | 2.60 | 0.94-7.21 | 2.72 | 0.91-8.12  

*Disease activity moderate (DAS28 3.2-5.1) or high (DAS28 >5.1) at inclusion
*Adjusted for sex, age, smoking, disease activity

Significance level for model, p=0.013
Conclusions

- Antibodies against MCV or modified MCV significantly predicted an inadequate response to TNF inhibitor after 3 months of therapy
- Presence of antibodies against MCV or modMCV combined with current smoking resulted in an 8-10 times increased risk of poor response compared with a non-smoker with a negative test
- The individual ACPA status could represent a predictive factor for response to TNF inhibitors, particularly in conjunction with smoking habits

Significance level for model, p=0.018