Detection of IgG4-Specific Autoantibodies in Rheumatoid Arthritis Serum Samples

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Keywords
rheumatoid arthritis, pathogenesis, diagnosis, autoantibodies, IgG4, rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA)

Comments
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Detection of IgG4-Specific Autoantibodies in Rheumatoid Arthritis Serum Samples

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Introduction

• Rheumatoid arthritis (RA) is a chronic multi-system autoimmune disease characterized by inflammatory synovitis.
• Autoantibodies, such as anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF), are important serological markers that distinguish RA from other forms of inflammatory arthritis; yet many patients with RA do not have measurable ACPA or RF.
• IgG4 is the second most abundant isotype of ACPA and RF, after RF; but, it is not detected by diagnostic assays typically available.
• Patients deemed “sero-negative” by standard assays may actually have high titers of the IgG4-specific isotype of ACPA and RF[1].

Background

Table 1: 2012 ACR/EULAR classification Criteria for RA

<table>
<thead>
<tr>
<th>Score</th>
<th>Joint Involvement:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 large joint</td>
</tr>
<tr>
<td>1</td>
<td>2-10 large joints</td>
</tr>
<tr>
<td>2</td>
<td>1-3 small joints</td>
</tr>
<tr>
<td>3</td>
<td>4-6 small joints</td>
</tr>
<tr>
<td>4</td>
<td>&gt;10 joints (at least 1 small joint)</td>
</tr>
</tbody>
</table>

ACPA and RF are important components of the 2010 American College of Rheumatology/European League Against Rheumatism, classification criteria for early diagnosis of RA [2].

Methods

• In this cross-sectional study, we aim to enroll 1000 patients with confirmed RA according to the 2010 ACR/EULAR classification criteria.
• We are collecting clinical information about each patient including demographics, current treatments, disease activity measures, laboratory test results, and radiographs.
• Concurrently, we are collecting serum samples from each patient that will be analyzed for 1) Total levels of IgG4 & IgG1; 2) Total ACPA & RF; 3) Levels of IgG1- and IgG4-specific ACPA & RF; 4) Cytokine levels (TNF, IL-1, IL-6, IL-17, IFN-γ, IL-21, & G-CSF).

Results

• To date, we have recruited 102 RA patients with the following demographics [Table 2].

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td>Males</td>
</tr>
<tr>
<td>68.6% (N=70)</td>
<td>31.4% (N=32)</td>
</tr>
</tbody>
</table>

Table 2: Demographics characteristics of recruited subjects

<table>
<thead>
<tr>
<th>Disease Activity Score using 28 joints (DAS28)</th>
<th>RF +/ACPA-</th>
<th>RF-/ACPA+</th>
<th>RF+/ACPA+</th>
<th>RF+/ACPA-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission (DAS28 &lt;2.6)</td>
<td>12.2% (N=12)</td>
<td>21.2% (N=21)</td>
<td>61.2% (N=61)</td>
<td>6.1% (N=6)</td>
</tr>
<tr>
<td>Low Disease Activity (DAS28 &gt;2.6 &amp; &lt;3.1)</td>
<td>3.67 ± 1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mod Disease Activity (DAS 28 ≥3.2 &amp; &lt;5.1)</td>
<td>3.67 ± 1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Disease Activity (DAS28 ≥5.1)</td>
<td>3.67 ± 1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Early initiation of therapy with Disease Modifying Anti-Rheumatic Drugs (DMARDs), especially within the first 3 months of diagnosis, significantly reduces disease progression and morbidity of RA [2].

• To quantitate and compare levels of IgG4-specific ACPA and IgG4-specific RF in patients with RA.
• To correlate levels of IgG4-specific ACPA with disease activity, therapy, and serum cytokine levels.
• To assess whether a diagnostic test that detects the IgG4 isotype of ACPA or of RF will allow earlier diagnosis of RA.

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Current Status

• In a combined effort from 2 large medical centers, UMASS Memorial & UVM, over 100 subjects have been recruited, of whom data and sera have been collected.
• IgG1- and IgG4-specific ACPA & RF testing is being performed by Dr. Mercedes Rincon at University of Vermont Medical Center.
• Results from this large cross-sectional study should help to elucidate the role of IgG4-specific autoantibodies in the pathogenesis of RA and may aid in its early diagnosis.

References