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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 IgG1; but, it is not detected by diagnostic assays typically available.
- Patients deemed “sero-negative” by standard assays may actually have high titer of the IgG4-specific isotype of ACPA and RF[1].

Objectives

- To quantitate and compare levels of IgG1- and IgG4-specific ACPA and IgG1- 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.

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 2: Demographics characteristics of recruited subjects

| Age Mean ± SD | 58.4 ± 12.4 years |
| Sex           | Females | 68.6% (N=70) |
|              | Males   | 31.4% (N=32) |
| Disease Activity Score using 28 joints (DAS28) | Mean ± SD | 3.67 ± 1.0 |
| Serologic testing (from medical record) | RF + RF – | 54.0% (N=47) |
|              | ACPA + ACPA – | 70.0% (N=60) |
|              | RF+/ACPA+ RF–/ACPA– | 49.4% (N=43) |
|              | RF+/ACPA+ RF–/ACPA– | 19.5% (N=17) |
|              | RF+/ACPA+ RF–/ACPA– | 4.5% (N=4) |
|              | RF+/ACPA+ RF–/ACPA– | 27.9% (N=24) |

Medications

- DmARD therapy: Methotrexate: 71.6% (N=73) Other DMARD: 26.5% (N=27)
- Biologic therapy: Anti-TNF biologics: 27.5% (N=28) Other biologics: 12.7% (N=13)

*Percentages exclude the 15 patients with unknown serologies.

Background

- 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].

- IgG4 autoantibodies contribute to the pathogenesis of autoimmune disease, but their specific roles have not yet been elucidated.

- A recent study has shown that patients who lack IgG1-specific ACPA, and thus test negative for “total” IgG ACPA, have detectable IgG4-specific ACPA[1].

- Treatment with tocilizumab, a humanized anti-IL-6 receptor monoclonal Ab, markedly decreases levels of IgG4-specific ACPA, but does not affect “total” ACPA or IgG1-specific ACPA[1].

References