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Detection of IgG4-Specific Autoantibodies in Rheumatoid Arthritis Serum Samples

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Comments
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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 titers of the IgG4-specific isotype of ACPA and RF[1].

Background

Table 1: 2012 ACR/EULAR classification Criteria for RA	Score
Joint involvement:	
1 large joint	1
2-10 large joints	2
1-3 small joints	3
4-10 small joints	4
>10 joints (at least 1 small joint)	5
Serology:	
RF- and ACPA-	0
Low + RF or low + ACPA	2
High +RF or high +ACPA	3
Acute Phase Reactants:	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of symptoms:	
<6 weeks	0
≥6 weeks	1
Score of ≥6 /10 indicates definite RA	

- 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].
- ACPA and RF are important components of the 2010 American College of Rheumatology/European League Against Rheumatism, classification criteria for early diagnosis of RA [3].
- 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 detectible 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].

Objectives

- To quantitate and compare levels of IgG1- and IgG4-specific ACPA and of 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, IFNγ, 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 Males	68.6% (N=70) 31.4% (N=32)
Disease Activity Score using 28 joints (DAS28)	Mean ±SD Remission (DAS28 <2.6) Low Disease Activity (DAS28 >2.6 & <3.1) Mod Disease Activity (DAS 28 >3.2 & <5.1) High Disease Activity (DAS28 >5.1)	3.67 ± 1.0 12.2% (N=12) 21.2% (N=21) 61.2% (N=61) 6.1% (N=6)
***Serologic testing (from medical record)**	RF + RF – ACPA + ACPA – RF+/ACPA+ RF-/ACPA+ RF+/ACPA- RF-/ACPA-	54.0% (N=47) 46.0% (N=40) 70.0% (N=60) 30.0% (N=27) 49.4% (N=43) 19.5% (N=17) 4.5% (N=4) 27.9% (N=24)
Medications	DMARD therapy: Methotrexate Other DMARD Biologic therapy: Anti-TNF biologics Other biologics	 71.6% (N=73) 26.5% (N=27) 27.5% (N=28) 12.7% (N=13)
*Percentages exclude the 15 patients with unknown serologies.		

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 .

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