

2015-04-29

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Azra Borogovac

*University of Massachusetts Medical School*

Younna Lahoud


*University of Massachusetts Medical School*

Janice Weaver

*University of Massachusetts Medical School*

*See next page for additional authors*

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## Repository Citation

Borogovac, Azra; Lahoud, Younna; Weaver, Janice; Cooper, Sheldon M.; Rincon, Mercedes; Kay, Jonathan; and Gravallesse, Ellen M., "Detection of IgG4-Specific Autoantibodies in Rheumatoid Arthritis Serum Samples" (2015). University of Massachusetts Medical School. *Senior Scholars Program*. Paper 192.  
<https://escholarship.umassmed.edu/ssp/192>

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## **Authors**

Azra Borogovac, Youmna Lahoud, Janice Weaver, Sheldon M. Cooper, Mercedes Rincon, Jonathan Kay, and Ellen M. Gravallese

## **Keywords**

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

## **Comments**

Poster presented on Senior Scholars Presentation Day at the University of Massachusetts Medical School, Worcester, MA, on April 29, 2015. Medical student Azra Borogovac participated in this study as part of the Senior Scholars research program at the University of Massachusetts Medical School.

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

Azra Borogovac, BA<sup>1</sup>; Youmna Lahoud, MD<sup>1</sup>; Janice Weaver, CCRP<sup>1</sup>;  
Sheldon M. Cooper, MD<sup>2</sup>; Mercedes Rincon, PhD<sup>2</sup>; Jonathan Kay, MD<sup>1</sup> and Ellen Gravallesse, MD<sup>1</sup>

<sup>1</sup>University of Massachusetts Medical School Worcester, MA

<sup>2</sup>University of Vermont Medical Center, Burlington, VT

## 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

Classification Criteria for RA	Score
<b>Joint involvement:</b>	
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
<b>Serology:</b>	
RF- and ACPA-	0
Low + RF or low + ACPA	2
High +RF or high +ACPA	3
<b>Acute Phase Reactants:</b>	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
<b>Duration of symptoms:</b>	
<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
  - Total levels of IgG4 & IgG1;
  - Total ACPA & RF;
  - Levels of IgG1- and IgG4-specific ACPA & RF;
  - Cytokine levels (TNF, IL-1, IL-6, IL-17, IFN $\gamma$ , IL-21, & G-CSF).

## 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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## Results

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

<b>Age</b>	Mean $\pm$ SD	58.4 $\pm$ 12.4 years
<b>Sex</b>	Females Males	68.6% (N=70) 31.4% (N=32)
<b>Disease Activity Score using 28 joints (DAS28)</b>	Mean $\pm$ 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 $\pm$ 1.0 12.2% (N=12) 21.2% (N=21) 61.2% (N=61) 6.1% (N=6)
<b>*Serologic testing (from medical record)</b>	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)
<b>Medications</b>	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.		