

Effect of methotrexate on response to Covid-19 mRNA vaccines in patients with Autoimmune Inflammatory Rheumatic Diseases: a longitudinal study



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Background/Purpose

Patients with autoimmune and inflammatory rheumatic diseases (AIIRD) have an increased risk of serious, life-threatening complications from COVID-19. These patients are treated with immunomodulatory medications, such as methotrexate (MTX) which has been shown to lower immune response to other vaccines. A number of studies indicate that the initial immune response to Covid-19 vaccine is decreased in patients on MTX. The CDC has recommended the administration of additional doses of COVID-19 vaccine in these patients. Longitudinal studies are required to assess the effect of MTX on the magnitude and quality of the immune response to the booster dose as compared to the initial COVID-19 vaccine. To this end, we evaluated the humoral response to Covid 19 mRNA vaccines at three timepoints: 8-12 weeks after the first dose of vaccine (postprime), 24-26 weeks after the first dose of vaccine (prebooster) and 2-4 weeks after booster (postbooster) in patients taking MTX in a multi-ethnic/racial cohort of patients with AIIRD. Control group consisted of vaccinated individuals without AIIRD.

METHODS

Participants:

- 22 patients with AIIRD on MTX receiving Covid-19 mRNA vaccine.
- 22 controls without AIIRD receiving Covid-19 mRNA vaccine.

Blood collection : 8-12 weeks after the first dose of vaccine (postprime)
24-26 weeks after the first dose of vaccine (prebooster)
2-4 weeks after booster (postbooster)

RBD and Spike binding IgG antibodies

Research-grade ELISA adapted from Mount Sinai protocol

RBD Ab: 96-well plates were coated with 2mg/ml of recombinant RBD protein and incubated overnight at 4°C. Plates were washed three times with PBS containing 0.1% Tween-20 blocked with PBS-T containing 3% (w/v) milk powder then incubated for 2h with samples diluted (1:50). Anti-human IgG horseradish peroxidase antibody diluted 1:3,000 was added.

Spike Ab : plates were processed as described above but using full-length spike protein for coating.

Neutralizing activity

V-PLEX SARS-CoV-2 pseudoneutralization assay (Meso Scale Discovery, Rockville, MD)

Precoated, multispot plates were blocked then reference standard, controls and samples diluted 1:100 and 1:1000 were added and incubated for 1h. MSD SULFO-TAG™ conjugated ACE-2 was added after which plates were read using a MESO SECTOR S 600 Reader. Percentage inhibition was calculated relative to the assay calibrator (maximum 100 % inhibition).

RESULTS

Table 1. Clinical and Demographic Characteristics of Study Participants

Characteristic	AIIRD (n=22)	Healthy (n=22)
Female, n (%)	18 (81.8)	17 (80.9)
Age mean (range) years	53.4 (23-73)	50.5 (30-67)
Race, n (%)		
Caucasian	12 (54.5)	11(50.0)
African American	9(40.9)	7(31.8)
Asian	1(4.5)	4(18.1)
Hispanic ethnicity	0(0.0)	0(0.0)
Diagnosis		
Rheumatoid arthritis	11(50.0)	--
Psoriatic arthritis	4(18.1)	--
Systemic Lupus Erythematosus	2(9.0)	--
Dermatomyositis	1(4.5)	--
Other connective tissue disease	2(9.0)	--
Sjögren's Disease	1(4.5)	--
Medication Exposure		
Mean dose, mg/wk (range)	17.8 (15-25)	--
Methotrexate monotherapy	12(54.5)	--
Methotrexate combination	10(45.4)	--
Tumor Necrosis Factor Inhibitor	5(22.7)	--
Hydroxychloroquine	2(9.0)	--
Prednisone	2(9.0)	--
Balimumab	1(4.5)	--
Abatacept	1(4.5)	--

SARS-CoV-2 specific IgG antibody

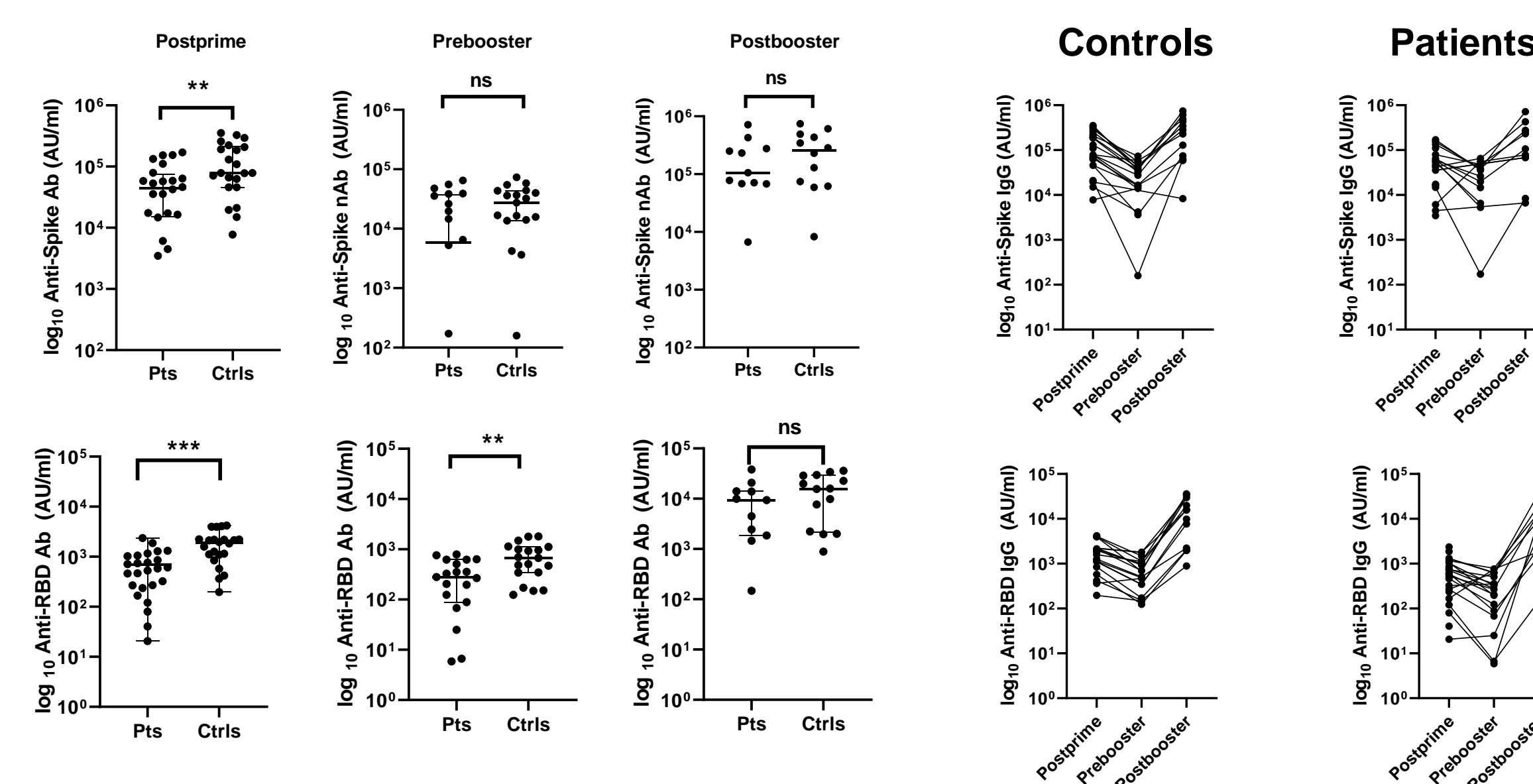


Figure 1. Participants received two doses of mRNA vaccines followed by a booster approx. 6 months later. Serum reactivity to Spike and RBD proteins was measured by ELISA at the specified timepoints. Data are shown as median ± IQR. Anti-Spike and anti-RBD IgG Abs could be detected in all study participants. Postprime titers were significantly lower in patients on MTX vs. controls and remained lower prebooster for anti-RBD but not anti-Spike Abs. Postbooster titers increased to levels similar to or higher than postprime levels and were comparable between groups.

Functional humoral immunogenicity

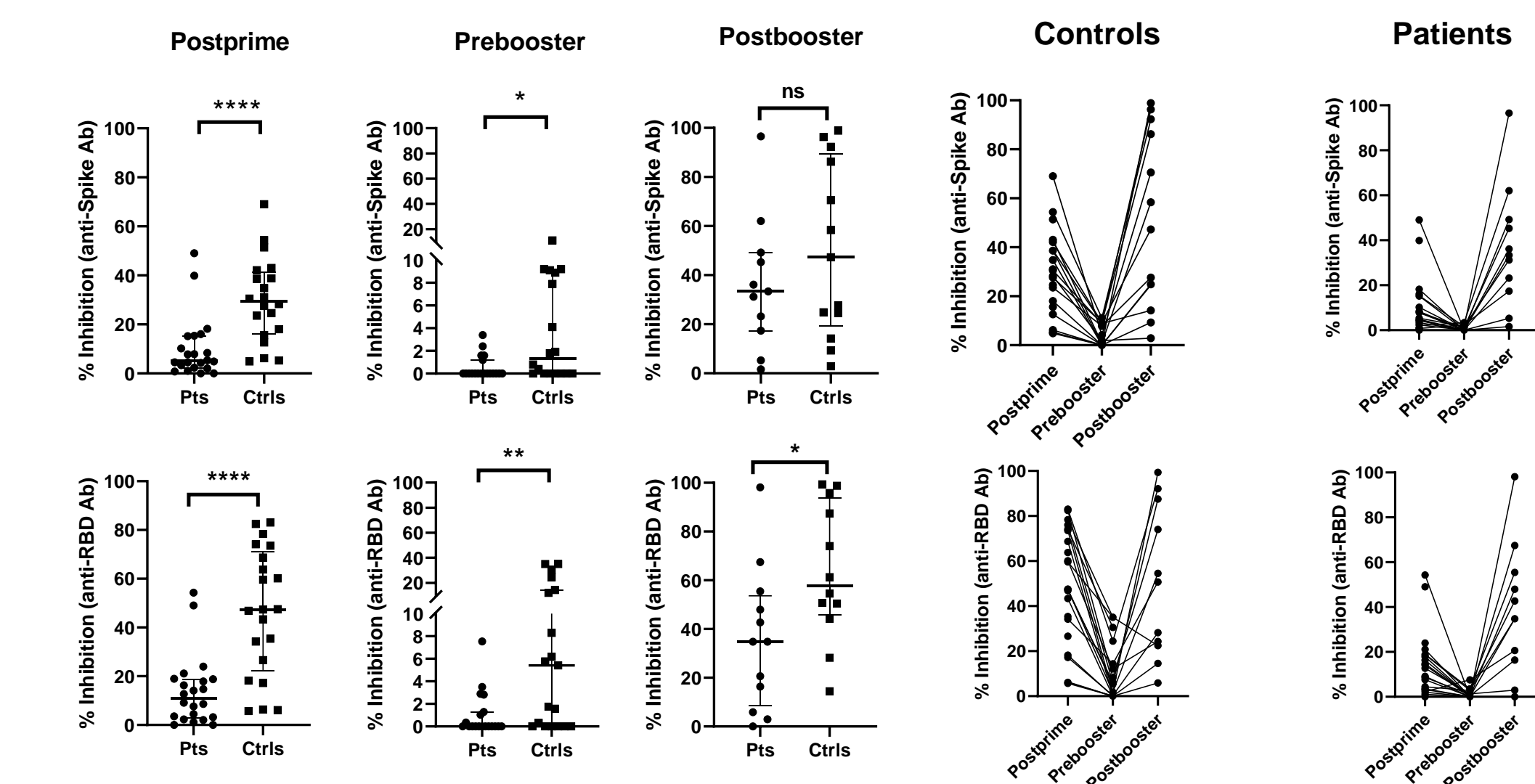


Figure 2. Neutralization capacity of serum anti-Spike and anti-RBD Abs against wild-type SARS-CoV-2. Significantly lower postprime and prebooster percentage inhibition in patients on MTX. Postbooster neutralizing activity of anti-Spike Abs increased to levels similar to or higher than postprime timepoint but remained significantly lower for RBD Abs in patients on MTX.

Impact of MTX discontinuation on vaccine response

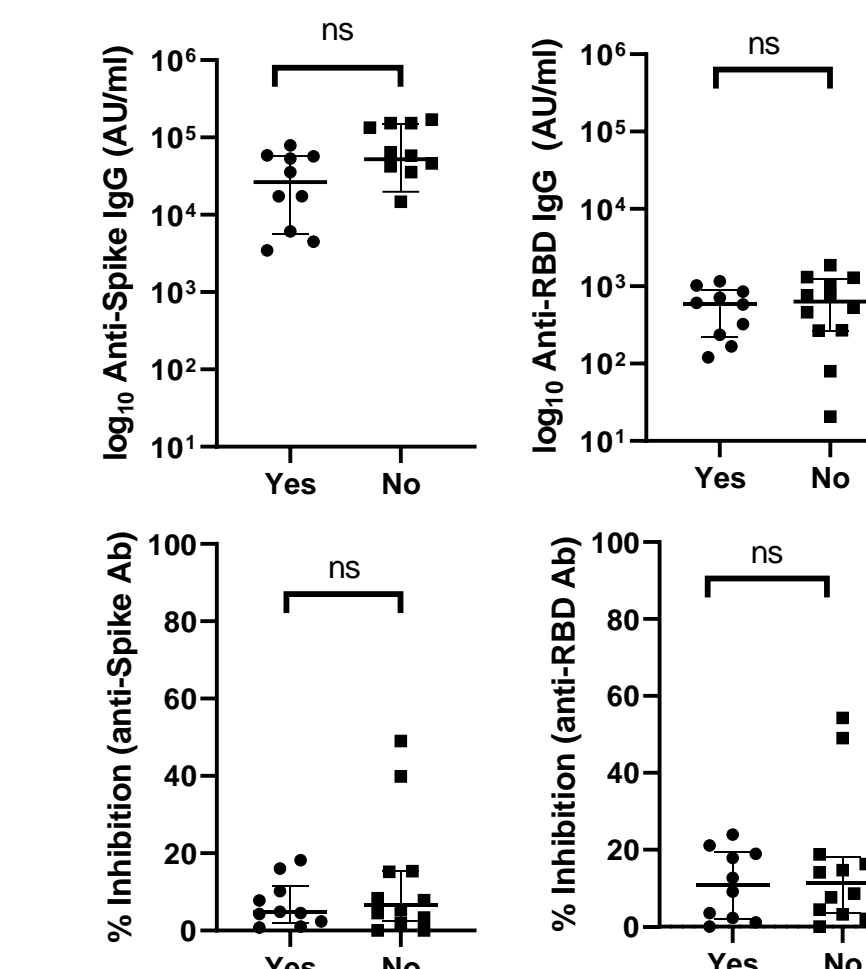


Figure 3. Temporary MTX discontinuation of variable duration after primary vaccine administration did not affect titers of anti-Spike or anti-RBD binding Abs or neutralizing activity.

CONCLUSIONS

- Patients with AIIRD on MTX had significantly reduced initial vaccine-induced humoral response as detected by binding and neutralizing assays for anti-Spike and RBD Abs
- The third mRNA booster significantly improved humoral response in AIIRD patients on MTX
- This study supports a third mRNA booster in AIIRD patients on MTX

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