Physical Activity Associates with Greater Antibody Persistence through 6 Months after the Second Dose of CoronaVac in Patients with Autoimmune Rheumatic Diseases

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Abstract

This study aimed to investigate the association between physical activity and persistent anti-SARS-CoV-2 antibodies 6 months after two-dose schedule of CoronaVac in autoimmune rheumatic diseases (ARD) patients. This was a prospective cohort study within an open-label, single-arm, phase 4 vaccination trial (clinicaltrials.gov #NCT04754698), conducted at a tertiary referral hospital in Sao Paulo, Brazil. ARD patients aged ≥18 underwent a two-dose schedule of CoronaVac (Sinovac Life Sciences, China). Persistent immunogenicity 6 months after the full-course vaccination was assessed using seroconversion rates of total anti-SARS-CoV-2 S1/S2 IgG, geometric mean titers of anti-S1/S2 IgG (GMT), and frequency of positive neutralizing antibodies (NAb). Physical activity was assessed trough questionnaire (active being defined as ≥150 min/week of moderate-to-vigorous physical activity). Physically active (n=421) and inactive (n=327) ARD patients were similar for most characteristics; however, active patients were significantly younger (p<0.001), had less chronic inflammatory arthritis (p<0.001) and less frequently used biologic agents (p<0.001) than inactive ones. Six months after full-course vaccination, being male (p<0.001), use of prednisone (p<0.01) and biologics (p<0.001) were associated with poor immunogenicity, while being physically active was associated with better humoral response (p<0.01). Adjusted point estimates from logistic regression models indicated greater odds of seroconversion rates (OR: 1.5 [95%CI: 1.1 to 2.1]) and NAb positivity (OR: 1.5 [95%CI: 1.0 to 2.1]) in physically active patients and approximately 43% greater GMT (42.8% [95%CI: 11.9 to 82.2]) than inactive ones. In conclusion, among immunocompromised patients, being physically active was associated with an increment in antibody persistence through 6 months after a full-course of an inactivated SARS-CoV-2 vaccine.

Introduction

Vaccine-induced antibody titers and effectiveness against symptomatic coronavirus infection disease 2019 (COVID-19) have been shown to wane over time. Neutralizing antibodies (NAb) against the B1.351 (Beta) variant were reduced considerably by 6 months among individuals who received the second dose of mRNA-1273 (Moderna's mRNA vaccine).[1] In addition, humoral response in general population was substantially decreased 6 months after receipt of the second dose of BNT162b2 (Pfizer–BioNTech's mRNA vaccine), especially among men, persons ≥ 65 years of age, and persons with immunosuppression, with a parallel increase in cases and hospitalization reported in Israel.[2,3] CoronaVac (Sinovac's inactivated vaccine) is a World Health Organization (WHO) approved vaccine for emergency use that has been shown to be effective in preventing severe cases of COVID-19[4] and is increasing the global supply through COVAX.[5] Individuals who received a two-dose schedule of CoronaVac also exhibited a decline in NAb seropositivity by 6 months after full course of vaccination in the general population.[6] Of note, the same pattern of immunity waning was observed for autoimmune rheumatic disease (ARD) patients vaccinated with CoronaVac, without a concomitant increase in cases or hospitalization, despite the Delta variant spread.[7]

In a global scenario with shortage and inequity of vaccines, and heterogeneous responses to vaccination, it is key to gathering knowledge on potential risk factors associated with poor persistence of immunity in order to develop strategies to enhance immunogenicity durability, as well as to prioritize individuals to receive a booster dose. In this regard, there is evidence suggesting that physical activity may act as an adjuvant to vaccines.[8,9] Among immunocompromised patients vaccinated with two doses of CoronaVac, those who were physically active exhibited higher titers and seroconversion rates than their inactive counterparts.[10] Whether active individuals show a greater persistence of antibodies than inactive ones remain unclear.

This study aimed to investigate the association between physical activity and persistent humoral immune response 6 months after a two-dose schedule of CoronaVac in patients with ARD.

Methods

This was a prospective cohort study within an open-label, single-arm, phase 4 vaccination trial (clinicaltrials.gov #NCT04754698), conducted at a tertiary referral hospital in Sao Paulo, Brazil. The protocol was approved by the institutional ethics committee. Written informed consent was obtained before participants' enrollment.

ARD patients aged ≥18 years and diagnosed with rheumatoid arthritis, systemic lupus erythematosus, axial spondyloarthritis, psoriatic arthritis, primary vasculitis, primary Sjögren's syndrome, systemic sclerosis, idiopathic inflammatory myopathies, and primary antiphospholipid syndrome were eligible. Detailed exclusion and inclusion criteria were described elsewhere.[11]

Patients underwent a two-dose schedule of CoronaVac (Sinovac Life Sciences, Beijing, China, batch #20200412).[11] The persistent immunogenicity 6 months after the full-course vaccination was assessed using seroconversion rates of total anti-SARS-CoV-2 S1/S2 IgG (considering values > 15.0 UA/mL), geometric mean titers of anti-S1/S2 IgG (GMT), and frequency of positive NAb (inhibition ≥ 30%). GMT and NAb assays are thoroughly described elsewhere. [10,11]

Using a telephone-based survey, typical levels of physical activity prior to vaccination were assessed in four domains: leisure time, household activities, work, and commuting. Participants were classified as physically active or inactive according to WHO Guidelines (i.e., physical inactivity defined as <150 min/week of moderate-to-vigorous intensity aerobic activity).[12]

Unadjusted analyses comparing active vs. inactive patients were performed using χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Model-based analyses were performed controlling for age (<60 or ≥60 years), sex, and body mass index (BMI) (<25 kg/m^2; 25–30 kg/m^2; >30 kg/m^2), use of prednisone, immunosuppressants and biologics. Immunogenicity data and physical activity status were added as fixed effects and we conducted logistic regression to estimate odds ratios (ORs) and 95%CIs with binary data obtained for rates of IgG seroconversion and NAb positivity. Also, we

conducted linear regressions for log transformed IgG. Linear regression coefficients and 95%CIs for log transformed dependent variables were back transformed and presented as percent changes. Analyses were conducted using R-statistical environment (R-4.1.0 for Windows).

Results

A total of 748 ARD patients were analyzed (Table 1 presents baseline characteristics). Physically active (n=421) and inactive (n=327) ARD patients were similar for most characteristics; however, active patients were significantly younger (p<0.001) had a lower frequency of chronic inflammatory arthritis (p<0.001), and less frequently used biologic (p<0.001) than inactive ones (Table 1).

Table 1
Baseline characteristics of patients with autoimmune rheumatic diseases (ARD) according to physical activity status.

	Active ARD (*n* = 421)	**Inactive ARD (*n* = 327)**	***p*-value**
Age, *years*	47.0 [39.0–59.0]	56.0 [45.0–65.0]	<0.001
Sex, f*emale*	322 (76.5)	248 (75.8)	0.838
Weight, *kg*	71.2 [61.3–82.0]	72.0 [60.0–83.6]	0.870
Height, *cm*	160.0 [155.0–166.0]	160.0 [154.0–167.0]	0.268
BMI, kg/m^2	27.5 [24.0–30.9]	27.5 [24.2–31.6]	
Overweight/obese	267 (63.6)	209 (63.9)	0.923
Caucasian race	218 (51.8)	187 (57.2)	0.141
Smoking	34 (8.1)	32 (9.8)	0.413
Comorbidities			
Systemic arterial hypertension	176 (41.8)	151 (46.2)	0.232
Diabetes mellitus	40 (9.5)	45 (13.8)	0.069
Dyslipidemia	114 (27.1)	99 (30.3)	0.337
Cardiomyopathy	27 (6.4)	19 (5.8)	0.734
Chronic renal disease	14 (3.3)	23 (7.0)	0.020
Chronic obstructive pulmonary disease	3 (0.7)	12 (3.7)	0.004
Asthma	17 (4.0)	12 (3.7)	0.796
Interstitial lung disease	21 (5.0)	39 (11.9)	0.001
Pulmonary hypertension	2 (0.5)	6 (1.8)	0.073
Hematologic disease	1 (0.2)	1 (0.3)	0.858
Hepatic disease	11 (2.6)	20 (6.1)	0.017
Cancer	4 (1.0)	4 (1.2)	0.719
Stroke	12 (2.9)	11 (3.4)	0.687
Tuberculosis	0 (0)	2 (0.6)	0.108
ARD			
Chronic inflammatory arthritis (RA, axSpA, PsA)	185 (43.9)	225 (69.1)	<0.001

	Active ARD (*n* = 421)	Inactive ARD (*n* = 327)	*p*-value
Other ARD (SLE, primary vasculitis, SSc, pSSj, IIM, PAPS)	236 (56.1)	102 (31.2)	<0.001
Current therapy			
Prednisone	155 (36.8)	138 (42.3)	0.126
Biologic	145 (34.4)	138 (42.2)	0.030
Immunosuppressants	263 (62.5)	216 (66.1)	0.311
Total physical activity, *min per week*	400.0 [252.0–720.0]	0.0 [0.0–75.0]	<0.001

Data are presented as median [interquartile range] and *n* (%). ARD, autoimmune rheumatic disease; BMI, body mass index; RA, rheumatoid arthritis; axSpA, axial spondyloarthritis; PsA, psoriatic arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; pSSj, primary Sjögren syndrome; IIM, idiopathic inflammatory myopathies; PAPS, primary antiphospholipid syndrome. Biologics include TNF inhibitor, abatacept, tocilizumab, belimumab, secukinumab, rituximab, ustekinumab. Immunosuppressants include methotrexate, leflunomide, mycophenolate mofetil, azathioprine, tofacitinib, cyclophosphamide, tacrolimus and cyclosporine. Total physical activity refers only to time spent in moderate-to-vigorous intensity activities.

Note: Missing data for weight and BMI (*n* = 1).

Figure 1 presents immunogenicity data for active vs. inactive ARD patients. Six months after vaccination, both seroconversion rates of total anti-SARS-CoV-2 S1/S2 IgG (53.1 vs. 40.7%; p=0.001) and frequency of positive NAb (31.2 vs. 22.0%; p=0.007) were significantly greater in ARD active vs. inactive patients. No differences were found in GMT between the two groups (both p>0.05).

Figure 2 presents the regression models controlling for covariates. Six months after the full course of vaccination, being male (p<0.001) and use of prednisone (p<0.01) and biologics (p<0.001) were associated with poor immunogenicity, while being physically active was associated with better immunogenicity (p<0.01).

Adjusted point estimates from logistic regression models indicated greater odds of seroconversion rates (OR: 1.5 [95%CI: 1.1 to 2.1]) and NAb positivity (OR: 1.5 [95%CI: 1.0 to 2.1]), and approximately 43% greater GMT (42.8% [95%CI: 11.9 to 82.2]) in physically active patients vs. inactive ones.

Discussion

This study shows that a physically active lifestyle associates with greater immunogenicity 6 months after a two-dose scheme of an inactivated SARS-CoV-2 vaccine among patients with dysfunctional immune system.

Immunocompromised individuals, such as those with ARD, may experience lower responses to different types of COVID-19 vaccines.[11,13] Booster doses have been considered for these individuals, but the shortage and inequitable distribution of vaccines across the globe may delay the delivery of extra doses for vulnerable populations. This might be a serious public health issue for many of the over 40 countries administering CoronaVac, particularly those with low and lower middle-income economies.

In this scenario, the identification of predictors of vaccine responses has major implications from clinical and public health perspectives. Recently, we showed that the ARD patients who were physically active exhibited greater seroconversion rates (OR: 1.4 [95%CI: 1.1-2.0]) and GMT (32% [95%CI: 8.8-60) vs. their inactive counterparts 6 weeks after the full course of vaccination.[10] Now, we extended this notion by showing that being physically active is also associated with greater persistent immune response 6 months after vaccination, evidenced by higher rates of seroconversion and neutralizing antibodies. Considering that the prevalence of seropositivity in response to CoronaVac decreased to 17% following 6 months in general population[14] and 23.8% in immunocompromised patients,[7] the 50% greater odds of IgG and NAb positivity rates observed herein in active vs. inactive ARD patients appears to be clinically meaningful. The associations observed also suggest that physical activity status may be more influential on antibody persistence than classical factors related to vaccine immunogenicity, such as older age and use of immunosuppressants.

Collectively, our studies conducted within this phase-4 trial suggest that the significant role of physical activity may not only enhance the humoral immunity to COVID-19 vaccination.[10], but also sustain its effects over time. This adds to numerous health benefits of being physically active, which includes prevention of several chronic diseases and protection against severe cases of COVID-19. In light of this, global strategies and public health policies focused on tackling physical inactivity become even more relevant and urgent, with special emphasis to individuals with dysfunctional immune system.

The main limitations of this study include its observational design, the lack of estimates of vaccine effectiveness and cell-mediated immune markers and the assessment of physical activity using a subjective tool. Finally, although this study used an inactivated vaccine, one may speculate that our results may be generalizable to other vaccine platforms that yield greater immunogenicity but that at the same time show a more pronounced 6-month decay in immunocompromised patients than Coronovac [2,7,11,13], suggesting a greater room for improvement with the other platforms.

In conclusion, among immunocompromised ARD patients, being physically activity was associated with greater antibody persistence through 6 months after a full-course of an inactivated SARS-CoV-2 vaccine.

Declarations

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AUTHOR CONTRIBUTIONS

N.E.A., S.G.P., A.C.M.R., C.G.S.S., E.F.N.Y, C.A.S. and E.B., conceived and designed the study, and supervised clinical data management. B.G., I.R.L., R.P.S., A.J.P., B.C.M., F.I.S., S.M.S., N.E.A., S.G.P., A.C.M.R., C.G.S.S., E.F.N.Y, C.A.S., H.R. and E.B participated in data collection. B.G., I.R.L., A.J.P., P.S., P.C.H. and H.R. analyzed and interpreted the data. B.G., H.R., and E.B. wrote the manuscript with inputs from all authors. All authors read and approved the final version.

COMPETING INTEREST STATEMENT

None declared.

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Data availability statement

All background and clinical information for ARD patients in this study are available from the corresponding author on reasonable request.

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Figures

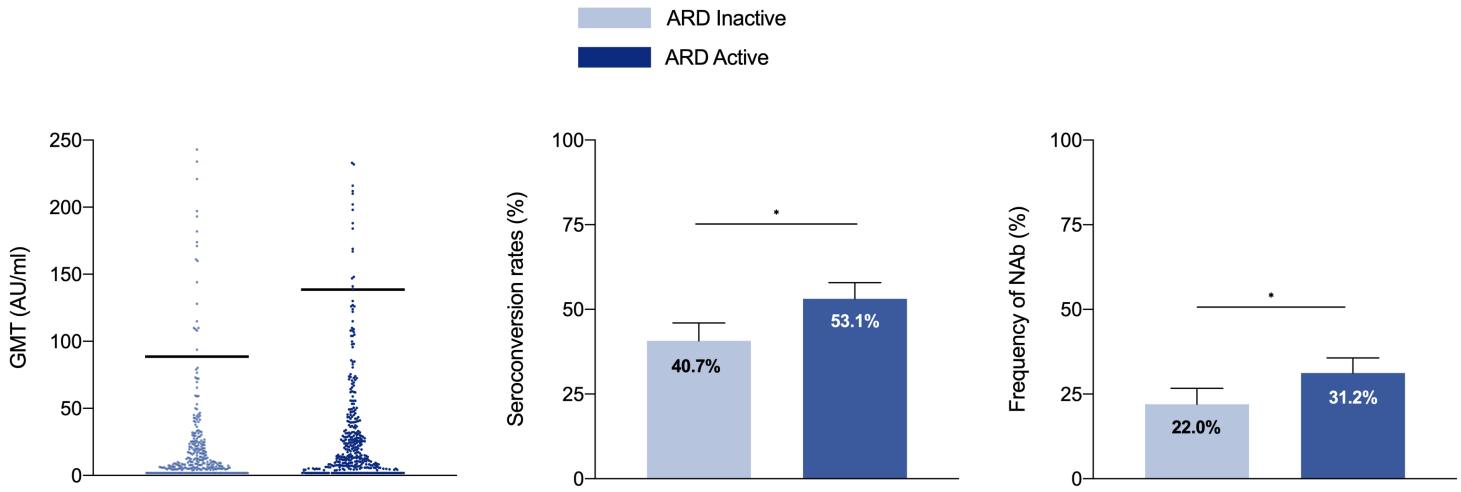

Figure 1

Unadjusted analysis for immunogenicity data in autoimmune rheumatic diseases patients (ARD) six months after full vaccination with CoronaVac.

*P<.05. Seroconversion was defined as a positive serology (IgG titer ≥ 15 AU/ml) for anti-SARS-CoV-2 S1/S2 IgG antibodies after vaccination (Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy). Positivity for NAb was defined as a neutralizing activity ≥ 30% (cPass sVNT Kit, GenScript, Piscataway, USA). Data are expressed as individual data, median and interquartile range for GMT and percentages and 95% confidence intervals (CIs) for frequency of seroconversion rates of total anti-SARS-Cov-2 S1/S2 IgG (SC) and neutralizing antibodies (NAb) positivity. Missing data for IgG (n = 3) and NAb (n = 43).

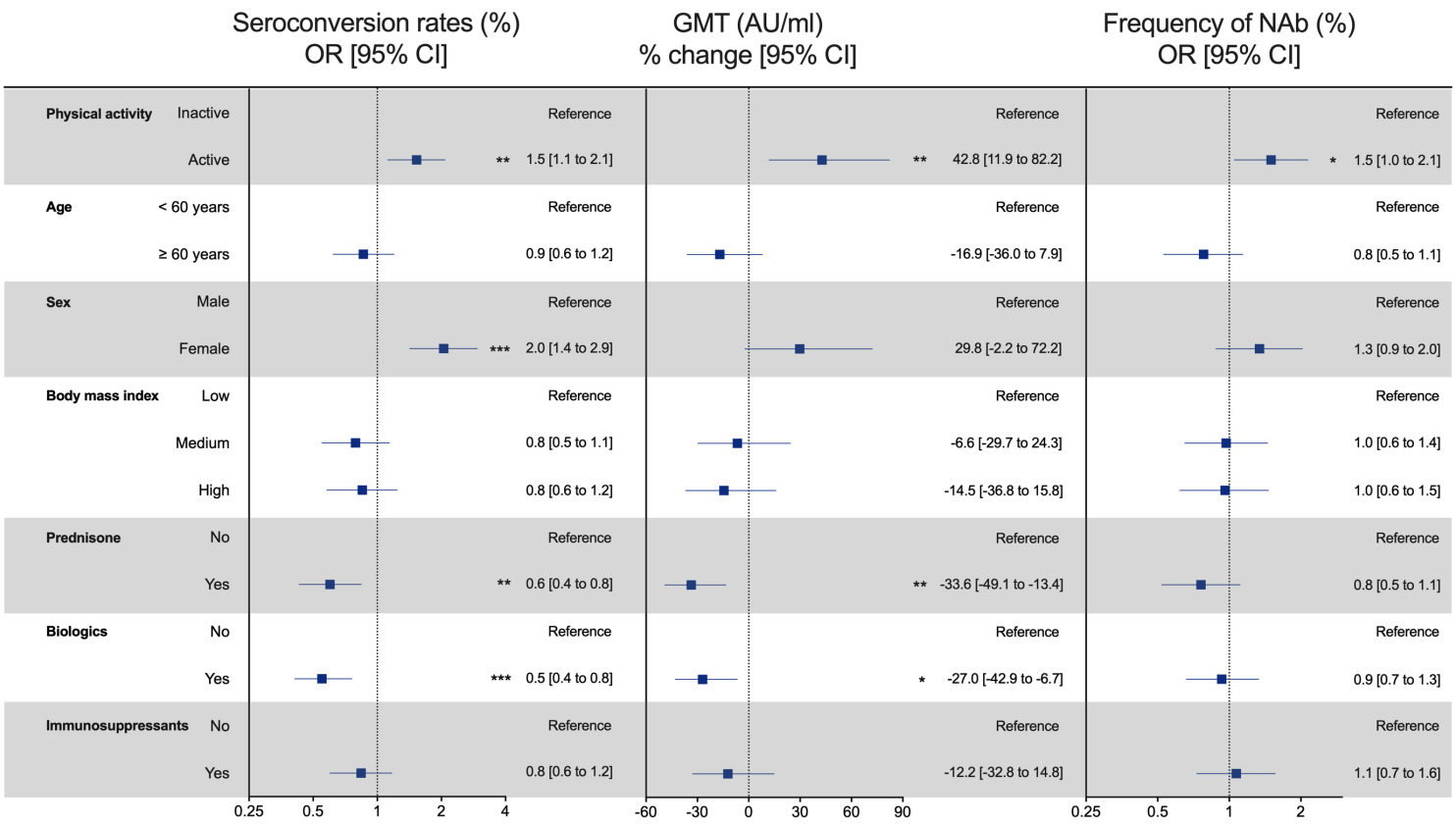

Figure 2

Adjusted risk factors for immunogenicity data in autoimmune rheumatic diseases (ARD) patients six months after full vaccination with CoronaVac.

Logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) with binary data obtained for frequency of seroconversion rates of total anti-SARS-Cov-2 S1/S2 IgG (SC) and neutralizing antibodies (NAb) positivity. Linear regression was used for natural log transformed GMT. Data expressed as percent change [95% CI]). Adjusted for age, sex, BMI, use of prednisone, immunosuppressants and biologics. *P<.05, **P<.01, ***P<.001. Seroconversion was defined as a positive serology (IgG titer ≥ 15 AU/ml) for anti-SARS-CoV-2 S1/S2 IgG antibodies after vaccination (Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy). Positivity for NAb was defined as a neutralizing activity ≥ 30% (cPass sVNT Kit, GenScript, Piscataway, USA). Missing data for IgG (n = 3) and NAb (n = 43).