DOI: 10.4274/TP.2022.36349
Trends in Pediatrics 2022;3(4):141-8

Original Article

Monitoring of Antibody Levels Following SARS-CoV-2 Infection in Children and Late Adolescents with Inflammatory Rheumatic Diseases

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Cite this article as: Haşlak F, Özbey D, Yıldız M, Adrovic Yıldız A, Şahin S, Köker O, Aliyeva A, Guliyeva V, Yalçın G, İnanlı G, Kocazeybek BS, Kasapçopur Ö, Barut K. Monitoring of Antibody Levels Following SARS-CoV-2 Infection in Children and Late Adolescents with Inflammatory Rheumatic Diseases. Trends in Pediatrics 2022;3(4):141-8

ABSTRACT

Objective: We monitored the severe acute respiratory syndrome-coronavirus-2 antibody levels in patients with inflammatory rheumatic diseases (IRD) and healthy children.

Methods: Healthy children and patients under 21 who were initially seropositive, were included in the study. Antibody levels of all subjects were measured again after the third and sixth months by the ELISA method. In this process, their symptoms were also questioned in terms of coronavirus disease-2019.

Results: The study included 35 participants (female/male: 1.69) (healthy control group: 10, patient group not receiving biological therapy: 19, patient group receiving biological therapy: 6). Their mean age was 14.27±5.49 years. Of the participants, 13 (37.1%) had a history of symptomatic infection, and 4 (11.4%) had a history of hospitalization. At the end of the six-month, a significant decrease was found in the immunoglobulin G levels of the participants (p=0.002). While no significant decrease was observed in the first trimester (p=0.085), there was a sharp decrease in the second trimester (p<0.001). Age, sex, presence of IRD and use of biological agents did not affect this decrease.

Conclusion: Although they decrease rapidly in the second trimester, we showed that antibodies acquired by infection in healthy children and children with IRD mostly stay at an acceptable level after six months. These data can be used to schedule vaccination programs. Besides, we showed that IRD and biological drugs do not affect the decrease in antibody levels. Therefore, no additional precautions may be required regarding vaccination in this patient group.

Keywords: Pediatrics, rheumatology, SARS-CoV-2, antibodies, viral

INTRODUCTION

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is responsible for the current pandemic. This novel virus causes a disease, which might be highly fatal named coronavirus disease-2019 (COVID-19). Although highly effective and safe vaccines against the virus are currently available, SARS-CoV-2 is still a major health concern worldwide.[1]

It was previously reported that increased age, male gender, and comorbidities such as cardiovascular diseases, diabetes, and hypertension are the main risk factors for poor outcomes.[2,3]

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Received: 01.11.2022 **Accepted:** 16.11.2022

Luckily, COVID-19 is often much milder in children than in adults.[4-6] Although a life-threatening condition named multisystem inflammatory syndrome in children was described in April 2020, it is an extremely rare complication of the virus.[7]

Due to conflicting data, it remains unclear whether individuals with inflammatory rheumatic diseases (IRD) are at increased risk of severe COVID-19.[8-11] However, it was recently reported in a large cohort that there is a significantly increased risk of both hospitalization and symptomatic infection in children with IRD.[12]

Another conundrum regarding the children with IRD during the pandemic was their active immunization after the SARS-CoV-2 infection. They were considered they may not be able to generate and sustain sufficient humoral immune response due to their immune-disturbed conditions caused by both their diseases and medication.[13] In this study, we primarily monitored the anti-SARS-CoV-2 immunoglobulin (Ig) G levels acquired by natural infection of seropositive children with and without IRD for six months. Secondary aim was to evaluate the clinical and demographic variables that may affect the decreasing pattern of the antibodies.

MATERIALS AND METHODS

Study Design

We conducted a prospective study. Those who were seropositive by measuring anti-SARS-CoV-2 IgA and IgG antibodies were included in the study regardless of the reason for their serological examination. Antibody levels of these seropositive subjects were measured again twice, 90 days and 180 days after the first measurement. Variables that may affect the lowering trend of the antibody levels with timing were evaluated. The study was started in July 2020, and the last antibody measuring test was performed in June 2021. We finished the study before August 2021, when children in our country were allowed to be vaccinated for the first time. Therefore, none of our subjects had been vaccinated against SARS-CoV-2.

Participants

In one of our previous works, which evaluated asymptomatic seropositivity, participants who were found to be seropositive by measuring anti-SARS-CoV-2 IgA or IgG antibodies were included in the study.[14] Additionally, those found to be seropositive by measuring antibodies 14-30 days after the contact history or COVID-19 suggestive symptoms had been started were also included. Patients diagnosed with any IRD before the age of 18 years and currently under 21 and healthy individuals under 18 years are included in the study. The children with IRD whose follow-up period was less than six months were excluded. During the intervals between the antibody measurements, COVID-19 suggestive symptoms were checked for each patient, and those with symptomatic infection or contact history were excluded from the study due to the possibility of affecting the results.

Children previously admitted to our center due to a non-specific and transient complaint before the pandemic and without any diagnosed underlying disease were established as the healthy control group. The patients with IRD who did not receive any biological treatment were called the non-biologic group, and the patients with IRD who were currently under biological treatment for at least six months at the first serologic evaluation time were called the biological group. Patients whose biological treatments were stopped during the antibody monitoring period were excluded from the study.

Antibody Measuring

The sera of the patients were removed from each subject's venous blood sample by centrifugation at 4.500 rpm and stored at -20 °C until testing. IgA and IgG detection against SARS-CoV-2 spike protein was assayed by the ELISA method using test kits based on the sandwich and semi-quantitative principles (EUROIMMUN AG, Lübeck, Germany). According to the manufacturer's instructions, assays were carried out with a dilution ratio of 1:100. Microplates were read at 450 nm (reference 620-650 nm) wavelength by an automated microplate reader (BioTek ELx800, Istanbul, Turkey). Then, absorbance (optical density, OD) was calculated for all samples.

Antibody ratios of samples were calculated by dividing the sample's OD by Calibrator's OD. While the ratios higher than 1.1 were classified as positive, those lower than 0.8 were classified as negative. Subjects with borderline ratios between 0.8 and 1.1 were classified as negative or positive based on the expert microbiologist's opinion.

Ethical Approval

The study protocol was approved by the Institutional Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (approval number: 04/16/20–29430533-604.01-01-54959). The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed in this study. We obtained informed consent from the participants and their parents.

Statistical Analysis

We performed the statistical analysis using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp). The chi-square test or Fisher's exact test was used to compare the categorical variables, expressed as numbers (percentages). Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. While those with a normal distribution were presented as mean ± standard deviation, those distributed abnormally were presented as median (minimum-maximum). Mann-Whitney U test or Student's t-test was used to compare the continuous variables when appropriate.

Repeated measures ANOVA was performed to assess the changing pattern of antibody levels of participants over time. A multivariate ANOVA test was performed to interpret the effects of variables such as age, gender, existing IRD, and receiving treatments on the lowering trend of antibody levels of the participants. Statistical

significance was defined as $p<0.05$. Prism software (Prism 8, GraphPad Software, San Diego, California) was used to graph data.

RESULTS

Baseline Characteristics of All Study Populations

Overall, 35 subjects (female/male: 1.69) were eligible for the study. Their mean age was 14.27±5.49 years. While there is not any underlying disease in ten (28.6%) subjects, nine (25.7%) had juvenile idiopathic arthritis (JIA), eight (22.9%) had Familial Mediterranean Fever (FMF), five (14.3%) had systemic lupus erythematosus (SLE), one (2.9%) had cryopyrin-associated periodic syndrome (CAPS), one (2.9%) had a deficiency of adenosine deaminase 2 (DADA2), and one (2.9%) subject had Sjögren's disease.

Six patients (17.1%) received biological disease-modifying anti-rheumatic drugs (bDMARDs) (adalimumab: 3, canakinumab: 2, etanercept: 1). Four of six (66.6%) had a contact history, and two patients (33.3%) (one with oligoarticular JIA and under adalimumab treatment, and the other one with systemic JIA under canakinumab treatment) who both had a contact history, had a history of symptomatic SARS-CoV-2 infection. However, none of them were hospitalized.

While eleven (31.4%) patients were under colchicine treatment, four (11.4%) patients were receiving steroids. During the whole study, ten (28.6%) were received at least one type of conventional disease-modifying anti-rheumatic drug (cDMARDs) (hydroxychloroquine: 8, methotrexate: 3, mycophenolate mofetil: 1, azathioprine: 1). Five of ten patients (50%) under cDMARD treatment had a contact history, and three of five had a history of symptomatic SARS-CoV-2 infection. All but one patient with symptomatic infection had a contact history, as well. Although two of them required hospitalization, both recovered completely.

Thirteen (37.1%) subjects (JIA: 5, FMF: 4, healthy children: 2, SLE: 1, Sjögren's disease: 1) (female: 61.5%) had a history of symptomatic SARS-CoV-2 infection. The most common symptom was fatigue, which was seen in nine (25.7%) subjects. The other symptoms were cough (n=7, 20%), sore throat (n=7, 20%), myalgia (n=7, 20%), rhinorrhea (n=6, 17.1%), diarrhea (n=5, 14.3%), fever (n=4, 11.4%), dyspnea (n=4, 11.4%), abdominal pain (n=4, 11.4%), rash (n=3, 8.6%), and vomiting (n=1, 2.9%), respectively.

Four (11.4%) patients were hospitalized. All were females. Patient 1 was 12.2 years old and was diagnosed with JIA. She was not receiving any medication. Patient 2 was 13.3 years old, diagnosed with Sjögren's disease and was receiving methotrexate and hydroxychloroquine. Patient 3 was 18.9 years old, diagnosed with SLE and was receiving hydroxychloroquine. Patients 4 was 19.7 years old, diagnosed with FMF and was under colchicine treatment. All but one with JIA had a contact history.

While twenty-two subjects (62.9%) had an asymptomatic infection, nine participants (25.7%) had mild-to-moderate COVID-19 disease course. Additionally, four patients (11.4%) who required hospitalization were considered to have a severe SARS-CoV-2 infection. Since those stating suspicious symptoms for COVID-19 or contact history were excluded during the study as we mentioned before, none of the included subjects were considered to have re-infection. In symptomatic cases, there was a 22.15±3.71 day-period between the first antibody measurement and the onset of COVID-19 symptoms. In asymptomatic but with contact history cases, the interval between the first serological evaluation and exposure date was 20.5±2.87 days. However, it was impossible to identify this period in incidental cases.

While the median IgA ratio of the patients was 1.55 (0.54-8.59), the mean IgG ratio was 3.56±2.67 on day 0. The mean IgG ratios on day 90 and day 180 were 2.92±2.08 and 1.98±1.33, respectively.

Comparisons Between the Groups

Those without underlying diseases were called the healthy control group (n=10). Among those with IRD (n=25), while those receiving bDMARDs (n=6) were called the biological group, the rest (n=19) were called the non-biologic group.

The median ages of the healthy control group, the biological group, and the non-biologic group were 9.55 (2.21-19.35), 17.49 (8.39-20.64), and 17.41 (3.90-20.80) years old, respectively. The participants of the healthy control group were significantly younger than the other group ($p=0.014$). There were no significant differences between the groups concerning antibody levels, and the frequencies of female gender, contact history, symptomatic SARS-CoV-2 infection, and hospitalization due to COVID-19 (Table 1).

Antibody Monitoring Data

While there was no significant difference between the IgG ratios on day 0 and day 90 ($p=0.085$), a significant decrease was observed from day 90 to day 180 ($p<0.001$). In total, the IgG ratios were significantly decreased from day 0 to day 180 ($p=0.002$) (Table 2). The IgG ratios of the participants for each group on day 0, day 90, and day 180 are available in Figure 1. Age, gender, the presence of IRD, receiving treatments such as steroids, colchicine, bDMARDs, and cDMARDs, contact history with a known infected case, symptomatic SARS-CoV-2 infection history, and hospitalization history due to COVID-19 were not found to be effective in the decreasing trend of IgG ratios of the subjects. The detailed data are given in Table 3.

Eight participants (22.9%) converted to seronegative at the end of the study: a nine-year old healthy boy, three patients with FMF under colchicine, a twenty-year old female with JIA under remission, an eight-year old boy with JIA receiving methotrexate, a twenty-year old female with SLE under hydroxychloroquine, and a nineteen-year old boy with JIA receiving adalimumab.

DISCUSSION

Anti-SARS-CoV-2 IgG levels of thirty-five seropositive children and late adolescents (healthy children: 10, those with IRD under

Table 1. Baseline characteristics of the subjects				
	Healthy control group (n=10)	**Non-biologic group (n=19)**	**Biologic group (n=6)**	**p-value**
Age [median (min-max)]	9.55 (2.21-19.35)	17.49 (8.39-20.64)	17.41 (3.90-20.80)	**0.014**
Female gender (n, %)	7 (70%)	11 (57.9%)	4 (66.7%)	0.892
Diagnosis				
FMF (n, %)	-	8 (42%)	-	
JIA (n, %)	-	5 (26.5%)	4 (66%)	
SLE (n, %)	-	5 (26.5%)	-	
CAPS (n, %)	-	-	1 (17%)	
DADA2 (n, %)	-	-	1 (17%)	
Sjögren (n, %)	-	1 (5%)	-	
Ongoing treatment				
Steroid (n, %)	-	2 (10.5%)	2 (33.3%)	
Colchicine (n, %)	-	10 (52.6%)	1 (16.7%)	
c-DMARD (n, %)	-	9 (47.4%)	1 (16.7%)	
Methotrexate (n)	-	2	1	
Mycophenolate mofetil (n)	-	1	-	
Hydroxychloroquine (n)	-	8	-	
Azathioprine (n)	-	1	-	
b-DMARD (n, %)	-	-	6 (100%)	
Adalimumab (n)	-	-	3	
Canakinumab (n)	-	-	2	
Etanercept (n)	-	-	1	
Contact history (n, %)	4 (40%)	10 (52.6%)	4 (66.7%)	0.665
Symptomatic infection (n, %)	2 (20%)	9 (47.4%)	2 (33.3%)	0.365
Symptoms				
Cough (n)	1	4	2	
Rhinorrhoea (n)	-	4	2	
Headache (n)	-	5	2	
Fatigue (n)	1	6	2	
Myalgia (n)	-	6	1	
Abdominal pain (n)	-	2	2	
Nausea-Vomiting (n)	-	1	-	
Diarrhea (n)	1	4	-	
Rash (n)	1	2	-	
Fever (n)	1	2	1	
Dyspnea (n)	-	4	-	
Hospitalization (n, %)	-	4 (21%)	-	0.263
IgA ratio [median (min-max)]	1.67 (0.73-8.59)	1.53 (0.32-5.35)	1.17 (0.05-5.35)	0.491
IgG ratio				
Day 0 (mean ± SD)	4.68±3.21	2.72±2.40	4.34±1.82	0.814
Day 90 (mean ± SD)	3.42±2.26	2.92±2.24	2.09±1.07	0.204
Day 180 (mean ± SD)	2.42±1.05	1.94±1.54	1.43±0.95	0.088

b-DMARD: Biologic disease modifying anti-rheumatic drugs, CAPS: Cryopyrin-associated periodic syndromes, c-DMARD: Conventional disease modifying anti-rheumatic drugs, DADA2: Deficiency of adenosine deaminase-2, FMF: Familial Mediterranean Fever; Ig: Immunoglobulin, JIA: Juvenile idiopathic arthritis, SLE: Systemic lupus erythematosus, min-max: Minimum-maximum, SD: Standard deviation

Table 2. Comparison of IgG ratios of all participants measured at three different times

	df	MS	F	p-value
Comparison of IgG ratios on day 0 and day 180	1.267	37.567	10.065	**0.002**
Comparison of IgG ratios on day 0 and day 90	1	21.122	3.184	0.085
Comparison of IgG ratios on day 90 and day 180	1	26.582	23.460	**<0.001**

Ig: Immunoglobulin

biological treatment: 6, those with IRD not under biological treatment: 19) were monitored for six months in this study. At the end of the six-month for each subject, a significant decrease was found in the SARS-CoV-2 IgG levels. While no significant decrease was observed in the first trimester, there was a sharp decrease in the second trimester. Nonetheless, most subjects (77%) remained seropositive after six months. Age, gender, presence of IRD, and use of biological agents did not affect the decreasing pattern of the antibodies.

There are scarce data regarding the antibody screening acquired by SARS-CoV-2 infection in children with IRD. A study from the United Kingdom evaluated the IgG levels against the seasonal coronaviruses of children with SLE, JIA, juvenile dermatomyositis, and healthy children by using the blood samples of these donors who were collected before the COVID-19 pandemic. Children with IRD were found to present comparable or stronger humoral immune responses than healthy children, even if they were under immunosuppressive medication.[15] The seroprevalence of SARS-CoV-2 in pediatric rheumatic patients was screened in New York, and 35 of 262 subjects were found to be SARS-CoV-2 IgG positive. Out of 35 seropositive patients, 18 were under anti-tumor necrose factor, 2 were anti-interleukin (IL)-6, one was under anti-IL-1, and one was under Janus kinase inhibitor treatment. Thus, this study showed that children with IRD, including those receiving biological treatment, may produce proper antibodies following the infection.[16] However, there are several studies have evaluated the humoral responses after SARS-CoV-2 vaccinations of children with IRD. A study from Turkey demonstrated that pediatric rheumatic patients can mount a sufficient humoral response after two doses of the BNT162b2 mRNA vaccine.[17] Although antibody titers after the vaccines were significantly lower in the

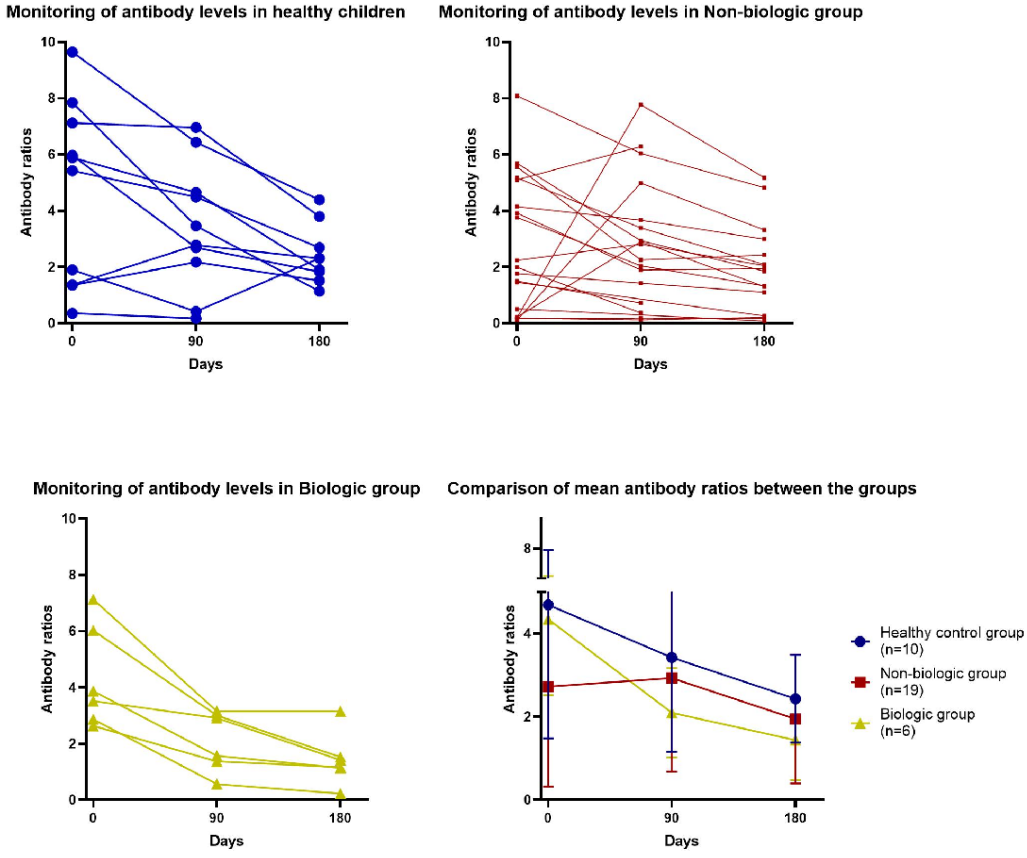

Figure 1. Anti-SARS-CoV-2 immunoglobulin G levels of the participants on day 0, day 90, and day 180

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2

Table 3. The effects of variables on the change of immunoglobulin G ratios of all subjects at three different times

	Day 0 IgG ratio	Day 90 IgG ratio	Day 180 IgG ratio	df	MS	F	p-value
Gender				1.262	0.247	0.064	0.857
Male	2.88±2.19	2.13±1.45	1.77±0.97				
Female	3.95±2.89	3.37±2.87	2.08±1.47				
Rheumatic disease				1.258	4.505	1.207	0.292
Yes	3.11±2.34	2.71±2.01	1.80±1.40				
No	4.68±3.21	3.42±2.26	2.42±1.05				
Group				2.587	7.673	2.293	0.104
Biologic group	4.34±1.82	2.09±1.07	1.43±0.95				
Non-biologic group	2.72±2.40	2.92±2.24	1.94±1.54				
Healthy control group	4.68±3.21	3.42±2.26	2.42±1.05				
Contact history				1.269	0.908	0.237	0.687
Yes	4.29±2.60	3.38±2.21	2.50±1.40				
No	2.78±2.59	2.43±1.88	1.36±0.95				
Symptomatic infection				1.259	1.113	0.289	0.647
Yes	3.37±2.23	2.81±1.75	2.13±1.25				
No	3.67±2.94	2.98±2.29	1.89±1.40				
Ongoing treatment							
b-DAMRD	4.34±1.82	2.09±1.07	1.43±0.95	1.280	6.356	1.767	0.180
c-DMARD	3.86±2.49	2.52±1.71	2.01±1.32	1.265	1.066	0.278	0.656
Colchicine	3.00±2.60	2.61±1.80	1.91±1.41	1.262	1.214	0.316	0.630
Steroid	4.93±2.33	3.09±2.16	2.30±1.73	1.272	2.072	0.548	0.505
Hospitalization				1.274	5.006	1.366	0.259
Yes	3.21±2.77	4.25±3.08	2.78±2.08				
No	3.59±2.70	2.79±1.98	1.90±1.25				

b-DMARD: Biologic disease modifying anti-rheumatic drugs, c-DMARD: Conventional disease modifying anti-rheumatic drugs, Ig: Immunoglobulin

adolescents with IRD than in their healthy peers, the seropositivity rate was not significantly different between the groups in a study by Heshin-Bekenstein et al.[18] A study from Spain demonstrated that neither humoral nor the cellular response to the BNT162b2 mRNA vaccines was different between the adolescents with and without IRD.[19] In our study, neither IgA nor IgG levels were different between the healthy children and those with IRD at the baseline. Similarly, no significant difference was shown between adults with IRD and healthy adults regarding the antibody levels following SARS-CoV-2 infection in several studies.[20,21]

The most common disease of our subjects was JIA (n=9), which is also the most common rheumatic disease in the childhood,[22] and the others were FMF (n=8), SLE (n=5), Sjögren's disease (n=1), CAPS (n=1), and DADA2 (n=1), respectively. Healthy children were significantly younger, which may be related to a mix of a relatively increased propensity of the parents of the younger children with IRD to apply strict isolation measures and a general diagnostic delay of IRD in childhood.

While three patients with JIA were under adalimumab treatment, one with systemic subtype was receiving canakinumab. The other patient under canakinumab was a CAPS patient, and one patient with DADA2 was receiving etanercept during the study process. Although thirteen (37.1%) subjects had a history of symptomatic SARS-CoV-2 infection, only four of them (11.4%) required hospitalization, and all of them recovered completely. Eleven of the thirteen symptomatic patients and all hospitalized patients were rheumatic patients. Consistent with our data, both symptomatic infection and hospitalization were found to be significantly more common in children with IRD than in healthy children in a previous study.[12]

While the most common symptoms of COVID-19 in the pediatric age are cough, pharyngeal erythema, and fever,[23] the most common ones in our study were fatigue, cough, sore throat, and myalgia. Only four of our thirty-five subjects had a fever, and this relatively decreased frequency of fever may be attributed to the fact that most of our subjects were under anti-inflammatory treatment regimens during the study.

Twenty-seven participants (77.1%) remained seropositive at the end of the six-months during the observation period. Similarly, it was shown in a prospective study that monitored the antibody levels acquired by SARS-CoV-2 infection that 80% of seropositive adults with SLE remained in their initial serological status until 30 weeks later.[24]

At the end of the six-month duration period of our study, a significant decrease, which was mainly observed in the second trimester, was found in the IgG levels of the participants. None of the tested variables, such as age, gender, presence of IRD, and use of biological agents, affected this decrease. Consistent with our results, Boekel et al.[25] showed that age, gender, hospitalization history, and receiving cDMARD/bDMARD except B-Cell targeting agents do not affect the development of long-lasting humoral immunity after the SARS-CoV-2 infection. However, none of our subjects were under rituximab treatment, which resulted in complete B lymphocyte depletion.

Study Limitations

The main limitation of the study is the limited number of cases. Unfortunately, we did not perform a power analysis due to the following reasons: 1) There is no study so far similar to ours. 2) We conducted this study among the seropositive subjects. Therefore, even if we need more patients to establish the optimal sample size, it is impossible to find. 3) Rheumatic diseases are seen very rare in childhood, already. 4) The costs of antibody measuring commercial kits are a significant economic burden. 5) There is a general unwillingness of asymptomatic SARS-CoV-2 seropositive children's parents to regular follow-up for antibody monitoring. Other limitations were that we could not assess the effects of immunosuppressive dosages, the durations of the diseases, and the medication lengths of the patients on the decreasing pattern of the antibodies due to the unavailable data. Additionally, the heterogeneity of the rheumatic diseases of our patients is another limitation, which can interfere with antibody levels in different ways. However, the main strength of our paper is that this is the only study to our best knowledge that presents the SARS-CoV-2 antibody levels acquired by the natural infection of children with IRD at three different times.

CONCLUSION

Although they decrease rapidly in the second trimester, we showed that antibodies acquired by infection in healthy children and children with IRD mostly stay at an acceptable level after six months. These data can be used to schedule vaccination programs. Besides, we showed that IRD and biological drugs do not affect the decrease in antibody levels. Therefore, no additional precautions may be required regarding vaccination in this patient group. However, due to the limited number of patients, the data of our study should be confirmed with studies involving a larger number of patients.

Ethics

Ethics Committee Approval: The study protocol was approved by the Institutional Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (approval number: 04/16/20–29430533-604.01-01-54959).

Informed Consent: Written informed consent was obtained from the participants included in this study and no identifying information of any participant was included in this paper.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.H., S.Ş., O.K., A.A., V.G., G.Y., G.İ., Ö.K., K.B., Concept: M.Y., A.A.Y., B.S.K., Ö.K., K.B., Design: B.S.K., K.B., Data Collection or Processing: F.H., D.Ö., S.Ş., O.K., A.A., V.G., G.Y., G.İ., Ö.K., K.B., Analysis or Interpretation: F.H., D.Ö., K.B., Literature Search: F.H., D.Ö., M.Y., A.A.Y., B.S.K., Ö.K., K.B., Writing: F.H., K.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Funding: This work was supported by the Scientific Research Projects Coordination Unit of İstanbul University-Cerrahpaşa. ID: 34942, Project code: TSA-2020-34942.

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