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Monitoring of immunoglobulin treatment compliance of patients with an inborn error of immunity during the pandemic period

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Abstract

Background During the coronavirus disease 2019 (COVID-19) pandemic, significant challenges have been encountered in managing patients with chronic diseases. This study aimed to evaluate the effects of the pandemic on follow-up and treatment adherence in patients receiving immunoglobulin replacement therapy (IRT).

Methods A study examining the changes in IRT application methods was conducted between March 2020 and September 2021. An online message line, under the control of nurses and doctors, was established for our patients, and their usage rates for this communication system were recorded.

Results A total of 169 patients, 93 males and 76 females, were included in the study. Among the patients, 124 (73.4%) received intravenous immunoglobulin (IVIG), and 45 (26.6%) received subcutaneous immunoglobulin (SCIG) treatment. Male sex was more common in both the IVIG and SCIG groups. Although all patients in the subcutaneous treatment group continued the treatments regularly, this rate was 80.6% in the IVIG group. During the pandemic, 26 patients switched from IVIG to SCIG treatment. Furthermore, 24 patients interrupted immunoglobulin treatment for various reasons. Patients who received subcutaneous treatment took a long break from their hospital controls, although they applied them properly at home. Routine immunoglobulin trough values were measured in only 17 (37.7%) patients who were on SCIG. In the presence of symptoms, 100% of SCIG patients contacted the remote medical team via the online message line, compared to 48.3% of IVIG patients.

Conclusion During the pandemic, the route of immunoglobulin treatment should be individualized based on each patient's characteristics and expectations. Telehealth services have emerged as a crucial tool for monitoring patients with chronic disorders, facilitating effective communication and personalized care.

Keywords COVID-19 pandemic, Immunoglobulin therapy, Telehealth services

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Introduction

Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, healthcare systems in different parts of the world have faced significant challenges in managing patients with chronic diseases. Patients with inborn error of immunity (IEI) were considered a risk group at the beginning of the pandemic [1, 2]. In subsequent periods, COVID-19 infection did not progress substantially in most patients with antibody production defects [3]. The spectrum of the disease varies from an asymptomatic course to severe respiratory illness and death in patients with IEI [4]. Severe COVID-19 infection seems to be more common in patients with type I interferon (IFN) production defects [2, 5, 6].

Since most patients with IEI have a defect in the number or functions of memory B cells that produce high-affinity antibodies, regular immunoglobulin therapy is vital in these patients [6].

Immunoglobulins play a crucial role in neutralizing both exogenous and endogenous pathogenic antigens, including those from bacterial and viral infections such as coronaviruses [7–9]. Immunoglobulin therapy modulates regulatory T-cell (Treg) activity, reduces inflammatory cytokine levels, and inhibits the production of matrix metalloproteinases, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6). As a result, it helps prevent cytokine-mediated interstitial and alveolar wall edema, which contributes to acute respiratory distress syndrome (ARDS) in COVID-19 patients [10–12]. Given these immunomodulatory effects, immunoglobulin therapy is considered a potential treatment option for acute COVID-19 infection and for managing post-infectious complications associated with the disease [13].

Immunodeficiency associations (IPOPI, ESID, INGID, APSID, ARAPID, ASID, CIS, LASID, SEAPID, and IUIS) have stated that regular immunoglobulin applications (intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG)) are indispensable for preventing different infections. Telemedicine helps to deliver health care, health education, and health information services via remote technologies. Telemedicine services have allowed many patients with IEI to avoid being exposed to infections.

This study aimed to evaluate the effects of the pandemic on follow-up and treatment compliance in IEI patients receiving immunoglobulin replacement therapy through telehealth.

Materials and methods

Intravenous immunoglobulin is typically administered at hospitals at 3- or 4-week intervals in Turkey. Frequent hospital attendance has been considered a breach of shielding and a risk of nosocomial exposure to COVID-19. Therefore, patients receiving hospital-based immunoglobulin replacement therapy (IRT) were assessed and, where possible, offered an emergency transition to home-based SCIG to minimize the risk of infection at the beginning of the pandemic. We informed the patients face-to-face about this issue. In case of dispute resolution, we activated an online message line for patients, under the control of nurses and doctors, before arriving at the hospital.

Firstly, a contact number was provided to all patients receiving immunoglobulin treatment, allowing them to send messages quickly. All patients and their families were informed about this contact number. The messaging line was established through WhatsApp for those with internet access and via Short Message Service (SMS) for those without. There were no restrictions on the time or day for messaging. This communication system enabled patients to quickly and easily reach out regarding health issues, medication supplies, and technical problems. Messages from all patients were reviewed by the remote team consisting of specialized nurses and doctors, and patients received feedback via text or phone calls.

Electronic file records of patients receiving immunoglobulin replacement therapy between March 2020 and September 2021 with a diagnosis of IEI, demographic characteristics, frequency of regular admissions, changes in treatment methods, and differences in vaccination records were retrospectively analyzed. The treatment information of our patients who received IVIG was recorded in the hospital's electronic file system. Patients receiving subcutaneous treatment were recorded in an online message group in which we communicated with patients receiving it at home. The rates of using the online communication line for our patients were recorded.

Patients who did not come for IVIG treatment were called through this system, and information about their health status was obtained. Bursa Uludag University Faculty of Medicine Ethics Committee approved our study in accordance with the Declaration of Helsinki (2022-11/22).

Statistics

Statistical analyses were performed via SPSS 28 (IBM Corp.). Categorical data are expressed as frequencies and percentages, and continuous data are reported as the mean ± standard deviation (SD) or median (minimum and maximum). Categorical variables were compared with the Pearson chi-square test.

Results

A total of 169 patients, 93 males and 76 females, were included in the study. The median age of the patients was 16 (1–79) years, and the median follow-up period was 3.25 (0.1–16) years. Among the patients, 124 (73.4%) were receiving IVIG, and 45 (26.6%) were receiving SCIG

treatment. Most of our patients were diagnosed with antibody production defects ($n=137$). The age groups of the patients in the study population and the diagnosis groups according to the International Union of Immunological Societies Expert Committee (IUIS) Human Inborn Errors of Immunity: 2022 have been given in Table 1 [14].

There were lower respiratory tract diseases in 17 (10%), endocrinologic diseases in 15 (8.9%), neurologic diseases in 14 (8.2%), cardiac diseases in 12 (7.1%), gastrointestinal system comorbidities in 11 (6.5%) and malignancies in 8 (4.7%) patients. Although all patients receiving classic subcutaneous or facilitated subcutaneous immunoglobulin (fSCIG) treatment continued these treatments regularly, the rate of continuing regular therapy in the group receiving IVIG was 80.6%.

During the pandemic, 145 patients (103 IVIG and 42 SCIG) continued immunoglobulin treatment, while 24 (21 IVIG and 3 SCIG) discontinued immunoglobulin treatment for various reasons. The diagnosis of 20 (83.3%) patients who discontinued treatment was predominantly antibody deficiency group. The most common reason for discontinuation was fear of hospitalization due to the risk of COVID-19 infection (Table 2). Of the 145 patients who continued immunoglobulin treatment, 84 (57.9%) experienced non-COVID-19 infections. Among these patients, 59 (57.2%) received intravenous immunoglobulin (IVIG), while 25 (59.5%) received subcutaneous immunoglobulin (SCIG). In contrast, among the patients who interrupted immunoglobulin treatment, non-COVID-19 infections were observed in

Table 1 Distribution of patients according to their diagnosis

Diagnosis	Number of children patients (< 18 age) *n* (%)	Number of adult patients (> 18 age) *n* (%)	Number of total patients *n* (%)
Predominantly antibody deficiencies (*n* = 137; 81%)			
Common variable immune deficiency	9 (5.3)	43	52 (30.7)
Hypogammaglobulinemia	33 (19.5)	3 (1.8)	36 (21.3)
IgG subclass deficiency	4 (2.4)	15 (8.8)	19 (11.2)
Secondary Hypogammaglobulinemia	12 (7.2)	3 (1.8)	15 (8.8)
X-linked agammaglobulinemia (XLA)	2 (1.2)	5 (3)	7 (4.2)
Hyper IgM syndrome	0 (0)	6 (3.6)	6 (3.5)
µ heavy chain deficiency	1 (0.6)	0 (0)	1 (0.6)
BLNK deficiency	0 (0)	1 (0.6)	1 (0.6)
Combined immunodeficiency associated with syndromic features (*n* = 18; 10.7%)			
Ataxia-telangiectasia	7 (4.2)	1 (0.6	8 (4.8)
Nijmegen breakage syndrome	1 (0.6)	2 (1.2)	3 (1.8)
Hyper IgE syndrome	2 (1.2)	1 (0.6)	3 (1.8))
Wiskott-Aldrich syndrome	0 (0)	1 (0.6)	1 (0.6)
DiGeorge syndrome	0 (0)	1 (0.6)	1 (0.6)
Anhidrotic Ectodermodysplasia	1 (0.6)	0 (0)	1 (0.6)
Purine nucleoside phosphorylase deficiency	1 (0.6)	0 (0)	1 (0.6)
Combined Immune Deficiency (*n* = 4; 2.4%)			
CD40 ligand deficiency	2 (1.2)	1 (0.6)	3 (1.7)
MHC class II deficiency	1 (0.6)	0 (0)	1 (0.6)
Severe Combined Immune Deficiency (*n* = 3; 1.8)			
Omenn Syndrome	1 (0.6)	0 (0)	1 (0.6)
RAG deficiency	1 (0.6)	0 (0)	1 (0.6)
DNA ligase IV deficiency	1 (0.6)	0 (0)	1(0.6)
Diseases of immune dysregulation (*n* = 2; 1.2%)			
LRBA deficiency	0 (0)	2 (1.2)	2 (1.2)
Defects in intrinsic and innate immunity (*n* = 2; 1.2%)			
STAT1 GOF	0 (0)	1 (0.6)	1 (0.6)
MDA5 deficiency	1 (0.6)	0 (0)	1 (0.6)
Phenocopies of inborn errors of immunity (*n* = 2;1.2%)			
Thymoma with hypogammaglobulinemia (Good syndrome)	0 (0)	2 (1.2)	2 (1.2)
Autoinflammatory disorders (*n* = 1; 0.6%)			
ADA2 deficiency	0 (0)	1 (0.6)	1 (0.6)
Total	80 (47.3)	89 (52.7)	169

Table 2 Reasons for interrupting Ig treatment

	Number of patients (%)
Fear of being in a hospital because of the risk of transmission	7 (29.2)
Settling in the countryside during the pandemic	5 (20.8)
Neglecting the treatment	5 (20.8)
Parents or patients were COVID-19 positive	3 (12.5)
Refusing infusion in COVID-19 quarantined service	2 (8.3)
Interruption due to business travel	2 (8.3)
Total	24

16 out of 24 (66.6%) individuals. Among those who continued immunoglobulin treatment and attended regular visits, 13 (8.9%) were diagnosed with COVID-19. Of these, ten were receiving IVIG, and three were on SCIG. Eight patients with COVID-19 were hospitalized. One of the five patients with lung involvement died. This patient was a 39-year-old woman who was receiving IVIG due to LRBA deficiency. Among the patients who interrupted their immunoglobulin treatment, 6 (25%) were diagnosed with COVID-19. Of those diagnosed, three with lung involvement were hospitalized. One of these patients died, while the others recovered without complications. The deceased was a 55-year-old male patient receiving IVIG due to IgG subclass deficiency. When all patients were evaluated during the pandemic, 68 (40%) patients were hospitalized for infectious and non-infectious reasons. The median hospitalization frequency during the study period was determined as 1 (0–19).

The number of patients transitioning from IVIG to classic SCIG was 22; four (3.2%) patients transitioned to fSCIG treatment. Application changes were observed during the pandemic period, such as irregular administration in 41 (33%) of the IVIG patients, changing the administration method in 26 (20.9%), and changing the hospital in 18 (14.5%). Eighteen (14.5%) patients who regularly received IVIG treatment at our center stated that they wanted to receive treatment at the nearest hospital to their home to eliminate the risk of contracting COVID-19 via public transport.

Seventeen (18.4%) of 92 patients over 18 years of age were not vaccinated against SARS-CoV-2. In addition, 15 (19.4%) of the 77 children under 18 years of age who lived with their parents had not been vaccinated. Among the reasons for refusing the vaccine were mistrust, fear of its side effects, and their belief that Ig therapy might be sufficient to protect against it. Three of our patients diagnosed with primary antibody deficiency were anti-vaccinationists. Although all the SCIG patients received their treatment at home regularly, they took a long break from hospital follow-ups. Routine immunoglobulin trough values were measured in only 17 (37.7%) of these patients.

Pandemic period, the rate at which our patients utilized the message line for health-related issues and other inquiries was 100% among those receiving subcutaneous treatment, compared to 48.3% for those receiving IVIG therapy. Overall, 105 out of 169 (62.3%) utilized the messaging service when we evaluated all our patients The average number of text messages sent (via WhatsApp and SMS) for per person during the study period was 15.6. Our medical infection and vaccination, medication usage issues, and proposed solutions.

Discussion

Immunoglobulins contain antibodies that neutralize microorganisms and their toxins in infectious diseases and are important in preventing infections in patients with primary immunodeficiency [15, 16].

In the consensus presented by the International Primary Immunodeficiency Societies, planning for home immunoglobulin replacement therapy, considering telehealth for routine follow-up, mild infections (otitis media, sinusitis, and superficial skin infections), and initial consultations of patients referred for possible immunodeficiency were suggested [1]. At the beginning of the SARS-CoV-2 pandemic, the Spanish Society for Primary Immunodeficiencies recommended following up with all adult patients with immunodeficiency by telephone at least once every two weeks [17].

In our country, there are no reports from official sites of the Ministry of Health or immunodeficiency associations in the form of procedures or recommendations regarding the follow-up and treatment process of immunocompromised patients during the pandemic.

In our study, while no interruption was observed in treatment or follow-up among all patients who received SCIG treatment during the pandemic, disruptions in their treatment were observed in 24 (19.3%) of the patients who received IVIG.

The proposed telehealth services for primary immunodeficiency patients are promising. Telehealth practices can offer an opportunity to provide patient care by minimizing the risks of face-to-face contact. Leimig et al. reported no significant differences in the follow-up of patients seen in hospitals face-to-face or followed by telehealth applications [18].

The use of telehealth reduces the burden on health systems. Therefore, telehealth keeps patients and health providers safe during the COVID-19 outbreak. Patients should be followed up via telehealth services and offered home treatment opportunities for those receiving regular treatment to reduce exposure to the SARS-CoV-2 virus. Recent research has shown that telehealth appointments are convenient for transplant recipients with secondary immunodeficiency during the COVID-19 pandemic [19–22]. Musaoglu et al. reported that the percentage of children

who underwent liver transplantation evaluated via the text message method during the pandemic period was 81.0%, whereas it was only 72.5% before the pandemic [23]. Telehealth has also been proposed and implemented in many centers where HIV-infected patients are cared for [24].

Emergency hospital appointments were arranged for all patients in our study who received both IVIG and SCIG when there was a significant health or technical problem. In the telehealth system we provide, all patients were interviewed about their prescription number, information about the problems encountered during the treatment, consultations about drug use, and hospital appointments.

When we considered the participation of all our patients, 62.3% of them used mobile health service messaging or called the responsible health personnel as the first step in reporting their complaints. However, 37.7% of the patients who applied subcutaneous treatment at home and reported their complaints to the doctor via telemedicine could not have their immunoglobulin trough levels checked because they did not come to their routine controls.

These findings suggest that telemedicine services will not replace doctor–patient face–to–face relationships, as reported in previous studies, but will help create more efficient treatment strategies and accelerate e-health strategies [25, 26].

Immunoglobulins have immunomodulatory activities, such as reducing phagocytosis-mediated cellular destruction, disrupting membrane attack complex formation with inhibition of the complement system, reducing IL-12 production, and increasing IL-10 production [27–30]. In one study, approximately 30% of patients with primary immunodeficiency who were diagnosed with COVID-19 were asymptomatic, and mild to moderate symptoms were observed in 50% of them [31]. In a multicenter study of 94 patients, ten patients were asymptomatic. Four of the ten asymptomatic patients had impaired antibody production. In these cases, SARS-CoV-2 testing was performed only because of travel, elective treatment, or the positivity of a symptomatic relative/close contact. In this cohort, nine patients (10%), including seven adults and two children, died. Six of the patients who died had antibody production defects [32]. Therefore, functional disorders of B cells might be protective against severe COVID-19 infection. Delavari et al. reported that Iranian patients with IEI had a 10-fold higher mortality than did the general population, especially among patients with combined immunodeficiency and immune dysregulation [2]. A total of 19 (11.2%) patients in our study group were diagnosed with COVID-19. Eleven of them were hospitalized. Seven patients had lung involvement. During our study, 2 (1.2%) adult patients who received IVIG died due to COVID-19 pneumonia. The other patients recovered without sequelae.

In a study conducted on 158 adult IEI patients in Italy, all 45 patients who received IVIG treatment switched to subcutaneous treatment during the pandemic [33]. Although it was recommended for all patients in another study by Cekic et al., only 18 (27.6%) of 65 patients receiving IVIG treatment agreed to switch to subcutaneous immunoglobulin treatment [34].

In our study, although all patients receiving IVIG were recommended to switch to subcutaneous treatment, 26 (20.9%) of 126 patients treated with IVIG switched to subcutaneous treatment. The most common reasons patients cited for not wanting to change their treatment route included avoiding frequent abdominal injections, concerns about developing adverse events at home, perceived lack of manual dexterity, and worries about maintaining hygienic conditions for injections at home.

In another study conducted in our department at the beginning of the pandemic, 12.7% ($n = 9$) of the patients reported not going to the hospital for routine controls to prevent SARS-CoV-2 transmission [34]. In our study, 24 (19.3%) patients treated with IVIG and 28 (62.2%) patients receiving subcutaneous Ig treatment delayed their hospital control examinations. When all the patients in our study were evaluated, this rate was 30.7%. Patients' adherence to follow-up and treatment attachment decreased as the pandemic progressed. Our study revealed that 24 (14.9%) patients interrupted immunoglobulin treatment for various reasons. All of these patients were in the group receiving IVIG treatment. All patients treated with SCIG received their treatment regularly during the pandemic process. The most common reason for discontinuing treatment (29.2%) was fear of going to the hospital because of the risk of COVID-19 transmission.

Conclusion

Our study is the first to reveal compliance problems with immunoglobulin treatment and their causes during the pandemic in patients with primary immunodeficiency. Since the continuity of immunoglobulin therapy is vital, planning for home immunoglobulin replacement therapy has been recommended at the beginning of any pandemic illness. We believe that patients with IEI should be monitored by telehealth services more frequently with respect to treatment continuity. Compliance with treatment was found to be greater in patients who were treated subcutaneously than in those who were treated via the IV route. During the pandemic, the immunoglobulin treatment method should be individualized according to patient characteristics and expectations.

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Authors' contributions
All the authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by YK, ZK, SC, IC and SSK. The first draft of the manuscript was written by YK and SSK, and all the authors commented on previous versions. All the authors read and approved the final manuscript.

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Data availability
The data that support the study findings are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Bursa Uludag University Faculty of Medicine Medical Research Ethics Committee for the study (2022–11/22). Informed consent was obtained from the parents or legal guardians of patients younger than 16 years of age for participation in the study and from the patients themselves for other patients.

Consent for publication
The participants gave permission to publish their data.

Competing interests
The authors declare no competing interests.

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