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Patient Compliance and Safety of Intravenous Biological Drug Treatments in Hospital During the COVID-19 Pandemic

COVID-19 Pandemi Sürecinde Hastanede İntravenöz Biyolojik Ajan Tedavilerinin Uyumu ve Güvenirliği

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This study was presented as an oral presentation in Türkiye Rheumatology E-Congress with International Attendance 2020, 13-15 November 2020, Online.

ABSTRACT Objective: This study aims to evaluate compliance and safety of treatments with intravenous (IV) biological drugs in hospital during the coronavirus disease-2019 (COVID-19) pandemic in patients with inflammatory rheumatic or bowel diseases. **Material and Methods:** The records of patients were retrospectively scanned from the hospital electronic database between 11.03.2020 and 30.09.2020. The patients with inflammatory rheumatic or bowel diseases who received intravenous (IV) biological therapy were included in the study. Demographic and clinic data, and information about COVID-19 infection were recorded. **Results:** The mean age of 103 patients included in the study was 45.3 years (minimum-maximum: 18-76 years) and 53 (51.5%) were women. The majority of patients (87 patients, 84.5%) had ankylosing spondylitis, rheumatoid arthritis, ulcerative colitis, and Crohn's disease. During the pandemic period, 77 (74.8%) patients continued routine follow-up, 18 (17.5%) patients extended the interval between visits, and 8 (7.7%) patients stopped follow-up. The biological drugs were switched to another in 12 (11.6%) patients due to secondary unresponsiveness, allergic reaction or unavailable drug. In this period, 6 patients were made COVID-polymerase chain reaction test and it was positive in 2 patients. They were receiving infliximab and rituximab treatment with the diagnosis of rheumatoid arthritis and systemic sclerosis, respectively. They continued the same treatment at the end of COVID-19 treatment. **Conclusion:** This study showed that most of the patients continued to routine follow-up and treatment, and these treatments did not increase the risk of COVID-19. Therefore, we think that IV biological treatments can be safely used during the pandemic process.

Keywords: Intravenous biological drugs; COVID-19 pandemic; safety and compliance; inflammatory disease

ÖZET Amaç: Bu çalışmanın amacı, inflamatuar romatizmal veya bağırsak hastalıkları olan hastalarda, koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] pandemisi sırasında hastanede intravenöz (IV) biyolojik ilaçların güvenliğini ve tedavi uyumunu değerlendirmektir. **Gereç ve Yöntemler:** Hastaların kayıtları 11.03.2020-30.09.2020 tarihleri arasında hastane elektronik veri tabanından geriye dönük olarak tarandı. İnflamatuar romatizmal veya bağırsak hastalığı olan ve IV biyolojik tedavi uygulanan hastalar çalışmaya dâhil edildi. Demografik ve klinik verilerle COVID-19 enfeksiyonuna ilişkin bilgiler kaydedildi. **Bulgular:** Çalışmaya dâhil edilen 103 hastanın yaş ortalaması 45,3 (minimum-maksimum: 18-76 yıl) ve 53'ü (%51,5) kadındı. Hastaların çoğunluğu (87 hasta, %84,5) ankilozan spondilit, romatoid artrit, ülseratif kolit ve Crohn hastalarından oluşuyordu. Pandemi döneminde, 77 (%74,8) hasta rutin takibe devam etti, 18 (%17,5) hasta takip aralığını uzattı ve 8 (%7,7) hasta takibi bıraktı. On iki (%11,6) hastada sekonder yanıtsızlık, alerjik reaksiyon veya ilaç bulunamaması nedeniyle biyolojik ajanlar değiştirildi. Bu dönemde, 6 hastaya COVID-polimeraz zincir reaksiyonu [polymerase chain reaction (PCR)] testi yapıldı ve 2 hastada pozitif çıktı. Bunlar sırasıyla romatoid artrit ve sistemik skleroz tanısı ile infliksimab ve rituksimab tedavisi alıyorlardı. COVID-19 tedavisinin sonunda da aynı tedaviye devam ettiler. **Sonuç:** Bu çalışma, hastaların çoğunun rutin takip ve tedaviye devam ettiğini ve bu tedavilerin COVID-19 riskini artırmadığını göstermiştir. Bu nedenle IV biyolojik tedavilerin pandemi sürecinde güvenle kullanılabileceğini düşünüyoruz.

Anahtar Kelimeler: İntravenöz biyolojik ilaçlar; COVID-19 pandemisi; güvenlik ve uyum; inflamatuar hastalık

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Biological agents are widely used in the treatment of both inflammatory rheumatic diseases and inflammatory bowel diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease and ulcerative colitis.[1] Both inflammatory diseases and their treatments are associated with an increased infection risk. In particular, biological treatments targeting cytokines involved in this inflammatory process increase the risk of viral, bacterial, and granulomatous infections, but there is no evidence yet that they increase the risk of coronavirus disease-2019 (COVID-19).[2-4]

A new coronavirus that caused severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was first detected at the end of 2019 in Hubei province, China. The clinical picture of this respiratory disease, called COVID-19, ranges from asymptomatic and influenza-like illness to severe disease with accompanying lung damage, multi-organ failure, and death. COVID-19, which spread rapidly all over the world, caused a life-threatening and still ongoing pandemic.[5,6]

Advanced ages and comorbid illnesses increase the risk of this disease. As a result of biological or other immunosuppressive treatments used in inflammatory rheumatic and inflammatory bowel diseases, patients have a risky immune system in terms of COVID-19. Despite this, the risk and prognosis for COVID-19 in patients treated with biological agents are unknown.[7,8]

On the other hand, research is ongoing on the potential of these agents to improve COVID-19.[9] Although data on the risks and consequences of COVID-19 infection in patients with inflammatory rheumatic or inflammatory bowel diseases are insufficient, patients continue to use biological immune modulatory agent therapies. Patients and clinicians are still hesitant about these treatments, as there is no evidence-based guideline for biological treatments. However, current guidelines are largely based on expert opinions.[9-11] Considering the prediction that the COVID-19 pandemic process will continue for a while, we think that the short-term results of our patients receiving intravenous (IV) biological treatment in the hospital will contribute to the literature.

MATERIAL AND METHODS

The records of 103 patients receiving IV biological drug therapy were scanned retrospectively from the electronic database of Mersin University Medical Faculty Hospital. The medical records of 2 clinics in a single center (department of physical medicine and rehabilitation and department of gastroenterology) were evaluated between 11.03.2020, when the first case of COVID-19 has been confirmed, and 30.09.2020. The patients who were treated with IV biological agents (infliximab, tocilizumab, rituximab, and vedolizumab) were included in the study. The patients treated with only nonbiological agents or subcutaneous biological agents or under 18 years of age were excluded. The demographic data (age, gender), diagnoses, treatments, laboratory values of the patients, and information about COVID-19 were recorded. The study was approved by Mersin University Local Research Ethics Committee (14.10.2020 and protocol number: 2020/698) and Ministry of Health of the Republic of Turkey (19.09.2020). The report was conducted in accordance with the Decleration of Helsinki, and written informed consent was obtained.

STATISTICAL ANALYSIS

Statistical analysis was performed using the statistical package SPSS software (Version 25.0, SPSS Inc., Chicago, IL, USA). If continuous variables were normal, they were described as the mean±standard deviation [$p>0.05$ in Kolmogorov-Smirnov test or Shapiro-Wilk ($n<30$)], and if the continuous variables were not normal, they were described as the median. Comparisons between groups were applied using Student t-test (group: patient and control) or Mann-Whitney U test was used for the data not normally distributed. Pre-post measures data were analyzed with Friedman test and Wilcoxon test. Values of $p<0.05$ were considered statistically significant.

RESULTS

The average age of 103 patients included in the study was 45.3 years (minimum-maximum: 18-76 years) and 50 (48.5%) patients were males, and 53 (51.5%) were females. The diagnosis and treatment informations of the patients have been shown in Table 1.

TABLE 1: Baseline characteristic of the patients.

Characteristics	All patients (n=103) Mean/range n/%
Age (years)	45.3 (18-76)
Females/males	53 (51.5%)/50(48.5%)
Diagnosis	
Rheumatoid arthritis	27 (26.2%)
Juvenile rheumatoid arthritis	1 (1.1%)
Ankylosing spondylitis	31 (30.1%)
Psoriatic arthritis	3 (2.9%)
Enteropathic arthritis	7 (6.8%)
Familial Mediterranean fever	1 (1%)
Systemic sclerosis	1 (1%)
Behçet's disease	3 (2.9%)
Ulcerative colitis	15 (14.6%)
Crohn's disease	14 (13.6%)
Biological therapies	
Tumor necrosis factor-α inhibitor (infliximab)	64 (62.1%)
Interleukin-6 receptor inhibitor (tocilizumab)	11 (10.7%)
Monoclonal antibodies	
Vedolizumab	21 (20.4%)
Rituximab	7 (6.8%)
COVID-19 symptoms	4 (3.9%)
Diagnosis of COVID-19	2 (1.9%)

While 84 (81.6%) patients were receiving biological therapy for more than 1 year, 9 (8.7%) patients started to receive biological therapy 3 months before the onset of the pandemic and 10 (9.7%) patients during the pandemic period. During the 6-months pandemic period, 11 (10.7%) patients 6 times, 13 (12.6%) patients 5 times, 24 (23.3%) patients 4 times, 30 (29.1%) patients 3 times, 10 (9.7%) patients twice, and 15 (14.6%) patients once had taken IV treatments.

In the pandemic period, the biological drugs were switched to another in 12 (11.6%) patients; in 5 due to secondary unresponsiveness to treatment, in 4 due to allergic reaction, and in 3 due to unavailability of the drug. While three of these patients continued treatment with a different IV biological agent, the others continued treatment with subcutaneous biological agents.

Within the study period, 77 (74.8%) patients continued routine follow-up and did not skip follow-up visits. Eighteen (17.5%) patients prolonged the time between the visits, 6 (5.8%) patients have not come for treatment after the initial therapy, and 2 (1.9%) patients have not come for treatment in the last 3 months. Of 26 patients that discontinued routine follow-up, 16 (15.5%) discontinued because of COVID-19 pandemic, 5 (4.8%) because of seasonal relocation, and 5 (4.8%) because of surgical procedure. Laboratory values of the patients, except for hemoglobin (Hb) (p=0.027), did not statistically significant change in the COVID-19 pandemic period compared to pre-pandemic period; the change in Hb values was clinically not significant (Table 2). In addition, when the patients who continued follow-up regularly and those who skipped control visits due to the COVID-19 pandemic were compared in terms of laboratory values, no statistically significant difference was determined (Table 3).

In addition to IV biological drugs, 9 (8.7%) patients were receiving antiviral agents for hepatitis, 5 (4.9%) patients steroid therapy, 9 patients nonsteroidal anti-inflammatory drugs, and 38 (36.9%) patients were receiving at least one conventional synthetic-disease-modifying antirheumatic drug (methotrexate, sulfasalazine, leflunomide, or hydroxychloroquine).

TABLE 2: Comparison of laboratory results at the last visit comparison with those before the pandemic.

	Before (n=103)	Last visit (n=103)	p value
CRP mg/L	4 (0.1-75.0)	3.2 (0.1-111)	0.061
ESR mm/h	15 (2-72)	12 (2-57)	0.068
Hb g/dL	13.7±1.5	13.4±1.5	0.027*
WBC (x10.e3/u)	8.11 (5.9-14.7)	8.03 (12.3-15.59)	0.976
PLT (x10.e3/u)	282 (110-765)	289 (116-538)	0.232
LYMP (x10.e3/u)	2.38 (0.71-5.33)	2.26 (0.48-5.64)	0.345

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; Hb: Hemoglobin; WBC: White blood cell; PLT: Platelet; LYMP: Lymphocytes.

TABLE 3: Comparison of laboratory results between regular and non-regular follow-up patients.

Before last*	Regular (n=77)	Non-regular (n=18)	p value
CRP mg/L	4.2 (0.1-75.0)	3.0 (0.2-47.0)	0.440
CRP* mg/L	3.0 (0.1-111.0)	3.9 (0.2-25.4)	0.894
Hb g/dL	13.7±1.6	13.8±1.3	0.703
Hb* g/dL	13.5±1.5	13.8±1.4	0.427
WBC (x10.e3/u)	7.66 (5.9-14.7)	8.66 (1.48-10.42)	0.547
WBC* (x10.e3/u)	8.00 (12.3-15.5)	8.60 (5.62-10.08)	0.514
PLT (x10.e3/u)	276 (110-765)	274.5 (143-468)	0.537
PLT* (x10.e3/u)	278 (116-538)	279 (182-383)	0.784
ESR mm/h	15 (2-72)	19 (2-61)	0.196
ESR* mm/h	11 (2-45.7)	13 (3-32)	0.439
LYMP (x10.e3/u)	2.29 (0.71-5.33)	2.39 (1.13-3.72)	0.585
LYMP*(x10.e3/u)	2.23 (0.48-4.54)	3.35 (1.68-3.82)	0.159

CRP: C-reactive protein; HB: Hemoglobin; WBC: White blood cell; PLT: Platelet; ESR: Erythrocyte sedimentation rate; LYMP: Lymphocytes.

During the study period, a total of 6 patients underwent the COVID-polymerase chain reaction (PCR) test (2 due to contact history, 3 due to fever, and 1 due to shortness of breath) and the tests of 2 patients were positive. They were receiving infliximab and rituximab treatment with the diagnosis of rheumatoid arthritis and systemic sclerosis, respectively (Table 4). At the end of the isolation period following the COVID-19 treatment, they continued treatment with the same IV biological drugs.

DISCUSSION

The effect of biological agents, which are widely used for the treatment of inflammatory rheumatic or bowel diseases, on the prognosis of COVID-19 is gaining critical importance for the management of treatment. There is yet no completed study focusing on the management of biological agents in the treatment of these diseases over the COVID-19 pandemic process. For this reason, multi-center studies are ongoing both in Turkey and in many other countries to observe the clinical outcomes of the patients using biologic agents. Since the use of anti-tumor necrosis factor (TNF) is associated with increased risk of infection, patients receiving anti-TNF have been considered in the high-risk group for COVID-19 and related complications.[12,13] Although the risk of certain viral, bacterial and granulomatous infections is high in the patients receiving anti-TNF, there is yet no evidence that anti-TNF in-

TABLE 4: Demographic and clinical data of the patients with the diagnosis of COVID-19.

	Patient 1	Patient 2
Diagnosis	Rheumatoid arthritis	Systemic sclerosis
Sex	Woman	Woman
Disease severity (last visit)	Pain (mild) DAS28:1.8	Mild
Disease duration	5 years	2 years
Steroid therapy/dose	No	Yes/10 mg prednisolone
Biological therapy	Infliximab	Rituximab
Date of infusion before COVID-19	2.7.2020	9.3.2020
Date of COVID-19 symptom	28.8.2020	22.8.2.2020
Duration between infusion and symptom	57 days	158 days
PCR test date	30.8.2020	24.8.2020
Date of infusion after COVID-19	16.10.2020	23.9.2020
Symptoms		
Fever	No	Yes
Non-productive cough	No	Yes
Sputum	No	No
Sore throat	No	Yes
Rhinorrhea	No	Yes
Anorexia	No	No
Fatigue	Yes	Yes
Myalgia	Yes	Yes
Arthralgia	No	No
Anosmia	Yes	No
Headache	Yes	No
Diarrhea	No	No
Nausea	No	No
Vomiting	No	No
CT scan/chest radiography	Infiltrative	Infiltrative

DAS28: Disease Activity Score-28; PCR: Polymerase chain reaction; CT: Computed tomography.

creases the risk for COVID-19.[4] Likewise, tocilizumab, vedolizumab and rituximab are known to be associated with increased risk of infection, but there is no evidence that they increase the risk of COVID-19.[14,15]

In the letter written by Duret et al., one of the limited number of publications, it was propounded that using a TNF inhibitor before a viral infection is not associated with severe clinical course of COVID-19.[16] However, the role of immune system and immune-modulating therapies on the course of COVID-19 remains debatable.[17,18] In the letter from New York, Haberman et al. evaluated auto-inflammatory patients diagnosed with COVID 19. In this study, it was emphasized that using biological agents is not associated with poor clinical outcomes of COVID-19.[19] A joint study conducted by 2 academic centers from France and Italy reported that 13 of 561 patients with inflammatory bowel disease receiving IV infliximab and vedolizumab were positive for COVID-19, and they emphasized that IV biological therapy does not enhance the risk of COVID-19.[20] Although the present study has larger spectrum of patients, the number of patients was lower because of single-center design of the study. Similarly, our patients have received IV infliximab, vedolizumab and tociluzumab therapy in the hospital; and the range of time was wider. Among the 103 patients we followed, only 6 underwent PCR testing for suspicious COVID-19 and 2 were found positive. The facts that our patients paid strict attention to social isolation, IV treatment in the hospital was performed in another unit separate from clinically positive COVID-19 patients, and healthcare personnel working in COVID-19 clinic were kept out of the follow-up and treatment of these patients can be considered as the reasons for detecting COVID-19 in only 2 patients.

Immunopathogenesis of COVID-19 infection has been associated with cytokine storm. TNF plays a role in the proinflammatory activity during cytokine storm by causing tissue damage, lung injury and shock due to increased vascular escape.[21,22] In vitro studies have demonstrated that TNF facilitates the interaction between SARS-CoV and angiotensin-converting enzyme 2, which is found in the viral entry.[21,23] Although it has been demonstrated that TNF-alpha inhibitors are not effective in the treatment of septic shock, whether cytokine blocking therapy will be effective in the cytokine storm associated with COVID-19 remains uncertain.[24-26] Studies including anti-TNF are ongoing on the ClinicalTrials.gov As the consequence of joint studies such as European League Against Rheumatism-COVID-19 database and COVID-19 Global Rheumatology Assembly in particular, new and more comprehensive evidences will be exposed about the rate and severity of affection of COVID-19 by the use of biological agents.

Cytokine storm including plasma inflammatory cytokines such as interleukins (IL-1, IL-6, IL-8, IL-12), TNF-alpha and interferon as well as chemokine is considered to play a role in the pathophysiology of COVID-19. Proinflammatory cytokines including IL-6 are increased in severe and fatal COVID-19 cases and thereby, the use of drugs inhibiting the IL-6 pathway has become a current issue for the prevention and treatment of the disease. Given that IL-6 activates the complement and coagulation system in the pathophysiology of disseminated intravascular coagulation, IL-6 can be considered as a quite critical molecule in cytokine storm. There are randomized and ongoing studies where tocilizumab, an IL-6 pathway inhibitor, is used for the treatment of COVID-19. Nevertheless, published studies suggest that these agents provide no benefit.[27-30]

Vedolizumab is a human monoclonal antibody that targets α4β7 integrin. It inhibits the migration of memory T-lymphocytes to the inflamed gastrointestinal tissue throughout the endothelium by selectively blocking the interaction of α4β7 with mucosal cell adhesion molecule-1. This intestine-selective action has been associated with lower risk of infection as compared to the other biological agents.[31] This indicates that the risk of COVID-19 infection might be lower with vedolizumab as compared to the other biological agents, but there is no study on this issue.

Rituximab is a chimeric monoclonal anti-CD20 antibody licensed for the treatment of rheumatoid arthritis, microscopic polyangiitis and granulomatosis with polyangiitis. Moreover, it is widely used also for the treatment of other systemic diseases such as systemic lupus erythematosus, Sjögren syndrome, systemic sclerosis and idiopathic inflammatory my-

opathies. CD20+ effects B cells and shows non-specific activity on the antibody titers by inducing complement-mediated cytotoxicity.[32]

Some studies reported higher risk of infection in rheumatoid arthritis patients treated with rituximab as compared to those treated with other biological disease-modifying antirheumatic drugs; however, these data have been retrospectively retrieved from the medical records. Effects of rituximab on the immune system response against SARS-CoV-2 infection have not been clarified yet.[33] The first study on rituximab published by Loarce-Martos et al. emphasized that patients receiving rituximab have higher risk of morbidity and mortality.[34] In the present study as well, the fact that one of our COVID-19-positive patients has been receiving rituximab appears to support this study. Long-term use of rituximab may impair the preparation of antibody responses to neutralize viral replication.

The continuity of treatment has been affected within this process either as the consequence of different clinical approaches such as postponing the treatment with biologics or expanding the intervals or due to patient-based personal reasons (anxiety, social media, unavailability of drug, etc.). Twenty-to-thirty percent of the physicians reported that their patients had experienced an exacerbation or delay in the diagnosis/intervention because of postponed appointments.[35] Although the majority of the patients that we followed have remained on their scheduled follow-up, it was observed that some of them had tendency to expand the treatment intervals or discontinue the treatment. During the 6-month pandemic period, while 74.8% of patients have continued follow-up, 17.5% of patients have extended the time between visits, and 7.7% of patients have stopped follow-up. Only 16 (15.5%) patients have discontinued or skipped follow-up visits because of the COVID-19 pandemic.

Earlier studies reported that some of the rheumatologists refrained from starting a new biological agent during pandemic process. In some clinics, biological therapies have been discontinued for a short time.[35,36] In our clinic, treatments of the patients with biologics have continued and new IV biologic agents have been started.

Studies revealed that face-to-face patient visits have been substantially reduced in many rheumatology clinics, instead the patients were reached via teleconferences, video calls or e-mail.[37,38] In the present study, tele-visit via teleconference, video or WhatsApp Inc USA was not performed because the patients received their IV therapies in the hospital, and they were evaluated by routine face-to-face clinical examination and analysis. In a study conducted in rheumatology clinics, it was reported that the number of examinations decreased by 53%.[39] However, SARS-CoV-2 as well can show atypical clinical manifestation due to the immunosuppressant agents widely used in the rheumatology and gastroenterology clinics, or the symptoms may be confused with the symptoms of auto-inflammatory diseases. Inflammatory markers of the patients can increase in either situation, fever response may be suppressed in the patients receiving steroid, or inflammatory markers may not be increased in the patients receiving IL-6 inhibitors. Despite the lacking evidence that the risk of having COVID-19 infection is higher among patients with auto-immune diseases treated with biological agent, such patients still potentially have the high risk of complications.[40] Therefore, particularly the patients that were diagnosed with auto-immune disease and have been receiving biological therapy should be monitored for COVID more attentively. Routine analysis prior to each session of IV treatment enables close monitoring for the patients receiving IV biological therapy in the hospital.

There has been a problem in the availability of tocilizumab since it has been used during the pandemic process. In the study conducted by Batu et al., 8.9% of the rheumatologists reported that they had problem in supplying tocilizumab.[35] In the present study as well, some of the patients receiving IV tocilizumab have switched to subcutaneous tocilizumab or another biological agent because of the problems in supplying the drug.

The present study is valuable in terms of evaluating the patients that have received IV biological agent for various indications. The patients' receiving their treatment by day hospitalization provided clinically close monitoring. Clinical, laboratory and con-

tact status of each patient in terms of COVID-19 was assessed prior to each session of treatment. However, PCR screening was not performed routinely as per pandemic management policy, or the patients could not be referred to a private center for PCR testing as it is forbidden.

CONCLUSION

COVID-19 infection rapidly spread all over the world and caused an ongoing and life-threatening pandemic. This study has shown that most of the patients continued routine follow-up and treatment, and these treatments did not increase the risk of COVID-19. Therefore, we think that IV biological treatments can be safely used during the pandemic process. In addition, we believe that long-term and multi-center studies are needed in the future.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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