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Original Article

Does Intravenous Immunoglobulin Therapy Have a Role in the Treatment of Severe Coronavirus-19 Patients?

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Abstract: *We wanted to evaluate the efficacy of intravenous immunoglobulin (IVIG) treatment in Covid-19 patients in the intensive care unit (ICU). Sixteen (66.7%) male and 8 (33.3%) female adult severe Covid-19 patients who were treated with IVIG in the tertiary ICU between April 2020 and October 2021 at Ankara City Hospital were retrospectively reviewed. The median age of the patients was 63 (interquartile range (IQR):19). The patients were evaluated in terms of laboratory values and clinical results before and after IVIG treatment. There was no statistically significant difference between survived and deceased Covid-19 patients treated with IVIG in terms of age, gender, the onset of symptoms, presence of concomitant diseases, APACHE-II scores, duration of mechanical ventilator support, and length of stay in the ICU. When the laboratory values before and after IVIG treatment were compared, a significant decrease was identified only in alanine transaminase levels (p=0.01). However, there was a statistically significant difference in mortality in 5 patients with Guillain-Barré syndrome who all survived (p=0.001). IVIG treatment was effective in Covid-19 patients with Guillain-Barré syndrome. However, IVIG treatment did not have a statistically significant effect on pre and post-treatment laboratory values, morbidity, and mortality of severe Covid-19 patients in the ICU.*

Keywords: *Covid-19, critical care, Guillain-Barré syndrome, Intravenous immunoglobulin*

INTRODUCTION

Coronavirus disease 2019 (Covid-19) is caused by a RNA virus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1,2]. Covid-19 can lead to asymptomatic infection, mild symptoms, or severe pulmonary symptoms with hyperinflammation [3]. In severe Covid-19 patients, management of hyperinflammation and cytokine storm with appropriate antiinflammatory agents is recommended [4]. Different anti-inflammatory agents have been tried on critically ill patients during the Covid-19 pandemic.

IVIG is a biological agent which contains pooled polyclonal immunoglobulin G from the plasma of approximately one thousand healthy blood donors [1]. IVIG is used for the treatment of immunodeficiency, autoimmune and inflammatory diseases [5]. IVIG has not only anti-inflammatory effects but also the ability to neutralize bacterial toxins [6]. IVIG treatment has also been tried in epidemic diseases related to viruses such as influenza A H1N1, Middle East Respiratory Syndrome (MERS-CoV-2), and Severe Acute Respiratory Syndrome (SARS), and it has been reported that IVIG treatment decreased viral load, caused clinical improvement and decreased mortality in patients with a severe course [7,8]. In light of experience, IVIG treatment has been recommended to be used for the management of patients with Covid-19 [1,9-13]. However, the role of IVIG treatment in patients with severe Covid-19 remains unclear. Thus, this study aimed to evaluate the efficacy of IVIG treatment administered to severe Covid-19 patients in the ICU.

MATERIALS AND METHODS

Local ethics committee approval for this study was obtained from Ankara City Hospital (E2-21-835). The electronic records of 640 Covid-19 patients who were followed up between April 2020 and October 2021 in tertiary ICU were retrospectively reviewed. Thereafter, sixteen (66.7%) male and 8 (33.3%) female adult Covid-19 patients who were treated with IVIG in

the ICU between April 2020 and October 2021 at Ankara City Hospital were included in this study for further analysis. The definitive Covid-19 diagnosis was based on both real-time reverse transcription polymerase chain reaction (RT-PCR) test results and ground glass appearance with pneumonia on thorax computed tomography. These severe Covid-19 patients had also respiratory distress with peripheral capillary oxygen saturation (SPO2) ≤ 93% in room air before admission to the ICU.

IVIG treatment was administered due to sepsis in 6 (25%) patients, Guillain-Barré syndrome in 5 (20.8%) patients, hematological disorders such as hemophagocytic syndrome, chronic lymphocytic leukemia and autoimmune hemolytic anemia in 9 (37.5%) patients, rheumatologic and immunological disorders such as immunodeficiency, systemic lupus erythematosus, myositis and vasculitis in 4 (16.7%) patients. In all patients, IVIG was administered at 0.4 g/kg/day for 3 consecutive days. These 24 patients were evaluated in terms of laboratory values before the first IVIG treatment session and after the third IVIG treatment session. Thus, neutrophil, lymphocyte and platelet count, neutrophil/lymphocyte ratio, lactate dehydrogenase, d-dimer, fibrinogen, ferritin, procalcitonin, c-reactive protein (CRP), interleukin-6, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values were noted. Demographic data, the onset of symptoms, concomitant diseases, APACHE II scores, duration of mechanical ventilator support, length of ICU stay, and mortality rates were also recorded.

For all statistical analysis, Statistical Packages for the Social Sciences (v17.0 SPSS 24 Inc. Chicago, IL) software was used. Categorical data were presented as numbers and percentages, while quantitative data were presented as mean standard deviation or median and interquartile range (IQR), as appropriate. The differences between the two groups were evaluated with the Mann-Whitney U test and the chi-square test. The statistical significance level was accepted as $p<0.05$.

RESULTS

The median age of the patients included in this study was 63 (IQR:19), and the median time to symptom onset was 6.5 days (IQR:6). The median APACHE II score of these patients was 16 (IQR:9). The median length of stay in the ICU was 22.5 (IQR:34) days, whereas the median mechanical ventilator time was 19 days (IQR:29) (Table 1). Eighteen (75%) patients had concomitant diseases such as diabetes mellitus type 2, hypertension, and coronary artery disease. The most common disease accompanying Covid-19 was hypertension in 13 (54.2%) patients. The most common symptom was dyspnea in 17 (70.8%) patients. Fever was present in 7 (29.1%) and cough in 5 (20.8%) patients. Other less frequent symptoms were headache, sore throat, nausea, vomiting, impaired taste and smell, myalgia, and weakness. Complications, which were not related to IVIG treatment, such as gastrointestinal bleeding in 2 patients, cerebrovascular accident in 1 patient, myocardial infarction in 1 patient, pneumothorax in 6 patients, and seizures in 2 patients were observed in total in 12 (50%) patients. Antibiotics were empirically administered in 15 (62.5%) of the patients. Unfortunately, 16 (66.7%) patients passed away due to complications related to Covid-19 (Table 1).

Table 1: Characteristics of the Intravenous Immunoglobulin Treated Covid-19 Patients

Characteristics of Covid-19 patients	Survived	Deceased	Total	*P* value
Gender (n, %) Male Female	 6 (75) 2 (25)	 10 (62.5) 6 (37.5)	 16 (66.7) 8 (33.3)	 0.67*
Age (years) (median, IQR)	61.5 (29)	63.5 (19)	63 (19)	0.85**
The onset of symptoms (days) (median, IQR)	6.5 (3)	6.5 (6)	6.5 (6)	0.60**
Length of ICU stay (days) (median, IQR)	29.5 (42)	22.0 (23)	22.5 (34)	0.42**
Mechanical ventilator duration (days) (median, IQR)	26 (59)	16 (27)	19 (29)	0.32**
Presence of concomitant disease (n, %) Diabetes mellitus type 2 Hypertension Coronary artery disease	7 (87.5) 4 (50) 6 (75) -	11 (68.8) 4 (25) 7 (43.8) 5 (100)	18 (75) 8 (33.3) 13 (54.2) 5 (20.8)	0.62* 0.36* 0.21* 0.13*
Complications (n, %)	5 (62.5)	7 (43.8)	12 (50)	0.67**
Antibiotic use (n, %)	4 (50)	11 (68.8)	15 (62.5)	0.41**
APACHE II score (median, IQR)	15 (9)	18.5 (12)	16 (9)	0.13**

*†IQR: interquartile range. ‡ICU: intensive care unit; *Chi-square test was used. **Mann-Whitney U test was used*

There was no statistically significant difference between survived and deceased patients in terms of gender, age, the onset of symptoms, length of stay in the ICU, duration of mechanical ventilator support, accompanying symptoms, concomitant diseases such as diabetes mellitus type 2, hypertension, coronary artery disease, complication development, antibiotic use, and APACHE II scores. However, a significant difference was identified in mortality when the effect of IVIG treatment administered for Guillain-Barré syndrome in 5 patients and other disorders were compared (p=0.001). All patients with Guillain-Barré syndrome survived after IVIG treatment. All 6 patients, who were treated with IVIG for sepsis, died. Three patients died and 1 patient survived with rheumatological and immunological diseases. Seven of 9 patients with hematological diseases passed away, whereas 2 patients survived (Table 1). When the laboratory values before and after IVIG treatment were compared, a significant decrease was found only in ALT levels (p=0.01) (Table 2).

Table 2: Laboratory Parameters of Covid-19 Patients Before and After IVIG Treatment

Laboratory parameters	Before IVIG treatment	After IVIG treatment	*P* value*
Neutrophil count x10^9/L	8.4 (6.5)	8.0 (7.8)	0.84
Lymphocyte count x10^9/L	0.59 (0.49)	0.59 (0.45)	0.26
Platelet count x10^9/L	206.5 (152)	210 (142)	0.48
Neutrophil/lymphocyte ratio	13.0 (10.4)	11.8 (7.0)	0.39
Lactate dehydrogenase (U/L)	456.5 (349)	459.5 (193)	0.18
D-dimer (mg/L)	2.79 (4.91)	2.69 (6.05)	0.74
Fibrinogen (g/L)	5.4 (2.9)	4.4 (2.8)	0.22
Ferritin (µg/L)	1011 (1417)	715 (1198)	0.38
Procalcitonin (µg/L)	0.30 (0.35)	0.51 (1.17)	0.10
C-reactive protein (g/L)	66 (136)	95 (151)	0.76
Interleukin-6 (pg/mL)	31.1 (34.3)	38.2 (61.4)	0.40
Aspartate aminotransferase (U/L)	44.5 (50)	40.5 (26)	0.21
Alanine aminotransferase (U/L)	52.5 (48)	34.5 (46)	0.01

*In all patients, IVIG was administered 0.4 g/kg/day for 3 consecutive days. Numerical data are given as a median and interquartile range. IVIG: intravenous immunoglobulin. *Wilcoxon test was used.*

DISCUSSION

The severity of the cases, the IVIG dose, and the time of administration should be considered when evaluating the effect of IVIG on Covid-19. In our study, the patients who underwent IVIG therapy were severe Covid-19 patients and all of the patients received IVIG treatment at the same dose and duration (0.4 g/kg/day for 3 consecutive days).

Huang et al. reported that 45 non-severe Covid-19 patients who were treated with IVIG had no benefit beyond standard therapy in terms of duration of fever, virus clearance time, length of hospital stay, and use of antibiotics [14]. However, after the initiation of IVIG therapy in Covid-19 patients, there have been several studies published reporting that IVIG treatment reduced mortality in Covid-19 patients. Gharebaghi et al. reported that 30 Covid-19 patients were treated with IVIG four vials daily for three days and the in-hospital mortality rate was significantly lower in the IVIG group compared to the control group (6 (20.0%) vs.14 (48.3%), p=0.022) [15]. Sakoulas et al. administered IVIG 0.5 g/kg/d for 3 days to 16 Covid-19 patients, reporting that patients treated with IVIG had shorter median ICU stay (2.5 vs 12.5 days, p=0.006) in addition to improvement of hypoxia compared to the control group [16]. Raman et al. reported that 50 Covid-19 patients were treated with IVIG, who had a significantly shorter hospital stay, and faster recovery with an improvement in oxygen saturation. Moreover, Raman et. al claimed that positive RT-PCR tests of Covid-19 patients treated with IVIG became negative in a shorter period compared to the control group (7 vs 18 days) [17]. Ali et al. administered each group with 10 patients with different doses of IVIG 0.15, 0.20, 0.25, and 0.30 g/kg. Even 10 of 40 participants (25%) passed away, Ali et al. reported that IVIG increased survival chances and reduced the risk of Covid-19 progression [18]. Esen et al. reported that 51 Covid-19 patients who received IVIG had prolonged median survival time and reduced CRP levels [19]. Shao et al. stated that early administration (admission ≤ 7 days) of high-dose IVIG (> 15 g per day) not only improved the prognosis but also reduced 60-day mortality in severe Covid-19 patients [20].

The latest Surviving Sepsis Campaign Guidelines did not recommend IVIG therapy for the treatment of sepsis due to the low quality of evidence from previous studies [21]. All of our 6 patients treated with IVIG for sepsis died, however, all patients with Guillain-Barré syndrome survived after IVIG treatment in this study. In addition, there are several case reports of Covid-19 patients who had neurological disorders such as acute disseminated encephalomyelitis and Guillain-Barré syndrome which were reported to be successfully treated with IVIG [22-27]. Moreover, IVIG treatment has been reported to be effective in Covid-19 related immunological diseases such as multisystem inflammatory disease, myocarditis, and Kawasaki disease [28].

However, there are several studies claiming that IVIG treatment did not affect the need for mechanical ventilation, improvement in chest tomography, and reduction in mortality in severe Covid-19 patients [29]. Tabarsi et al. administered 400 mg/kg IVIG daily for three days to 52 patients, in addition to hydroxychloroquine and lopinavir/ritonavir treatment. IVIG treatment was initiated after 3.84 ± 3.35 days of admission and Tabarsi et al. did not identify any significant difference between the IVIG and control group in terms of the need for mechanical ventilation and mortality [29]. Hou et al. reported that 113 Covid-19 patients were treated with IVIG. Patients who received IVIG had a longer hospital stay of 23.0 days (19.0–31.0) with a higher mortality rate than the control group (9 (19.1%) vs 4 (6.1%), p= 0.032) [30]. Hou et al. stated that IVIG improved neither in-hospital mortality nor the need for mechanical ventilation in severe Covid-19 patients. Liu et al. stated that they treated 421 severe Covid-19 patients with IVIG and they observed no significant differences in 28-day mortality, acute respiratory distress syndrome, acute hepatic injury, acute kidney injury, diffuse intravascular coagulation, myocardial injury, shock and invasive mechanical ventilation between the IVIG and control group [31]. Focosi et al. evaluated 2401 Covid-19 patients from 10 studies and concluded that IVIG was not associated with reduced death risk, thus the current evidence from the medical literature did not support IVIG therapy in Covid-19 patients [32]. In a recently published retrospective, multi-center cohort study of critically ill Covid-19 patients, 109 patients treated with standard therapy and 74 patients who received IVIG therapy were compared [33]. Salehi et al. reported that there was no difference in length of stay in the ICU, duration of mechanical ventilation, and mortality between standard therapy and IVIG therapy groups. Thus, Salehi et al. concluded that IVIG therapy was not beneficial in critically ill Covid-19 patients [33].

Within our study, there was no statistically significant difference in mechanical ventilation duration and length of stay in the ICU between critically ill Covid-19 patients who survived or died (p=0.32 and p=0.42, respectively). However, we did not have the opportunity to compare critically ill Covid-19 patients who received IVIG therapy plus standard treatment and only standard treatment.

Moreover, the effect of IVIG on mild Covid-19 cases requires further research. Huang et al. reported that 45 non-severe Covid-19 patients who were treated with IVIG had no benefit beyond standard therapy in terms of duration of fever, virus clearance time, length of hospital stay, and use of antibiotics [14].

In this study, laboratory parameters before and after IVIG treatment were evaluated. There was neither a statistically significant increase nor decrease in acute phase reactants such as CRP, procalcitonin, ferritin, and fibrinogen before and after IVIG therapy (p=0.76, p=0.10, p=0.38, and p=0.22, respectively.) The only laboratory parameter which had a statistically significant decrease after IVIG therapy was ALT in critically ill Covid-19 patients (p=0.01) (Table 2).

IVIG may slightly increase liver function tests. However, Chen et al. reported that IVIG was effective in alleviating hepatic ischemia-reperfusion injury in a rat model by reducing ALT, AST, IL-6, and TNF-alpha [34]. Moreover, Omma et al. reported improvement in liver function tests including ALT after IVIG treatment [3].

IVIG treatment is an expensive therapy option in developing countries. Therefore, we had to administer IVIG as a salvage therapy only to severe Covid-19 patients. Unfortunately, 16 (66.7%) of 24 severe Covid-19 patients passed away despite IVIG treatment.

IVIG therapy has the risk of several side effects such as thromboembolism, renal failure, meningoencephalitis, and anaphylaxis [35]. We have encountered no side effects during IVIG therapy in our ICU.

The main limitation of this retrospective study was the small sample size. A larger sample size will help to learn more about the positive and negative effects of IVIG therapy in Covid-19 patients. As our intensive care unit was reserved for only severe Covid-19 patients during the pandemic, this study lacked a control group. The effect of IVIG on severe Covid-19 cases requires further well-designed prospective randomized controlled studies.

CONCLUSION

IVIG treatment was effective in Covid-19 patients with Guillain-Barré syndrome. However, IVIG treatment did not have a statistically significant effect on pre and post-treatment laboratory values, morbidity, and mortality of severe Covid-19 patients in the ICU.

Conflicts of interest and sources of funding
The authors declare no conflict of interest.
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Authors' contribution
AConceptualization, S.G.I., C.M.A., M.E.Y., S.I.; methodology, M.E.Y., S.I.; software, M.E.Y.; validation, S.G.I., C.M.A., M.E.Y., S.I.; formal analysis, M.E.Y.; investigation, M.E.Y.; resources, S.G.I., C.M.A., M.E.Y., S.I.; data curation, S.G.I, C.M.A, M.E.Y., S.I.; writing-original draft preparation, M.E.Y.; writing-review and editing, S.G.I., C.M.A., M.E.Y., S.I.; visualization, M.E.Y.; supervision, S.I.; project administration, S.I. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate
The study was conducted under the Declaration of Helsinki, and local ethics committee approval for this study was obtained from Ankara City Hospital (E2-21-835).

References:

1. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol 2020, 39, 2085-94. doi: 10.1007/s10067-020-05190-5.

2. Hu B, Guo H, Zhou P, Shi Z-L. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol 2021, 19, 141-54. doi: 10.1038/s41579-020-00459-7.

3. Omma A, Erden A, Armağan B, Güven SC, Karakaş Ö, Şahiner ES, et al. A single center experience of intravenous immunoglobulin treatment in Covid-19. Int Immunopharmacol 2021, 98, 107891. doi: 10.1016/j.intimp.2021.107891.

4. Pourahmad R, Moazzami B, Rezaei N. Efficacy of Plasmapheresis and Immunoglobulin Replacement Therapy (IVIG) on Patients with COVID-19. SN Compr Clin Med 2020, 2, 1407-11. doi: 10.1007/s42399-020-00438-2.

5. Saghazadeh A, Rezaei N. Towards treatment planning of COVID-19: Rationale and hypothesis for the use of multiple immunosuppressive agents: Anti-antibodies, immunoglobulins, and corticosteroids. Int Immunopharmacol 2020, 84, 106560. doi: 10.1016/j.intimp.2020.106560.

6. Wang JT, Sheng WH, Fang CT, Chen YC, Wang JL, Yu CJ, et al. Clinical manifestations, laboratory findings, and treatment outcomes of SARS patients. Emerg Infect Dis, 2004, 10, 818-24. doi: 10.3201/eid1005.030640.

7. Hung IFN, To KKW, Lee CK, Lee KL, Yan WW, Chan K, et al. Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. Chest 2013, 144, 464-73. doi: 10.1378/chest.12-2907.

8. Loutfy MR, Blatt LM, Siminovitch KA, Ward S, Wolff B, Lho H, et al. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. JAMA 2003, 290, 3222-8. doi: 10.1001/jama.290.24.3222.

9. Arumugham VB, Rayi A. Intravenous Immunoglobulin (IVIG). StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.

10. Liu X, Cao W, Li T. High-Dose Intravenous Immunoglobulins in the Treatment of Severe Acute Viral Pneumonia: The Known Mechanisms and Clinical Effects. Front Immunol 2020, 11, 1660. doi: 10.3389/fimmu.2020.01660.

11. Yaqinuddin A, Ambia AR, Elgazzar TA, AlSaud MBM, Kashir J. Application of intravenous immunoglobulin (IVIG) to modulate inflammation in critical COVID-19-A theoretical perspective. Med Hypotheses 2021, 151, 110592. doi: 10.1016/j.mehy.2021.110592.

12. Xiang HR, Cheng X, Li Y, Luo WW, Zhang QZ, Peng WX. Efficacy of IVIG (intravenous immunoglobulin) for corona virus disease 2019 (COVID-19): A meta-analysis. Int Immunopharmacol 2021, 96, 107732. doi: 10.1016/j.intimp.2021.107732.

13. Moradimajd P, Samaee H, Sedigh-Maroufi S, Kourosh-Aami M, Mohsenzadagan M. Administration of intravenous immunoglobulin in the treatment of COVID-19: A review of available evidence. J Med Virol 2021, 93, 2675-82. doi: 10.1002/jmv.26727.

14. Huang C, Fei L, Li W, Xu W, Xie X, Li Q, et al. Efficacy evaluation of intravenous immunoglobulin in non-severe patients with COVID-19: A retrospective cohort study based on propensity score matching. Int J Infect Dis 2021, 105, 525-31. doi: 10.1016/j.ijid.2021.01.009.

15. Gharebaghi N, Nejadrahim R, Mousavi SJ, Sadat-Ebrahimi SR, Hajizadeh R. The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial. BMC Infect Dis 2020, 20, 786. doi: 10.1186/s12879-020-05507-4.

16. Sakoulas G, Geriak M, Kullar R, Greenwood KL, Habib M, Vyas A, et al. Intravenous Immunoglobulin Plus Methylprednisolone Mitigate Respiratory Morbidity in Coronavirus Disease 2019. Crit Care Explor 2020, 2, e0280. doi: 10.1097/CCE.0000000000000280.

17. Raman RS, Bhagwan Barge V, Anil Kumar D, Dandu H, Rakesh Kartha R, Bafna V, et al. A Phase II Safety and Efficacy Study on Prognosis of Moderate Pneumonia in Coronavirus Disease 2019 Patients With Regular Intravenous Immunoglobulin Therapy. J Infect Dis 2021, 223, 1538-43. doi: 10.1093/infdis/jiab098.

18. Ali S, Uddin SM, Shalim E, Sayeed MA, Anjum F, Saleem F, et al. Hyperimmune anti-COVID-19 IVIG (C-IVIG) treatment in severe and critical COVID-19 patients: A phase I/II randomized control trial. EClinicalMedicine 2021, 36, 100926. doi: 10.1016/j.eclinm.2021.100926.

19. Esen F, Özcan PE, Orhun G, Polat Ö, Anaklı İ, Alay G, et al. Effects of adjunct treatment with intravenous immunoglobulins on the course of severe COVID-19: results from a retrospective cohort study. Curr Med Res Opin 2021, 37, 543-8. doi: 10.1080/03007995.2020.1856058.

20. Shao Z, Feng Y, Zhong L, Xie Q, Lei M, Liu Z, et al. Clinical efficacy of intravenous immunoglobulin therapy in critical ill patients with COVID-19: a multicenter retrospective cohort study. Clin Transl Immunology 2020, 9, e1192. doi: 10.1002/cti2.1192.

21. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021, 47, 1181-247. doi: 10.1007/s00134-021-06506-y.

22. Parsons T, Banks S, Bae C, Gelber J, Alahmadi H, Tichauer M. COVID-19-associated acute disseminated encephalomyelitis (ADEM). J Neurol 2020, 267, 2799-802. doi: 10.1007/s00415-020-09951-9.

23. Scheidl E, Canseco DD, Hadji-Naumov A, Bereznai B. Guillain-Barré syndrome during SARS-CoV-2 pandemic: A case report and review of recent literature. J Peripher Nerv Syst 2020; 25, 204-7. doi: 10.1111/jns.12382.

24. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain-Barré Syndrome Associated with SARS-CoV-2. N Engl J Med 2020, 382, 2574-6. doi: 10.1056/NEJMc2009191.

25. Sedaghat Z, Karimi N. Guillain Barre syndrome associated with

COVID-19 infection: A case report. J Clin Neurosci 2020, 76, 233-5. doi: 10.1016/j.jocn.2020.04.062.

26. Virani A, Rabold E, Hanson T, Haag A, Elrufay R, Cheema T, et al. Guillain-Barré Syndrome associated with SARS-CoV-2 infection. IDCases 2020, 20, e00771. doi: 10.1016/j.idcr.2020.e00771.

27. Paliwal VK, Garg RK, Gupta A, Tejan N. Neuromuscular presentations in patients with COVID-19. Neurol Sci 2020, 41, 3039-56. doi: 10.1007/s10072-020-04708-8.

28. Wang Z, Zhao S, Tang Y, Wang Z, Shi Q, Dang X, et al. Potentially effective drugs for the treatment of COVID-19 or MIS-C in children: a systematic review. Eur J Pediatr 2022, 181, 2135-46. doi: 10.1007/s00431-022-04388-w.

29. Tabarsi P, Barati S, Jamaati H, Haseli S, Marjani M, Moniri A, et al. Evaluating the effects of Intravenous Immunoglobulin (IVIg) on the management of severe COVID-19 cases: A randomized controlled trial. Int Immunopharmacol 2021, 90, 107205. doi: 10.1016/j.intimp.2020.107205.

30. Hou X, Tian L, Zhou L, Jia X, Kong L, Xue Y, et al. Intravenous immunoglobulin-based adjuvant therapy for severe COVID-19: a single-center retrospective cohort study. Virol J 2021, 18, 101. doi: 10.1186/s12985-021-01575-3.

31. Liu J, Chen Y, Li R, Wu Z, Xu Q, Li Z, et al. Intravenous immunoglobulin treatment for patients with severe COVID-19: a retrospective multicentre study. Clin Microbiol Infect 2021, 27, 1488-93. doi: 10.1016/j.cmi.2021.05.012.

32. Focosi D, Franchini M, Tuccori M, Cruciani M. Efficacy of High-Dose Polyclonal Intravenous Immunoglobulin in COVID-19: A Systematic Review. Vaccines (Basel) 2022, 10, 94. doi: 10.3390/vaccines10010094.

33. Salehi M, Barkhori Mehni M, Akbarian M, Fattah Ghazi S, Khajavi Rad N, Moradi Moghaddam O, et al. The outcome of using intravenous immunoglobulin (IVIG) in critically ill COVID-19 patients': a retrospective, multi-centric cohort study. Eur J Med Res 2022, 27, 18. doi: 10.1186/s40001-022-00637-8.

34. Chen Z, Lin R, Zhuo H, Xu F, Liu X. Intravenous immunoglobulin is effective in alleviating hepatic ischemia-reperfusion injury: a rat model study. Mol Biol Rep 2022, 49, 341-9. doi: 10.1007/s11033-021-06879-9.

35. Shankar-Hari M, Spencer J, Sewell WA, Rowan KM, Singer M. Bench-to-bedside review: Immunoglobulin therapy for sepsis-biological plausibility from a critical care perspective. Crit Care 2012, 16, 206. doi: 10.1186/cc10597.