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Orijinal Araştırma / Original Article

Treatment of COVID-19-Releated Hyperinflammatory Response in Intensive Care Unit: Pulse Steroid, Anticytokines, IVIG, Plasmapheresis

COVID-19'a Bağlı Gelişen Hiperinflamatuvar Yanıtın Yoğun Bakımda Tedavisi: Antisitokinler, Plazmaferez, IVIG, Sitokin Filtresi

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Abstract

Aim: In our study, we aimed to see whether there is a difference in the survival effects of the treatments in 144 covid-19 patients who developed HIS.

Material and Method: Between Nov 2020 and Jan 2021; we retrospectively evaluated 650 patients who were admitted in to intensive care unit (ICU). Among these patients, we analyzed 144 patients whom recieved pulse steroid, anticytokine, plasmapheresis and IVIG treatment alone or in combination. The treatment planning of Covid-19 in our hospital is organized and implemented by a multidisciplinary treatment board. Accordingly, pulse was administered to patients whom had shown HIS findings after the day 7 of the initial diagnosis. If there is no contraindication; transition to anticytokine treatment and then plasmapheresis and / or IVIG was applied.

Results: When all the treatments were examined, no difference was found between the survival rates according to the application. While the mortality rate was %68 in all patients hospitalized in our ICU's with Covid-19, this rate was found to be %81 in our patients with HIS.

Conclusion: There is an obvious condition that an amount of time is needed for supposed positive results of our admitted treatments. While our mortality rate was lower in all patients we followed up; in accordance with our expectations, we can say that the mortality rate is high in patients with HIS. The fact that no superiority of treatment modalities was observed in our study; we can still attribute the fact that the clinics of Covid-19 patients are not homogeneous and that there is no definite standardization regarding treatment yet.

Keywords: Critical care, COVID-19, hyperinflamatory response, acute respiratory distress syndrome, steroids.

Öz

Amaç: Çalışmamızda, COVID-19 ilişkili hiperinflamatuvar yanıt (HIS) gelişen 144 hastamızda uyguladığımız tedavilerin sağkalıma etkilerini incelemeyi amaçladık.

Gereç Ve Yöntem: 1 Kasım 2020 ve 31 Ocak 2021 aralığında COVID-19' a bağlı ağır solunum yetmezliği ile yoğun bakımlarımızda takip ettiğimiz 650 hasta retrospektif olarak taranmıştır. Bu hastalardan 144 kişide COVID-19'a bağlı HIS varlığı düşünülerek tedavilerinde pulse steroid, antisitokin ajanlar, plazmaferez ve IVIG uygulamalarına yer verilmiştir. Bu tedavi uygulamalarının bir kısmı tek başına bir kısmı bir arada kullanılmıştır. Hastanemizde COVID-19 ilişkili hastalık tablosunun yönetimi, multidisipliner bir komite tarafından yürütülmektedir. Bu komitenin kararları doğrultusunda, tanıdan yaklaşık 7 gün geçtikten sonra hiperinflamatuvar yanıt bulguları gelişen hastalara pulse steroid verilmiştir. Daha ileri tedavi gerekliliği gösteren hastalarda, kontrendikasyon olmaması gözetilerek; antisitokin ajanlara, plazmaferez ve IVIG' e geçilmiştir.

Bulgular: Tüm tedavi ajanları değerlendirildiğinde, sağkalım üzerindeki etkilerinde farklılık gözlenmemiştir. Çalışmanın kapsadığı dönemde, yoğun bakımda takip ettiğimiz tüm COVID-19 hastalarımızın mortalite oranı %68 iken, HIS gelişmiş olan hastalarımızın mortalitesi %81 olarak bulunmuştur.

Sonuç: Takip ettiğimiz tüm hastalarda mortalite oranımız daha düşük iken; beklentilerimiz doğrultusunda HIS görülen hastalarda mortalite oranının yüksek olduğunu söyleyebiliriz. Çalışmamızda tedavi modalitelerinin birbirine üstünlüğünün görülmemesini, COVID-19 hastalarının homojen olmamasına ve kanıtlı tedavilerin henüz olmamasına bağlamaktayız.

Anahtar Kelimeler: Yoğun bakım, COVID-19, hiperinflamatuvar yanıt, akut respiratuvar distress sendromu, steroidler,

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INTRODUCTION

Physical damage due to hyperinflammatory response is one of the primary factors affecting the severity of the course of the disease. Even though the Covid-19 pandemic has been present for almost 2 years, we still lack laboratory parameters with high specificity, radiological markers, scoring systems or clinical results utilizable for predicting which patients are likely to develop severe inflammatory responses. Furthermore, there is a prevailing uncertainty regarding the development of HIS, a factor that can independently affect high mortality. Rescue treatment applied for HIS has disadvantages, possibly leading to mortal results. In this study, we aim to investigate the effects of pulse steroid, tocilizumab, anakinra, IVIG and plasmapheresis treatments in in ICU patients who developed HIS due to severe course of the disease.

MATERIAL AND METHOD

After receiving approval from the Ethical Board for Scientific Research (Decision number: KAEK/2021.03.21), we searched the hospital database for patients who received pandemic ICU-care due to Covid-19 or related syndromes (e.g. ARDS and other organ failures) in our hospital, between November 1, 2020 and January 31, 2021. Of the 650 patients turning up in the results, 144 who had developed HIS were included in the study. 144 patients who had received HIS diagnosis in the ICU were closely evaluated through the hospital database and archive files. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

HIS diagnosis was given to patients presenting at least 3 of the following criteria: persistent fever, increase in oxygen demand, increase in ferritin, d-dimer, CRP, LDH, SGOT and SGPT, and advancing lymphopenia. All the Covid-19 patients who met the criteria for HIS diagnosis were included in the study. Patients with known rheumatic or hematological diseases, patients with diagnosed malignancy and patients receiving any kind of immunosuppressant treatment were excluded.

All Covid-19 patients admitted to ICU were, as a first step, received a standart treatment consisting of favipravir, low molecular weight heparin (LMWH), acetylsalicylic acid (ASA) and metilprednizolon. Favipiravir was ordered as 2X1600 mg peroral (po) loading for the first dose, followed by 2X600 maintenance dose. The remaining drugs were prescribed according to the following regimen: Metilprednizolon 1 mg/kg/day intravenously (iv), DMAH 0,01 U/kg, acetylsalicylic acid 100 mg po. As for the ventilation, invasive and noninvasive protective mechanical ventilation strategies, high-flow nasal oxygen (HFNOT) and non-breather masks were utilized. Prone position was preferred in all patients when there were no contrindications. First choice in empirical antimicrobial treatment was moxifloxasin. D-dimer, aPTT, ferritin, CRP, procalsitoninin (PCT), fibrinogen, complete blood count, SGOT-SGPT, LDH, urea, creatinine, and bilirubin levels of all patients were monitored on a daily basis. Anteroposterior chest radiography was routinely performed 2 times a week, except for patients requiring more frequent investigation. Furthermore, patients were monitorised closely and treated when necessary in terms of fluid balance, nutrition, analgesia and sedation.

Patients who were pre-diagnosed with HIS were presented to the Covid-19 treatment committee of the hospital, which consists of a ICU specialist, a rheumatologist, a hematologist and an infectious diseases specialist. Following the decision of the committee, patients first received pulse steroid (250-1000 mg/day, for 3 days). Patients who were considered to be non-responsive to steroid within 24-48 hours were represented to the committee and were evaluated for anticytokine therapy, intravenous immunoglobulin treatment (IVIG) and plasmapheresis. Choice for further treatment was based on PCT value and surveillance cultures indicating possible secondary infections. If there were not any indicators of infection and if the PCT level was not high, patient was considered to be in a persistent hyperinflammatory condition, and received one of the anticytokine therapy options. In the anticytokine treatment regimen, patients either received IL-6 inhibitor tosulizumab 400 mg/day for consecutive 2 days or IL-1 inhibitor anakinra 3X200 mg/day (3 days), 3X100 mg/day (3 days) adding up to 10 days depending on the response. If a secondary infection was found to be most likely (PCT is high and cultures indicate growth or pre-growth), the decision was targeted antibiotic therapy usually with either plasmapheresis or IVIG. If there were findings of a secondary infection or damage in end organs consistent with septic shock, IVIG was the first choice. If the patient did not respond to an IVIG treatment regimen of 0,4 mg/kg/day after 5 days, we moved on to plasmapheresis. After 2 consecutive days of plasmapheresis, depending on the response, the treatment was continued for a maximum of 5 days, being applied every other day. Expected response in these treatments is improvement in clinical presentation and laboratory results.

We used NCSS (Number Cruncher Statistical System) Statistical Software (Utah, USA) for statistical analyses. Data were evaluated based on descriptive statistical methods (mean, standard deviation, median, frequency, ratio, IQR) as well as Shapiro Wilk test and box plot graphics to compare variables to normal distribution. For variables found to be non-normally distributed, we used Mann Whitney U test for between-group comparisons, and Wilcoxon signed-rank test for within-group comparisons. Survival evaluations were made using Kaplan Meier survival analysis and Log rank test. Significance level was determined as $p<0.05$.

RESULTS

Cases included in the study has an age range of 26 to 92 years. Demographical qualities, comorbid diseases, APACHE II scores within the first 24 hours after ICU-admission, number of intubated and not intubated patients, number of discharged patients and number of exitus cases, duration of of ICU-care were presented in **Table 1**.

Table 1. Distribution of descriptive factors		
Age	Min-Max (Median)	26-92 (65)
	Mean±SD	64.63±11.76
Gender	Female	56 (38.9)
	Male	88 (61.1)
Comorbidities	No	34 (23.6)
	Yes	110 (76.4)
Diseases (n=110)	Diabetes Mellitus	55 (50.0)
	Hypertension	70 (63.6)
	Hyperlipidemia	2 (1.8)
	COPD	17 (15.5)
	Malignancy	15 (13.6)
	CF/ACS	25 (22.7)
	Rheumatic diseases	1 (0.9)
	Cerebrovascular disease	6 (5.5)
	Dementia/Alzheimer's	4 (3.6)
	Other	35 (31.8)
APACHE-II	Min-Max (Median)	7-48 (19.5)
	Mean±SD	21.68±9.17
Intubation	No	128 (88.9)
	Yes	16 (11.1)
Result	Discharge	26 (18.1)
	Ex	118 (81.9)
Duration	Min-Max (Median)	1-71 (11)
	Mean±SD	13.63±11.38

COPD: Chronic obstrictive pulmonary disease, CF: Cardiac failure, ACS: Acute coronary syndrom.

We have found that 91.7% of our patient received pulse steroids (250 mg/day) for 3 days. Based on clinical and laboratory data, number of patients we estimate to be non-resposive to pulse steroid at the second day was 64 **Table 2**.

Table 2. Distribution based on treatment		
		Number of Patients n (%)
Treatment	Pulse	132 (91.7)
	Anakinra	40 (27.8)
	Tocilizumab	14 (9.7)
	Plazmapheresis	20 (13.9)
	IVIG	26 (18.1)

Of the total number of 144 cases, 91.7% received pulse steroids while 27.8% received Anakinra, 9.8% received Tocilizumab, 13.9% plasmapheresis and 18.1% IVIG treatment. Some of our patients were found to receive a combination of these treatments, Pulse+Anakinra being the most frequent combination (25.7%, n=37). 2.1% cases did not receive any treatment at all while 51.7% was found to use single medicine, whereas 31.9 used two medicines, 12.5% used three medicines and 2.1% used four medicines.

Among the cases not receiving pulse treatment, 3(25%) cases were observed to survive, whereas 9(75%) did not survive, and the average survival period was 17.96±2.92 days. As for the group receiving the treatment, 23(17.4%) cases survived, 109(82.6%) patients were exitus, and the average survival period was 16.32±1.53 days.

In cases not receiving Anakira treatment, 19(18.3%) cases survived, whereas 85 did not survive, and the average survival period was 17,29±1,81 days. As for the group receiving the treatment, 7(17.5%) cases survived, 33(82.5%) patients were exitus, and the average survival period was 13.85±1.49 days.

In cases not receiving Tocilizumab treatment, 23(17.7%) cases survived, whereas 107 did not survive and the average survival period was 16.69±1.56 days. As for the group receiving the treatment, 3(21.4%) cases survived, 11(78.6%) patients were exitus, and the average survival period was 14.28±2.39 days.

In cases not receiving plasmapheresis treatment, 25(20.2%) cases survived, whereas 99 did not survive and the average survival period was 17.02±1.77 days. As for the group receiving the treatment, 1(5%) cases survived, 19 patients were exitus, and the average survival period was 16.57±1.86 days.

In cases not receiving IVIG treatment, 24(20.3%) cases survived, whereas 94 did not survive and the average survival period was 17.23±1.83 days. As for the group receiving the treatment, 2(7.7%) cases survived, 24 patients were exitus, and the average survival period was 15.10±1.30 days. The relationship between survival rate and type of treatment was not significant for any of the treatments.

DISCUSSION

Covid-19-related HIS or Covid-19-related cytokine storm syndrome (CSS) is based on the former concept of cytokine storm. Cytokine storm was first observed in graft-versus-host-disease, and was later described for viral infections (e.g. influenza, SARS), autoimmune diseases (systemic lupus eritematozus and juvenile rheumatoid arthiritis) and hematological diseases (hemophagositic lymphohistiosytosis-HLH). CSS results from inappropriate activation of lymphocyte and macrophage, which causes extensive release of cytokine/chemokine, initiating systemic inflammation, and leading to multiple organ failure and high mortality(1). In Covid-19-related disease, similar symptoms and HIS develops usually by the end of the first week. Persistent fever, intensification of lymphopenia, increase in ferritin, d-dimer, LDH and CRP, worsening clinical and radiological findings (increased need of oxygen and increased pulmonary infiltrates) were evaluated as HIS-development and these patients were treated with advanced treatment agents.

Even though case series from the early days of the Covid-19 pandemic and retrospective cohort analyses are encouraging in terms of steroid use for Covid-19-associated diseases, many guidelines still suggest its use only for severe cases (2). Based on previous experiences with SARS and MERS pandemics, steroids have been among the first choices due to their systemic affects and their suppressing effect on lung inflammation. However, there are still reservations, since steroids may decrease viral clearance and increase viral load (3). A meta-analysis covering 73 studies reported that 53% of the ICU-patients received steroids, and that steroids are

favorable in severe Covid-19 patients in terms of mortality. However, there were not any significant differences between high or low doses (4). Results of the Recovery study announced on February 2021 indicate that even though patient groups were heterogenous, when patients who do nor do not use dexamethasone were compared, the dexamethasone group was found to have less mortality within 28 days (5). National Health Commission of the PRC, Surviving Sepsis Committee, WHO and Turkish Republic Ministry of Health all suggest, albeit in different evidence levels and dosages, use of steroids in severe conditions. In our study, when patients who were on a 1mg/kg/day metilprednizolon regimen developed HIS, they received pulse steroid 250 mg (IV) for 3 days, and the mortality rate was a high 82.6%. However, we cannot argue that pulse steroid treatment was the direct cause of this mortality rate. Retrospectively, we observed that number of patients who did not receive pulse steroids even though they developed HIS was very limited. If a prospective study with a matching control group could be designed, more conclusive implications could be made.

We used anticytokine treatment for patients who did not respond to pulse steroids after 48 hours, who did not present secondary infection findings, and for whom the suspicion of an infection was low. Major cytokines responsible for the cytokine storm include interleukins (IL-1, IL-6, IL-8), tumor necrosis factor (TNF-α), many of the pro-inflammatory chemokines and interferons (IFN-γ) (6). For the anticytokine treatment, we used anakinra and tocilizumab as antibodies against IL-1 and IL-6, respectively. Tocilizumab is a monoclonal antibody developed against the membrane-bound and soluble IL-6 receptor. Formerly used in chimeric antigen receptor (CAR) T-cell therapies, it was first tried on Covid-19-associated cytokine storm by Xu and colleagues in China (7). In a meta-analysis by Aziz et.al., this treatment regimen was reported to decrease mortality and need for mechanical ventilation, after which it began to appear in international guidelines (8). Covid-19 treatment guideline of Turkish Ministry of Health suggests off-treatment use of tosilizumab or anakinra in cases with macrophage activation syndrome and unresponsive to glucocorticoid treatment or cases with fast-progressing macrophage activation syndrome (9). According to the regimen prescribed in this guideline, we provided patients with 400 mg of tocilizumab as the first dose, and repeated the same dosage intravenously 24 hours later. Our data indicates that mortality rate for patients receiving tocilizumab treatment was 78.6%.

We also used another anticytokine treatment agent, the IL-1 antagonist anakinra, in the light of present literature. We could say that, during anakinra treatment, the declining trend follow-up with CRP and ferritine, compared to the late response with tocilizumab, makes it easier for us to judge the response to the drug.Iglesisas-Julian and colleagues conducted a high-dose subcutaneous anakinra study with severe Covid-19 patients who developed cytokine storm, and reported that 55.6% of the patients benefited from high-dose anakinra, that they observed decrease in CRP, ferritin and d-dimer levels, and that there were not any secondary infections. In our retrospective study, we found that patients who received anakinra in 2-10 mg/kg, mortaliy rate was 82.5%. This high mortality rare raises up questions regarding the timing of the anticytokine treatment. We have, unfortunately, failed to access any clear suggestions on this matter in the present literature. However, limited information and comments seem to suggest starting the treatment early. Another important factor is that in case of pandemics, especially during the peak periods, additional intensive care units are established. Furthermore, in these conditions, problems in standard care procedures are most possible. In the case of ICUs, even the presence of such a possibility could lead to negative results on mortality. Statistically, we have found that of the 54 patients who received tocilizumab or anakinra, 10 were discharged from the ICU. Even though this is not a significant ratio, we still consider these treatment regimen as a viable life-saving option, and think that turning to multiple anticytokine treatment combinations in the light of further research is probable.

IVIG and plasmapheresis treatments seem to fall behind anticytokines in HIS treatments. IVIG is produced from human plasma collected from general population. It is used in primary and secondary immune deficiencies and hyperinflammatory conditions as an immunomodulator. On the other hand, as we see with Covid-19, its lack of antibodies against new pathogens raises questions about its efficiency (10). In the studies on IVIG use in Covid-19, some clinicians report to use it as a prophylaxis option while others indicate to prefer it as a treatment option in various patient groups, ranging from mild symptoms to severe ICU patients (11, 12). Furthermore, some authors report better results for IVIG when it is ordered within the first 14 days after the initial symptoms of the disease, and that the response rate is not as good as expected after the 14th day. According to the hypothesis presented by these authors, viremic phase of Covid-19 is the first of the three defined phases, and it is the phase where IVIG is expected to lead to significant results. There are also studies on both IVIG and plasmapheresis treatments indicating better results for the first 10-14 days. Similarly, in our study, we have found that IVIG and plasmapheresis treatment was applied within the first 15 days.

Plasmapheresis is selective removal of the plasma from the blood. The most commonly used method of plasmapheresis, membrane filtration, has the advantage of separating especially large molecules. Due to the positive results it provides, it is preferred in diseases such as myasthenia gravis, Guillian-Barre syndrome, thrombotic microangiopathies, and some reno-vascular syndromes. Studies indicate its successful use in both MERS and SARS infections (11). Since antibodies, complementary products, lipoproteins, immune complexes, cryoglobulins, myeloma proteins, ADAMTS-13, protein-bound toxins, platelets and WBC are components removable by plasmapheresis, this method is preferred in cytokine storms

(13). Plasmapheresis have also been formerly used in Hepatitis C virus infections for reducing viral load and, therefore, the inflammatory response (14). Although there are randomized controlled trials supporting plasmapheresis use in cytokine storm/HIS development related to Covid-19, some authors still argue that the response is not significant. Faqihi and colleagues reported lower mortality rates in plasma exchange group, in comparison to standard treatments they apply in ICU, but their results were not statistically significant (15). In our study, 19 of the 20 patients who received plasmapheresis treatment after developing HIS did not survive. Convalescent plasma transfusion, which is another method of plasma exchange, has been recently on the focus of researchers in Turkey, and is expected to be a topic of further interest in the near future.

One of the major limitations of this study was its retrospective design. For this reason, factors such as start of treatment and standardization criteria are not included in the analyses. Our results are based on the data of first group patients who received advanced treatment due to Covid-19-associated HIS development. Furthermore, due to the high number of patients related to the pandemic, treatment was provided with additional units and health staff, and the problems the staff may have come across in training and practice may have led to setbacks in standard intensive care procedures. We are currently conducting a prospective design within the peak period we are still in, standardizing the treatments based on the experience we have gained from this patient group.

CONCLUSION

Covid-19 is a disease on a pandemic level, which is capable of frequent mutations, and yet lacks a standardized treatment. Due to high mortality rates it causes in ICU, search for an evidence-based treatment procedure continues. In this retrospective study, we shared our treatment plans and the results we obtained. However, based on the available data, we are currently unable to report an efficient model regarding mortality. Further research on Covid-19 and sharing the most recent information obtained is of high importance for establishing an effective treatment model..

ETHICAL DECLARATIONS

Ethics Committee Approval: This study has recieved approval from Başakşehir Çam and Sakura City Hospital's Ethical Board for Scientific Research (Decision number: KAEK/2021.03.21)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. England JT, Abdulla A, Biggs CM et al. Weathering the COVID-19 storm: Lessons from hematologic cytokine syndromes. Blood Rev. 2021;45:100707.
2. TC Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü, COVID-19 Ağır Pnömoni, ARDS, Sepsis, Septik Şok Yönetimi Bilimsel Danışma Kurulu Çalışması, 23 Ekim 2020.
3. Halaçlı B, Topeli A. Treatment of the Cytokine storm in COVID-19. J Crit Intensive Care 2020; 11(Suppl.1):36–40.
4. Cano EJ, Fuentes XF, Campioli CC et al. Impact of corticosteroids in coronavirus disease 2019 outcomes. Chest 2021; 159(3): 1019–40.
5. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021; 384:693-704
6. COVID-19 Tanı ve Tedavisinde Kanıta Dayalı Öneriler ve Türk Toraks Derneği COVID-19 Görev Grubu Görüş Raporu, Türk Toraks Derneği COVID-19 E-Kitapları Serisi, Aralık 2020.
7. Xu X, Han M, Li T et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci USA. 2020;117:10970-5.
8. Aziz M, Haghbin H, Abu Sitta E et al. Efficacy of tocilizumab in COVID-19: A systematic review and meta-analysis. J Med Virol. 2021;93:1620–30.
9. TC Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü, Antisitokin-Antiinflamatuar Tedaviler, Koagülopati Yönetimi, 07 Kasım 2020.
10. Nguyen AA, Habiballah SB, Platt CD et al. Immunoglobulins in the treatment of COVID-19 infection: Proceed with caution! Clinical Immunology 2020;216:108459.
11. Pourahmad R, Moazzami B, Rezaei N. Efficacy of plasmapheresis and immunoglobulin replacement therapy (IVIG) on patients with COVID-19. SN Compr Clin Med. 2.1407–11.
12. Keith P, Day M, Choe C, Perkins L. The successful use of therapeutic plasma exchange for severe COVID-19 acute respiratory distress syndrome with multiple organ failure. SAGE Open Med Case Rep 2020;8: 1–4.
13. Kaplan AA. Therapeutic plasma exchange: a technical and operational review. J Clin Apher 2013;28(1):3–10.
14. Ishikawa T, Abe S, Kojima Y et al. Prediction of a sustained viral response in chronic hepatitis C patients who undergo induction therapy with double filtration plasmapheresis plus interferon-β/ribavirin. Exp Ther Med. 2015;9(5):1646-50.
15. Faqihi F, Alharthy A, Alodat M et al. A pilot study of therapeutic plasma exchange for serious SARS CoV-2 disease (COVID-19): A structured summary of a randomized controlled trial study protocol. Trials 2020;21:506.