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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Efficacy of intravenous immunoglobulin in the treatment of a COVID-19 patient

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SUMMARY

Introduction Diabetes mellitus patients are a vulnerable group of people who are prone to getting infected with severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). The virus has a high binding affinity to angiotensin-converting enzyme 2 receptor, which allows efficient host cell entering, prolonged virus retention, and a possibility of insulin resistance and ketoacidosis development.

Case outline We describe a case of a 20-year-old patient with a past medical history of type 1 diabetes mellitus who presented with bilateral COVID-19 pneumonia. Initially, treatment with polyvitamin therapy, corticosteroids, tocilizumab, and convalescent plasma did not improve the patient's condition, but might have led to the worsening of the underlying disease, high blood glucose level, and ketoacidosis. Patient developed a rapid progression of the disease and severe pneumonia that required intubation and mechanical ventilation. Intravenous immunoglobulin (IVIg) was administrated in order to suppress a hyperactive immune response through its immunomodulatory effect. Forty-eight hours later, respiratory gas exchange was improved, almost complete regression of changes in the lungs was seen, normalization of metabolic and gas exchange parameters was detected. After 14 days of hospitalization, the patient was discharged in good general condition.

Conclusion COVID-19 complicated by diabetes mellitus leads to a poor outcome of the disease, but antiviral and anti-inflammatory activity of IVIg suggests that it may be a useful therapeutic agent in cases of COVID-19. In the presented case, the application of IVIg led to a rapid improvement in the patient's condition.

Keywords: COVID-19; diabetic ketoacidosis; immunoglobulin; pneumonia

INTRODUCTION

Corona virus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), a virus with strong transmissibility that has rapidly evolved into a pandemic [1]. The disease spreads rapidly and has a high mortality rate. About 14% of patients require hospitalization and oxygen therapy and 5% of patients require admission to the intensive care unit (ICU) [2]. SARS-CoV-2 activates both innate and acquired immune response. Infected endothelial cells, mononuclear macrophages, neutrophils and maturated dendritic cells (innate immunity) produce pro-inflammatory mediators, such as interferon, cytokines [tumor necrosis factor α, interleukin (IL)-6] and chemokines, which recruit other components of the immune system [3]. The subsequent acquired immune responses including T lymphocytes (CD4+ and CD8+ T cells) and B lymphocytes play an important role in the defense. CD4+ T cells stimulate B cells to produce virus-specific antibodies, while CD8+ T cells are able to directly kill virus-infected cells. However, SARS-CoV-2 can induce excessive and prolonged inflammatory responses, known as the cytokine storm. Excessive neutrophil extracellular traps production, by neutrophils, can enhance tissue damage and may contribute to the cytokine storm, while activated B cells may contribute by production of IL-6. In patients with severe COVID-19, the cytokine storm causes acute respiratory distress syndrome or multiple-organ dysfunction [3].

Since SARS-CoV-2 affects the host immune system, there is a possibility of introducing intravenous immunoglobulin (IVIg) administration in the therapy of COVID-19 with the aim of improving immune response of the host [4].

CASE REPORT

A 20-year-old female, body mass index 22 kg/m^2, was admitted to the temporary COVID hospital of Zvezdara University Medical Center with positive real-time reverse transcription polymerase chain reaction (rRT-PCR) assay for SARS-CoV-2 and with a radiographic diagnosis of bilateral pneumonia (Figure 1). Six days prior to presentation, the patient complained of fatigue, tiredness and dry cough. On admission, the patient presented conscious, adynamic, pale skin and visible mucous membranes, highly febrile with a pronounced dry cough and breath that smelled like acetone. She had a history of

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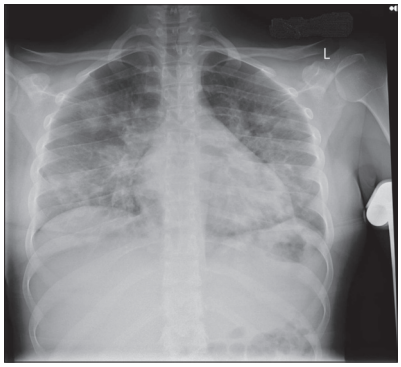

Figure 1. Chest radiograph at admission to the hospital

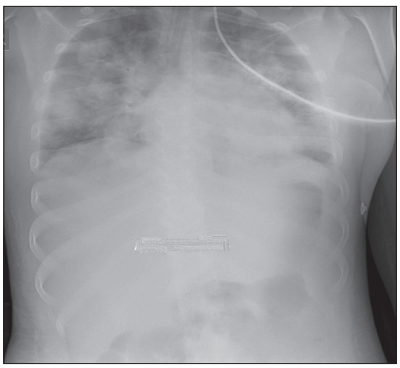

Figure 2. Chest radiograph at admission to the intensive care unit (11 days from the onset of the disease)

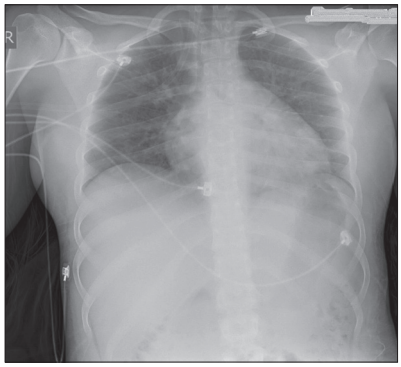

Figure 3. Chest radiograph 48 hours after immunoglobulin administration

type 1 diabetes mellitus diagnosed at the age of 13 and she was being treated with insulin. Hematologic, biochemistry and acid-base analysis before and after the treatments in ICU are presented in Tables 1 and 2.

Table 1. Hematologic and biochemistry analysis before and after the treatments

Parameters	On admission to the hospital	Before immunoglobulin administration	Forty-eight hours after immunoglobulin administration	At ICU discharge	At hospital discharge
WBC (10^9/L)	11	10.3	10.2	16.6	12.3
PLT count (10^9/L)	374	447	546	482	389
Neutrophil count (%)	76.7	66.8	68.9	77.7	67.3
Lymphocyt count (%)	11.7	19.7	18.2	11.1	23.7
CRP (mg/L)	96.1	163.1	81.5	24.5	4.2
Feritin (ng/ml)	427	402	265	184	156
LDH (U/L)	702	739	624	613	689
K^+ (mmol/L)	4.24	1.6	2.7	3.7	4
Glucose (mmol/L)	14	19.5	8.6	7.5	6.7

WBC – white blood cells; PLT – platelets; CRP – C-reactive protein; LDH – lactate dehydrogenase; K+ – potassium, ICU – intensive care unit

Table 2. Acid-base analysis before and after the treatments

Parameters	On admission to the hospital	Before immunoglobulin administration	Forty-eight hours after immunoglobulin administration	At ICU discharge	At hospital discharge
pH	7	7.13	7.52	7.54	7.34
pO_2 (mmHg)	120.6	74.7	96	88.5	110
pCO_2 (mmHg)	9.9	14.1	27.2	23.1	34
spO_2 (%)	90	90	97	97	97
HCO_3^- (mmol/L)	2.8	8.5	15.6	18.7	19.2
BE (mmol/L)	-3.5	-22.2	-12.7	-4.2	2.3
Lactate (mmol/L)	2.8	3.27	1.1	1.2	1.1

ICU – intensive care unit; pO_2 – oxygen partial pressure; pCO_2 – carbon dioxide partial pressure; spO_2 – oxygen saturation in the blood; HCO_3^- – bicarbonates; BE – basic excess

On the first day of hospitalization, the treatment was provided with vitamins (alphacalcidiol tablets 1 × 2 mcg, vitamin C 1 × 1 g), anticoagulant therapy (nadroparin 4000 U s.c.), corticosteroid therapy (prednisone tablets 0.5 mg/kg twice daily), proton pump inhibitors for gastric protection. Diabetic ketoacidosis (DKA) management was started (insulin and crystalloid fluids infusion, bicarbonate compensation) and antibiotic for bacterial super infection prevention was also performed (third-generation cephalosporin, ceftriaxone 2 g). Twenty-four hours after admission, somnolence, high fever (39°C), fatigue, hypotension (90/50 mmHg), tachycardia (hearth rate above 120 beats/min), tachypnea (respiratory rate 35 breaths/min), shortness of breath, blood oxygen saturation (spO_2) of 90% and normal glucose level (6.6 mmol/L) were observed. Oxygen supplementation was provided by a mask and oxygen flow of 5 l/min and spO_2 increased up to 97%. The next day blood analysis showed IL-6 value of 44.6 pg/ml, immunosuppressant (tocilizumab 600 mg) and convalescent plasma were administered. This did not result in clinical improvement – after 48 hours she became extremely dyspneic, tachypneic, tachycardic, hypotensive, blood tests revealed high glucose level (19.5 mmol/L) and ketoacidosis, while chest radiography showed progression of pneumonia (Figure 2). Due to the worsening of the general condition, the patient was transferred from the ward to the ICU. Since the blood gas exchange worsened, invasive mechanical ventilation with lung protection strategies was initiated immediately upon admission to the ICU (11 days from the onset of the disease). Due to the rapid disease progression complicated with ketoacidosis and unsatisfactory response to the applied therapy, it was decided to continue with the local therapeutical protocol and apply IVIg (10 g once). Forty-eight hours later, chest radiography showed almost complete regression of the changes in the lungs (Figure 3), inflammatory markers were decreased, metabolic disorder corrected, blood gas exchange was normalized and the patient was extubated. After 14 days in the hospital, the patient was discharged home without oxygen supplementation, afebrile, eupneic, with normal system function, normal laboratory and metabolic findings, and with a negative PCR test.

This case report was approved by the institutional ethics committee, and written consent was obtained from the

patient for the publication of this report and any accompanying images.

DISCUSSION

COVID-19 is a disease that leads to a high mortality rate. Local guidelines on the treatment of patients with COVID-19 exist, but mainly include symptomatic treatment and supportive care. Clinical manifestations of COVID-19 are non-specific, the disease can be asymptomatic or it can present with symptoms such as fever, dry cough, myalgia, fatigue, headache, diarrhea, and many others [5]. COVID-19 is classified as mild, moderate, or severe disease. However, COVID-19 can sometimes have a fulminant evolution rapidly leading to death [6]. It is assumed that a history of the underlying diseases can be associated with the development of severe illness [7].

Prevalence of diabetes in COVID-19 patients is high and is associated with the increased risk of complications and poor outcome. The majority of COVID-19 patients are patients with type 2 diabetes mellitus (9.7–10.9%) [8]. DKA prevalence before the pandemic was 0.72% and during the pandemic it increased up to 3.14%, while DKA mortality rate during the pandemic increased from 18% up to 46.3% [9]. Diabetes is causally associated with upregulated angiotensin-converting enzyme 2 receptor (ACE_2) expressions in the lungs, which may increase susceptibility to the SARS-CoV-2. The virus has a high binding affinity to the ACE_2 receptor [10], which allows efficient host cell entering and prolonged virus retention. ACE_2 is widely expressed in multiple organs, including pancreas, so the virus infection can lead to the pancreatic damage resulting in the development of insulin resistance and ketoacidosis. Elevated glucose levels directly increase SARS-CoV-2 replication. In this way hyperglycemia might support viral proliferation [10].

In addition, the virus directly damages the cells, especially T cell function, which can be reduced. CD4+ T lymphocytes are quickly activated into T helper-1 cells, leading to the high secretion of inflammatory cytokines (IL-6) [11]. IL-6 is an important cytokine of hyperinflammation in COVID-19, which is already increased in patients with underlying type 1 diabetes mellitus and triggers ketogenesis [11].

This case report shows the application of a local therapeutical protocol for COVID-19 and the management of DKA at the same time. Since the patient had rapid disease progression and all therapeutical options were exhausted, IVIg was used as a potent and safe immune modulator [12]. IVIg is a therapeutical product of normal human polyclonal IgG obtained from the pooled plasma of a large number of healthy donors. IVIg product used in this case (Ig VENA, Kedrion S.p.A., Barga, Italy) contains human normal immunoglobulin, mainly IgG (at least 95%). Initially, IVIg was used as a replacement therapy in patients with immunodeficiency disease in order to prevent infections by pathogen neutralization [13]. Today, it's widely used for a number of autoimmune and inflammatory diseases, including viral pneumonias. Several published studies showed potential benefits of IVIg therapy in SARS, MERS, influenza, and RSV infections and that's why it has been considered for COVID-19. These viral infections are associated with an excessive and uncontrolled complement activation, which contributes to tissue damage and hyperinflammation. IVIg treatment of this infections may reduce complement activation, bind and block C5a and C3a, leading to the decrease of hyperinflammation [14]. IVIg has numerous modes of action, such as inhibition of T-cell activation and proliferation, down-regulation of antibodies' production by B cells, interruption of complement activation cascade, and cytokine modulation (neutralization of inflammatory cytokines, chemokines and complement fragments by endogenous antigen-specific IgG which are present in IVIg), inhibition of neutrophil recruitment and activation and limitation of the differentiation of macrophages (these effects may be induced by blocking the activation of Fcγ receptors on innate immune effector cells), and many more [3, 14].

To date, the possitive effects of IVIg therapy in severe COVID-19 patients have been described in several case reports and studies, where IVIg therapy differs in doses, lenght of administration, and comorbidites. Currently, there is no consensus on IVIg treatment for COVID-19. A big multicentre retrospective study showed that 28-day mortality was not different between the group of COVID-19 patients treated with IVIg and non-IVIg group, so further investigations of efficacy of IVIg administration are needed [15]. Studies also showed that the administration of a high dose of IVIg within first 48 h promotes benefits such as the reduction of the use of mechanical ventilation and shorter ICU length of stay and the reduction of the mortality rate [16]. Several case reports of multisystem inflammatory syndrome in adults that presents 2–6 weeks after COVID-19 infection have been published thus far. In these cases, the combined administration of a high dose of corticosteroids and IVIg had better results compared to corticosteroid or IVIg monotherapy [17]. In contrast to previous studies, in the present case, high doses of corticosteroids and lower doses of IVIg were administered during the period when mechanical ventilation was applied, which led to an improvement in the condition. Therefore, further studies are needed to determine the dose and the timing of IVIg administration, as well as at what stage of the disease should the therapy be applied.

This case report showed that initially applied therapy did not result in clinical improvement; the disease had rapid progression complicated by an underlying condition and an inadequate immune response, which led to the decision to apply the last step of the protocol algorithm. Shortly after the IVIg administration, the patient improved clinically, a significant decrease of white blood cells, ferritin and lactate dehydrogenase levels was seen, gas exchange improved and chest radiography showed significant improvement as well. The patient was extubated and after 14 days of hospitalization she was discharged in stable condition.

The main limitation of this case report is that the patient received tocilizumab, convalescent plasma, and higher doses of corticosteroids prior to IVIg. Some of these

drugs may have influenced the course of the viral disease and enhanced the efficacy of IVIg. The lack of efficacy of convalescent plasma could have resulted from insufficient titers of neutralizing antibodies or the timing of administration, while the anti-inflammatory and immunemodulatory effects on the various immune cells of IVIg may account for its clinical benefits.

Considering the immunomodulatory effects of IVIg its application has a potential role in the treatment of the severe COVID-19. Intravenous immunoglobulins are in use for severe and critically ill COVID-19 patients, but available data is still limited and without clinical confirmation. Therefore, additional detailed well-designed studies of IVIg administration in severe COVID-19 patients are needed.

Conflict of interest: None declared.

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Ефикасност интравенских имуноглобулина у лечењу болесника са ковидом 19

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САЖЕТАК

Увод Оболели од шећерне болести представљају осетљиву групу људи склону инфекцији коронавирусом 2, који изазива тешки акутни респираторни синдром (*SARS-CoV*-2). Вирус има већи афинитет везивања за рецепторе ензима за конверзију ангиотензина, што омогућава ефикасан улазак вируса у ћелију, дуже задржавање вируса и могућност настанка инсулинске резистенције и развој кетоацидозе.

Приказ болесника Приказан је случај особе старости 20 година која болује од шећерне болести типа I са билатералном ковид 19 пнеумонијом. Примењена поливитаминска, кортикостероидна терапија, тоцилизумаб и плазма реконвалесцената нису довели до побољшања стања, а постоји могућност да су довели до погоршања основне болести, појаве високе вредности шећера у крви и развоја кетоацидозе. Због рапидног напредовања болести и погоршања упале плућа болесница је интубирана и механички вентилирана. У терапију су уведени имуноглобулини (*IVIg*) због своје способности модулације имунитета. Након 48 сати долази до побољшања гасне размене, скоро потпуне регресије промена на плућима, нормализације метаболичких и параметара гасне размене. Болесница је након 14 дана отпуштена на кућно лечење у добром општем стању.

Закључак Ковид 19 компликован шећерном болешћу доводи до лошег исхода болести, али антивирусна и противупална активност *IVIg* наводи на размишљање да може представљати корисно терапијско средство и у случају ковида 19. Код приказаног случаја примена *IVIg* је врло брзо довела до побољшања стања болесника.

Кључне речи: ковид 19; дијабетесна кетоацидоза; имуноглобулини; запаљење плућа