Case Report / Приказ болесника

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

Ефикасност интравенских имуноглобулина у лечењу болесника са ковидом 19

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SUMMARY
Introduction Diabetes mellitus patients represent a vulnerable group of people who are prone to getting infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus has a high binding affinity to angiotensin-converting enzyme 2 receptor which allows efficient host cell entry, prolonged virus retention and 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 condition, but might have led to the worsening of 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) has been administrated in order to suppress a hyperactive immune response through its immunomodulatory effect. Forty-eight hours later respiratory gas exchange had been improved, almost complete regression of changes in the lungs have been seen, normalization of metabolic and gas exchange parameters have been detected. After 14 days in the hospital the patient was discharged home 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 they may be useful therapeutic agent and in the case of COVID-19. In the presented case, the application of IVIg very fast led to an 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 coronavirus 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 (IFN), cytokines (tumor necrosis factor (TNF)-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 cytokine storm, while activated B cells may contribute by production of IL-6. In patients with severe COVID-19 cytokine storm causes acute respiratory distress syndrome or multiple-organ dysfunction [3].

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

CASE REPORT

A 20-year-old female, body mass index 22 kg/m², 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 mucus membranes, highly febrile with a pronounced dry cough and breathe that smelled like acetone. She had a history of 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 Table 1 and Table 2.
At the first day in the hospital treatment was provided with vitamins (Alphacalcidiol tablets 1x2 mcg, vitamin C 1x1g), 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 2gr). Twenty-four hours after admission somnolence, high fever (39°C), fatigue, hypotension (90/50 mmHg), tachycardia (hearth rate above 120/min), tachypnea (respiratory rate 35/min), shortness of breath, blood oxygen saturation (spO₂) 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 spO₂ 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 didn’t result in clinical improvement, after 48 hours she became extremely dispneic, tachipneic, 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 got worsened invasive mechanical ventilation with lung protection strategies was initiated immediately upon admission to 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 had been 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 patient was extubated. After 14 days in the hospital, the patient was discharged home without oxygen supplementation, afebrile, eupnoic, with normal system function, normal laboratory and metabolic findings and with 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 case report and any accompanying images.
DISCUSSION

The 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, 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, sometimes COVID-19 can have a fulminant evolution rapidly leading to death [6]. It is assumed that a history of underlying diseases can be associated with development of severe illness [7].

Prevalence of diabetes in COVID-19 patients is high and it 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 had increased from 18% up to 46.3% [9]. Diabetes is causally associated with upregulated angiotensin-converting enzyme 2 receptor (ACE2) expressions in the lungs, which may increase susceptibility to the SARS-CoV-2. The virus has a high binding affinity to ACE2 receptor [10] which allows efficient host cell entering and prolonged virus retention. ACE2 is widely expressed in multiple organs, including pancreas, so virus 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, 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 hyper inflammation in COVID-19, it’s already increased in patients with underlying type-1 diabetes mellitus and it 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 (IgVena) 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’s been considered for COVID-19. This viral infections are associated with an excessive and uncontrolled complement activation which contribute 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 like 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 (this effects may be induced by blocking the activation of Fcγ receptors on innate immune effector cells) and many more [3,14].

To date, the positive effects of IVIg therapy in severe COVID-19 patients have been described in the several case reports and studies, where IVIg therapy differs in doses, length of administration and comorbidities. 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 administration of a high dose of IVIg within first 48 h promotes better benefits such as 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 up to today. In this cases, the combined administration of a high dose 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 timing of IVIg administration and at what stage of the disease.
This case report showed that initially applied therapy didn’t result in clinical improvement; disease had rapid progression complicated with underlying condition and inadequate immune response which led to the decision to apply the last step of the protocol algorithm. Shortly after the IVIg administration patient was clinically improved, significant decrease of white blood cells, ferritin and lactate dehydrogenase levels was seen, gas exchange has been improved and chest radiography showed significant improvement. Patient was extubated and after 14 days in the hospital she was discharged home 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 efficacy of the 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 immune-modulatory 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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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                   |
| Ferritin (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                 |
| pO₂ (mmHg) | 120.6                       | 74.7                                 | 96                                            | 88.5            | 110                  |
| pCO₂ (mmHg)| 9.9                         | 14.1                                 | 27.2                                          | 23.1            | 34                   |
| spO₂ (%)  | 90                          | 90                                   | 97                                            | 97              | 97                   |
| HCO₃⁻ (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; pO₂ – oxygen partial pressure; pCO₂ – carbon dioxide partial pressure; spO₂ – oxygen saturation in the blood; HCO₃⁻ – bicarbonates; BE – basic excess
**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