

Pulse Therapy with Corticosteroids and Intravenous Immunoglobulin in the Management of Severe Tocilizumab-Resistant COVID-19. A report of three clinical cases.

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Abstract

Three patients with severe life-threatening COVID-19 who failed to achieve substantial improvement on tocilizumab, received pulse therapy with corticosteroids (methylprednisolone, 1000 mg/day IV for three consecutive days) and intravenous immunoglobulin (20 g/day IV). This was associated with a prompt resolution of respiratory failure, elimination of cytokine release syndrome, and reversal of pulmonary CT changes. The treatment was generally safe and well tolerated. There was no evidence of protracted persistence of the virus in the patients who received pulse therapy. Randomized controlled trials are necessary to specify the efficacy and safety of high-dose methylprednisolone and intravenous immunoglobulin in the treatment of severe life-threatening COVID-19 separately or in combination.

Keywords: SARS-CoV-2; COVID-19; pulse therapy; corticosteroids; immunoglobulin

Introduction

Clinical presentations of CoronaVirus Disease-2019 (COVID-19) range from asymptomatic cases, through mildly symptomatic flu-like forms (81%), to severe (14%) and critical (5%) disease manifesting with pneumonia, hepatic, cardiac, and other organ involvement.¹ Respiratory failure and acute respiratory distress syndrome (ARDS) are common complications.² Multi-organ failure and disseminated intravascular coagulation (DIC) can also be observed.^{2,3} Aforementioned problems determine the need in intensive care in 17–20% of hospitalized patients.⁴ The main cause of death in infected patients worldwide is a combination of both ARDS and DIC leading to a fatal outcome in 11-15% of hospitalized persons.^{4,5} The average COVID-19 associated mortality rate reached 3.7% of reported cases.⁴

Factors, associated with the development of severe respiratory failure, admission to the intensive care unit and death, include older age, comorbid conditions, elevated body mass index, lymphopenia, elevated blood levels of transaminases, lactate dehydrogenase, C-reactive protein, D-dimer, ferritin, and soluble interleukin-2 receptor.^{2,6,7} This configuration of features resembles a family of syndromes gathered under the umbrella term of the cytokine release syndrome (CRS), in which hyperinflammation and multiorgan disease arise through excessive cytokine release from uncontrolled immune activation. Rheumatologists face this phenomenon regularly in systemic juvenile idiopathic arthritis, adult-onset Still's disease, systemic lupus erythematosus, and other disorders.⁸ There is a growing evidence that in patients with SARS-CoV-2 infection, the virus can induce an excessive and aberrant host immune response resulting in the development of CRS leading to severe lung impairment including ARDS and other organ damage.^{9,10} A growing awareness of the role of immune factors and CRS in particular in the thanatogenesis in SARS-CoV-2 infection stimulates the investigation of immunomodulatory drugs as a potential treatment for COVID-19 patients, especially suffering of pronounced and the most severe forms of the disease.^{10,11} Experience from hyperinflammation syndromes in systemic juvenile idiopathic arthritis, hemophagocytic lymphohistiocytosis and other cytokine storm syndromes suggests that early intervention is essential to avoid life-threatening tissue damage.⁸ In this context, it is difficult to ignore the opinion of specialists suggesting that in patients with COVID-19 who exhibit the evidence of CRS, treatment with glucocorticoids, intravenous immunoglobulin, and/or anticytokine therapies should be used, with the aim of preventing and/or reversing the dramatic inflammatory pathway triggered by the virus, which ultimately leads to ARDS, thus saving the lives of the patients.^{8,11} And in light of this, it is also difficult to dispute with the point of view that the recommendation against the use of glucocorticoids for the treatment of COVID-19¹² needs reconsideration.⁸

Recently a number of publications appeared suggesting a positive role of specific IL-6 inhibitor tocilizumab in the treatment of severe COVID-19 complicated with respiratory failure.¹³⁻¹⁵ Nonetheless, there exists a number of COVID-19 patients in whom it is not possible to achieve a sustained improvement with the use of this drug.¹⁶ Secondly, tocilizumab and other interleukin blockers belong to the group of relatively expensive drugs that may hamper their use in wide-scale epidemics or in less prosperous healthcare systems. Everything said forces us to look for other possibilities in the treatment of severe, life-threatening cases of COVID-19 disease.

Here we present a description of three cases of successful treatment of severe tocilizumab-resistant COVID-19 with a combination of methylprednisolone pulse therapy and intravenous immunoglobulin.

Description of cases

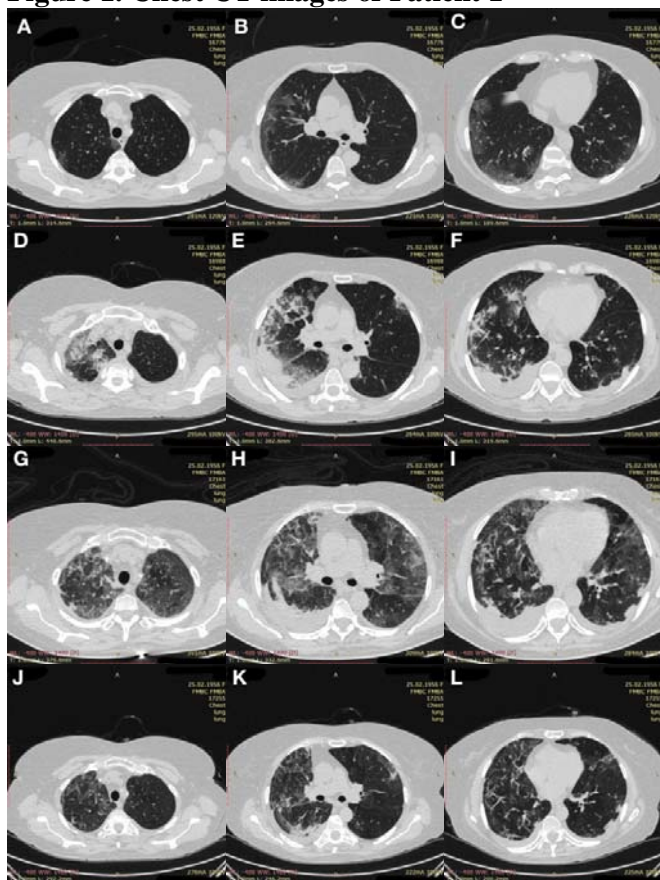
Case 1

A 64-year-old woman, was admitted to Infectious Disease Department of Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency of Russia (SRC-FMBC FMBA) on April 6, 2020 complaining of dry exhausting cough, dyspnea (Modified Medical Research Council Dyspnea Scale (mMRC) grade 3),¹⁷ and fever up to 38,8°C. The symptoms developed suddenly on March 29, 2020 against the background of a complete physical and emotional well-being. The patient had no identified contacts with persons having proven diagnosis of COVID-19. She also did not travel abroad in the current year.

The patient was obese (BMI, 37 kg/m²), had a history of bronchial asthma and received a long-term therapy with inhaled budesonide (320 mcg daily) and formoterol (9 mcg daily). No clinical manifestations of asthma were present in the month preceding hospitalization. No history of other chronic conditions was available.

Nasopharyngeal swab specimens for acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acid collected at an outpatient facility three days before admission were positive. The patient received paracetamol and amoxicillin/clavulanate for five consecutive days before admission and was later on referred to the hospital because of clinical deterioration and positive SARS-CoV-2 test results.

Figure 1. Chest CT images of Patient 1



(A-C) Chest CT images on admittance. (D-F) Chest CT images on day 11. (G-I) Chest CT images on day 17. (J-L) Chest CT images on day 22.

On admission, physical examination revealed body temperature, 36.2°C; pulse, 96 per minute; blood pressure, 160/100 mm Hg; respiratory rate, 22 breaths per minute. The patient's peripheral oxygen saturation (SpO₂) was 93% on room air.

Immediately after admission, computed tomography (CT) imaging of the chest was performed in the patient showing multiple bilateral ground-glass opacities predominantly in subpleural regions of the lower and middle regions of both lungs. Reticular changes were also seen in the same zones (Figure 1, A-C).

Laboratory tests were approximately normal except for a moderate C-reactive protein increase to 11.58 mg/L (Table 1). Procalcitonin level on admission was normal (< 0,5 ng/ml).

Basing on typical symptoms, CT changes in the lungs, and positive swab test for SARS-CoV-2, the patient was diagnosed a severe form of COVID-19 infection complicated with a bilateral multilobar pneumonia and acute respiratory failure.

On admission, oxygen supplementation via nasal cannula (5 L/min) was maintained in the patient leading to an increase in SpO₂ level to 96% with improvement in respiratory discomfort. The patient was started on clarithromycin 1000 mg/day orally (PO), hydroxychloroquine 800 mg PO on the first day followed by a dose reduction to 400 mg daily from the second day, ceftriaxone 2000 mg/day via intravenous infusion (IV), and tilorone 125 mg PO daily for antiviral treatment.

On April 9, 2020 (day 4 of hospitalization), the patient's condition began to deteriorate with increasing shortness of breath and progressive fall in SpO₂ from 93% on day 4 to 90% by day 11 despite noninvasive low-flow oxygenation. The patient was transferred to an alternative treatment including antiviral agents lopinavir 800 mg PO daily, ritonavir 200 mg PO daily, and umifenovir 400 mg PO daily. Antimicrobial therapy was changed to meropenem 3000 mg IV daily.

Table 1. Laboratory results in Patient 1

Laboratory parameter	Normal range	Results				
		On admission	Day 11	Day 14	Day 17	Day 22
WBC, x10 ⁹ /L	4.0 – 9.0	5.7	9.3	10.1	12.2	10.9
Neutrophils (Absolute), x10 ⁹ /L	1.7 – 7.7	3.8	7.2	8.3	11.3	8.5
Lymphocytes (Absolute), x10 ⁹ /L	0.4 – 4.4	1.5	1.5	1.1	0.8	2.0
Hemoglobin, g/L	130 - 170	135	117	115	120	112
Platelets, x10 ⁹ /L	120 - 380	198	408	426	421	231
ALT, U/L	5 - 33	15	20	53	45	22
AST, U/L	5 - 32	23	26	68	61	53
Total Bilirubin, mmol/L	5.0 – 21.0	6.0	-	9.0	12.0	4.0
Creatinine, mmol/L	44 - 80	61	46	51	49	38
Glucose, mmol/L	3.9 – 6.05	4.8	5.0	7.1	7.7	5.6
Sodium, mmol/L	136 - 145	142	142	143	147	143
Potassium, mmol/L	3.5 – 5.1	4.3	3.7	3.56	3,2	3.9
D-Dimer, mg/L	0.00 – 0.55	-	1.77	-	1.52	-
C-Reactive Protein, mg/L	0.00 – 5.00	11.58	52.63	54.15	7.91	1.47
Procalcitonin, ng/mL	0.00 – 0.50	<0.5	0.05	<0.05	0.08	0.03
SARS-CoV-2 RNA	Negative	Positive	-	-	Positive	Negative

WBC = white blood cell count, AST = aspartate aminotransferase (serum glutamic-oxaloacetic transaminase), ALT = alanine aminotransferase (serum glutamic-pyruvic transaminase), SARS-CoV-2 = severe acute respiratory syndrome-related coronavirus 2, RNA = ribonucleic acid

No positive change in the patient was obtained by day 11. Chest CT on hospital day 11 showed multiple bilateral ground-glass opacities with new obfuscation zones appearing in subpleural and central regions of the middle and upper right lobes and having a noticeable reticular pattern. The density of previously seen opacities increased, subpleural areas of consolidation appeared in the right lung (Figure 1, D-F). Overall involvement of pulmonary tissue reached 75% in the right lung and 30-50% in the left one. Laboratory data showed high

level of C-reactive protein (52.63 mg/L). Other changes included increased D-dimer level (1.77 mg/L). Body temperature and procalcitonin level were normal. Considering high risk of progression to severe respiratory failure and intubation, a moderate dose of methylprednisolone (125 mg daily IV) was prescribed to the patient and was given on days 11 to 14. Antimicrobial therapy with meropenem was continued.

After temporary stabilization, the patient's condition went on worsening. On day 14, SpO₂ reached 86% on low-flow oxygenation in prone position. The patient was fully conscious but suffered of severe dyspnea and fatigue. Chest X-ray on day 14 showed diffuse round multiple opacities without definite borders all over the lungs with a tendency to merger. Opacification involved more than 75% of the right lung and at least 50% of the left lung tissue. Laboratory data showed the same changes as on day 11.

Because of respiratory failure, the patient was transferred to the medical ICU, where she was started on high-flow oxygen therapy 45 L/min via nasal cannula. This raised SpO₂ to 90-93% with blood oxygen saturation dropping back to 80% on room air. The patient was given tocilizumab (400 mg IV), 1 time on day 14.

On days 14 and 15, the condition of the patient remained extremely severe, without any improvement. Hypoxemia with SpO₂, 88-90% persisted despite high-flow oxygenation up to 50 L/min and prone-positioning of the patient.

Considering the severe, life-threatening course of COVID-19 disease in a high-risk patient, lack of sufficient clinical response to tocilizumab, emerging perspective of intubation with subsequent fatality risk of more than 90%,² the multidisciplinary team decided to prescribe the patient a pulse therapy with a high dose of methylprednisolone (1000 mg/day IV for three consecutive days) as a potentially life-saving compassion treatment. Pulse therapy with methylprednisolone was accompanied by intravenous immunoglobulin 20 g/day IV for three consecutive days to prevent steroid-induced immunodeficiency and for its own immunomodulatory effect. This treatment was conducted on hospital days 15 to 17.

In the evening of day 15, SpO₂ stabilized in the patient at 95-96% on decreased high-flow oxygen 10 L/min with respiratory rate, 14-15 breaths per minute. On day 16, SpO₂ reached 99% on high-flow oxygenation 10 L/min. On day 17, high-flow oxygenation was discontinued, and the patient sustained SpO₂ at 95-97% on low-flow oxygenation 5 L/min. Chest CT imaging on day 17 showed multidirectional changes. Multiple confluent ground-glass opacities increased in size. However, initial positive change was also found: bilateral subpleural pulmonary infiltrates lost their density to the degree of ground-glass opacity and decreased in size (Figure 1, G-I). Further positive changes were seen on CT images on day 22: opacification in the left lung mostly resolved, the range and density of obfuscation in the right lung have clearly decreased (Figure 1, J-L).

During the following days, clinical condition of the patient continued to improve. Respiratory failure resolved, and the patient was able to sustain normal (97-98%) blood oxygen saturation on room air by day 25. Respiratory rate, blood pressure, and heart rate also returned to normal values. Respiratory symptoms decreased leaving a small degree of dyspnea (mMRC 2) and fatigue. First SARS-CoV-2 negative nasopharyngeal swab was obtained on day 20 and confirmed 2 days later. The patient was declared to be cured and discharged from the hospital on May 5, 2020 (hospital day 30).

Case 2

A 60-year-old woman, was admitted to SRC-FMBC FMBA Infectious Disease Department on April 20, 2020 with fever above 39°C, dry cough, weakness, and chest pain in the left hemithorax on inspiration. On April, 9 2020 she had a documented contact with a COVID-19 patient. The disease manifested on April, 16 2020 with fever and malaise. Concomitant conditions: obesity (BMI, 35 kg/m²), chronic pancreatitis, idiopathic frequent supraventricular premature beats, on chronic treatment with lappaconitine hydrobromide. No known allergies.

Nasopharyngeal swab specimens for SARS-CoV-2 were twice positive. Previous treatment: paracetamol, ascorbic acid, ceftriaxone 2000 mg/day intramuscularly (IM). The patient was referred to the hospital because of high fever and typical picture of COVID-19 pneumonia on an outpatient chest CT.

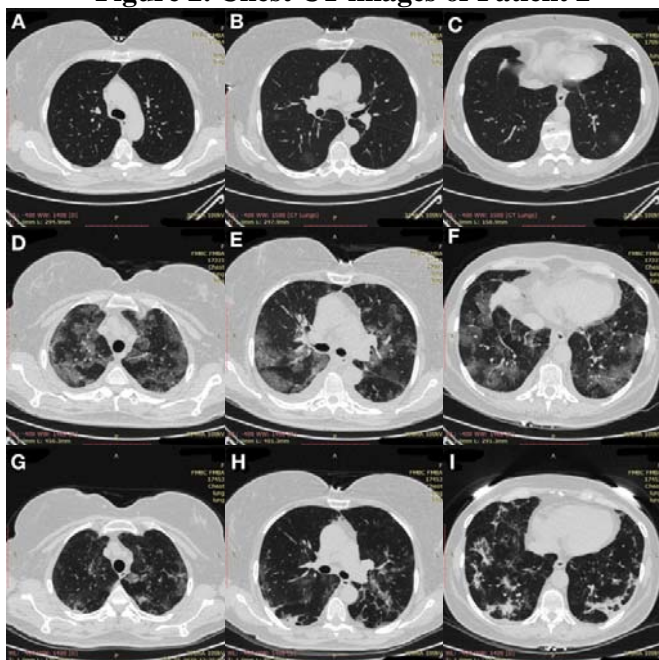
Physical examination results on admission: body temperature, 38.8°C; pulse, 85 per minute; blood pressure, 125/80 mm Hg; and respiratory rate, 22 breaths per minute. Peripheral oxygen saturation (SpO₂) was 95% on room air.

CT data of April 19, 2020: multiple ground-glass opacities up to 3 cm in size in the majority of segments of both lungs, predominantly in the lower and middle regions, affecting less than 50% of the lung parenchyma (Figure 2, A-C). Laboratory tests were approximately normal except for slightly increased levels of C-reactive protein and D-dimer (Table 2).

Basing on clinical symptoms, typical CT changes in the lungs, and twice positive swab test for SARS-CoV-2, the patient was diagnosed a moderately severe form of COVID-19 complicated with a bilateral viral pneumonia without an acute respiratory failure.

The patient was started on clarithromycin, hydroxychloroquine, ceftriaxone, and tilorone as described earlier. For the next two days, the patients demonstrated persistent fever (37.7-38.5°C), cough, and malaise. Respiratory rate and blood oxygen saturation were normal.

Figure 2. Chest CT images of Patient 2



(A-C) Chest CT images on admittance. (D-F) Chest CT images on day 10. (G-I) Chest CT images on day 23.

On hospital day 3, the patient suffered sudden deterioration with appearance of dyspnea (mMRC 4), aggravation of fever and chills. Blood oxygen saturation dropped to 87-91% on room air that required noninvasive oxygenation via nasal cannula. On low-flow oxygen 5 L/min, SpO₂ raised to 92-95% at rest. Tachypnea, 25 breaths per minute, and arterial hypotension, 90/70 mm Hg were also seen.

The CT scan of day 3 demonstrated an obvious progression of pathological changes with enlargement of pre-existing and appearance of new ground-glass opacities with a tendency to merger into large subpleural opacification areas affecting up to 50% of pulmonary tissue. Laboratory tests demonstrated a high level of CRP and ferritin (Table 2).

Considering the progression of the disease according to clinical and roentgenological data and significantly elevated markers of inflammation, the patient has been diagnosed with CRS. A

moderate dose of corticosteroids (methylprednisolone 125 mg/day IV) and low molecular weight heparin (enoxaparin 40 mg subcutaneously (SC) twice daily) were added to therapy. The patient was switched to an alternative antiviral drug scheme. Lopinavir 800 mg PO daily, ritonavir 200 mg PO daily, and umifenovir 400 mg PO daily were prescribed. During the next four days, the condition of the patient improved and she was relatively stable with comfortable breathing, body temperature, 37.2 – 37.3°C; blood oxygen saturation, 94 – 96% on low-flow oxygen 3-5 L/min; respiratory rate, 20-22 breaths per minute; and blood pressure, 115-120/70-80 mm Hg.

On day 7, the patient's condition worsened again with a surge of body temperature to 39.3°C and decrease of SpO₂ to 88-90% on low-flow oxygen. She also reported a decrease in urine output to less than 300 mL/day. CT scan of day 8 revealed an increase of pre-existing opacities in size and density. New ground-glass shadows appeared in upper and lower zones of the lungs merging into large subpleural opacification areas. In the left lung, small foci of consolidation were seen. Interlobular septal thickening could be noted in various parts of the lungs. In total, pathological changes involved at least 75% of pulmonary tissue. Laboratory data of day 8 showed a high ferritin level that did not match a moderate elevation of C-reactive protein (Table 2). The level of D-dimer and aminotransferases were moderately increased.

Basing on above described picture, acute multiple organ failure (acute kidney injury, respiratory failure) was diagnosed in the patient. All drugs were discontinued except for steroids. The patient was transferred to the medical ICU where she was started on continuous veno-venous hemodiafiltration and high-flow oxygenation 40 L/min via nasal cannula. Because of severe and progressive course of COVID-19 despite treatment and the development of multiple organ failure without signs of secondary bacterial infection (procalcitonin level, < 0.5 ng/ml), on day 7 the patient was given tocilizumab 400 mg IV.

Table 2. Laboratory results in Patient 2

Laboratory parameter	Normal range	Results				
		On admission	Day 3	Day 8	Day 10	Day 21
WBC, x10 ⁹ /L	4.0 – 9.0	3.3	4.3	8.6	4.8	4.0
Neutrophils (Absolute), x10 ⁹ /L	1.7 – 7.7	1.7	3.1	7.7	3.5	2.3
Lymphocytes (Absolute), x10 ⁹ /L	0.4 – 4.4	1.1	0.9	0.8	1.2	1.4
Hemoglobin, g/L	130 - 170	128	121	111	110	116
Platelets, x10 ⁹ /L	120 - 380	176	163	279	305	271
ALT, U/L	5 - 33	37	101	93	100	126
AST, U/L	5 - 32	38	87	55	80	51
Total Bilirubin, mmol/L	5.0 – 21.0	4	4	7	7	8.9
Creatinine, mmol/L	44 - 80	48	50	43	45	48
Glucose, mmol/L	3.9 – 6.05	6.0	7.1	7.5	9.0	
Sodium, mmol/L	136 - 145	141	-	140	136	142
Potassium, mmol/L	3.5 – 5.1	4.2	-	3.4	3.2	3.8
D-Dimer, mg/L	0.00 – 0.55	1.36	0.75	0.92	1.54	0.42
C-Reactive Protein, mg/L	0.00 – 5.00	7.52	34.77	17.34	5.80	0.69
Procalcitonin, ng/mL	0,00 - 0,50	0.05	0.04	0.02	<0.5	-
Ferritin, ng/mL	28 - 365	-	868	797	-	-
SARS-CoV-2 RNA	Negative	Positive	Positive	Positive	Positive	Negative

WBC = white blood cell count, AST = aspartate aminotransferase (serum glutamic-oxaloacetic transaminase), ALT = alanine aminotransferase (serum glutamic-pyruvic transaminase), SARS-CoV-2 = severe acute respiratory syndrome-related coronavirus 2, RNA = ribonucleic acid

On the above-mentioned treatment, the patient increased in urine output to 2900 mL/day, the level of creatinine stayed normal (Table 2). However, for the next three days her condition remained unstable and required intensive care. It was not possible to achieve her SpO₂ above 94%, and high-flow oxygen supplementation up to 50 L/min via nasal cannula was required to reach this. The patient continued to experience persistent fever, pronounced dyspnea and fatigue. On day 10, the patient had body temperature, 38°C; blood pressure, 125/80 mm Hg; respiratory rate, 20 breathing movements per minute; and SpO₂, 88-94% on high-flow oxygenation 45-50 L/min, FiO₂, 50%. Computed tomography of the chest on day 10 showed no significant change compared to day 8. Merging ground glass opacities could be seen in all regions of both lungs involving up to 75% of pulmonary tissue (Figure 2, D-F). Laboratory tests revealed increased aminotransferases and D-dimer, mild anemia, and moderate elevation of CRP. Other parameters were approximately normal (Table 2).

Thus, it became clear that the patient failed to achieve enough clinical improvement with tocilizumab. Given the severe, life-threatening course of COVID-19 and insufficient effectiveness of previous therapy, the multidisciplinary team decided to give the patient a pulse therapy with 1000 mg of IV methylprednisolone for three consecutive days. Corticosteroid pulse therapy was accompanied by intravenous immunoglobulin 20 g/day IV for three consecutive days. This treatment was conducted on hospital days 10 to 12.

By the evening of day 10 (first day of pulse therapy), the patient decreased body temperature to 36,6°C. Saturation stabilized at 97% on high-flow oxygen 45 L/min, FiO₂, 50%. By the evening of day 11 (second day of pulse therapy), high-flow oxygenation was discontinued, SpO₂ reached 97% on oxygen supplementation via nasal cannula 4 L/min. Body temperature was 36,8°C; respiratory rate, 20 breaths per minute; heart rate, 72 per minute; blood pressure, 100/60 mm Hg. On day 12, pulse therapy was completed. The patient experienced significant improvement having moderate residual weakness and dyspnea (mMRC 2), normal body temperature (36.4 - 36.7°C) and blood oxygen saturation (96-98%) on room air. On day 13, the patient returned to the regular ward, and was discharged in good clinical condition on day 23 with two negative swab tests for SARS-CoV-2 proving her to be cured. Chest CT at discharge showed partial or complete resolution of the opacities in both lungs with the amount of involved pulmonary tissue decreased to less than 50%. A portion of opacities in all segments of the lungs turned into consolidation (Figure 2, G-I). However, no clinical or laboratory sign proved that change complying with secondary infection.

Case 3

A 33-year-old man, was admitted to Infectious Disease Department on April 21, 2020 complaining of weakness, fever above 39°C, dizziness, and loss of appetite. No documented contacts with COVID-19 patients. The disease manifested on April, 14 2020 with head ache and weakness. A day later the patient noticed fever up to 39.5°C and for several days used to take paracetamol and ibuprofen to decrease the fever. On April 19, 2020 the patient consulted a general practitioner and was referred to CT of the chest with suspected COVID-19. The CT scan revealed a typical bilateral pneumonia. Nasopharyngeal swab specimens for SARS-CoV-2 were positive. The patient was started on azithromycin and hydroxychloroquine. He complied with the treatment for two days but the symptoms persisted. On April 21, 2020 he was taken to hospital because of worsening condition. The patient had no concomitant diseases and allergies.

Physical examination results on admission: body temperature, 36.7°C; pulse, 66 per minute; blood pressure, 110/80 mm Hg; respiratory rate, 24 breaths per minute. The patient's peripheral oxygen saturation was 94% on room air.

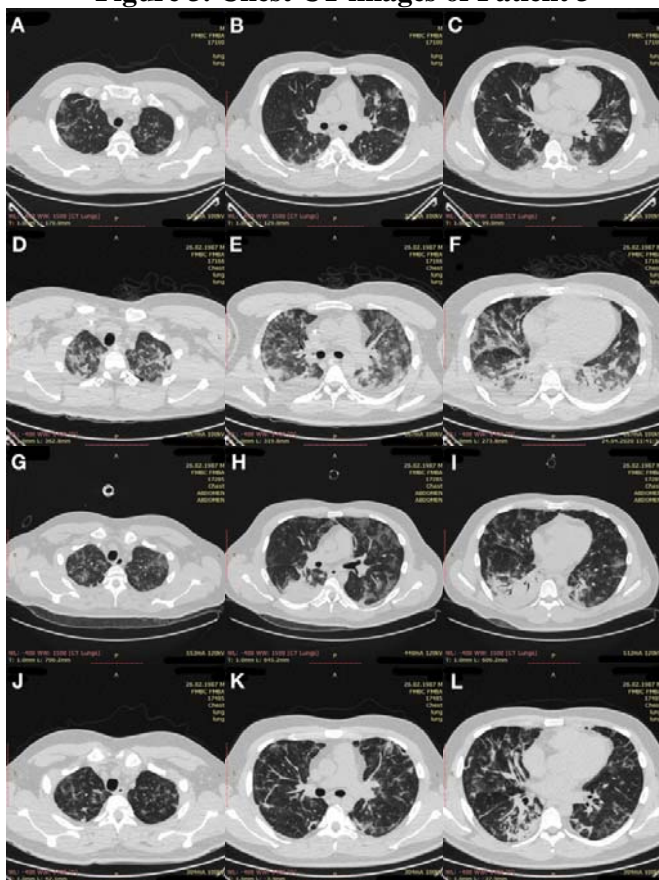
Chest CT data of April 21, 2020: multiple ground-glass opacities and areas of pulmonary consolidation in all segments of the lungs. The opacities involved more than 75% of pulmonary tissue (Figure 3, A-C). Blood tests on admission revealed an extra-high level of ferritin and noticeably increased C-reactive protein and aminotransferases (Table 3). Procalcitonin level was normal.

Because of a pronounced pulmonary involvement according to CT and clinical data suggestive of CRS, the patient was diagnosed a severe, potentially life-threatening form of COVID-19 despite respiratory failure was not seen on admission. He was started on methylprednisolone 125 mg/day IV, enoxaparin 80 mg SC twice daily, lopinavir 800 mg PO daily, ritonavir 200 mg PO daily, umifenovir 400 mg PO daily, and ceftriaxone 2000 mg IV daily. Despite treatment, during the first two hospital days he experienced severe symptoms including transient elevations of body temperature to 38°C with chills, cough, shortness of breath, dizziness, and insomnia. Blood oxygen saturation decreased to 85-90% on room air demanding for noninvasive low-flow oxygenation with a growth in SpO₂ to 90-92% on 5 L/min oxygen via facial mask. The patient was fully conscious, complied with recommendations of the personnel, and was put to a prone-position for 2 hours every 2 hours.

On day 3, the patient experienced a serious deterioration with severe dyspnea at rest, aggravation of fever (38.1°C) and chills. Blood oxygen saturation fell to 87% on low-flow oxygenation with tachypnea 28 breaths per minute. The patient was transferred to the medical ICU where he was given 400 mg tocilizumab IV.

To the end of day 3, the body temperature decreased in the patient to 37.1°C. On oxygen supplementation via facial mask 4-5 L/min, blood oxygen saturation fluctuated around 92% with rapid desaturation to 87% on room air, respiratory rate was 22-24 breaths per minute. The patient was hemodynamically stable with blood pressure, 130/70 mm Hg and heart rate, 94 per minute.

Figure 3. Chest CT images of Patient 3



(A-C) Chest CT images on admittance. (D-F) Chest CT images on day 4. (G-I) Chest CT images on day 9. (J-L) Chest CT images on day 23.

In the night of hospital day 4, a threatening progression of respiratory insufficiency occurred. There was registered a fall of SpO₂ to 80% on 8 L/min oxygen via facial mask, the patient became agitated, respiratory rate increased to 42-44 per minute, blood pressure reached

175/94 mmHg, heart rate increased to 135 per minute. Arterial blood gas analysis revealed pH=7.33, $p_aO_2=59$ mmHg, $p_aCO_2=35.7$ mmHg. The patient was intubated, and mechanical ventilation with low tidal volume was initiated. This enabled to stabilize the clinical condition of the patient. Blood oxygen saturation increased to 98%, blood pressure decreased to 120/70 mmHg, heart rate was 85 per minute. CT scan at day 4 demonstrated the appearance of multiple new merging ground-glass opacities and areas of consolidation in all segments of the lungs. Partial atelectasis of both lower lobes was also noted. In general, pathological changes involved more than 75% of pulmonary tissue. CT picture was suspicious of ARDS (Figure 3, D-F).

Facing the risk of unfavorable future course of the disease because of massive pulmonary involvement and severe respiratory insufficiency requiring mechanical ventilation and considering the lack of conventional ways of treatment escalation, the multidisciplinary team in charge of treatment decided to perform in the patient a pulse therapy with a high dose of methylprednisolone. On days 4 to 6, he received methylprednisolone 1000 mg/day in the form of a prolonged IV infusion.

By the end of day 4, it was possible in the patient to reduce FiO_2 twice to 45% keeping $SpO_2>95\%$. By the end of day 5, respiratory index (PaO_2/FiO_2) increased to 275 mmHg, $SpO_2=98\%$. On day 6, the regimen of invasive ventilation was switched to spontaneous assisted ventilation. On subsequent days, sedation was discontinued, and the patient demonstrated $SpO_2=98\%$ on spontaneous ventilation. He was fully conscious and available to non-verbal contact.

Table 3. Laboratory results in Patient 3

Laboratory parameter	Normal range	Results				
		On admission	Day 4	Day 9	Day 17	Day 23
WBC, $\times 10^9/L$	4.0 – 9.0	9.7	9.9	34.7	5.9	5.1
Neutrophils (Absolute), $\times 10^9/L$	1.7 – 7.7	7.80	8.40	33.20	3.90	2.80
Lymphocytes (Absolute), $\times 10^9/L$	0.4 – 4.4	1.50	1.30	1.20	1.50	2.0
Hemoglobin, g/L	130 - 170	154	145	114	117	138
Platelets, $\times 10^9/L$	120 - 380	206	230	331	223	250
ALT, U/L	5 - 33	124	160	61	65	54
AST, U/L	5 - 32	161	156	57	31	30
Total Bilirubin, mmol/L	5.0 – 21.0	4	8	11	7	13.5
Creatinine, mmol/L	44 - 80	85	86	122	71	87
Glucose, mmol/L	3.9 – 6.05	5.8	9.4	8.5	5.9	5.0
Sodium, mmol/L	136 - 145	142	141	136	140	141
Potassium, mmol/L	3.5 – 5.1	4.2	4.0	4.6	4.5	4.3
D-Dimer, mg/L	0.00 – 0.55	1.41	0.49	1.34	1.29	-
C-Reactive Protein, mg/L	0.00–5.00	44.64	2.85	119.67	8.25	2.08
Procalcitonin, ng/mL	0,00-0,50	0.08	< 0.50	> 2	< 0.50	< 0.50
Ferritin, ng/mL	28- 365	2540	1140	-	644	-
SARS-CoV-2 RNA	Negative	Positive	Positive	Positive	Positive	Negative

WBC = white blood cell count, AST = aspartate aminotransferase (serum glutamic-oxaloacetic transaminase), ALT = alanine aminotransferase (serum glutamic-pyruvic transaminase), SARS-CoV-2 = severe acute respiratory syndrome-related coronavirus 2, RNA = ribonucleic acid

On day 8, the patient experienced another transient deterioration with elevation of body temperature to 40.1°C at maximum, SpO_2 decrease to 94%, and hemodynamic compromise with blood pressure lowering to 88/55 mm Hg demanding a norepinephrine drip. Chest CT performed on day 9 showed a distinct positive change in CT picture compared to that of day 4. The ground

glass opacities noticeably decreased in amount and density all over the lungs. Pneumatized parenchyma could be seen again in all pulmonary segments. The total volume of affected lung tissue lowered to approximately 50%. However, a new zone of pulmonary tissue consolidation with a symptom of air bronchogram was found in the lower lobe of the right lung suggestive of pneumonia (Figure 3, G-I). Blood analysis of day 9 revealed a pronounced neutrophil leukocytosis, mild normochromic anemia, elevation of C-reactive protein and a high level of procalcitonin.

The patient was diagnosed with nosocomial pneumonia. After a seven-day course of meropenem 3000 mg/day IV and an infusion of intravenous immunoglobulin 20 g/day IV, he finally improved, was weaned from the ventilator on day 14 and returned to the regular ward on day 16 having SpO₂, 99% on oxygen supplementation via nasal cannula 3 L/min. The patient was discharged home on day 23 having no symptoms, normal blood oxygen saturation (95% on room air), and negative nasopharyngeal swab test for SARS-CoV-2. Chest CT of May 07, 2020 revealed partial resolution of pulmonary tissue consolidation in the right lower lobe and further decrease of size and density of ground-glass opacities all over the lungs (Figure 3, J-L).

Discussion

In this presentation we describe a cohort of three patients with severe life-threatening COVID-19, who failed to improve after consecutive use of moderate doses of corticosteroids, specific IL-6 inhibitor tocilizumab, and demonstrated a favorable response to pulse therapy with high doses of methylprednisolone and intravenous human immunoglobulin.

In two of the patients, deterioration was associated with clinical features suggestive of hyperinflammation possibly due to cytokine release syndrome (high fever, (multi)organ failure, pronounced elevation of C-reactive protein, ferritin, D-dimer, and aminotransferases). In one patient, vast pulmonary involvement and respiratory failure were accompanied by a relatively modest increase in CRP and D-dimer, ALT, AST levels. Considering the evidence of immunopathological nature of COVID-19-associated severe pneumonia, a specific IL-6 inhibitor tocilizumab was selected to fight the rampant exacerbation in these patients. Unfortunately, usually effective in hours according to our clinical experience, tocilizumab did not render a prompt clinical relief in this cohort.

Patients with severe COVID-19 have increased levels of multiple cytokines.^{7,11} The blockade of only one of them, namely IL-6, may have not enough power to suppress the development of such a threatening COVID-19 complication as CRS, which, as we can suppose now, stimulates severe pulmonary and other organ damage and can lead to a fatal outcome.¹¹ To be fully effective in the treatment of CRS in COVID-19 patients, immunomodulating therapies are awaited to suppress multiple proinflammatory cytokine pathways. And in such situations, corticosteroids along with intravenous immunoglobulin are usually named first.⁸

Facing continuous worsening of the patients, the multidisciplinary group in charge of treatment decided to use pulse therapy with high doses of corticosteroids and intravenous immunoglobulin as *ultima ratio* before the obvious indications to intubation occur or immediately after intubation given the unpredictable outcome on mechanical ventilation.

The result seemed overwhelmingly positive to us. During the first day of pulse therapy, the patients stabilized blood oxygen saturation, hemodynamics, and decreased body temperature, if elevated. To the end of a three-day course, there was no need in high-flow oxygenation any more in two of the patients. The third patient, who was intubated prior to pulse therapy, was switched to spontaneous ventilation and was capable of sustaining a 98% blood oxygen saturation on this regimen. In all the patients, clinical improvement was accompanied by a rapid positive dynamic of the CT picture in the lungs. The patients were soon discharged in a good condition with negative swab tests for SARS-CoV-2. Patients with a similar catastrophic course of the disease often died or needed prolonged mechanical ventilation with unpredictable outcome.²

To our knowledge, pulse therapy with high doses of corticosteroids was not previously used for treatment of severe lung impairment in COVID-19. And we have managed to find only one report of successful use of intravenous immunoglobulin in three patients with severe COVID-19.²⁴ But we considered such therapy justified as both steroids and intravenous immunoglobulin are positioned as a first-line cure for a cytokine release syndrome.⁸

Pulse therapy with methylprednisolone and intravenous immunoglobulin was generally safe and well tolerated. We did not observe serious side effects in described patients. There were noticeable fluctuations of glucose and electrolytes level surrounding pulse therapy, but they were not critical and could be effectively managed in a hospital setting. Heart rhythm disturbances, uncontrolled hypertension, and gastrointestinal bleeding were not registered in connection with pulse therapy.

The period of viral shedding amounted 20-23 days in described patients. This correlates well with the data from other authors who found the average time to viral clearance in SARS-CoV-2 infection to be 20 (17-24) days.² Hence, there was no evidence of protracted persistence of the virus in patients who received pulse therapy with high doses of methylprednisolone and intravenous immunoglobulin.

We used pulse therapy with methylprednisolone in combination with intravenous immunoglobulin in order to prevent infectious complications and basing on the own immunomodulating effect of immunoglobulin.^{8,22,23} The effectiveness and safety of these components, either used separately or in combination, require further evaluation in randomized controlled studies.

Conclusions

1. Pulse therapy with high doses of methylprednisolone and intravenous immunoglobulin was associated with a prompt suppression of lung damage and respiratory failure, elimination of clinical manifestations of cytokine release syndrome, and reversal of pulmonary CT changes in patients with severe COVID-19 in case of insufficient efficacy of moderate doses of corticosteroids and tocilizumab.

2. Pulse therapy with methylprednisolone in combination with intravenous immunoglobulin was safe and well tolerated.

3. Pulse therapy with methylprednisolone and intravenous immunoglobulin correlated with rapid and pronounced improvement in severe COVID-19 regardless of the initial level of biomarkers of inflammation.

4. Randomized controlled trials are necessary to specify the efficacy of high-dose methylprednisolone and intravenous immunoglobulin in the treatment of severe life-threatening COVID-19 separately or in combination.

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