High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with Coronavirus Disease 2019

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Abstract:

The outbreak of Coronavirus Disease 2019 (COVID-19) has spread rapidly in China. Till now, no definite effective treatment has been identified. We reported on three patients of severe COVID-19 who received high-dose intravenous immunoglobulin (IVIg) with satisfactory recovery. Based on these observations, randomized studies of high-dose IVIg should be considered in deteriorating patients infected with COVID-19.

Keywords: Coronavirus Disease 2019, SARS-COV-2, high-dose intravenous immunoglobulin, immunomodulation

The outbreak of pneumonia of unknown cause that first occurred in Wuhan, China, December 2019, has recently been assessed by WHO as a pandemic. The pneumonia is caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-COV-2, previously known as 2019-nCoV), and the disease it caused was later designated coronavirus disease 2019 (COVID-19) by WHO. As of March 12, 2020, a total of 80981 cases had been reported in China, including 3173 reported deaths. Meanwhile, number of confirmed patients continues to grow out of China and 45309 cases had already been reported[1]. The relatively high infectivity, rapid progression of lung involvement, and lack of definite effective treatment, make it urgent to develop efficient measures of management based on the pathogenesis of COVID-19. Although many empirical therapeutic options have been introduced on several operational recommendations, including existing and new generation of antivirals, steroids, and traditional Chinese medicine, the optimal strategy for severe COVID-19 remains unclear.

The clinical spectrum of SARS-CoV-2 infection is quite wide, and includes asymptomatic infection, mild type with only upper respiratory tract illness, common type with pulmonary infiltrations, severe type with respiratory distress and critically ill patients that needs intubation or intensive care[2]. Clinical features of those with pneumonia include fever, cough, and in many cases a sudden and accelerating respiratory distress originated from interstitial pneumonia. In those who rapidly progressed to critical conditions, reduced peripheral lymphocyte counts and elevated inflammatory factors were observed, indicating an overwhelming immune response[3,

4]. Previous experiences in SARS showed that the main pathogenesis of organ dysfunction lay on the overall cytokine dysregulation. Similarly, the point when status deterioration starts in patients with COVID-19 should be a critical window of opportunity for intervention. Here we reported on three patients with COVID-19, who received high-dose intravenous immunoglobulin (IVIg) at the time of respiratory distress initiation, with satisfactory clinical and radiographic recovery.

Case presentation

Patient 1

On Jan 22, 2020, a 56-year-old man was admitted to Jin Yin-tan Hospital, Wuhan, China. Patient had sore throat since Jan 19, and reported fever for two days before admission, with the highest temperature of 38.2 degrees Celsius. He was given oseltamivir and azithromycin by a local clinic to empirically cover community-acquired respiratory pathogens, yet without any improvement. On Jan 21, he came to the Emergency Department of Jin Yin-tan Hospital, and a CT scan was done showing scattered interstitial patches and pleural thickening on the right side (Figure 1). Oropharyngeal swab was positive for SARS-COV2 by real-time reverse-transcriptase–polymerase-chain-reaction (rRT-PCR) assay. He was previously generally healthy, and denied any exposure or direct contact with the Huanan seafood market.

On admission, he was afebrile, with the blood pressure 125/80mmHg, pulse 86 beats per minute, respiratory rate 20 breaths per minute, and oxygen saturation 96% when breathing ambient air. Both lungs were clear on auscultation, and the remainder

of the examination was unremarkable. Laboratory results reflected a significant lymphocytopenia with a lymphocyte count 0.48×10^9/L (1.1-3.2). His inflammatory markers were elevated, with the erythrocyte sedimentation rate (ESR) 49mm/1h (0-15), and the high-sensitive C-reactive protein (hsCRP) 57.8mg/L (0-5). The liver and renal functions were within the normal range (Table 1). Detections of antigens were negative for Influenza A and B, as well as for H7 subtype avian influenza virus.

The patient was diagnosed COVID-19, common type. Supportive care and empirical moxifloxacin were given with a close monitoring of the clinical status. He had intermittent fever, but the vital signs remained largely stable until Jan 26 when cough and shortness of breath developed. The oxygen saturation decreased to 91% at ambient air, and hsCRP further elevated to 106.2mg/L. A CT scan on Jan 29 showed progressing infiltrations bilaterally compared to that of Jan 21(Figure 1A).

The diagnosis was modified to COVID-19, severe type. High-dose IVIg was started from Jan 28 (hospital day 7), at 25 grams per day for five days (body weight 66 kilograms). Moxifloxacin was continued till Feb 2. On the same day following IVIg infusion, patient became afebrile. No adverse event was reported. Over the next few days, his clinical status gradually improved. The supplemental oxygen was discontinued, and his oxygen saturation level returned to 97 to 98% on Feb 3 at ambient air. Test results on Feb 5 showed recovered lymphocyte count to 1.6×10^9/L. The ESR decreased to 31mm/h, and hsCRP returned to normal range. The CT scan showed partial resolution of previous lesions (Figure 1A). Two consecutive oropharyngeal swabs on Feb 2 and 3 were both negative for 2019-nCoV. Patient was discharged on Feb 5.

Patient 2

A 34-year-old man presented with fever and dry cough for 10 days, and was admitted on Jan 29, 2020 to Jin Yin-tan Hospital. Patient reported fever up to 38.5 degrees Celsius with dry cough. On Jan 28, he began to feel short of breath and came to a local hospital. An oropharyngeal swab was confirmed positive for SARS-COV2, and patient was transferred to Jin Yin-tan Hospital the next day. He had a two-year history of hypertension well controlled by valsartan and felodipine, and denied any exposure or direct contact with the seafood market.

The physical examination showed a body temperature of 37.5°C, blood pressure 138/90 mmHg, pulse 86 beats per minute, respiratory rate 26 breaths per minute, and oxygen saturation was 90% when breathing ambient air. Laboratory results on admission reflected mild thrombocytopenia at 97×10^9/L (120-350), and moderately elevated inflammation markers including ESR 58mm/1h and hsCRP 82mg/L. The level of creatine kinase was elevated at 1081U/L (50-310), and myoglobin was mildly increased to 153.8ng/ml (0-146.9) (Table 1). IgM tests for respiratory pathogens were negative for influenza A and B, parainfluenza, respiratory syncytial virus (RSV), adenovirus, mumps virus and microvirus B19. A CT scan on Jan 30 indicated bilateral infiltrations and opacities, more prominent on the right side (Figure1B).

Patient was diagnosed COVID-19, severe type. IVIg was administered immediately at the dose of 25 grams per day for five days (body weight 63kg). Patient became afebrile from the second day of IVIg treatment, with a gradual improvement of

breathing difficulty. CT scan was repeated on Feb 3, showing prominent absorption compared with that of Jan 30 (Figure 1B). The nasal PCR testing turned negative for SARS-COV2 on Feb 3, and he was discharged on Feb 5.

Patient 3

A 35-year-old woman was admitted to Jin Yin-tan Hospital on Jan 24, 2020. She reported malaise and low-grade fever (maximal 37.3 degrees Celsius) with mild coughing since Jan 19. A CT scan from local hospital showed mild ground-glass opacities. Her nasopharyngeal swab was positive for 2019-nCoV, and oral lopinavir/ritonavir was prescribed while being closely monitored. Patient developed high-degree fever around 39 degrees Celsius on Jan 22 yet with no obvious shortness of breath, and got admitted on Jan 24. She was previous generally healthy, but reported close contact with her colleague who had been diagnosed COVID-19 a few days before.

On admission, she was afebrile, with the blood pressure 105/68 mmHg, pulse 91 beats per minute, respiratory rate 20 breaths per minute, and oxygen saturation was 98% with ambient air. Her lungs were clear to auscultation. Laboratory studies revealed mild lymphocytopenia with a lymphocyte count of 0.85×10^9/L, and slightly elevated hsCRP at 41.4mg/L (Table 1). IgM tests for respiratory pathogens were reported negative for influenza A and B, parainfluenza, RSV, adenovirus, mumps virus and microvirus B19. A chest CT scan on Jan 24 showed multiple ground-glass opacities and infiltrations bilaterally, more advanced than that of Jan 20 (Figure 1C).

Lopinavir/ritonavir was continued to complete the two-week course. Patient's

temperature was between 37.5-38.5 degrees Celsius. On Jan 29, she developed shortness of breath, and the oxygen saturation decreased to 92% at ambient air. Prominent deterioration was also noticed from chest CT, accompanied by further reduction of lymphocyte counts to 0.6×10^9/L, and elevation of hsCRP to 69.5mg/L (Figure 1C).

Her clinical diagnosis grading was modified from common to severe type, and IVIg was administered from Jan 29 at 25 grams per day for five days (body weight 56kg). Meanwhile, methylprednisolone 40mg per day was given for three days. Fever subsided after the first day of enhanced treatment. Her symptoms improved significantly two days later when oxygen saturation returned to 98% at ambient air. Negative PCR testing for SARS-COV2 were confirmed on Feb 2 and 3. The chest CT scan revealed radiographic resolution (Figure 1C). She was discharged on Feb 9.

Discussion

Although confirmed cases of COVID-19 rapidly accumulated during the past two months, our understanding of the clinical spectrum and pathophysiological changes of this infection still remains very limited. Nevertheless, no definite treatment has been identified, which makes it extremely difficult for clinical management. Here we report a case series of COVID-19, all of whom were successfully treated by high-dose IVIg at the early stage of clinical deterioration. Based on these observations, a high-dose IVIg administered at the appropriate point, could successfully block the progression of disease cascade, and finally improve the outcome of COVID-19.

The natural history of SARS-CoV-2 infection does not simply resemble any of the previously known coronaviruses. Up to date, we have noticed quite a wide clinical spectrum of SARS-CoV-2 infection, including asymptomatic infection, mild upper respiratory tract illness, and those with pulmonary infiltrations. A large proportion of reported symptomatic cases including our patients and many others, followed a similar track of progression. The infection often started with mild or moderate unspecific symptoms, including but is not limited to low-grade fever, sore throat, coughing, fatigue and malaise, similar to that of a common cold. The initial symptoms would alleviate or persist for around 3-7 days, when high-grade fever developed and respiratory distress became quite prominent. Some of these patients would also have gastrointestinal symptoms during this period. However, if we look at the CT series as shown here, which were quite typical of most COVID-19 patients, we would have a very strong impression that most of the lesions started from the peripheral, especially the subpleural region when ARDS developed[5]. These features indicated an hematogenous or lymphatic distribution or spreading of pathogenic factors rather than direct inspiration.

Based on these observations, we deduced that symptomatic COVID-19 mainly consists of three phases, including a starting phase, spanning the acquisition of the virus and subsequent viremia; and in many but not all patients an accelerating phase, when virus-induced secondary damage of targeting organs and tissue occurs, including the lungs, the heart, the gastrointestinal tract, and even an overall inflammatory storm. The third phase is the final recovery phase. This was demonstrated by not only the clinical features but also the laboratory dynamics, including progressive lymphocytopenia and

elevated inflammation markers at the time of acceleration. Therefore, strategies against COVID-19 should also be specified according to the course of infection. The best timing of antivirals, if there are any, may lie on the phase before acceleration. When clinical deterioration began, the first few days of deterioration may present a critical point when potent suppression of inflammatory cascade could save the patients from fatal immune-mediated injuries, as shown here. Moreover, from the experiences of our patients, once if the acceleration of disease could be stopped, it seemed to work well even no effective antiviral drugs were given.

As a result, high-dose IVIg at 0.3-0.5g per kg weight per day for five days was used in our patients as a potent and safe immune modulator. Dose of IVIg was determined based on the well-established practice in immune modulation therapy for other diseases, including the neuromuscular disorders, autoimmune thrombocytopenic purpura, et al[6, 7], with a consideration of potential cardiac or renal impairment in severe COVID-19 patients. None of the three patients reported any adverse events. All patients were clinically improved shortly following the administration, with the temperature back to normal in one to two days, and breathing difficulties alleviating in 3-5 days. Confounding factors did exist, including the use of different antivirals in two of the three patients at various time points, and short course of steroids in Patient 3. Moreover, in Patient 2, valsartan, an angiotensin receptor 1 blocker (AT1R), had been used for treating hypertension. As angiotensin-converting enzyme 2 (ACE2) has been identified as the major receptor binding domain of SARS-CoV-2[8, 9], there has been a hypothesis that higher expression of ACE2 following chronically medication of AT1R

may protect SARS-CoV-2 infected patients against acute lung injury rather than putting them at higher risk, though currently remains unproved[10]. Nevertheless, from the timeline and patterns of disease course in these three patients, it was most probable that high-dose IVIg was playing the leading role in their recovery.

IVIg is a blood product containing polyclonal immunoglobulin G isolated and pooled from healthy donors, and has been used for over 30 years. As a complex preparation, it contains a large number of bioactive moieties, and the entirety of effects is not yet fully understood. IVIg of higher dose has been a choice of immunomodulatory therapy for autoimmune or inflammatory disease, and for prophylaxis and treatment of severe infections especially in immunocompromised patients[11, 12]. Several theories have been proposed to explain its potential immunomodulatory mechanisms, including the Fc-mediated and Fab-mediated approaches[13, 14]. In previous studies of SARS and Middle East respiratory syndrome (MERS), IVIg therapy has exhibited various clinical benefits with good tolerance [15-17]. Considering its efficacy in improving passive immunity and modulating immune inflammation, and the overall safety profile, high-dose IVIg could be considered a promising option at the early stage of clinical deterioration of patents with COVID-19.

Our report is limited by the small numbers of patients we included, and more evidence is needed to confirm the conclusion. However, it provided an important therapeutic clue under current situation of rapid disease spreading. The timing of IVIg administration is very critical in practice. Patients might not receive much benefit when overall systemic damage has already taken place. Currently, a randomized controlled

trial evaluating the efficiency of high-dose IVIg therapy in severe COVID-19 has been initiated (NCT 04261426), which would bring more evidence for IVIg using in treating such patients.

Acknowledgement

We are grateful to the patients for their consent to publish this case series. We thank all the nurses and clinical staff who provided care for these patients and who are providing continuous care to other patients in China.

Author contribution

T.L. and W.C designed the use of IVIg in these patients. W.C and X.L drafted the manuscript. L.R, T.B., K.H and H.S took clinical care of these three patients and collected all the data and imaging studies. H.F, Y.H and L.L reviewed the literature and critically revised the manuscript. All authors reviewed the manuscript, provided feedback and approved the manuscript in its final form.

Competing interests

All authors declared no competing financial interests.

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Table 1. Laboratory tests of the three patients before and after infusion of high-dose intravenous immunoglobulin.

		Patient 1[a]			Patient 2[b]		Patient 3[c]		
Measure	Reference Range	Illness Day 4, Hospital Day 1	Illness Day 9, Hospital Day 6	Illness Day 18, Hospital Day 15	Illness Day 12, Hospital Day 2	Illness Day 16, Hospital Day 6	Illness Day 6, Hospital Day 1	Illness Day 11, Hospital Day 6	Illness Day 14, Hospital Day 9
WBC (10^9/L)	3.5-9.5	4.22	6.61	8.74	4.74	3.91	3.06↓	3.39↓	4.4
RBC (10^{12}/L)	4.3-5.8	4.4	4.26↓	4.02↓	5.21	4.92	4.25	4.34	3.83
Hb (g/L)	130-175	144	139	128↓	147	139	127	126	114
PLT (10^9/L)	120-350	147	210	241	97↓	—	153	274	287
NEUT# (10^9/L)	1.8-6.3	3.4	5.82	6.51↑	3.11	2.27	1.86	2.46	3.42
LYM# (10^9/L)	1.1-3.2	0.48↓	0.58↓	1.63	1.2	1.04↓	0.85↓	0.60↓	0.85↓
ESR (mm/h)	0-15	49↑	—	31↑	58.8↑	—		40↑	41.5↑
hsCRP (mg/L)	0-5	57.8↑	106.2↑	4.3	82.0↑	25.1↑	41.1↑	69.5↑	6.6↑
Mb (ng/mL)	0-146.9	96.3	36.5	—	153.8↑	—	16.6	—	—
hsTnI (pg/mL)	0-28	1.1	1.3	—	3.6	—	0	—	—
SF (ng/mL)	21.8-274.66	459.57↑	—	563.02↑	806.99↑	632.55↑	85.91	—	232.62↑
PCT (ng/mL)	<0.05	—	<0.05	<0.05	<0.05	0.05	<0.05	<0.05	<0.05
TBIL (μmol/L)	0-26	15.5	15.4	6.5	15	—	8.4	—	5.9
ALT (U/L)	9-50	20	14	60↑	52↑	—	15	—	20
AST (U/L)	14-40	36	34	40	54↑	—	25	—	11↓
ALB (g/L)	40-55	39.3↓	34.2↓	39.6↓	32.4↓	—	33.4↓	—	33.0↓
ALP (U/L)	45-125	47	47	46	60	—	47	—	26↓
γ-GT (U/L)	10-60	17	19	29	87↑	—	15	—	33
CRE (μmol/L)	57-97	88.8	69.2	63	72.7	—	51.6	—	47
UA (μmol/L)	208-428	191↓	99↓	195↓	472↑	—	201	—	131↓
CK (U/L)	50-310	267	81	51	1081↑	—	46	—	32↓

LDH (U/L)	120-250	308↑	315↑	296↑	651↑	—	163	—	222
D-dimer (ug/mL)	0-1.5	0.37	—	—	0.43	—	—	—	1.55↑
PT (sec)	10.5-13.5	10.6	—	10.2↓	11.3	—	—	—	—
PTA (%)	0.8-1.2	129.7↑	—	117.4	95.5	—	—	—	—
FIB (g/L)	2-4	4.1↑	—	3.7	4.4↑	—	—	—	—

[a]IVIg was initiated on hospital day 7.

[b]IVIg was initiated on hospital day 2.

[c]IVIg was initiated on hospital day 6.

↓The value in the patient was below normal.

↑The value in the patient was above normal.

Abbreviation: WBC, white-cell count; RBC, red-cell count; Hb, hemoglobn; PLT, platelet count; NEUT#, absolute neutrophil count; LYM#, absolute lymphocyte count; ESR, erythrocyte sedimentation rate; hsCRP, hypersensitive C-reactive protein; Mb, myoglobin; hsTn, hypersensitive troponin; SF, serum ferritin; PCT, procalcitonin; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartase aminotransferase; ALB, albumin; ALP, alkaline phosphatase; γ-GT, γ -glutamyltransferase; CRE, creatinine; UA, urine acid; CK, creatinekinase; LDH, lactate dehydrogenase; PT, prothrombin time; PTA, prothrombin activity; FIB, fibrinogen.

Figure Legends

Figure 1 Chest CT scan of Patient 1(A), Patient 2(B) and Patient 3(C) before and following high-dose intravenous immunoglobulin (IVIg) with days of illness.