Intravenous immunoglobulin as a therapeutic option for patients with worsening COVID-19 under rituximab

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SUMMARY

Severe cases of the new COVID-19 are being reported in immunosuppressed patients. The risk seems to depend on the type of immunosuppressive agents used and it is particularly important in patients under the long-lasting effect of rituximab. Information regarding the best therapeutic approach to these patients is scarce and further studies are needed. We present a case of a young woman with rheumatoid arthritis treated with rituximab (last administration 4 months before her admission). She presented with a deteriorating and prolonged SARS-CoV-2 infection, with persistent fever, significant elevation of inflammatory markers and radiological progression. Glucocorticoids and antibiotic therapy were initiated, with no response. Intravenous immunoglobulin was then used with a rapid and exuberant response, anticipating a promising role of this therapy in immunosuppressed patients with COVID-19 under the effect of rituximab.

BACKGROUND

In March 2020, the new COVID-19 was declared a pandemic disease by the WHO.[1] It has spread all over the world and still no definite treatment has been identified, making its management a continuous challenge. Previous studies did not confirm that immunosuppressed patients, under biological disease-modifying antirheumatic drugs (bDMARDs) were at particularly higher risk of severe COVID-19;[2 3] however, that might not be the truth for all immunosuppressive agents, and we should consider the possibility of different risks depending on the type of biological agents used. In fact, rituximab (RTX) has been associated to unfavourable prognosis in patients with COVID-19 with frequent hospitalisations and a high mortality rate described in a Spanish cohort (61.5% and 23.1%, respectively).[4]

RTX is a chimeric murine/human monoclonal antibody targeting CD20, highly expressed on B cells.[5] It causes a rapid, profound and long-lasting (6–12 months) B-cell depletion as it compromises replenishment of mature plasma cells (with associated hypogammaglobulinemia in some patients), leading to a well-established risk of infectious events.[5 6] Additionally, RTX also seems to impact T-cells' function, namely disturbing crosstalk between B and T cells and their activation, as well as other immunomodulatory functions.[6] These effects are even more notorious in patients with prior exposure to other immunosuppressive drugs such as glucocorticoids.[5] RTX was approved in 2008 to treat rheumatoid arthritis (RA) and since then it is largely used to treat patients with moderate to severe disease that do not respond adequately to other treatments.[7]

The specific long-lasting effects of RTX raise concerns in the current COVID-19 pandemic scenario.[8] Neutralising antibody responses against SARS-CoV-2 include IgG and IgM antibodies, and those can be found in the serum of infected patients around day 14 of symptoms.[9 10] Administration of RTX might compromise priming of antibody responses, explaining adverse outcomes in patients with COVID-19; it may also cause impairment of immunological memory after SARS-CoV-2 infection or vaccination, raising the risk of (re) infection. However, interrupting RTX can lead to uncontrolled inflammatory disease and the need to increase or add immunosuppressive drugs, which can also have deleterious effects. Further studies are needed to enlighten on the best approach to these patients.

We present a case of COVID-19 in a patient under RTX with persistent fever, analytical and radiological deterioration, who has markedly improved after intravenous immunoglobulin (IVIg) administration.

CASE PRESENTATION

On 29 November 2020, she was diagnosed with COVID-19 (RT-PCR in nasopharyngeal swab) after attending the emergency department (ED) with complaints of fever, headache, myalgia, non-productive cough and chest pain in the previous 24 hours. Physical examination, chest radiograph and laboratory findings were unremarkable (normal haemogram and leucogram, 288 000 platelets $\times 10^9$/LμL and C reactive protein (CRP) 1.93 mg/dL) and she was discharged from hospital. Her mother and daughter, who both lived with her, were also diagnosed with COVID-19.

We report the case of a 43-year-old woman who has been treated with RTX for the last 6 years (in addition to prednisolone 5–10 mg daily), for a seropositive rheumatoid factor and anticyclic citrullinated peptide RA. She had done 12 courses of RTX (two 1 g intravenous infusions 2 weeks apart) by the time of our evaluation (last administration 4 months prior, in August 2020). She had taken other immunosuppressive drugs (methotrexate, sulfasalazine and hydroxychloroquine), which she did not tolerate. The choice of RTX as first bDMARD had

to do with the history of thyroid cancer 5 years before, in a seropositive RA patient. There were no major infectious events since the beginning of RTX, or the need to postpone cycles for clinical or analytical reasons. She tolerated and responded well to this maintenance therapy. Besides RA, other relevant comorbidities included postsurgical hypothyroidism (thyroid neoplasm), dyslipidaemia and depressive syndrome and she was taking pantoprazole, levothyroxine, fluoxetine and fenofibrate.

She returned to the ED on 14 December 2020 (15 days after) with persistent fever (three to four times a day, maximum axillary temperature of 40°C), headache, myalgia, cough and pleuritic chest pain, as well as asthenia and nausea. She denied shortness of breath, other gastrointestinal or urinary symptoms. She was admitted to the COVID-19 ward on 15 December 2020.

INVESTIGATIONS

On admission, blood pressure was 125/80 mm Hg, pulse 90 beats/min, oxygen saturation 96% (ambient air); both lungs were normal on auscultation, with the remainder of the physical examination unremarkable. She had interstitial and subpleural infiltrates with ground-glass opacities with moderate involvement on both chest radiograph and CT. Arterial blood gas test showed respiratory alkalemia with subtle hypoxemia (pH, 7.50; pCO_2, 30 mm Hg; pO_2, 74 mm Hg; HCO_3, 22.1 mmol/L; lactate, 1.3 mmol/L) and her analyses showed haemoglobin, 137 g/L; CRP, 3.08 mg/dL; 7400 leucocytes x10^9/L; 1060 lymphocytes (14%); negative D-dimers, 384 000 plateletsx10^9/L; creatinine, 0.72 mg/dL; normal transaminases and ferritin 900 ng/mL.

We assumed a case of SARS-CoV-2 pneumonia, in an immunosuppressed patient, admitted 15 days after the diagnosis and the beginning of symptoms. She started oxygen therapy (1 L/min, nasal cannula) and we increased prednisolone to 40 mg/day (equivalent to dexamethasone 6 mg id). Flow cytometry showed 1830 lymphocytes/μL, with 805 CD4 (44%) and no efficient B cells (CD19+); quantitative serum immunoglobulin test revealed low levels of IgG and IgM (IgG 452 mg/dL (600–1500)/IgM 37.8 mg/dL (50–300)) and COVID-19 serology test (IgG and IgM) was negative.

Despite treatment, the patient remained highly febrile, experiencing elevation of inflammatory markers (CRP 20.6 mg/dL; procalcitonin 0.11 ng/mL; erythrocyte sedimentation rate 70 mm/hour and maximum ferritin 1028 ng/mL) and radiological progression (figure 1). There weren't, however, any other analytical alterations worth mentioning (no cytopenia, normal triglycerides, no hepatic or renal alterations, normal coagulation tests). Although persistently symptomatic, no obvious clinical aggravation occurred and no additional oxygen therapy was needed. Also, no signs of cutaneous erythematosus rash, adenopathies or serositis, were ever evident. A broad-spectrum antibiotic (piperacillin–tazobactam) was initiated on day 20 (D20) of symptoms, but with no clinical, analytical or radiological response. Blood and urine cultures were all negative, as well as pneumococcal urinary antigen testing.

TREATMENT

On D25 of symptoms (D5 of antibiotic), considering the lack of response, and after discussion with rheumatology department, it was decided to initiate a 5-day course of human immunoglobulin (0.4 mg/kg/day—total dose of 2 g/kg) and adjust dexamethasone to 9 mg id. One day after the initiation of IVIg, the patient became afebrile, with no adverse effects observed. Throughout the next days, there was a remarkable clinical, analytical and radiographic recovery: oxygen supplementation was suspended, and the patient remained afebrile and asymptomatic. She was discharged on D32, 48 hours after finishing the 5 days course of IVIg.

OUTCOME AND FOLLOW-UP

The patient was evaluated in our outpatient clinic 2 and 6 weeks after discharge. She was afebrile and asymptomatic and had resumed her normal activities and work. Her laboratory results revealed no abnormal findings and a significant radiologic improvement was noticed (figure 1). She initiated and has been tolerating corticosteroid tapering. She had no measurable SARS-CoV-2 antibodies 6 weeks after discharge, confirming the anticipated impaired immunological response of seroconversion.

DISCUSSION

Despite cumulative experience and multiple pharmacologic therapies considered or used in patients with COVID-19,

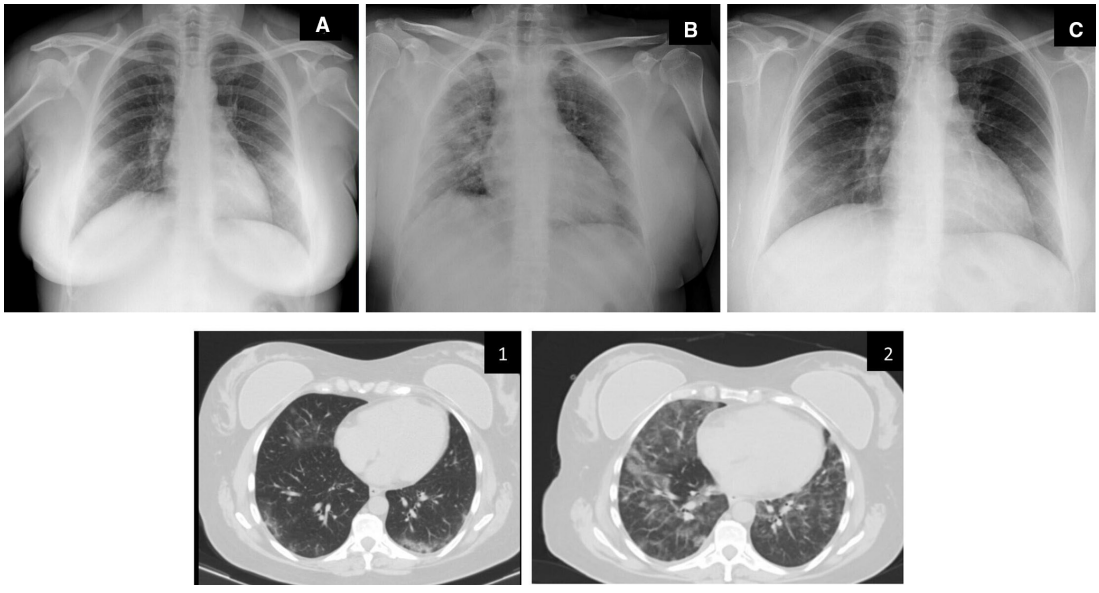

Figure 1 Patient's radiological evolution: (A) on admission; (B) day 25 of symptoms, before intravenous immunoglobulin treatment and (C) 2 weeks after discharge.

there is not a definite and consensual treatment, and constant updates are being made according to new and rapidly emerging literature.

IVIg is one of the treatments considered for COVID-19. It is a blood product obtained from healthy donors, containing polyclonal gamma immunoglobulin. Admitting that the population from which it is derived includes an increasing number of patients already exposed to SARS-CoV-2, there is a clear possibility that it also contains protective antibodies against it.[11 12] IVIg is already used as an immunomodulatory therapy in autoimmune and inflammatory diseases and for prophylaxis and treatment of severe infections in immunocompromised patients. It was also considered a therapeutic option in patients infected with previous SARS and Middle East respiratory syndrome, with favourable outcomes.[13 14] It seems reasonable to expect that IVIg can prevent the progression of the inflammatory cascade and improve passive immunity. In fact, previous case reports from China revealed a remarkable clinical and radiologic response after IVIg.[12] Also, a randomised placebo-controlled double-blind clinical trial from Gharebaghi *et al*[11] showed satisfactory results in severe COVID-19 (SpO_2 ≤96% on ≥4 L O_2, but not on mechanical ventilation), with improvement of clinical outcomes and reduced mortality in the IVIg group.

On immunocompromised patients under RTX, IVIg may particularly improve immune balance, preventing or fighting fatal or severe infections associated to B-cell depletion.[15] In fact, IVIg has been successfully used to treat or prevent infections in patients with autoimmune or lymphoproliferative diseases and RTX-induced hypogammaglobulinemia.[16 17]

Multiple autoimmune and rheumatic manifestations have been described in patients with COVID-19, such as cytokine storm or multisystem inflammatory syndromes, which have similarities to other life-threatening hyperinflammatory states such as haemophagocytic lymphohistiocytosis. These should be considered in a case like this, where such a deleterious infectious event occurred on top of an autoinflammatory disease. The use of IVIg has been reported to be beneficial in both situations.[18 19] Although considered, severe hyperinflammatory states just mentioned were not confirmed in this patient. As previously reported, in addition to the worsening of SARS-CoV-2 pneumonia and persistent high fever, with maintained elevation of inflammatory markers, no other organ dysfunction was noted and no substantial analytical evidence supporting them was found.

IVIg dose used was based on the already established practice for other diseases, and there were no reported adverse effects. However, it should be noted that the most severe effects (although rare) reported with IVIg include acute renal failure and thromboembolic events (TEs), and the population at most risk (advanced age, previous TE diseases or renal failure, diabetes mellitus, hypertension and dyslipidaemia) is virtually the same that is at risk to develop serious SARS-CoV-2 infection.[20] Nevertheless, IVIg is being perceived as a promising therapeutic option in patients with deteriorating COVID-19 considering its immunomodulatory role, and it can have a particular benefit on young and immunocompromised patients under the effect of RTX.

Patient's perspective

As soon as I knew I had COVID-19, I immediately became very anxious and worried. Considering I was immunosuppressed, I had done a lot of effort to prevent infection and felt miserable when I realised it had struck me. I had persistent fever, permanent discomfort and aggravating tiredness.
The second time I went to the emergency department (ED) I was really nervous because I feared hospitalisation. I was experiencing recurrent episodes of fever, headache, pain, cough and exhaustion. The doctors in the ED told me I needed hospitalisation since I was worsening, had persistent fever and needed supplemental oxygen therapy. Everyone in the hospital treated me incredibly well, which really helped me, especially considering I was in an isolation ward and could only talk to my friends and relatives on the phone. They explained the treatment that I was being given and they ran a lot of tests on me, but I was not improving despite their efforts … I felt miserable. After a while they told me they were going to try a different treatment, the IVIg. I was partially hopeful that it might work but I had never imagined the results would be so rapid. The day after I had started treatment I really felt better, had no fever and had a lot more energy, even my roommate noticed it! After a few days, the doctors told me my blood tests and radiograph were improving and I can't describe how happy I was when I found out that I was going to leave the hospital and return to my family. This was a really scary experience to me, but fortunately I recovered. I am finally with my family, returning to 'normal' life, feeling very grateful. I want to thank all the health professionals involved for their effort, work and kindness and my family, for all the support given.

Learning points

- Despite some contradictory data, COVID-19 can lead to serious disease in immunosuppressed patients. This seems to differ according to the type of immunosuppressive agents involved and, namely, rituximab (RTX) has been associated to severe COVID-19 disease.
- There isn't a definite and consensual COVID-19 treatment, and therapeutic recommendations are regularly updated and revised. We particularly emphasise the scarcity of robust information regarding treatment in immunosuppressed patients with COVID-19.
- We present a case of a patient with deteriorating COVID-19 under the effect of RTX, who experienced a rapid and notable improvement after IVIg treatment. Despite lacking strong evidence, IVIg might be a promising therapeutic choice in RTX-treated patients and its use considered in this population.

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REFERENCES

1 WHO.int. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Available: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-member-states-information-session-on-covid-19-11-march-2021
2 Monti S, Balduzzi S, Delvino P, *et al*. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. *Ann Rheum Dis* 2020;79:667–8.
3 Haberman R, Axelrad J, Chen A, *et al*. Covid-19 in Immune-Mediated Inflammatory Diseases - Case Series from New York. *N Engl J Med* 2020;383:85–8.
4 Loarce-Martos J, García-Fernández A, López-Gutiérrez F, *et al*. High rates of severe disease and death due to SARS-CoV-2 infection in rheumatic disease patients treated with rituximab: a descriptive study. *Rheumatol Int* 2020;40:2015–21.
5 Marco H, Smith RM, Jones RB, *et al*. The effect of rituximab therapy on immunoglobulin levels in patients with multisystem autoimmune disease. *BMC Musculoskelet Disord* 2014;15:178.
6 Tudesq J-J, Cartron G, Rivière S, *et al*. Clinical and microbiological characteristics of the infections in patients treated with rituximab for autoimmune and/or malignant hematological disorders. *Autoimmun Rev* 2018;17:115–24.
7 Pateinakis P, Pyrpasopoulou A. CD20+ B cell depletion in systemic autoimmune diseases: common mechanism of inhibition or disease-specific effect on humoral immunity? *Biomed Res Int* 2014;2014:1–5.
8 Mehta P, Porter JC, Chambers RC, *et al*. B-Cell depletion with rituximab in the COVID-19 pandemic: where do we stand? *Lancet Rheumatol* 2020;2:e589–90.
9 Kow CS, Hasan SS. Use of rituximab and the risk of adverse clinical outcomes in COVID-19 patients with systemic rheumatic disease. *Rheumatol Int* 2020;40:2117–8.
10 Zhao J, Yuan Q, Wang H, *et al*. Antibody responses to SARS-CoV-2 in patients with novel coronavirus disease 2019. *Clin Infect Dis* 2020;71:2027–34.
11 Gharebaghi N, Nejadrahim R, Mousavi SJ. The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial. *BMC Infect Dis* 2020;20.
12 Cao W, Liu X, Bai T, *et al*. High-Dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. *Open Forum Infect Dis* 2020;7:ofaa102.
13 Wang J-T, Sheng W-H, Fang C-T, *et al*. Clinical manifestations, laboratory findings, and treatment outcomes of SARS patients. *Emerg Infect Dis* 2004;10:818–24.
14 Arabi YM, Arifi AA, Balkhy HH, *et al*. Clinical course and outcomes of critically ill patients with middle East respiratory syndrome coronavirus infection. *Ann Intern Med* 2014;160:389-397–97.
15 Ahmed AR, Kaveri S. Reversing autoimmunity combination of rituximab and intravenous immunoglobulin. *Front Immunol* 2018;9:1189.
16 Roberts DM, Jones RB, Smith RM, *et al*. Immunoglobulin G replacement for the treatment of infective complications of rituximab-associated hypogammaglobulinemia in autoimmune disease: a case series. *J Autoimmun* 2015;57:24–9.
17 Casulo C, Maragulia J, Zelenetz AD. Incidence of hypogammaglobulinemia in patients receiving rituximab and the use of intravenous immunoglobulin for recurrent infections. *Clin Lymphoma Myeloma Leuk* 2013;13:106–11.
18 Tang K-T, Hsu B-C, Chen D-Y. Autoimmune and rheumatic manifestations associated with COVID-19 in adults: an updated systematic review. *Front Immunol* 2021;12.
19 Fernandez-Ruiz R, Paredes JL, Niewold TB. COVID-19 in patients with systemic lupus erythematosus: lessons learned from the inflammatory disease. *Transl Res* 2021;232:13–36.
20 Katz U, Achiron A, Sherer Y, *et al*. Safety of intravenous immunoglobulin (IVIg) therapy. *Autoimmun Rev* 2007;6:257–9.