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Case Presentation

Tocilizumab for Severe SARS-COV-2 Infection in Patients with Lymphoma

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Abstract

The pathogenesis of severe SARS-COV-2 infection is often based on the release of proinflammatory cytokines including Interleukin-6 (IL-6). Off-label use of tocilizumab, a humanized anti-human IL-6 receptor antibody, has been successful for the management of severe COVID-19 manifestations with rapid relief of respiratory symptoms, resolution of fever and reduction in CRP being the most relevant clinical manifestations of efficacy. Actually several guidelines available support the use of IL-6 receptor blockage following reports of successful outcomes in patients with severe SARS-COV-2 and elevated IL-6 serum levels. Early use of tocilizumab in patients with progressive respiratory failure might result in reduction in hospital stays and admissions to the intensive care units Reports on experience of tocilizumab in hematological patients are virtually absent in the literature. We hereby contribute to currently available experience. While awaiting the results of clinical trials we encourage this approach in such patients provided no contraindications exist.

Keywords: Tocilizumab; SARS-COV-2; Lymphoma

Abbreviations

IL-6: Interleukin-6; ICU: Intensive Care Unit

Background

Since the first outbreak of SARS-COV-2 infection in China the search of effective therapies against the virus has been a major challenge with lopinavir/ritonavir, remdesevir, hydroxychloroquine±azythromycin and convalescent plasma having failed to prove any strong influence in disease outcomes and mortality so far while awaiting the results of ongoing trials. Although most infected individuals (about 80%) exhibit a mild illness, 14% have serious and 5% have critical illness. Approximately 10% will require hospital admission due to COVID-19 pneumonia, of which approximately 10% will require Intensive Care Unit (ICU) care due to multiple organ dysfunction, including invasive ventilation due to acute respiratory distress syndrome [1]. The pathogenesis of such adverse clinical outcomes has been suggested to involve a cytokine release syndrome-like clinical picture comprising elevated IL-6 levels and this the rationale behind the possibility of therapeutically using tocilizumab, a humanized anti-human IL-6 receptor antibody of the IgG1 subclass [2].

Early administration of tocilizumab in cases with adverse clinical course (rapid clinical and/or radiological worsening) might have a quick anti-inflammatory effect avoiding progressive organ failure, coagulopathy, ICU admissions and potentially reducing mortality. Some promising favorable experience with tocilizumab in the severe SARS-COV-2 infection setting has been reported but no solid evidence to recommend routine use of this drug is available yet [3,4].

To date the only published experience of tocilizumab use in haematological patients has been successful administration in a multiple myeloma patient in China [5]. We report our single-centre experience with tocilizumab in 3 patients diagnosed with lymphoma who were admitted to hospital due to SARS-COV-2 pneumonia. Patient characteristics on admission can be found in (Table 1).

Case Presentation

Case 1 was a patient diagnosed with follicular lymphoma and has remained in Complete Remission (CR) after 6 cycles of bendamustine-rituximab and 2-year rituximab maintenance which he had ended up 13 months before admission. Four days after hospitalization he developed a high temperature and severe respiratory failure. No improvement was noticed with corticosteroid pulses. D-dimer, clotting screen and procalcitonin were normal at the time whereas ferritin (3200 ng/mL), CRP (159 mg/L), IL-6 (145 pg/mL) and LDH (268 U/L) levels were elevated. Two standard doses (8 mg/kg) of tocilizumab with a 12-hour interval were administered with rapid clinical and analytical (PCR 15 mg/L) improvement 48 hours later. He was discharged 11 days after admission.

Case 2 was in CR of mantle-cell lymphoma following 6 VRCAP courses and ongoing rituximab maintenance. Ten days after admission he developed progressive respiratory failure and new infiltrates in his chest X-ray unresponsive to corticosteroid pulses. Segmentary pulmonary embolism was also diagnosed and therapeutic-dose enoxaparin started with no change in respiratory status. Once IL-6 levels were found to be high (160 pg/pL) 2 standard tocilizumab doses were prescribed. At the time ferritin (4300 ng/mL), CRP (69 mg/L), LDH (459 U/L), D-dimer (2.5 pg/mL) and INR (1.5) were also found to be raised. Despite tocilizumab administration his respiratory failure continued to worsen and analytical parameters did not significantly change. He passed away 14 days after admission.

Case 3 was also a patient with mantle-cell lymphoma in CR following R-CHOP/R-DHAP (6 courses) and consolidation with autologous stem cell transplantation. He was on rituximab

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Table 1: Characteristics of the patients reported.

	Case 1	Case 2	Case 3
Age (years)	68	80	55
Sex	M	M	M
Type of lymphoma	Follicular	Mantle cell	Mantle cell
Time from diagnosis (months)	47	36	45
1st line/time from last course (months)	BR/42	VRCAP/29	RCHOP-RDHAP/40
Time on rituximab maintenance (months)	24	26	33
Last rituximab dose (months)	13	2	3
Disease status	CR	CR	CR
COVID-19 severity	Moderate	Severe	Severe
Lymphocyte count (x10^9/L)	0.67	0.28	0.47
Neutrophil count (x10^9/L)	5.4	5.8	3
TP ratio	1.1	1.01	1.16
TTPA ratio	1.3	1.13	1.17
D-dimer (n<0.5 mg/ml)	0.6	0.6	2.6
PCR (n <5 ng/mL)	147	38.2	300
Procalcitonin (n <0.5 ng/mL)	0.26	0.27	0.88
LDH (n 135-250 U/L)	376	280	671
Comorbidities	HT	None	DM, HT, CRF
IgG (n 700-1600 mg/dL)	1278	603	394
IgA (n 70-400 mg/dL)	125	38	41
IgM (n 40-230 mg/dL)	89	17	9
Oxygen saturation (%)	98	89	88
Pneumococcal/Legionella antigen urine	Neg/Neg	Neg/Neg	Neg/Neg
Intensive care unit	No	No	No
Treatment			
Hydroxychloroquine	Yes	Yes	Yes
Azytromycin	Yes	Yes	Yes
Corticosteroids	Yes	Yes	Yes
Ceftriaxone	Yes	Yes	Yes
Symptoms resolved/Death	Resolved	Death	Resolved
Days for resolution/Death	21	16	28

HT: Hypertension; DM: Diabetes Mellitus; CRF: Chronic Renal Failure; CR: Complete Remission.
All data provided were recorded on admission.

maintenance when he presented with SARS-COV-2 pneumonia. After 6 days in hospital he developed progressive respiratory failure, persistence of high fever and no improvement in his X-ray findings. IL-6 (243 pg/mL), ferritin (2350 ng/mL) and LDH (457 U/L) levels were found to be very elevated. He received 2 doses of tocilizumab with important clinical improvement within the next 2 days. Despite his comorbidities his clinical course was favorable and was discharged 17 days after admission.

Discussion/Conclusions

Since the arrival of COVID19 and the evidence of an involvement of a release of proinflammatory cytokines including Interleukins-6 (IL-6) during the clinical illness, especially in severe cases, there has been an interest in the potential benefits of this drug for the treatment of severe SARS-COV-2 infection. Preliminary data from short series of patients have been encouraging but any evidence behind these data is lacking. In the hematological setting tocilizumab has only been licensed for the treatment of the cytokine release syndrome following CAR-T cell therapy [6]. IDSA guidelines support the use of tocilizumab in the setting on ongoing clinical trials whereas Italian guidelines of SARS-COV-2 infection management find off-label use of this drug acceptable in severe cases especially if IL-6 levels are >40 pg [7,8]. Measurement of serum IL-6 levels is important for decision making but not for further monitoring of treatment effectiveness. Contraindications to the use of tocilizumab comprise abnormal liver function tests (transaminase level >5 fold the upper limit of normal), low neutrophil or platelet count (<0.5 and 50x10^9/L respectively), documented sepsis (high procalcitonine levels may be indicative), complicated diverticulitis/intestinal perforation, cutaneous infection and immunosuppressive anti-rejection therapy). There are FDA black box warnings of serious infections with tocilizumab which makes involved physicians be particularly cautious with patient selection before use is raised.

Our report show that actually tocilizumab therapy might be of clinical interest in patients with lymphoma and severe SARS-COV-2 infection. Development of early intervention strategies aimed to avoid progressive respiratory failure eventually leading to longer hospital stays and ICU admission (even invasive ventilation) is key in severe COVID19 management. Results of ongoing trials must be awaited before any conclusions can be drawn but in the meantime off-label use of well selected patients may be of benefit and should be encouraged.

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