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Ruxolitinib for Severe COVID-19-Related Hyperinflammation in Nonresponders to Steroids

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Abstract
Introduction: Currently, severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection is a major public health problem worldwide. Although most patients present a mild infection, effective strategies are required for patients who develop the severe disease. Anti-inflammatory treatment with JAK inhibitors has been considered in SARS-CoV-2. ***Methods:*** In this study, we presented our experience in a group of severe SARS-CoV-2 Chilean patients. This prospective study was performed on consecutive patients presenting severe respiratory failure owing to COVID-19 or high-risk clinical condition associated with SARS-CoV-2, and who were treated with ruxolitinib for management of associated inflammation. Overall, 18 patients presenting SARS-CoV-2 viral-induced hyperinflammation were treated with ruxolitinib, with 16 patients previously treated with steroids, 4 with tocilizumab, and 3 with both treatments. ***Results:*** Ten patients evolved with favorable response, including 7 patients admitted with severe respiratory failure (PaFi less than 200 mm Hg in high-flow nasal cannula), presenting complete regression of hyperinflammation, regression of the lung lesions, and subsequent discharge. In the remaining 8 patients, 25% showed reduced inflammation, but early discharge was not achieved owing to the slow evolution of respiratory failure. Unfortunately, 3 patients demonstrated a severe respiratory failure. The early initiation of ruxolitinib was found to be associated with better clinical evolution ($p < 0.005$). ***Conclusion:*** In this study, ruxolitinib resolved hyperinflammatory state in 55% of the patients, regardless of the previous steroid or tocilizumab therapy. Unfortunately, few patients demonstrated severe evolution despite ruxolitinib therapy. Notably, the treatment starting time appears to play an important role in achieving good outcomes. Further validation in randomized controlled trials is crucial.

Introduction

Currently, the COVID-19 pandemic has incurred a severe impact on human lives worldwide. Owing to the high death toll associated with this disease, establishing appropriate strategies to mitigate the deleterious effects of this

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infection remains a priority. The strategies being explored include prevention with vaccines, public health measures, and antiviral agents, as well as treatment of the viral-induced inflammation, which in many cases produces more damage than the virus itself. During early infection, the pathophysiology of severe acute respiratory syndrome coronavirus (SARS-CoV-2) promotes the increased secretion of cytokines, including interleukin (IL)-18, monocyte chemoattractant protein-1 (MCO1), interferon gamma-induced protein-10 (IP10), and macrophage inflammatory protein (MIP1a). During the second phase, lymphocytes, macrophages, and granulocytes are recruited and trigger the intense secretion of IL-15, interferon (IFN) a/IFNb, IL-12, and IL-21 necessary for the viral clearance, along with an excess of IL-6 which is a pivotal step in pathogenesis of severe infections. This allows for an intense elevation of cytokines including tumor necrosis factor (TNF), IL-17a, granulocyte macrophage-colony-stimulating factor (GM-CSF), and granulocyte colony-stimulating factor, consequently resulting in a state of systemic and pulmonary hyperinflammation [1, 2]. With the massive release of cytokines (cytokine storm), critically ill patients present an elevated levels of macrophage activation markers, including high levels of ferritin and sCD25 (IL-2RA). If this situation remains persistent and progressive, it leads to respiratory distress and multiple organ failure. Lymphocyte activation occurs via different pathways, which can be inhibited through pharmacological treatment. In recent years, it has been reported that the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway plays a key role in various conditions presenting excessive inflammation, including graft-versus-host disease (GVHD), rheumatoid arthritis, ulcerative colitis, psoriasis, and hemophagocytic syndrome [3, 4]. Ruxolitinib is an oral JAK1/JAK2 inhibitor, approved by the Food and Drug Administration for myeloproliferative neoplasm and GVHD. In vitro, it decreases the secretion of IL-6, IL-13, MCP-1, and TNF-α [5]. The inhibition of the JAK/STAT pathway could rapidly arrest the activation and recruitment of inflammatory lymphocytes, without inducing severe immunosuppression. Reportedly, steroid-refractory acute GVHD has shown excellent results following ruxolitinib therapy, with a good safety profile [3]. Furthermore, this effect has been observed in the following treatment with chimeric antigen receptor T-cell therapy, where the use of ruxolitinib prevents the cytokine release syndrome, without reducing the effectiveness of the cell therapy [6]. Recently, JAK 2 inhibitors have been used in SARS-CoV-2 COVID-19 hyperinflammatory state with encouraging results [7, 8]. Furthermore, it has been recently described that there are genetic hallmarks that would allow severe SARS-CoV-2, such as the overexpression of TYK2, which is a substrate for the JAK2-STAT [9]. Therefore, a drug inhibitory of this pathway is very attractive. In this study, we reported our experience in treating 18 consecutive patients with ruxolitinib on a compassionate basis. The rationale of this treatment is to seek a prompt reduction in the hyperinflammation state, to achieve clinical improvement while avoiding intensive care unit (ICU) admission for major respiratory failure.

Methods

This study is a single-arm nonrandomized analysis of a cohort of patients treated with ruxolitinib in our institution. For all the patients with COVID-19 treated with ruxolitinib, clinical, radiological, and laboratory findings were prospectively recorded since April 2020. Additionally, we collected the demographic data and recorded the time evolution of ferritin, D-dimer, C-reactive protein, and lactate dehydrogenase (LDH), as well as absolute counts of neutrophils and platelets, hemoglobin levels, radiological tests, and arterial blood gases. To determine the improvements in the hyperinflammation state, we established the following parameters: a reduction of >50% of baseline altered levels of ferritin, LDH, D-dimer, and C-reactive protein, complete resolution of the clinical hyperinflammation status, recovery of respiratory failure, improvements in radiological findings, time to ruxolitinib start since diagnosis of SARS-CoV-2 infection, length of hospital stay, and improvement/discharge from hospitalization.

Patients

Between April and June of 2020, Chile, as well as our hospital, experienced a maximal and historical number of patients hospitalized owing to severe COVID-19. The compassionate use of ruxolitinib was initiated in patients presenting treatment failure, or progression to other treatments in our institutional protocol at that time, including steroids (methylprednisolone or dexamethasone), and tocilizumab, as well as hydroxychloroquine and lopinavir/ritonavir during the early phase of the pandemic. For ruxolitinib therapy, we excluded patients on mechanical ventilation or participating in other investigational interventions like randomized controlled trials (i.e., convalescent plasma). In total, 18 consecutively hospitalized patients in basic or intermediate care units were treated with ruxolitinib. Inclusion criteria were as follows: (1) aged 18 or older; (2) SARS-CoV-2 active infection confirmed by reverse transcription-polymerase chain reaction; and (3) diagnosis of viral pneumonia according to the WHO criteria [7].

Intervention

Ruxolitinib was administered as a 15-day regimen, consisting of 10 mg BID for 7 days, followed by 5 mg BID for 6 days, and finally, 5 mg each day for 2 days, similar to doses recommended for this condition [10]. Despite the short duration of treatment, we used a tapering schedule to avoid the theoretical risk of withdrawal syndrome and cytokine storm, as described with the abrupt discon-

Table 1. Demographic and clinical characteristics of patients at baseline

Age, years median (range)	60 (29–80)
Gender	Male, *n* = 15; female, *n* = 3
Blood group type	A, *n* = 6 B, *n* = 3 AB, *n* = 2 O, *n* = 4 Not available, *n* = 3
Preexisting conditions	Arterial hypertension, *n* = 6 Diabetes mellitus, *n* = 8 Asthma, *n* = 2 Acute lymphoblastic leukemia, *n* = 2 Hodgkin lymphoma, *n* = 1 Multiple myeloma, *n* = 2 Hairy cell leukemia, *n* = 1 Obesity, *n* = 10 Cirrhosis, *n* = 1
Median SpO_2/FiO_2, mm Hg at admission (range)	240 (80–300)
Median media blood pressure, mm Hg at admission (range)	62 (45–90)
Median leukocytes count, cells/μL at admission (range)	8 (3.4–38)
Median neutrophils count, cells/μL at admission (range)	6 (2.3–39)
Median platelets count, cells × 10^3/μL at admission (range)	184 (22–285)
Median lymphocytes count, cells/μL at admission (range)	0.63 (0.5-1-3)
Median D-dimer, U/L at admission (range)	1,089 (800–1,600)
Median C-reactive protein, mg/dL at admission (range)	13 (3–30)
Median ferritin, ng/mL at admission (range)	2,557 (450–13,000)
Median IL-6, pg/mL at admission (range)	122 (17–390)
Time from admission to ruxolitinib start in days (range)	14 (6–28)
Previous treatment	Corticoids, *n* = 16 Tocilizumab, *n* = 4 Hydroxychloroquine, *n* = 1 Antibiotics, *n* = 14 Ritonavir/lopinavir, *n* = 1

tinuation of ruxolitinib [10, 11]. In the event of thrombocytopenia with <100,000 cells/μL, the dosage was reduced by 50%, and if <50,000 cells/μL, treatment was discontinued and transfusion support was initiated to maintain counts greater than the observed value. If the presence of neutropenia <1,000 cells/μL, the dosage was adjusted to 50%, and if neutropenia presented <500 cells/μL, the drug was discontinued, with no granulocyte colony-stimulating factor therapy owing to the theoretical risk of worsening the cytokine storm. No dose adjustment was performed in patients with liver dysfunction. In patients with acute renal failure presenting a creatinine clearance <30 mL/min, the dose was reduced to 25% per day, every other day. Although there is evidence that supports the administration of ruxolitinib by nasogastric or enteral tube, this route of administration was not used in severely ill patients.

Statistical Analysis

Demographic and baseline characteristics are presented as median and ranges. A comparison between the clinical and laboratory characteristics was performed using GraphPad Prism V 7.01 (GraphPad Software, La Jolla, CA, USA). Statistical analysis of laboratory values was performed using Friedman, and Kruskal-Wallis tests for parametric and nonparametric data. For clinical outcomes such as resolution of inflammation, stay and use of mechanical ventilation analysis were performed and an N1 proportion test appropriate for the samples of reduced size. For the analysis, the early initiation of ruxolitinib was established in the first 7 days from the first positive SARS-CoV-2 test. Differences with $p < 0.005$ were considered statistically significant.

Table 2. Changes of inflammation parameters pre- and post-ruxolitinib

	At admission	At ruxo start	+8	+15
D-dimer median/range, normal value 0–500 U/L	1,089 (460–1,940)	3,291 (843–17,712)	2,660 (438–3,586)	1,649 (299–3,082)
C-reactive protein median/range, normal value 0–5 mg/dL	12 (3–45)	11 (2–31)	5 (0.6–25)	2.2 (0.13–10.2)
Ferritin median/range, normal value 20–200 ng/mL	2,557 (382–13,000)	3,456 (481–13,000)	2,471 (800–2338)	1,228 (757–4,352)
IL-6 median/range, normal value 0–16 pg/mL	190 (17–390)	330 (90–2343)	393 (14–1,890)	93 (15–181)
LDH median/range, normal value 160–224 U/L	393 (78–1,400)	479 (192–1,560)	331 (179–456)	322 (195–487)

LDH, lactate dehydrogenase; IL, interleukin.

Table 3. Effect of clinical variables on improvements after ruxolitinib treatment

	Complete resolution group (n = 10)	Slow or no improvement group		p value
		late responders (partial remission of respiratory dysfunction group) (n = 5)	progression to catastrophic respiratory failure group (n = 3)	
Age, n (%)				
<40 years	40	0	0	0.003
41–59 years	40	0	0	
>60 years	20	100	100	
Gender, n (%)				
Male	80	60	70	0.004
Female	20	40	30	
HFNC/IMV at diagnosis, n (%)	66	100	40	0.02
Regression of pulmonary infiltrates, n (%)	100	0	66	0.0002
Early start of ruxolitinib, n (%)	100	20	33	0.006
SARS-CoV-2 nasal-oropharyngeal swab negativization, n (%)	100	88	60	0.007

HFNC, high-flow nasal cannula; IMV, invasive mechanical ventilation; SARS-CoV-2, severe acute respiratory syndrome coronavirus. Regression of pulmonary infiltrates: normalization of chest X-ray or CT scan.

Results

Clinical Characteristics of Patients

The baseline characteristics of patients are summarized in Table 1. In this cohort, 80% of patients were male. The median age was 60 years and all the patients, except 2, presented preexisting conditions such as obesity, arterial hypertension, cirrhosis, and malignancy. As expected, all admitted patients presented elevated levels of ferritin, D-dimer, and C-reactive protein.

Ruxolitinib Effect on Hyperinflammatory State

In the present study, 89% of patients treated with ruxolitinib demonstrated a significant reduction in all inflammation markers that were elevated at the diagnosis of the viral disease, including C-reactive protein, LDH, ferritin, and D-dimer ($p < 0.001$) as shown in Table 2. IL-6 was available for follow-up analysis in 10 patients and a persistent reduction was observed after starting ruxolitinib treatment. There were 2 individuals who afterward showed a new inflammation stress due to post viral-bacterial pneumonia. Improvement in inflammation was not associated with sustained clinical improvement in all the patients, as 40% of the patients presented a torpid evolution in terms of lung deterioration despite adequate control of inflammation. Clinical evolution of the cohort allowed the recognition of 3 groups of patients: rapid responders with complete resolution of the hyperinflammatory state (n = 10), late responders with partial remission of respiratory dysfunction (n = 5), and patients with progression to catastrophic respiratory failure and/or restrictive organized pneumonia (n = 3). Based on these findings, a multivariate analysis was performed and ruxolitinib use, younger age, and regression of in-

Table 4. Imagenologic and ventilatory patterns

	Imagenological changes		Evolution of artificial ventilatory	
	CT or chest X-ray at diagnosis	CT or chest X-ray at 8 weeks follow-up	ventilatory support at dx	ventilatory state at 8 weeks follow-up
Complete response group (n = 10)	Diffuse pattern of COVID 70% lobar viral pneumonia 30%	100% resolution	HFNC 70% facial mask FiO_2 0.3 30%	Normal respiratory function 100%
Late responders (partial remission of respiratory dysfunction group) (n = 5)	Diffuse pattern of COVID 100%	Deterioration and progression 60% stability 20% mild improvement 20%	HFNC 60% IMV 40%	Prolonged ICU stay with IMV 40% Use of domiciliary O_2 40% Hospitalized with FiO_2 0.4 20%
Progression to catastrophic respiratory failure group (n = 3)	Diffuse pattern of COVID 100%	100% organized pneumonia with fibrotic bands	IMV 100%	100% deceased

HFNC, high-flow nasal cannula; IMV, invasive mechanical ventilation; ICU, intensive care unit.

flammation were associated with improvements in the clinical condition and possibility of discharge, whereas advanced age, incomplete resolution, gender, and prolonged hospital stay were associated with the inferior clinical evolution (Table 3).

Toxicity

Treatment with ruxolitinib was well tolerated. In total, 14 (77%) patients completed the schedule without adverse reactions. In 2 patients (1 with cirrhosis and other with central venous catheter infection/sepsis), ruxolitinib was suspended owing to severe thrombocytopenia. No other hematological alterations were detected. Ruxolitinib is not associated with delayed viral clearance as shown in Table 2.

Respiratory Function and Image Evolution

At diagnosis, most patients presented diffuse bilateral lung involvement owing to SARS-CoV-2 pneumonia; after ruxolitinib treatment, 56% evolved into complete radiologic resolution. At the start of ruxolitinib therapy, 10 of the 18 patients were receiving high-flow nasal cannula oxygen, and 28% of the entire group required further support with invasive mechanical ventilation, among which 60% died (Table 4).

Overall Response and Mortality

In this study, 10 patients (55%) demonstrated the complete resolution of all the manifestations of viral-induced inflammation and pulmonary disease. Of these patients, 3 started and maintained ruxolitinib therapy without ventilatory support, and 7 started ruxolitinib during the severe respiratory failure (6 were treated under vigilant pronation with high-flow nasal cannula and 1 was treated under invasive mechanical ventilation) and achieved complete disease regression; these 10 patients were then discharged. Of the remaining patients, 5 evolved with a complete response to hyperinflammation but developed organized pneumonia with extremely restrictive lung dysfunction and required prolonged hospitalization.

In this cohort, 3 patients demonstrated a sudden progression to severe respiratory failure and severe acute respiratory distress syndrome, necessitating the mechanical invasive ventilation. In 2 of these patients, deterioration occurred within the first 24 h after initiating ruxolitinib, and on transfer to the ICU, the oral route and medication were both interrupted. The third patient completed the ruxolitinib regimen; however, regression of the severe lung involvement was not observed. Therefore, the mortality rate in this cohort at 4 months of follow-up was 15% (n = 3). 40% of the patients had hematological diseases (multiple myeloma n = 3, acute lymphoblastic leukemia n = 2, Hodgkin disease n = 1, Hairy cell leukemia b = 1). In this group, mortality was 28%, in 1 patient with multiple myeloma and 1 patient with Hodgkin's disease. However, these patients who had a catastrophic evolution received no >2 days of ruxolitinib treatment.

Discussion

The inhibition of the JAK/STAT pathway with ruxolitinib could be beneficial in patients presenting severe SARS-CoV-2 infection and a hyperinflammatory state, with a low potential for serious adverse effects, based on

low doses and the short treatment duration [11, 12]. In this study, we analyzed the effect of ruxolitinib in our population and observed encouraging results despite the previous use of steroids or tocilizumab. Ruxolitinib therapy enabled the discharge of 50% of our patients presenting severe disease, with regression of the hyperinflammatory state, pulmonary dysfunction, and pulmonary infiltrates. Notably, this effect was mainly observed in patients who were promptly treated with ruxolitinib. In our study, we observed good tolerance to the investigated medication, with mild adverse reactions. Although a marginal increase in reactivation of the viruses of the Herpesviridae family and Hepatitis B has been reported with ruxolitinib therapy [10], we observed no virus reactivation. In the context of the COVID-19 pandemic, a recent randomized controlled trial conducted by Cao et al. [13] has shown that in patients with "severe COVID-19" (defined as having hypoxemia in room air or respiratory rate >30 breaths/min), treatment with 5 mg of ruxolitinib BID (20 patients) demonstrated a significant early improvement in the computed tomography lung scan versus placebo, and reduced the risk of intubation and death (not significant). Furthermore, in a case series presenting 14 patients with SARS-CoV-2 and hyperinflammation treated with ruxolitinib, multiorgan failure was reportedly reduced, with mild adverse effects [14]. Moreover, recently published case reports in hematological patients have revealed excellent responses to ruxolitinib in terms of viral infection control [15, 16]. This aspect must be considered when selecting treatment against COVID, as in cases with concomitant hematological diseases, with increased activity of the JAK/STAT pathway, the benefit of therapy with selective inhibitors would allow adequate control of the viral infection, as well as therapeutic efficacy without worsening the underlying disease. Recently, Capochiani et al. [17] in a case series of 18 critically ill patients with COVID-19 and acute respiratory distress syndrome, reported that ruxolitinib treatment resulted in global improvement in 89% of patients and complete resolution in 60%. One possible explanation for the differences with our results is that patients in our analysis had worse baseline risk conditions such as cancer (40 vs. 5%) or metabolic disease [17].

Unfortunately, in our cohort, a group of patients progressed to severe respiratory failure despite several treatment strategies. This alarming situation has been consistently reported by various authors. In a multicentric randomized study in the United Kingdom [18], the RECOVERY Collaborative Group randomly allocated 2,104 patients to receive dexamethasone and compared these patients with 4,321 patients treated with usual care; their findings reported significant improvement in overall survival, but proportional and absolute mortality rate reductions varied significantly depending on the level of respiratory support at randomization. Reportedly, dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation ($p < 0.001$) and by one-fifth in patients receiving oxygen without invasive mechanical ventilation ($p = 0.002$) but did not reduce mortality in patients not receiving respiratory support at randomization ($p = 0.14$). Therefore, in absolute counts, the RECOVERY Collaborative Group reported that 454 patients allocated in dexamethasone and 1,065 in the best support group died, which reveals the magnitude of the lethality of the viral infection. The catastrophic evolution of patients with prolonged respiratory failure is a major unresolved challenge. These patients demand longer ICU stays and with the potential to develop organizing pneumonia, lung fibrosis, disability, and the risk of death [19]. Certainly, the fact that not all patients develop this serious complication demonstrates that there exists a certain individual predisposition [20]. In this regard, patients with genomic alterations have demonstrated deficits in interleukin immune function [21].

There are several limitations in our study that include the small size of sample, the nonrandomized intervention, and the compassionate basis of our protocol. It is well known that randomized clinical trials are the cornerstone of clinical data, but prospective and real-world data remain valuable. The possibility of treating patients outside the strict limits of the randomized clinical trials allows the treatment of more heterogenous populations or those with comorbidities usually excluded from the randomized clinical trials.

In conclusion, in this cohort, ruxolitinib therapy enabled both the resolution of hyperinflammation and discharge without sequelae in 55% of patients with severe COVID-19 infections, regardless of previous utilization of steroids and/or tocilizumab. Unfortunately, a small group of patients evolved to severe respiratory failure, despite the management of inflammation and critical care support. Undoubtedly, better therapies are needed to treat this subgroup of patients. Ongoing clinical trials will present the complete landscape of immunomodulation in severe SARS-CoV-2 infection. Indeed, the RECOVERY initiative has included baricitinib, another JAK inhibitor as a possible treatment for COVID-19 refractory to corticoid therapy [22]. Like other interventions in SARS-CoV-2 severe infection, maybe the early use of ruxolitinib could prove to be helpful and deserves further investigation.

Statement of Ethics

All patients provided signed informed consent for ruxolitinib use and publication of relevant clinical data with the protection of identity. Clinical informed consent was regulated by the Ethical Board of Hospital Clínico de la Pontificia Universidad Católica de Chile with number IB 6723 100/1-ARI. This work acts in accordance with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Due to the descriptive methods and cohort analysis of the compassionate use of ruxolitinib, the Institutional Review Board approved it and received the Ethics Committee clearance.

Conflict of Interest Statement

There are no conflicts of interest.

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Author Contributions

P.R. and M.S. conceived and designed the study; N.T., J.C., M.O., M.J.G., P.B., and J.P. enrolled patients and contributed to the data; P.R., J.J., and M.S. interpreted the data and wrote the manuscript; all the authors reviewed the manuscript and approved the final version.

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