

Coronavirus Pandemic

Ruxolitinib as a treatment strategy for SARS-CoV-2 pneumonia: clinical experience in a real-world setting

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Abstract

Introduction: Severe acute respiratory syndrome-related coronavirus (SARS-CoV-2) infection is characterised by a viral phase and a severe pro-inflammatory phase. The inhibition of the JAK/STAT pathway limits the pro-inflammatory state in moderate to severe COVID-19.

Methodology: We analysed the data obtained by an observational cohort of patients with SARS-CoV-2 pneumonia treated with ruxolitinib in 22 hospitals of Mexico. The applied dose was determined based on physician's criteria. The benefit of ruxolitinib was evaluated using the 8-points ordinal scale developed by the NIH in the ACTT1 trial. Duration of hospital stay, changes in pro-inflammatory laboratory values, mortality, and toxicity were also measured.

Results: A total of 287 patients were reported at 22 sites in Mexico from March to June 2020; 80.8% received ruxolitinib 5 mg BID and 19.16% received ruxolitinib 10 mg BID plus standard of care. At beginning of treatment, 223 patients were on oxygen support and 59 on invasive

ventilation. The percentage of patients on invasive ventilation was 53% in the 10 mg and 13% in the 5 mg cohort. A statistically significant improvement measured as a reduction by 2 points on the 8-point ordinal scale was described (baseline 5.39 ± 0.93 , final 3.67 ± 2.98 , $p = 0.0001$). There were 74 deaths. Serious adverse events were presented in 6.9% of the patients.

Conclusions: Ruxolitinib appears to be safe in COVID-19 patients, with clinical benefits observed in terms of decrease in the 8-point ordinal scale and pro-inflammatory state. Further studies must be done to ensure efficacy against mortality.

Key words: COVID-19; pneumonia; ruxolitinib; JAK/STAT inhibitors.

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Introduction

At the end of 2019, multiple cases of severe pneumonia characterized by cough, dyspnoea, and lung damage with an unknown aetiology were reported in Wuhan, China. This disease, named as coronavirus disease-19 (COVID-19), was declared a pandemic in March 2020 by the World Health Organization and the causative agent was identified to be a novel coronavirus, severe acute respiratory syndrome-related coronavirus (SARS-CoV-2) [1]. As of January 2021, a total of 93,956,883 cases and 2,029,084 deaths were reported globally [2]. During the same month, in Mexico, the Department of Health reported a total of 1,839,876 confirmed COVID-19 cases and 160,151 deaths [2,3].

SARS-CoV-2 enters the body and adheres to the alveolar epithelium. Consequently, there is an activation of innate and adaptive immune responses through the activation of CD4+ and CD8+ T lymphocytes. CD4+ T cells induce early innate inflammatory response in the tissue, contributing to the control of virus by increasing the synthesis and release of various cytokines. From what is known so far of COVID-19 infection is that in moderate to severe cases, the infection evolves into a severe pro-inflammatory state with subsequently tissue injury. The cytokine storm observed in COVID-19 is characterised by high levels of IL-2, IL-6, IL-7, IL-10, granulocyte colony-stimulating factor, 10 kDa interferon-gamma-induced protein (IP-10), monocyte chemo-attractant protein-1 (MCP-1), macrophage inflammatory protein 1 α (MIP-1 α), and tumour necrosis factor (TNF). Based on these characteristics, different phases of COVID-19 infection have been described—the first or early phase called the ‘viral response’, transitions through a ‘pulmonary phase’ with increase in severity and inflammation, to a ‘hyper-inflammation phase’ [4,5].

While there is no standard treatment for COVID-19, immunomodulators, cytokine inhibitors, antivirals,

antibiotics, and mechanical measures are being employed for treatment in several hospitals. IL-6 and TNF- α evince special interest because they are two of the multiple cytokines related to the Janus kinase/Signal Transducer and Transcription Activator (JAK/STAT) activation pathway, specifically JAK 1 and JAK 2, and are indirect activators of this signalling and transcription pathway [6,7]. Early initiation of immunomodulators and immunosuppression is recommended in the pulmonary phase, when inflammation begins in the host [8]. With this understanding, the present therapies proposed for COVID-19 target the cytokine pathways; these include treatments with anti-IL-6 and anti-TNF agents, and with agents that inhibit the JAK-STAT pathway [9].

Ruxolitinib is a janus kinase (JAK) inhibitor, with selectivity for subtypes JAK1 and JAK2. It blocks the activation and nuclear translocation of STAT and inhibits the synthesis and release of IL-6, which as mentioned above, is highly related with the pathophysiology of severe cases of COVID-19 [7,8]. The anti-inflammatory effects of ruxolitinib, have been evidenced in multiple clinical studies on myeloproliferative neoplasms, haemophagocytosis, and graft-versus-host disease. This drug decreases the plasma levels of pro-inflammatory cytokines, including IFN- α , IL-6, IL-8, IL-16, and IL-18, as well as C-reactive protein [11].

The first experience with the use of ruxolitinib in patients with COVID-19 came from an Italian group that reported favourable results in a small group of patients with moderate disease [12]. In Mexico, a favourable response to ruxolitinib was reported for a small group of patients relative to that in a control group [13]. Herein, we report the results obtained in patients with COVID-19 pneumonia administered ruxolitinib as an off-label and compassionate exemption treatment at multiple medical centres in Mexico.

Methodology

Study design and treatment

The data obtained from a cohort of patients with SARS-CoV-2 pneumonia treated with ruxolitinib in 22 hospitals of Mexico was analysed. Ruxolitinib (Jakavi®, Novartis Farmacéutica S.A. de C.V., México) was administered to most patients under a Novartis' compassionate use program, the remaining patients received it as an off-label treatment. The patients were considered by their treating physicians with moderate to severe pneumonia given the need of oxygen supplementation or hospital admission. These patients were invited to participate in a prospective observational registry. Patients included were ≥ 18 years, had a positive real-time polymerase chain reaction test for SARS-CoV-2, and radiological evidence of pneumonia by chest x-ray or CT-scan. Informed consent was obtained for all patients in accordance with local regulations and the registry was approved by the Hospital Angeles Lomas's Ethics Committee.

Ruxolitinib was administered at a dose of 5 mg twice a day or 10 mg twice a day as determined by investigator's criteria at each site. Supportive treatment

was given at the discretion of the clinician depending on the hospital's standard of care for COVID-19.

Novartis was neither involved in the collection, analysis of the data nor in the decision to submit the manuscript.

Procedures

Laboratory and clinical data were collected at baseline, days 5, 10, and 15 of treatment and/or on the last date of follow-up. Patients were categorized according to the 8-point ordinal scale as follows: 1) Not hospitalised, without limitation on activities; 2) Not hospitalised, with limitation on activities and/or requiring home oxygen; 3) Hospitalised, not requiring supplemental oxygen and without on-going medical care; 4) Hospitalised, not requiring supplemental oxygen, with on-going medical care; 5) Hospitalised, requiring supplemental oxygen; 6) Hospitalised, on non-invasive ventilation using high-flow oxygen devices; 7) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation; 8) dead. This scale was developed by the National Institutes of Health for the Adaptive COVID-19 Treatment Trial (clinicaltrials.gov NCT04280705).

Statistics

Patient registration was done in Office Excel® spreadsheets. The statistical analysis was conducted with the IBM SPSS Statistics version 26. Kolmorov–Smirnov and Shapiro–Wilk tests were performed to define data distribution. The descriptive analysis was carried out with measures of central tendency using mean \pm standard deviation values and interquartile data. The Mann–Whitney U test was performed for non-parametric values and Pearson's chi-squared test was done for categorical data. *p* values ≤ 0.05 were considered statistically significant.

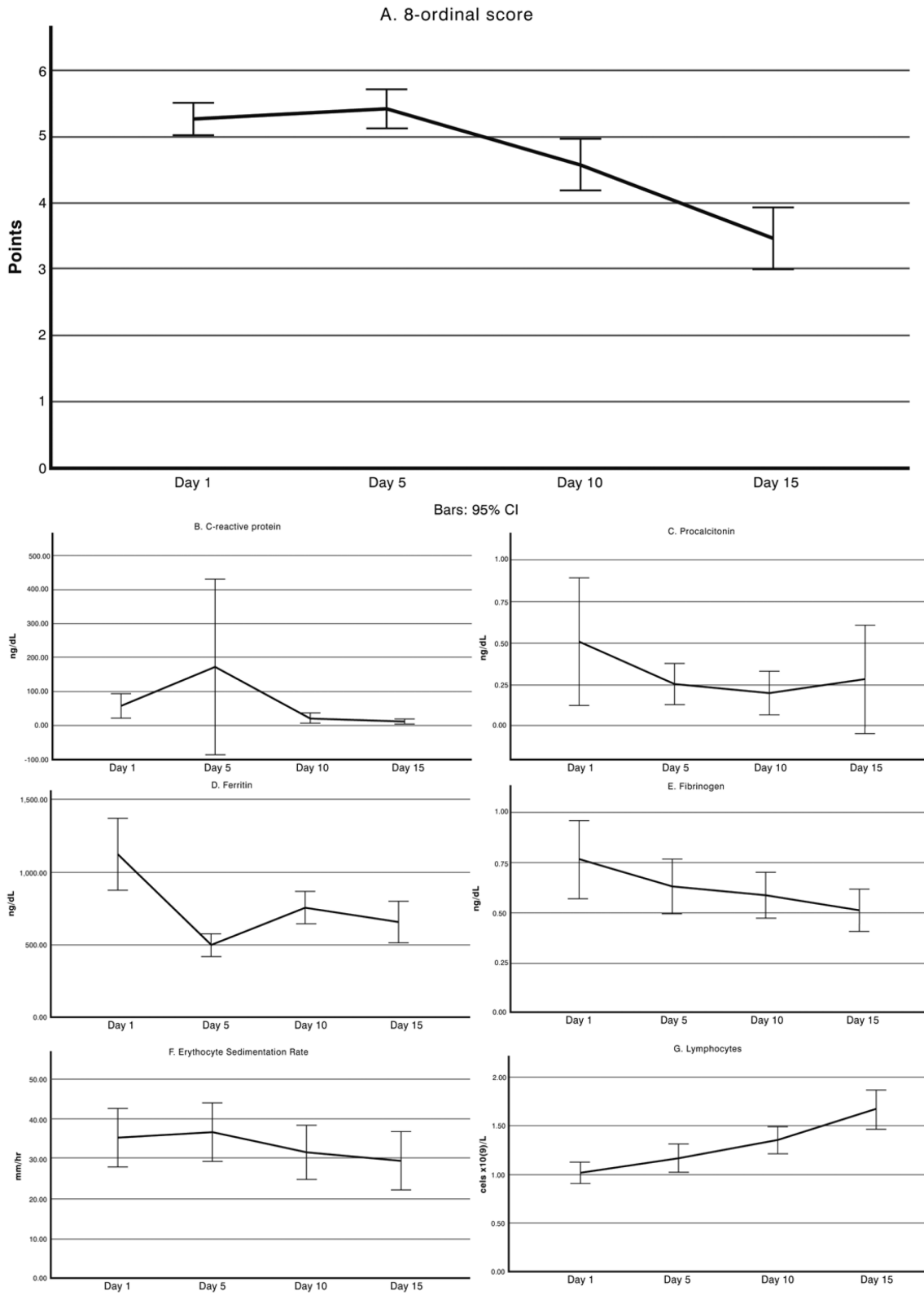
Results

From March 2020 to June 2020, 287 patients at 22 sites in 13 cities of Mexico fulfilled the inclusion criteria (102 (35.5%) women and 185 (64.5%) men, with an average age of 54 ± 14 years). Among these, 232 (80.8%) patients received at least one dose twice daily of 5 mg oral ruxolitinib and 55 (19.16%) patients received 10 mg oral ruxolitinib. The comorbidities observed were hypertension in 36%, diabetes in 30%, pneumopathy in 4.5%, cardiopathy in 3.1%, and arrhythmias in 2.1% patients. Obesity was reported in 41% patients. The values for the remaining parameters are shown in Table 1 and Supplementary Table 1.

Table 1. Baseline characteristics of patients treated with ruxolitinib.

Characteristics	All Patients (N = 287)
Age – mean (IQR)	54 \pm 14
Sex – n (%)	
Male	185 (64.5)
Female	102 (35.5)
Comorbidities – n (%)	
Obesity – BMI ≥ 30	118 (41)
Hypertension	104 (36)
Type 2 Diabetes	87 (30)
Chronic pneumopathy	13 (4.5)
Chronic cardiopathy	9 (3.1)
Invasive Mechanical Ventilation	59 (20.6)
Vasopressor use	26(9.1)
Body Mass Index – n	30 \pm 6
Charlson Comorbidity Index – mean (range)	0 (0-7)
Laboratory Values	
Hemoglobin - g/dL	13 \pm 0.75
Leucocytes – cells $\times 10^9/L$	11.5 \pm 4.8
Lymphocytes - cells $\times 10^9/L$	1.1 \pm 0.32
Neutrophils - cells $\times 10^9/L$	8 \pm 1.5
Platelets - cells $\times 10^9/L$	337 \pm 39
Glucose - mg/dL	133 \pm 22
Creatinine – mg/dL	1.14 \pm 3.95
Albumin - mg/dL	2.9 \pm 0.34
Erythrocyte sedimentation rate - mm/hr	31 \pm 6
C-reactive protein - mg/dL	44.84 \pm 80.11
Procalcitonin - ng/mL	1.27 \pm 3.95
Lactate Dehydrogenase - UI/L	395 \pm 132
Ferritin - ng/dL	939 \pm 278
Fibrinogen - mg/dL	486 \pm 120
D-dimer - ng/mL	2593.76 \pm 4762.75

Figure 1. Clinical and laboratory evolution at baseline and days 5, 10 and 15.

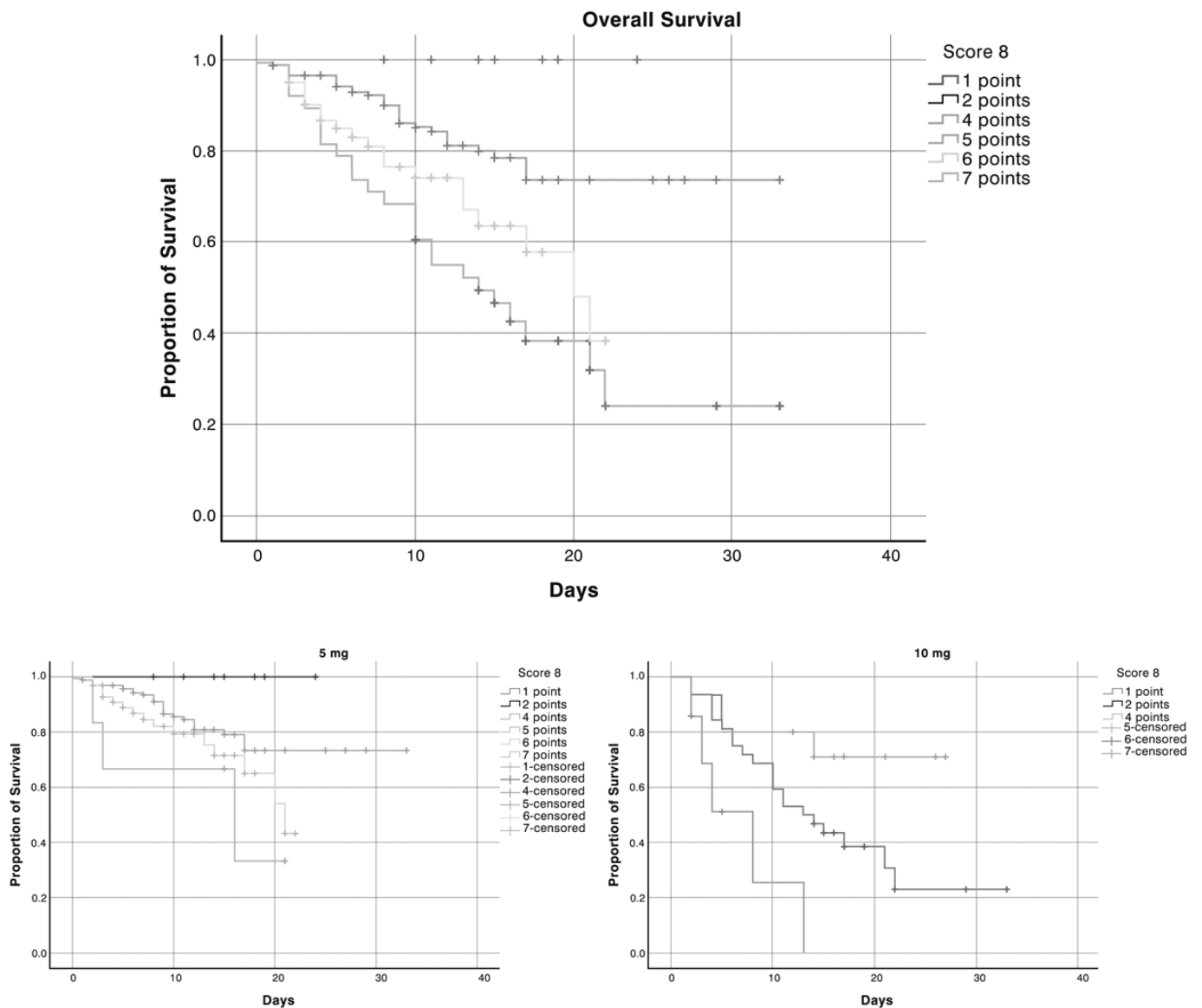


95% Confidence Interval. Evolution of A) 8-ordinal score (points) B) C-Reactive protein (ng/dL), C) Procalcitonin (mg/dL), D) Ferritin (ng/dL) E) Fibrinogen (mg/dL), F) Erythrocyte Sedimentation Rate (mm/hr) and G) Lymphocytes (cells x10(9)/L)

Table 2. Hospital length distributed by oxygen support at admission.

Oxygen support at admission	Ruxolitinib 5 mg n = 232		Ruxolitinib 10 mg n = 55	
	Cases n (%)	Hospital days Mean ± SD	Cases n (%)	Hospital days Mean ± SD
None	62 (27)	11 ± 6	2 (4)	11 ± 8
Nasal cannula	79 (34)	11 ± 6	7 (13)	17 ± 7
Oxygen mask	42 (18)	11 ± 8	6 (11)	13 ± 12
High flow nasal cannula	2 (0.8)	12 ± 8	1 (2)	29
High flow oxygen mask	16 (6.8)	10 ± 5	6 (11)	17 ± 7
Non-invasive mechanical ventilation	1 (0.4)	31	4 (7)	9 ± 8
Invasive mechanical ventilation	30 (13)	14 ± 7	29 (53)	16 ± 7

Figure 2. Kaplan Meier Cumulative Deaths.



Cumulative proportion of mortality measured by days. A) Proportion shown by their baseline 8-point ordinal score. B) Proportion measured in the 5 mg group. C) Proportion measured in the 10 mg group.

The number of days from the appearance of initial symptoms to diagnosis was 6 ± 4.8 . Most of the patients received an antibiotic (azithromycin being the most frequent; 178 cases) in combination with an antimalarial (83 cases; hydroxychloroquine in 69 cases and chloroquine in 14 cases). Ritonavir/lopinavir was administered to 35 patients. Among the 276 patients treated with anticoagulants, 252 received enoxaparin. A total of 45.3% patients received systemic corticosteroids (54 received methylprednisolone, 44 received dexamethasone, and 9 received prednisone). All the patients received ruxolitinib twice a day; 232 patients received a 5 mg dose and 55 patients received a 10 mg dose. The time from the appearance of symptoms to hospital admission was 6.7 ± 4.5 days and that from admission to ruxolitinib initiation was 2.72 ± 3.56 days.

At the beginning of treatment, 223 patients were on oxygen support, with 86 on nasal cannula, 48 on conventional oxygen mask, 25 on high-flow support, 5 on non-invasive mechanical ventilation, and 59 on invasive ventilation. There were more patients on invasive ventilation in the 10 mg group compared to that in the 5 mg group. The distribution of oxygen support and the duration of hospital stay are shown in Table 2. At the end of treatment, 45 patients progressed to invasive mechanical ventilation (IMV) and 93 patients were off supplemental oxygen.

At admission, the 8-point ordinal scale score was 5.39 ± 0.93 , with a final score of 3.67 ± 2.98 ($p = 0.0001$). The score in the 5 mg dose group was 5 ± 1 points at day 1, 5 ± 1 points at day 5, 4 ± 2 points at day 10, and 3 ± 2 points at day 15 of treatment. Patients in the 10 mg group had a score of 6 ± 1 points on day 1, 7 ± 0.5 points on day 5, 6 ± 1 points on day 10, and 5 ± 2 points on day 15; the scores for both the groups were statistically significant ($p = 0.001$).

The average duration of hospital stay was 7 ± 5 days for the 5 mg dose group and 6 ± 3 days for the 10 mg

dose group. The rate of invasive or non-invasive mechanical ventilation was 60% (33 patients) in the 10 mg group versus 13.3% (31 patients) in the 5 mg group.

Laboratory parameters were also influenced by ruxolitinib, with decrease observed in the levels of c-reactive protein, lactic dehydrogenase, and ferritin as well as in the erythrocyte sedimentation rate (Figure 1). However, for the two dose groups, the differences were statistically significant only for c-reactive protein, lactic dehydrogenase, and ferritin (Supplementary Figure 1).

There were 74 deaths in total—44/232 (19%) in the 5 mg group and 30/55 (58%) in the 10 mg group. The cause of death was respiratory failure in 51 patients, multiple organ failure in 14 patients, cardiogenic failure in 3 patients, nosocomial pneumonia in 5 patients, and cerebral hemorrhage in 1 patient. Among the 74 patients who died, 44 (59.45%) were on IMV since the start of treatment. The overall survival associated with the initial 8-point score is shown in Figure 2. Sixteen of the 74 deaths were within the first 4 doses of treatment. There was no statistically significant difference in mortality with the use of systemic corticosteroids.

Sixty-six patients presented with one or more adverse events; these were mostly grade 1 in 52 patients being the most frequent thrombocytosis without bleeding or thrombosis (25 cases). There were 15 grade 3/4 events with 6 deaths resulted from bacterial pneumonia. There were no fungal infections. A list of adverse events is presented in Table 3.

Discussion

Herein, we present the data for 287 patients treated with ruxolitinib as an immunomodulator for COVID-19. The primary endpoint was to evaluate the clinical response measured on the 8-ordinal point scale. There was a significant reduction of 2 points at 15 days after the start of treatment, mostly in patients administered a 5 mg dose rather than in patients administered a 10 mg dose. Both the schemes of 5 and 10 mg doses seem to

Table 3. Adverse Events in Patients treated with Ruxolitinib.

	Grade 1-2	Grade 3-4	Grade 5
Fever	1	0	0
Hypertriglyceridemia	13	3	0
Transaminasemia	9	0	0
Lactate Dehydrogenase Increase	1	0	0
Bilirubin Increase	1	0	0
Alkaline Phosphatase Increase	2	0	0
Creatinine Increase	4	5	0
Anemia	11	1	0
Lymphopenia	7	2	0
Neutropenia	0	0	0
Thrombocytopenia	0	1	0
Pneumonia	0	2	6

have good clinical response, differentiated by the clinical characteristics of the patients at admission being poor in the 10 mg group. It is important to mention that the 10 mg dose was given in consideration of the severity of COVID-19 pneumonia and, therefore, it was expected that the patients treated with this dose would have a poor prognosis. It is also remarkable that in the 5 mg group, only 13.3% of the patients were on mechanical ventilation (MV) whereas in the 10 mg group, more than half (60%) of the patients were initially on MV. The progression to MV was 15.6%, being acceptable compared to the values of 16%–42.9% reported for severe cases in the literature [14–16].

As of date, in Mexico, the mortality caused by COVID-19 fluctuates around 10%. This percentage is based on all the reported infections. However, for moderate to severe cases, mortality has been reported to be 21% in the New York Area, 61.5% in severe cases in China, as 33% and 61.5% in other Latin-American countries for severe cases and for MV cases, respectively [17–20]. In Mexico, case series of 125 hospitalised patients, a global mortality of 43.2%, with a mean overall survival of 18 days, was reported [16]. In our cohort, the global mortality was 25.8%, which is within the expected value for the currently registered moderate to severe cases. However, when mortality was analysed for the dose given, it was 19% in the 5 mg group, which is lower than that expected in moderate to severe cases. In the 10 mg ruxolitinib group, the mortality was 58%, similar to that registered in Latin Americans with other treatments [19]. This results suggest that the main difference between the two treatment doses was the clinical deterioration observed in patients administered the 10 mg dose, resulting in poor prognosis. Thus, more than the dose itself, the difference was based on the patient's status, with a higher percentage of patients with MV in the 10 mg group.

Several studies have shown the efficacy of JAK inhibitors in severe COVID-19. Among the first of these studies to show the efficacy of ruxolitinib was a report by La Rosée *et al.* who reported the treatment of 14 cases of severe COVID-19 with 7.5 mg twice a day, with a 25% reduction in their COVID inflammation score by 5th day and 42% reduction by 7th day. In three patients with insufficient response, the dose was escalated to 15 mg BID; however, two of these patients died. The median number of days of hospitalisation was 18, with remarkable suppression of inflammation measured in terms of ferritin, CRP, and IL-6 levels [21]. Cao *et al.* conducted a single-blind randomised controlled trial in severe cases, with 20 patients treated

with ruxolitinib 5 mg BID plus standard of care versus 21 patients given placebo plus standard of care as the control group. They reported no difference in the time to clinical improvement, which was the primary endpoint. Nevertheless, the improvement, as evidenced by CT scans, was higher in the ruxolitinib group (90% vs. 61.9%), with no deaths in the treatment arm versus 14.3% mortality in the control group at 28 days [22].

Another JAK inhibitor that has shown efficacy is baricitinib. The first report on the use of this inhibitor in COVID-19 patients was a pilot study by Fabrizio Cantini *et al.* They reported that 12 patients treated with baricitinib plus lopinavir/ritonavir and hydroxychloroquine showed improvement in fever, SpO₂, PaO₂/FiO₂, laboratory parameters, and ICU requirement, with no serious adverse events [23]. The same group released the results of a multicentre trial with 113 patients treated with baricitinib 4 mg/day compared to 78 patients treated with placebo plus lopinavir/ritonavir; they reported a significantly lower fatality rate at 15 days in the baricitinib-arm compared with that in the controls (0% vs. 6.4%), with a higher discharge rate at one week (9.7% vs. 1.3%) [24]. A group in Spain also demonstrated the efficacy of baricitinib, showing as their primary endpoint, a death rate or progression to MV in 16.9% of patients in the baricitinib-treated group compared to 34.9% in the control group ($p < 0.001$) [15].

Exploring another treatments, in the final report of the ACTT-1 trial, remdesivir, the only antiviral approved by FDA for COVID-19, was reported to have an estimated mortality by day 15 of 6.7% versus 11.9% in patients administered placebo, with serious adverse effects reported in 24.6% of remdesivir-treated patients [26]. Corticosteroids have also shown efficacy; Nevertheless, it is important to mention that in some of the studies, patients expected to die in the next 24 hours were excluded. The response to treatment with dexamethasone in the COALITION COVID-19 Brazil study was demonstrated by a reduction in MV days and a reduction of 10% in the mortality rate, with a total of 56.3% deaths in the treatment arm [19]. Tocilizumab has also shown good response in several studies. A case series of 77 patients with severe COVID-19, with a mean follow up of 83 days, showed ICU admission in 54.5% patients and MV in 49.4% patients with hospital stay duration of 16 days and global mortality of 12.9% [14]. Another report on 63 patients described a mortality of 11% at 14 days in moderate to severe COVID-19 patients with a rapid response on CRP and d-dimer and a stable response on ferritin, as the pro-inflammatory values analysed [26].

Based on the ACTT-2 trial, we now have knowledge of the clinical results of treatment with a JAK inhibitor and remdesivir together. In this phase 3 placebo-controlled trial, 1033 severe COVID-19 patients were randomised into remdesivir plus baricitinib or remdesivir plus placebo groups. There were better responses in the JAK inhibitor group, with 1 day less required for recovery, which was remarkable in the group of high-flow oxygen or non-invasive ventilation at enrolment, with a time to recovery of 10 days with the combination versus 18 days with remdesivir plus placebo. Also, there was an improvement in mortality, with 2.7% less at 28 days versus placebo. There were fewer severe adverse events in the combination group [27]. These results support the notion that JAK inhibitors alone or in combination with viral response treatments are useful in moderate to severe cases of COVID-19.

The findings of the adverse events upon treatment with the JAK inhibitor in this study were similar to those in other studies in which JAK inhibitors were found to be mostly safe in the COVID-19 scenario. The adverse events reported by La Rosée *et al.* were moderate increase in transaminases and anaemia in patients with pre-existing anaemia [21]. Cao *et al.* reported no serious adverse events in patients treated with ruxolitinib [22]. Most important, the deaths reported as adverse events were caused by bacterial pneumonia, a common complication in viral pneumonia and in intubated patients with even a bigger percentage of bacterial complications with other immunosuppressors. In our study, 2.87% of the cases had serious infections versus 14.2% in cases treated with tocilizumab. In fact, a review of bacterial and fungal infections in SARS-COV2 revealed a rate of co-infection ranging from 4.8% to 38.9%, hospital acquired pneumonia ranging from 0% to 31% whereas septic shock was reported in 4% to 33.1% of the patients [14,28]. In our study, thrombocytosis was frequently reported as an adverse event, nevertheless this effect was found in patients by the time of recovery with a favourable response.

In this case series, the delay in the administration of ruxolitinib was approximately 9 days from the appearance of initial symptoms. Studies on the immunosuppressor, tocilizumab, showed a better response upon early use, with a better prognosis of survival when the drug was administered within 6 days of admission in the hospital (HR = 2.2, 95% CI = 1.3–6.7) [26]. A better clinical response was also reported with baricitinib plus remdesivir in patients with non-invasive ventilation [27]. In our study, when mortality

was determined using the Kaplan–Meier curve, as expected, the outcome was poor in patients with a higher score on the 8-point scale at baseline. Based on this information as well as on the global evolution of the group, it can be said that when ruxolitinib is given early in moderate cases, the response and prevention of mortality appears to be favourable with no toxicity limiting events.

It is important to highlight that in this multicentre study, there was a broad diversity in the population as well as in the treatments granted as ‘standard of care’. Moreover, the study was performed at reference centres where the admission of patients was late and, in some occasions, the patients were in deteriorated conditions at the start of treatment. We consider these points to be the main limitations of the present study. However, it is also pertinent to note that in a country where the use of remdesivir and tocilizumab is limited, it is important to have other effective, safe, and achievable therapeutic options, such as ruxolitinib. The results of this study should be evaluated with those of the phase III placebo-controlled study organized by Novartis (RUXCOVID – clinicaltrials.gov NCT04362137).

Conclusions

Patients treated with ruxolitinib showed clinical improvement presented as a reduction of 2 points in an ordinal 8-points scale. There was also a reduction in C-reactive protein, erythrocyte sedimentation rate, ferritin, fibrinogen without compromise of lymphocyte count. Only 6.9% of the patients showed adverse events grade 3 or higher. With this findings Ruxolitinib appears to be a safe option in patients with COVID-19 pneumonia where other resources are limited.

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Annex – Supplementary Items

Supplementary Table 1. Demographic characteristics of patients demonstrated by their ruxolitinib dose treatment.

	Total	Ruxolitinib		p value
		5 mg (n = 232)	10 mg (n = 55)	
Comorbidities:				
Age	54 ± 14	54 ± 14	55 ± 14	NS
Body Mass Index	30 ± 6	30 ± 6	31 ± 6	NS
Charlson index	0 (0-7)	0 (0-7)	0 (0-6)	NS
Hypertension	104 (36)	82 (35.3)	22 (40)	NS
Diabetes	87 (30)	67 (29)	21 (38)	NS
Chronic lung disease	13 (4.5)	12 (5)	1 (1.8)	NS
Chronic heart disease	9 (3.1)	7 (3)	2 (3.6)	NS
Arrythmia	6 (2.1)	5 (2)	1 (1.8)	NS
Chronic liver disease	4 (1.4)	3 (1)	1 (1.8)	NS
Treatment used:				
Azithromycin	178	136 (59)	42 (76)	0.02
Hydroxychloroquine	69	52 (22)	17 (31)	NS
Chloroquine	14	14 (6)	0	0.07
Liponavir/Ritonavir	35	19 (8)	16	NS
Enoxaparin	252	200 (86)	52 (95)	NS
Rivaroxaban	12	12 (5)	0	NS
Apixaban	7	7 (3)	0	NS
NF-Heparin	3	2 (0.8)	1 (1.8)	NS
Methylprednisolone	54	34 (14.6)	20 (36.3)	0.0005
Dexamethasone	44	30 (13)	14 (25.4)	0.03
Hydrocortisone	23	17 (7)	6 (11)	NS
Prednisone	9	7 (3)	2 (3.6)	NS

NS: Non-significant.

Supplementary Figure 1. Evolution of 8-point ordinal scale and proinflammatory values on day 1, 5, 10 and 15 day of ruxolitinib with 5 mg and 10 mg doses.

