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Ruxolitinib as treatment against COVID-19 in Mexican population.

Ruxolitinib como tratamiento contra el COVID-19 en población mexicana

Roberto Ovilla-Martínez,[1] Xóchitl Cota-Rangel,[1] José Antonio De La Peña-Celaya,[1] Aarón Molina-Jaimes,[2] Mariana Alejandra Alvarado-Zepeda,[3] Karla Erika Rojas-Vértiz Contreras,[4] Nora Ivonne Araujo-Martínez,[3,4] Rodolfo Ruiz-Luján,[5] Alejandro Ortiz-Arroyo,[1] Pamela Elena Báez-Islas[1]

Abstract

BACKGROUND: Many of the cytokines involved in COVID-19 are triggered by the JAK/STAT signal pathway. JAK inhibitors have been proposed as treatment for moderate to severe SARS-CoV-2 infection.

OBJECTIVES: To measure clinical changes by the 8-point ordinal scale; secondary endpoint was to determine hospitalization days, proinflammatory changes, progression to ICU, mechanical ventilation, deaths and adverse events.

MATERIAL AND METHOD: A control paired case series of patients under compassionate-use of ruxolitinib with confirmed diagnosis of SARS-CoV-2 pneumonia manifestations.

RESULTS: We analyzed 20 cases with COVID-19 pneumonia with supplemental oxygen requirement. The 8-point ordinal scale was 5 points in 9/10 and 6 points in 1/10 in the intervention group; 5 points in 8/10 and 6 points in 2/10 in the control group. By the end of study all the ruxolitinib patients had < 2 points while 3 patients died (8 points) in the control group. The hospitalization length was shorter for the intervention group with 9.7 (range 5-19 SD 5.27) *versus* 16.2 days (range 8-25 SD 4.78). No serious adverse events were reported in the intervention group.

CONCLUSIONS: Ruxolitinib patients had better clinical course with shorter hospital length without major toxicity. This preliminary study has promising effects to continue with larger trials.

KEYWORDS: COVID-19; Ruxolitinib; Cytokine release syndrome.

Resumen

ANTECEDENTES: Varias de las citocinas elevadas en COVID-19 son generadas por la vía de JAK/STAT. Los inhibidores de JAK se han propuesto como tratamiento contra la infección por SARS-CoV-2 moderada a severa.

OBJETIVOS: Medir los cambios clínicos mediante la escala ordinal de 8 puntos; el objetivo secundario fue determinar los días de hospitalización, cambios en estados proinflamatorios, progresión a UCI, ventilación mecánica, defunciones y eventos adversos.

MATERIAL Y MÉTODO: Estudio de serie de casos y controles tratados con ruxolitinib mediante uso compasivo en pacientes con neumonía por SARS-CoV-2.

RESULTADOS: Se analizaron 10 casos con neumonía por COVID-19 tratados con ruxolitinib con escala inicial de 8 puntos de 5 en 9/10 y 6 en 1/10 en comparación con 10 controles con 5 en 9/10 y 6 en 1/10 pacientes. Al final todos los pacientes con ruxolitinib tenían menos de dos puntos, mientras que 3 pacientes del grupo control murieron. El tiempo de hospitalización fue menor en el grupo intervenido. No se reportaron eventos adversos graves en el grupo de casos.

CONCLUSIONES: Los pacientes tratados con ruxolitinib tuvieron mejor evolución clínica y menor tiempo de hospitalización sin mayor toxicidad. Estos resultados preliminares deberán continuar con ensayos clínicos mayores.

PALABRAS CLAVE: COVID-19; ruxolitinib; síndrome de liberación de citocinas.

[1] Hematology Division. Hospital Ángeles Lomas, Estado de México, México.
[2] Infectology Service. ISSSTE Hospital Regional de Alta Especialidad Bicentenario de la Independencia, Estado de México, México.
[3] Internal Medicine Division. Centro Médico de Especialidades de Ciudad Juárez, Ciudad Juárez, Chihuahua, México.
[4] Internal Medicine Division. ISSSTE Hospital General B de Zona Ciudad Juárez, Ciudad Juárez, Chihuahua, México.
[5] Infectology Division. Hospital General de Mexicali, Mexicali, Baja California, México.

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Correspondence
Pamela Elena Báez Islas
drabaez.hematologia@gmail.com

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INTRODUCTION

Coronavirus disease 19 has affected more than 16 million people and caused death in above 650,000.[1] The infection is originated by a coronavirus family virus named SARS-CoV-2, an acronym for severe acute respiratory syndrome by coronavirus-2, coined on February 2020 by the WHO; its clinical manifestations are known as COVID-19 an acronym of coronavirus disease 2019".[2]

The immune response is vital for the control and resolution but is also responsible for the severity of the respiratory condition. The first report of patients with COVID-19 showed that several cytokines were elevated: IL-1, IL-7, IL-8, IL-9, bFGF, GMCSF, IP-10, MCP-1, MIP-1α, VEGF, IFN-γ and TNF-α with higher concentrations found on those who required intensive care unit (ICU).[3] Another group found higher expression of interleukin-2 receptor (IL-2R) and serum levels of interleukin-6 in severe cases.[4] Based on these reports the use of immunosuppressors or immunomodulators as a therapeutic approach on moderate to severe COVID-19 has been proposed.[5-8]

Many of the cytokines involved in COVID-19 are triggered by the signal pathway of Janus Kinase (JAK)/signal transducers and activators of transcription (STAT) which has already been described as the cause of various systemic inflammatory responses and autoimmune diseases. The transduction pathway is initiated by the union of the cytokines to its receptor which enables JAK activation. Once activated, JAKs phosphorylate STATs which translocate into the nucleus where they bind their cognate promoter elements to regulate transcription of target genes, unraveling intracellular signals that generate a storm of diverse cytokines.[9]

Ruxolitinib, a JAK 1/2 inhibitor, is a drug approved for polycythemia vera and myelofibrosis and has shown efficacy in other proinflammatory states such as graft versus host disease, systemic mastocytosis, refractory juvenile dermatomyositis and hemophagocytic lymphohistiocytosis. Ruxolitonib causes a reduction in proinflammatory cytokines (IL-6, TNF-α, GM-CSF, MCP-1, and MIP-1α) and suppression of the proliferation of cytotoxic T-cells with activation and promotion of phenotypic changes to CD4+ lymphocytes as T-reg cells CD8+CD25+.[10-17] With all this information, ruxolitinib has been used in Mexico as a compassionate treatment in patients with COVID-19 pneumonia. Here we comment on the preliminary results of the first patients reported receiving this treatment.

MATERIAL AND METHOD

We analyzed patients treated with ruxolitinib using the inclusion criteria age ≥18 years, confirmed COVID-19 diagnosis by polymerase chain reaction (PCR), informed consent and radiology evidence of pneumonia by chest x-ray or CT-scan. We excluded those patients whose data was incomplete for analysis of the primary objective as those patients with invasive mechanical ventilation or use of other target therapy as tocilizumab or another JAK-inhibitor.

Ruxolitinib (Jakavi®) was provided by Novartis' medical access program. Request approval was reserved for hospitalized patients who had SARS-CoV-2 infection confirmed by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay with radiology evidence of pneumonia by chest x-ray or CT-scan and need for oxygen support determined by clinicians. The treatment was avoided in pregnancy, breastfeeding, end stage chronic renal disease thrombocytopenia ≤ 20,000 cells/mm^3, neutropenia ≤ 500 cells/mm^3, active HIV infection, hepatitis C, hepatitis B, herpes zoster or *Mycobacterium tuberculosis* infection.

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The recommended dose was 5 mg twice a day. Informed consent was obtained for all patients in accordance with local regulations and the registry was approved by the local Ethics Committee. The drug sponsor was not involved in the recollection and analysis of the data nor the decision to submit the manuscript. Supportive therapy as antibiotics and antivirals were given at the discretion of the clinician and each hospital's standard of care for COVID-19.

The primary endpoint was to determine the clinical improvement by the 8-point ordinal scale consisting on: *1)* not hospitalized and without limitation on activities; *2)* not hospitalized with limitation on activities and/or requiring supplemental oxygen; *3)* hospitalized, not requiring supplemental oxygen without ongoing medical care; *4)* hospitalized, not requiring supplemental oxygen with ongoing medical care; *5)* hospitalized, requiring supplemental oxygen; *6)* hospitalized on non-invasive ventilation of high flow oxygen devices; *7)* hospitalized on invasive mechanical ventilation or extracorporeal membrane oxygenation; *8)* death.

Secondary endpoints were number of days in hospital, changes in proinflammatory parameters (erythrocyte sedimentation rate [ESR], lactic dehydrogenase [LDH], C-reactive protein [CRP], ferritin, fibrinogen and d-dimer [DD]), rate of patients with progression to invasive mechanical ventilation, proportion of deaths and rate of adverse events secondary to ruxolitinib. These parameters were measured at the beginning of treatment, day 5, day 10 and 15.

Registry was done in Office Excel® spreadsheets. The statistical analysis was conducted with 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 with standard deviation, interquartile data. U-Mann-Whitney for non-parametric values and Pearson's χ^2 test for categorical data.

RESULTS

We report the first 10 patients who received the treatment with ruxolitinib and 10 patients without ruxolitinib from five hospitals in Mexico on March and April 2020. Seven patients were female. Mean age was 56.7 years (range 33-74 SD 12.07). The mean time from admission to start ruxolitinib in the treatment group was 3.6 days (range 0-9 SD 3.86). Their main baseline characteristics are described in **Table 1**.

All the patients had antibiotics on their therapeutic schemes, with the most frequently used being azithromycin and clarithromycin. Only one patient received antiviral, atazanavir/ritonavir, in the case group while seven patients received antiviral in the control group, one received atazanavir/ritonavir and the rest lopinavir/ritonavir. The use of hydroxychloroquine or chloroquine was reported in sixteen of the patients: four patients received hydroxychloroquine in the ruxolitinib group and seven patients in the control group; there were five patients on chloroquine in the ruxolitinib group. Seven patients had anticoagulation with enoxaparin in the ruxolitinb group while nine had it on control. The use of corticosteroids was reported in six patients on the ruxolitinib group, none on control.

On the first evaluation, all the patients required oxygen supplementation by regular nasal cannula or face mask. In the intervention group, at day 1 of ruxolitinib treatment, 7/10 patients had peripheral oxygen saturation (SpO2) lower than 90% (mean of 87.4% [range 75-96 SD 6.5]), while the mean SpO2 in the control group was 85.7% (range 78-91 SD 3.97). PaO_2/FiO_2 was measured with a mean for the intervention group in 109.9 and 252 for the control group.

Table 1. Demographic, clinical and laboratory baseline characteristics

Characteristics	Ruxolitinib N = 10	Control N =10	p value
Age, mean (IQR)	55 (47.47-62.25)	58.4 (52.75-69.50)	0.49
Sex, no.			
Male	6	7	
Female	4	3	0.63
Hypertension, no.	5	6	0.65
Type 2 diabetes, no.	5	3	0.36
Body mass index, no.			
Normal	2	4	
Overweight	5	4	
Obesity	3	3	0.43
Charlson Comorbidity Index, mean (IQR)	0.7 (0-1)	1.6 (0-2.25)	0.35
Laboratory values*, mean (IQR)			0.10
PaO_2/FiO_2	109.6 (49-249.25)	252 (232.25-292)	0.009
Hemoglobin, g/dL	13.9 (13.0-15.5)	14.7 (13.5-16.6)	0.48
Leucocytes, $x10^9$/L	7.24 (4.96-8.86)	8.79 (7.34-10.51)	0.12
Lymphocytes, cells $x10^9$/L	0.87 (0.64-1.07)	0.82 (1.06-1.25)	0.16
Neutrophils, cells $x10^9$/L	6.14 (4.0-7.35)	7.09 (5.68-9.13)	0.27
Platelets, cells $x10^9$/L	308.7 (197.5-407.25)	216.8 (153.5-244.5)	0.14
Glucose, mg/dL	137.5 (94-7-136.5)	148 (106.7-168.7)	0.10
Creatinine, mg/dL	0.82 (0.64-0.96)	1.5 (0.71-1.15)	0.48
Erythrocyte sedimentation rate, mm/hr	44.3 (20.0-73.75)	21 (11.75-32.50)	0.93
C-reactive protein, mg/dL	32.70 (11.70-44.13)	15.9 (6.03-22.29)	0.25
Procalcitonin, ng/mL	0.59 (0.08-1.32)	0.20 (0.10-0.35)	0.73
Lactate dehydrogenase, UI/L	553.88 (333.5-742.0)	565.3 (421.75-719.25)	0.89
Ferritin, ng/dL	1266.01 (486.75-1619.07)	415 (350 - NA)	0.26
Fibrinogen, mg/dL	805.33 (599.25 -1077.75)	389.98 (228.5-587.57)	0.06
D-dimer, ng/mL	1117.01 (235.25-1755.00)	5198.60 (812.5-6005.0)	0.43
8-ordinal scale			
5 points	9	8	
6 points	1	2	0.53

Four patients suspended ruxolitinib treatment before two weeks due to major improvement with hospital discharge decided by their physicians. Two patients received treatment for 10 days, one for 11 days and one for 12 days, the rest of them completed 15 days of treatment even in out-of-hospital context. The intervention group had a follow up mean of 16.3 days (range 10-25 SD 4.16).

At beginning all patients had an 8-point ordinal scale above 5 in the intervention group. At the end of treatment just one patient had 2 points while the rest had 1 point, which means all pa-

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tients in the intervention group were out-hospital with just one still symptomatic. In the control group, nine patients began with 5 points and one with 6 points. At the end, the control group had four patients with 1 point, three had 2 points and three had 8 points representing 3 deaths in the control group while there were any on the ruxolitinib group. The evolution on day 1, 5, 10 and 15 of this scale is shown in **Figure 1**.

The changes on the proinflammatory values are shown in **Figure 2** for both groups. After starting ruxolitinib treatment, no patient required subsequent invasive mechanical ventilation or admission to intensive care unit, in contrast two patients in the control group required invasive mechanical ventilation with progression to death in both cases. The mean number of days in-hospital for the intervention group was 9.7 days (range 5-19 SD 5.27) with a follow up of 16.3 days (range 10-25 SD 4.16) meanwhile the in-hospital stay mean was longer in the control group with 16.2 days (range 8-25 SD 4.78). We also found important improve in chest imaging; chest x-ray and CT evolution of two cases of ruxolitinib group are shown in **Figures 3 and 4**.

In the intervention group all patients remain alive and there was no serious adverse event reported. Two patients presented thrombocytosis in out-of-hospital context related to inflammation recovery. One patient had grade 1 transaminase increase. No other adverse events were seen.

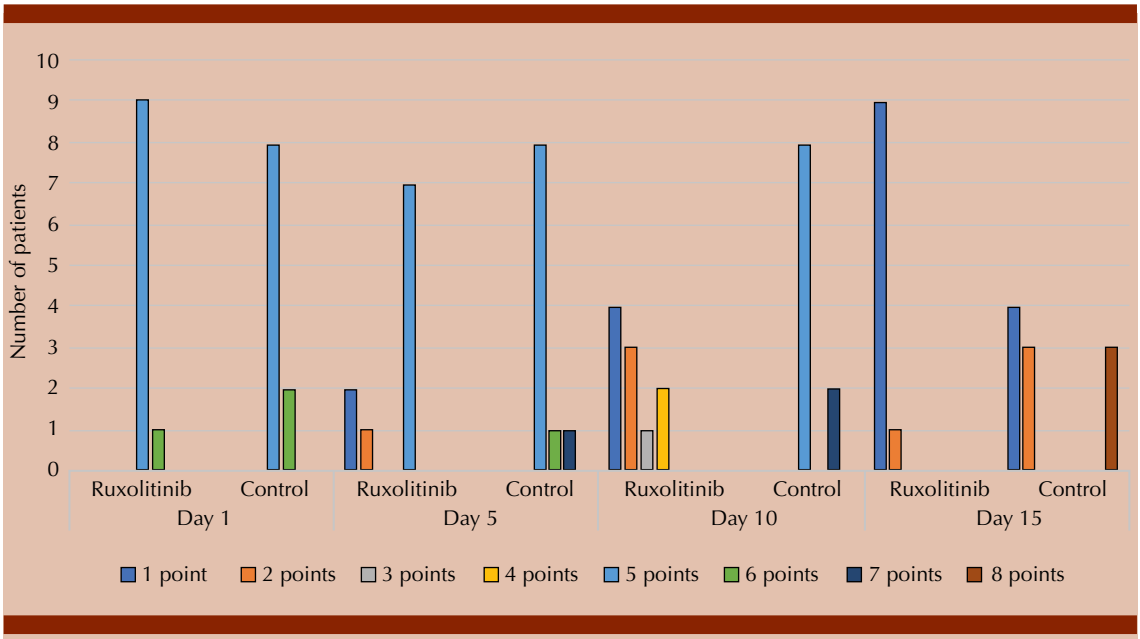

Figure 1. Evolution of the 8- point ordinal scale in the treated group and control group. The scale was measured at day 1, 5, 10 and 15 in ruxolitinib and control group. The score is: 1 point for not hospitalized and without limitations, 2 points for not hospitalized with limited activity and/or home oxygen supplementation, 3 points for hospitalized without supplemental oxygen nor ongoing medical care, 4 points for hospitalized without supplemental oxygen with ongoing medical care, 5 points for hospitalized with requiring supplemental oxygen, 6 points for non-invasive ventilation or need of high flow oxygen devices, 7 points for invasive mechanical ventilation or extracorporeal membrane oxygenation, and 8 points for death.

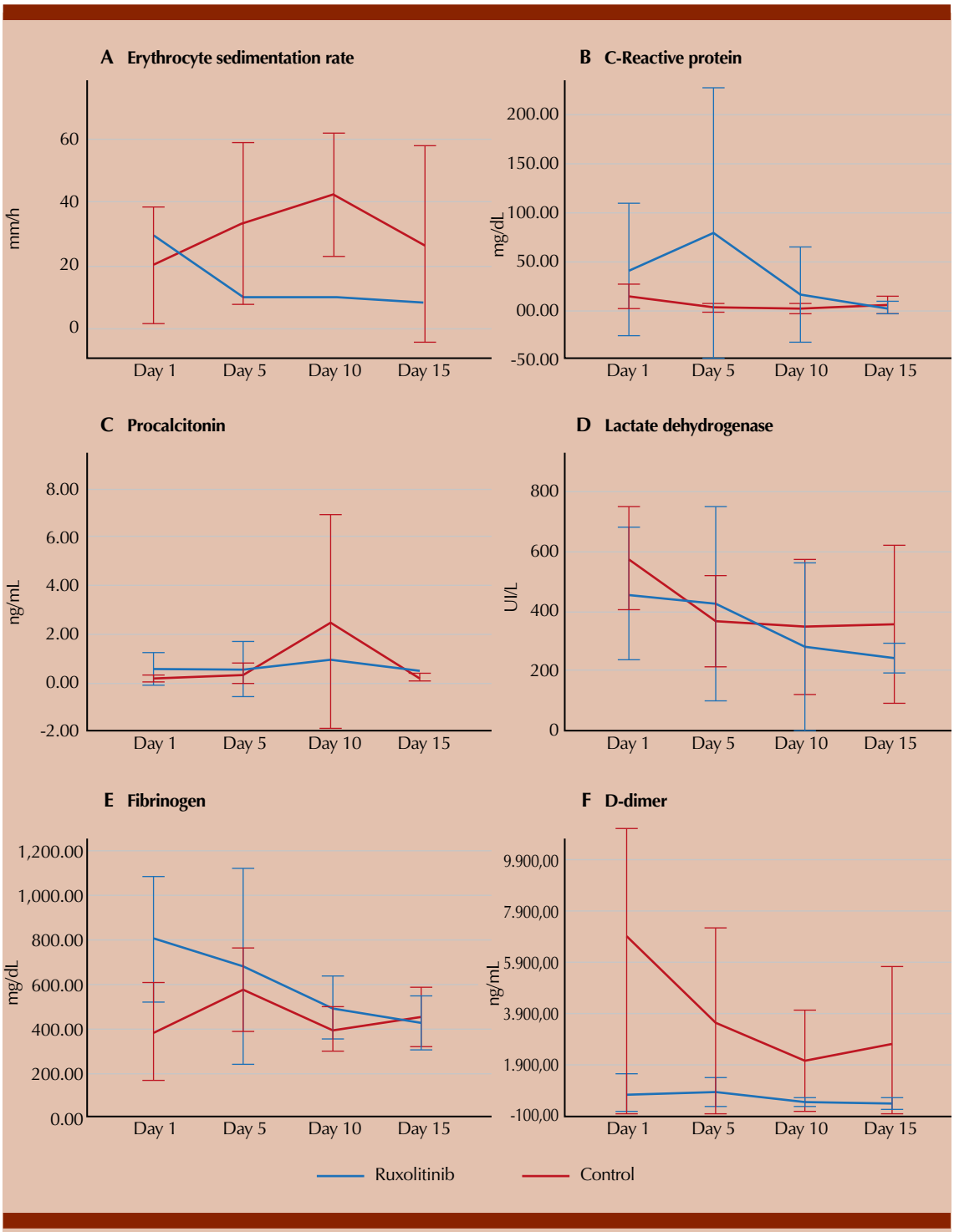

Figure 2. Evolution on proinflammatory values from baseline to day 5, 10 and 15. Proinflammatory values expressed in means, I bars indicate 95% confidence intervals at day baseline (day 1), 5, 10 and 15 of follow-up.

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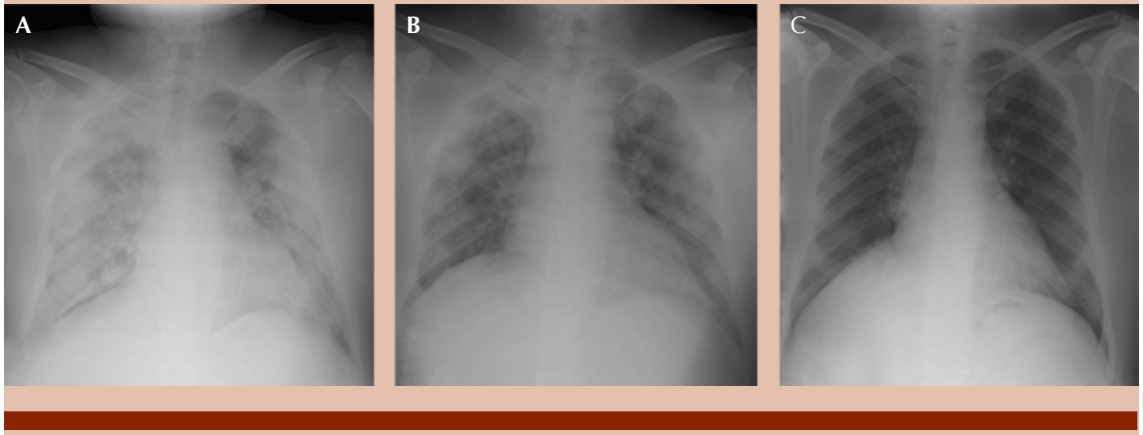

Figure 3. X-ray changes under ruxolitinib treatment. Image evolution of intervention-group patient #7, a 54 year-old-male. **A.** Image at diagnosis on April 29th. **B.** Image after five days of treatment on May 6th. **C.** Image after 10 days of treatment on May 11th.

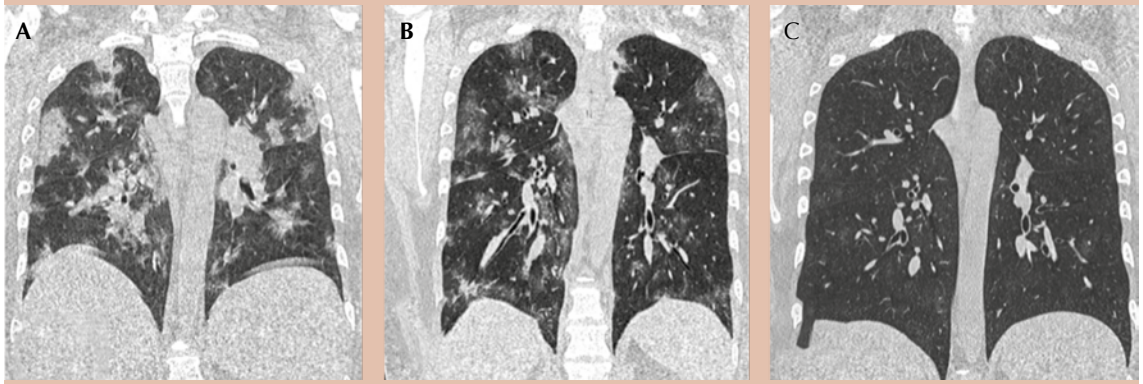

Figure 4. Chest CT-scan changes under ruxolitinib treatment. Radiographic evolution of intervention-group patient #5, a 33 year-old-female. **A.** Image at diagnosis on April 27th. **B.** Image after six days of treatment on May 3rd. **C.** Image after completion of treatment on May 14th. *These images are courtesy of Dra. Christina del Bosque.

DISCUSSION

At sixteen days of follow-up, this study found that ruxolitinib was efficient in the clinical state improvement based on the 8-point ordinal scale compared to the control group. Patients in both groups (intervention and control) were on similar situations at the start, but by the end of treatment all the patients with ruxolitinib were discharged from hospital with a difference in mean hospital stay of 5 days compared to the control group (intervention group mean 9.7 days [range 5-19 days, SD 5.27] versus control group mean 16.2 days [range 8-25, SD 4.78]). Even more relevant, there was no progression to invasive mechanical ventilation nor deaths in the ruxolitinib

group compared to two progression to invasive mechanical ventilation and admission to ICU and three deaths in the control group. Another relevant finding was the lack of serious adverse events in the intervention group.

After recognition of SARS-CoV-2, the cytokines that play a main role in the innate immune response are type I interferons (IFNs-I) which stimulates monocyte-macrophages and dendritic cells to produce IL6, TNF-α and IL1-β, cytokines that are upregulated in severe forms of COVID-19.[3,8] Some of those cytokines stimulate NK cells and several T cells (CD8+, CD4+, Tregs), provoking a second wave of numerous cytokines contributing to a cytokine release syndrome, also known as cytokine storm.[8,18,19] IFNs-I also upregulate the expression of angiotensin-converting enzyme 2 (ACE2) which is also the SARS-CoV-2 receptor.[20] IFNs-I also plays a role in the overactivation of the coagulation system in bacterial and viral infection leading to disseminated intravascular coagulation (DIC).[19] This model has been replicated in mice infected with SARS-CoV demonstrating that dysregulated IFNs-I are a potential therapeutic target to diminish the lethal expression of SARS-CoV.[18] This information is relevant because type I IFNs signal through cell surface IFN-αβ receptor to activate the JAK/STAT pathway explaining the action mechanism of JAK inhibitors in SARS-CoV-2.[8,18]

This study supports previous results with JAK inhibitors for moderate to severe COVID-19. An Italian series showed efficacy on 12 patients treated with baricitinib compared with a historical group showing improvement in fever, SpO2, PaO2/FiO2, CRP with seven discharged patients at week 2 and no admissions to ICU compared to just one patient discharged and seven progressions to ICU in the control group; the only adverse event reported was grade 2 transaminase increase.[6] A randomized phase II trial in China reported the use of ruxolitinib in 20 patients compared to 21 patients in the control group with severe COVID-19; the reported serious adverse events were one case of grade 3 lymphopenia and one grade 3 hypertension event with no statistical difference in terms of clinical improvement, although it was reported a shorter time to improvement and significant progress in chest CT-scan with improvement in 90% of treated patients versus 61% in the control group. More importantly, there were no deaths in the ruxolitinib group *versus* 3 deaths in the control group.[21] More recently, there was a report in Germany of COVID-19 patients in which 14 cases were treated with ruxolitinib; in this group the treatment dose was 7.5 mg twice a day showing efficacy (measured as a reduction of 25% of their COVID inflammation score) in 12 of the 14 patients by the 7th day of treatment with a median time of hospitalization of 18 days with demonstration of decrease in serum ferritin, CRP and IL-6; only one patient died and there was 3 grade 3 adverse events none of which had long term effects.[22]

Comparing the evidence with JAK inhibitors with tocilizumab, one of the most commonly used immunosuppressors in COVID-19, we found two case series where the clinical improvement on ventilation was reported in 65% to 75% of patients and a third case series of fifteen patients where one showed improvement, nine had clinical stabilization, two had disease aggravation and three died; serious adverse events reported on this three studies were septic shock and death in two patients and one gastrointestinal perforation.[23-25] This could justify the use of ruxolitinib as a broader anti-cytokine therapy instead of IL-6 only inhibition. Nevertheless, it's important to recognize that most of the patients treated with tocilizumab in these case series were under invasive mechanical ventilation at the start of treatment.

The challenge of COVID-19 treatment is that, until now, there is no specific therapy for the

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disease with unsatisfactory results on lopinavir/ritonavir[26] and a recently described increased risk of mortality with hydroxychloroquine and/or azithromycin.[27] The first report on remdesivir on a compassionate-use basis demonstrated that patients had improvement in oxygen support achieving extubation in 57% of the invasive mechanical ventilation group.[28] A randomized placebo controlled study of remdesivir showed shorter recovery time as benefit in patients requiring supplemental oxygen in the treatment group but not in those who were in high flow oxygen support, nor on invasive mechanical ventilation, and there was no significative statistical difference in mortality between both groups.[29] With this data we are still without an efficient treatment for this disease making it more complex in those patients who are in a severe state secondary to cytokine storm.

This study limitations are based on its retrospective design and the low number of cases described restraining significant differences in outcomes measures. Another significant constraint was our limitation to measure cytokines like IL1, IL6 and TNF, nevertheless we indirectly watched the cytokine storm by regular proinflammatory markers. Even with limited cases, this report shows the use of ruxolitinib in ten patients treated under compassionate-use with promising results to support larger trials. Given the nature of the study the principal restrictions were missing values in follow-up for secondary endpoints.

This study shows ruxolitinib treatment safety in patients with COVID-19, the next step should be a prospective analysis of its safety and efficacy with a longer follow-up.

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