ramr
Revista Americana de Medicina Respiratoria
American Review of Respiratory Medicine

ORIGINAL ARTICLE

ISSN 1852 - 236X

Compassionate-Use Ruxolitinib for Covid-19 Compared to Treatment with Chloroquines. Report on 100 cases at the Hospital de Especialidades Portoviejo, Ecuador

Ruxolitinib como uso compasivo para la Covid-19 frente al tratamiento con cloroquinas: Reporte de 100 casos en el Hospital de Especialidades Portoviejo - Ecuador

Guillen Cuadros, Mayra[1]; Wittong Montesdeoca, Raquel[1]; Cornejo Lago, Silvia[1]; Macías Zambrano, Daniel[2]

Recibido: 11/10/2021
Aceptado: 07/04/2022

Correspondence
Dra. Mayra Guillen Cuadros
Email:
neumoguillen@hotmail.com
Portoviejo, Ecuador

ABSTRACT

The group with compassionate use of ruxolitinib for Covid-19 showed improved chest images and a larger number of discharged patients, compared to group 1 (chloroquines and azithromycin), with a decrease in inflammatory markers. There is one article that described a case which refractory to anti-IL6 therapy but responded to Jak-Stat inhibition with ruxolitinib.[1] The most common comorbidity in both groups was arterial hypertension, followed by diabetes type 2; group 1 showed a larger number of patients without comorbidities (18 patients).

The number of male patients with the disease caused by SARS-CoV2 was larger in group 1, with 31 males (62.0%), compared to a total of 19 females (38.0%), whereas in group 2, 25.0% were males, and 25.0% females. The severity of Covid-19 was defined as **moderate:** adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, tachypnea), particularly $SpO_2 \geq 90\%$ on ambient air; and **severe:** adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, tachypnea) plus some of the following: respiratory rate > 30 breaths/min, severe respiratory distress or $SpO_2 < 90\%$ on ambient air.[2]

The acute respiratory distress syndrome (ARDS) in both groups had an average ratio of pressure arterial oxygen and fraction of inspired oxygen (PaFi) of 135.3 mmHg in the ruxolitinib group versus 138.9 mmHg in the control group.

Efficacy was defined as: decrease in inflammatory markers, gasometric improvement in the PaFi, lower oxygen requirement, lower number of patients with severe symptoms admitted to the Intensive Care Unit, proof of the drug's safety 10 days after use, and detailed number of discharged patients.

Key words: Coronavirus Infection; Cytokines; Respiratory Distress Syndrome, Adult; SARS-CoV2; Chloroquines

Rev Am Med Resp 2022;22:218-224
https://doi.org./10.56538/ramr.GWFC3776

[1] Hospital de Especialidades Portoviejo, Ministry of Health.
[2] Hospital Instituto Ecuatoriano de Seguridad Social (IESS).

RESUMEN

El uso compasivo de ruxolitinib en la covid-19 demostró una mejoría en las imágenes de tórax y mayor número de altas en el grupo que lo usó vs. el grupo 1 (cloroquinas y azitromicina), con descenso de los marcadores inflamatorios. Existe un artículo que señaló que un caso que fue refractario a la terapia anti-IL6, pero respondió a la inhibición de Jak-Stat con ruxolitinib.[1] La comorbilidad más frecuente en ambos grupos fue la hipertensión arterial, seguida por la diabetes tipo 2; el grupo 1 presentó un mayor número de pacientes que no presentaban comorbilidades (18 pacientes).

El número de hombres con enfermedad por SARS-CoV2 fue mayor en el grupo 1, con 31 hombres (62,0%) frente un total de 19 mujeres (38,0%), mientras que, en el grupo 2, el 25,0% eran hombres y mujeres, el 25,0%. La gravedad de la covid-19 fue definida como **moderada**: adolescente o adulto con signos clínicos de neumonía (fiebre, tos, disnea, taquipnea), en particular $SpO_2 \geq 90\%$ con aire ambiente; y **grave**: adolescente o adulto con signos clínicos de neumonía (fiebre, tos, disnea, taquipnea) más alguno de los siguientes: frecuencia respiratoria > 30 inspiraciones/min, dificultad respiratoria grave o $SpO_2 < 90\%$ con aire ambiente.[2]

El síndrome de dificultad respiratoria aguda (SDRA) en ambos grupos fue de un promedio de relación entre la presión arterial de oxígeno y la fracción inspirada de oxígeno (PaFi) en el grupo ruxolitinib 135,3 mmHg vs. Grupo control PaFi 138,9 mmHg.

Se definió la eficacia por descenso de los marcadores inflamatorios, mejoría gasométrica de la PaFi, menor requerimiento de oxígeno, disminución del ingreso a unidad de cuidados intensivos de los pacientes con sintomatología grave, demostración de la seguridad del fármaco en los 10 días posteriores a su uso y detallado del número de casos con alta médica.

Palabras clave: Ruxolitinib; Infecciones por coronavirus; Citocinas; Síndrome de Dificultad Respiratoria del Adulto; SARS-CoV2; Cloroquinas

INTRODUCTION

The Covid-19 pandemic presented approximately 10 874 146 million cases and around 521 355 deaths on a worldwide level.[3]

In Ecuador, the rate was 147 033 cases confirmed by RT-PCR (reverse transcription-polymerase chain reaction), with more than 10 800 deaths.[4]

The city of Guayaquil was one of the most affected areas, with the largest number of confirmed cases (17 973); whereas in the Manabí province, 10 151 cases confirmed with swab PCR tests have been reported up to now.[5]

The Intensive Care Units around the country collapsed during the first four weeks. There was a group of patients who couldn't have access to a ventilator. The mortality rate was 7%.

The Hospital de Especialidades Portoviejo received during the first 6 months more than 12 000 cases of suspected Covid-19 based on clinical and epidemiological criteria and chest imaging, with 491 deaths from SARS-CoV-2; and the highest mortality rate occurred in the Intensive Care Unit (48.8%) (Table1).

In view of the severity of this disease, the Pulmonology and Infectology Service of the Hospital de Especialidades Portoviejo, based on poor pharmacological and therapeutic evidence about the Covid-19 pandemic, created a protocol for the compassionate use of medication with ruxolitinib. It was used in SARS-CoV-2 cases with increased inflammatory markers (Ldh [lactate dehydrogenase], ferritin, D-dimer, IL6) and those with more than 50% of radiologic involvement in chest images, at the IIB stage of the disease with hypoxemia. The hypothesis included the fact that the use of ruxolitinib could provide a benefit, because it reduces the cytokine levels, and so it could reduce the number of patients admitted to the Critical Care Units with moderate and severe acute respiratory distress syndrome; this would cause radiological improvement and faster lymphocyte recovery.[6]

TABLE 1. Number of deaths from March to September, 2020, due to Covid-19 at the Hospital de Especialidades Portoviejo

Deceased	Total sum	Percentage
ICU	240	48.88%
Infectology	42	8.55%
Internal medicine	73	14.87%
Neonatology	13	2.65%
Pediatric icu	9	1.83%
Emergency	114	23.22%
Overall total	491	100.00%

Secondary hemophagocytic lymphohistiocytosis (sHLH) is a hyperinflammatory syndrome secondary to several triggers, including sepsis, characterized by strong increase in cytokines with multi-organ failure and a very high mortality rate.[7]

Ruxolitinib reduces the spleen volume and circulating levels of proinflammatory interleukins, particularly IL-6 and TNF-alpha.[8] Recently, preliminary data from 7 patients with sHLH who were treated with ruxolitinib 15 mg (twice a day) showed promising results regarding global survival, and improvement has been observed in the inflammatory markers such as ferritin and soluble IL-2 receptor.[9]

MATERIALS AND METHODS

Patients were studied from April 2020 to June 2020 at the Hospital de Especialidades Portoviejo.

Inclusion criteria

Patients who met the following criteria:

- High suspicion and diagnosis of Covid-19.
- Chest X-ray and tomographies showing more than 50% of radiologic involvement.
- PaFi ≤ 250 mmHg.
- Rapidly worsening respiratory failure requiring invasive ventilation.
- Increase in any of the systemic inflammatory response indicators: LDH 300 U/L, ferritin 1000 ng/mL, D-dimer 1500 ng/mL.
- SpO_2 ≤ 93%.

Exclusion criteria

- Patients diagnosed with Covid-19 plus chronic renal failure with clearance of less than 30 mL/h.
- Infectious diseases, such as tuberculosis, HIV.
- Hypersensitivity to the active principle.
- Pregnant women.
- Patients who weigh less than 50 kg.
- Platelets <50,000 cells/mmc.
- Hemoglobin < 8 g/dL.
- Neutrophils < 500 cells/mmc.
- Sepsis documented by pathogens other than SARS-CoV2.
- Patients who didn't sign consent to the use of ruxolitinib.

DATA ANALYSIS

In the analysis of the information gathered from the medical records of Covid patients, we applied the quantitative paradigm through the use of descriptive statistics and the creation of contingency tables, absolute and relative frequencies, and the calculation of mean values, standard deviation and minimum and maximum values. Inferential statistics is also applied to support the research hypothesis through student-t techniques for independent samples and chi square test, as applicable, depending on the type of variable. For data processing we used the program Excel for windows and the statistical program SPSS, version 21.

Treatment as compassionate use

Patients were randomly selected; 1:1 ratio. They were divided in two groups, 50 patients each, with a total of 100 patients diagnosed with Covid-19 through PCR: **group 1 received 250 mg chloroquine phosphate** every 12 h, for 7 days; **group 2 received 5 mg ruxolitinib**, twice a day, for 10 days. Also, systemic corticoids were used during 3 days, plus general measures (Figure 1).

We performed daily electrocardiogram control and suspended medication in patients with prolonged QT interval ≥ 500 ms.

RESULTS

This study intends to compare the use of two types of treatment in patients admitted to the Hospital Especialidades Portoviejo, Ecuador, an institution in the province of Manabí with the sentinel surveillance system for cases of SARS-CoV-2. Group 1 includes patients who receive **chloroquine + azithromycin;** and in group 2 patients receive **ruxolitinib + methylprednisolone**.

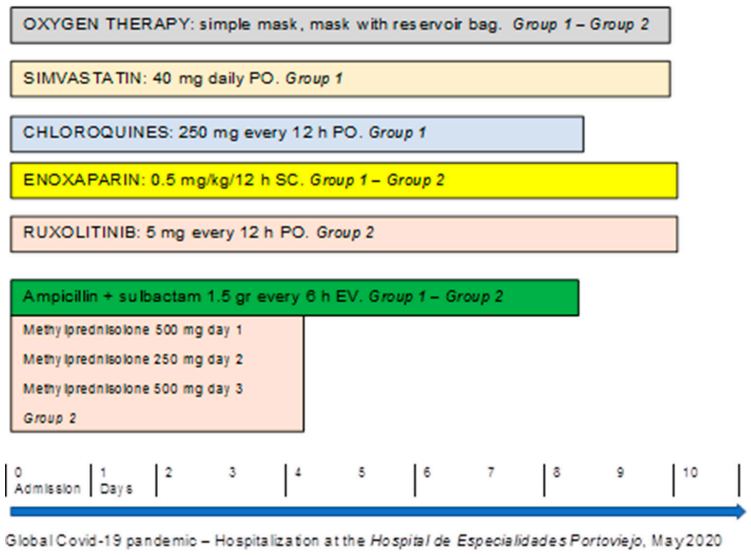

Figure 1. Use of compassionate treatment for patients with pneumonia caused by Covid-19

Table 2 shows the clinical aspects of the cases according to the treatment group. One of the variables is "age", where patients aged 60 or older predominate in both groups (62% in group 1 and 58% in group 2). Mean age was 60.9 ± 10.7 years and 62.2 ± 12.7 years, respectively.

Regarding sex, males predominate in group 1 (62%), and account for 50% in group 2.

The degree of severity that is most frequently presented is "severe" (70.0% in group 1 and 78.0% in group 2). With regard to comorbidities, the presence of an underlying disease (40% in group 1 vs. 34% in group 2), or two or more associated diseases (22% in both groups) predominate in both groups. The most frequently found conditions were: hypertension (22% vs. 16%), hypertension and diabetes (12% vs. 14%), and diabetes (8% vs. 2%), group 1 vs. group 2, respectively.

Table 3 shows some of the clinical parameters used for the Covid diagnosis protocol. SaO_2 was measured upon admission, and similar mean values were observed in both groups (82.94 ± 12.2 in group 1, and 84.12 ± 8.6 in group 2). Also, upon admission, we carried out chest X-ray or lung tomography in patients who were able to move in order to observe the percentage of involvement of the pulmonary parenchyma, and found 51.55 ± 11.9 in group 1, and 54.4 ± 12.7 in group 2. Then, 72% of the patients underwent a control chest X-ray, and a lower percentage of involvement was found in patients treated with ruxolitinib + methylprednisolone (79.1 ± 30.3 in group 2). An assay conducted in China showed significant improvement in the chest computed tomographies of 43 patients who received ruxolitinib. [10]

In order to show the differences between the groups regarding the percentages of lung involvement through imaging, we applied the student-t for independent samples. The results showed that there weren't any statistical differences between the groups in relation to the percentage of lung involvement ($p > 0.05$; at 95% CI).

Adverse effects

Group 1: chloroquines + azithromycin: 4 out of 50 patients had prolonged QT interval, so treatment with chloroquines was suspended. Those patients, who were older than 70 years, died on days 7, 8 and 10 of hospitalization. On day 4 of hospitalization, another patient showed lower gastrointestinal bleeding; it is worth mentioning that the patient had arterial hypertension, diabetes mellitus and nephrectomy due to clear cell cancer. Four patients had sudden death on days 6 and 7 of hospitalization.

Group 2: ruxolitinib + methylprednisolone: 1 out of 50 patients died on day 5 due to a stroke. The other symptoms presented by 4 patients were mild, such as cephalea, insomnia and nervousness on days 1 to 3 of hospitalization; we couldn't determine if those symptoms were characteristic of the ongoing disease.

TABLE 2. Clinical aspects according to the treatment group. Cases of covid-19. Hospital de especialidades portoviejo. Period: May, year 2020

Clinical aspect	Group 1 Chloroquine + Azithromycin (*n* = 50)		Group 2 Ruxolitinib + Methylprednisolone (*n* = 50)	
	Number	%	Number	%
Age in years (mean ± SD):	(60.9 ± 10.7 años)		(62.2 ± 12.7 años)	
< 50	7	14.0	8	16.0
50-59	12	24.0	13	26.0
≥ 60	31	62.0	29	58
Sex				
Male	31	62.0	25	50.0
Female	19	38.0	25	50.0
Severity				
Moderate	15	30.0	11	22.0
Severe	35	70.0	39	78.0
Comorbidities:				
No comorbidities	19	38.0	7	14.0
One comorbidity	20	40.0	17	34.0
Two or more comorbidities	11	22.0	11	22.0
Most common comorbidities:				
Arterial hypertension (AHT)	11	22.0	8	16.0
AHT/DM	6	12.0	7	14.0
Diabetes mellitus (DM)	4	8.0	1	2.0
Other*	29	58.0	34	68.0

* Refers to diseases such as obesity, smoking, asthma and several comorbidities

TABLE 3. Clinical parameters according to the treatment group. Cases of COVID-19. Hospital de especialidades portoviejo. Period: May, year 2020

Parameter	Group 1 Chloroquine + Azithromycin (*n* = 50)	Group 2 Ruxolitinib + Methylprednisolone (*n* = 50)
Initial SO_2		
Mean ± sd	82.94 ± 12.2	84.12 ± 8.6
Minimum value	25	25
Maximum value	93	75
% Initial xr		
Mean ± sd	51.55 ± 11.9	54.4 ± 12.7
Minimum value	20	45
Maximum value	75	95
% Control RX 72 hours**		
Mean ± sd	82.78 ± 32.7	79.1 ± 30.3
Minimum value	25	25
Maximum value	100	100

**Differences between the mean value of % of control RX 72 h according to study group: STUDENT-T, for independent samples (t: 0.5) p (95%): >0.05.

The stroke could have been a matter of causality, considering the hypercoagulability syndrome of Covid-19. The bibliography describes venous thrombosis in patients diagnosed with Sars-CoV-2[11], of 5%-15% in patients outside the ICU, and up to 35% in patients inside the ICU.

Table 4 compares the adverse effects found in patients treated with chloroquine + azithromycin (group 1) vs. those treated with ruxolitinib + methylprednisone (group 2). A higher number of adverse effects and intercurrent conditions was observed in group 1 (64.3%) compared to group 2 (35.7%). Some of the adverse effects are: prolonged QT interval, gastrointestinal bleeding, sudden death, UTI (group 1), and stroke, insomnia, nervousness (group 2). However, the research hypothesis about the differences between the groups according to the treatment couldn't be supported when applying the chi square, obtaining a *p* value > 0.05, 95% CI.

Likewise, there are new lines of research that would show with greater certainty the adverse effects that could be caused by the compassionate use of these treatments for this re-emerging disease and its different variants.

It is necessary to mention there was a limitation upon this research, since we couldn't ask for the autopsy, given the measures imposed by the Ministry of Public Health for the management of corpses of patients diagnosed with Covid-19. Thus, it wasn't possible to determine the real cause of death of these patients, whose treatment (with its adverse effects and complications) is showing effectivity up to this day, and is being evaluated by specialists around the world.

The number of patients referred to the Intensive Care Unit was higher in group 1: 30 patients. Only one of those patients was discharged (3.3%), whereas 14 patients from group 2 were referred to the ICU, and 4 of them recovered (28.5%).

CONCLUSION

We can't attribute the decrease in mortality and ICU admissions to the group using ruxolitinib, since patients from this group received systemic corticosteroids; but, the increase in the number of patients being discharged and the lower number of adverse effects found in group 2 (ruxolitinib +

TABLE 4. Adverse effects and intercurrent conditions according to the treatment group*. Cases of COVID-19. Hospital de especialidades portoviejo. Period: May, year 2020

Intercurrent Conditions adverse effects	Group 1 Chloroquine + Azithromycin (*n* = 50)		Group 2 Ruxolitinib + Methylprednisolone (*n* = 50)		Total	
	Number	%	Number	%	Number	%
None	41	47.7	45	52.3	86	100
Present	9**	64.3	5***	35.7	14	100

*Pearson's CHI^2: 1.32 p (95%): 0.24.
**Group 1: prolonged QT interval, gastrointestinal bleeding, sudden death, UTI (urinary tract infection).
***Group 2: stroke, cephalea, insomnia, nervousness.

TABLE 5. Evolución de la enfermedad según grupo de tratamiento*. Casos COVID-19, hospital de especialidades portoviejo. Período: mayo, año 2020

Evolution	Group 1 Chloroquine + Azithromycin (*n* = 50)		Group 2 Ruxolitinib + Methylprednisolone (*n* = 50)	
	Number	%	Number	%
Discharge	11	22.0	37	74.0
Death	39	78.0	13	26.0

**Pearson's CHI^2: 27.08 p (95%): 0.000.

methylprednisolone) are surprising. A significant increase in mortality was seen with the use of chloroquines and azithromycin.

This case report invites health professionals to conduct studies with more statistical weight to evaluate drugs that inhibit the cytokine storm induced by Covid-19.

Conflict of interest

Authors have no conflict of interest to declare.

REFERENCES

. Innes AJ, Cook LB, Marks S, et al. Ruxolitinib para la infección por COVID-19 grave resistente al tratamiento con tocilizumab. Br J Haematol. 2020;190:e181–e232. https://doi.org/10.1111/bjh.16979

2. OMS: Organización Mundial de la Salud. [Internet]. Manejo clínico de la COVID-19: Orientaciones provisionales. 2020;16. [citado 27 de Mayo 2020].Disponible en: https://apps.who.int/iris/bitstream/handle/10665/332638/WHO-2019-nCoV-clinical-2020.5-spa.pdf
3. News.google [Internet].Coronavirus covid19. Ecuador. 2020; [actualizado 8 septiembre 2020]. Disponible en: https://news.google.com/covid19/map?hl=es419&mid=/m/02j71&gl=US&ceid=US:es419
4. Salud.gob.ec. [Internet].Covid-19 Ministerio de Salud Pública. Ecuador:2020;1-2. BoletinN°196. [Actualizado 12/09/20208]. Disponible en : https://www.salud.gob.ec/wp-content/uploads/2020/09/Boletin-196_Nacional_MSP.pdf
5. Salud.gob.ec. [Internet]. Situación nacional por covid-19 infografía n°227. Ecuador:2020; 1-5. [Inicio 29/02/2020 Corte 11/10/2020]. Disponible en :https://www.salud.gob.ec/wp-content/uploads/2020/10/INFOGRAFIA-NACIONALCOVID19-COE-NACIONAL-08h00-11102020_new.pdf
6. Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. J AllergyClin Immunol. 2020;146:137-46.e.3. https://doi.org/10.1016/j.jaci.2020.05.019
7. Puja M, Daniel F, Michael B, et al. COVID-19: considere los síndromes de tormenta de citocinas y la inmunosupresión. Lancet 2020;395.
8. Caocci G, La Nasa G. Could ruxolitinib be effective in patients with COVID-19 infection at risk of acute respiratory distress syndrome (ARDS)? Ann Hematol. 2020;99:1675-6. . https://doi.org/10.1007/s00277-020-04067-6
9. Swamy Y, Paul S, Timothy B, et al.Inhibición de la señalización de citocinas por ruxolitinib e implicaciones para el tratamiento con COVID-19. Clin Immunol. 2020;218.
10. Cao Y, Wei J, Wang G, et al. Reply. J Allergy Clin Immunol. 2020;146:1453-4. https://doi.org/10.1016/j.jaci.2020.07.037
11. Lopez Reyes, Oscullo G, Jimenez D, et al. Riesgo trombótico y Covid-19: revisión de la evidencia actual para un mejor enfoque diagnóstico y terapéutico. Arch Bronconeumol. 2021;57:55-64. https://doi.org/10.1016/j.arbres.2020.07.033