Ruxolitinib in severe COVID-19. Results of a multicenter, prospective, single arm, open-label clinical study to investigate the efficacy and safety of ruxolitinib in patients with COVID-19 and severe acute respiratory syndrome

Ruxolitinib en COVID-19 grave. Resultados de un estudio multicéntrico, prospectivo, de brazo único y diseño abierto para evaluar la eficacia y seguridad del ruxolitinib en pacientes con COVID-19 y síndrome respiratorio agudo grave

Ruxolitinibe em COVID-19 grave. Resultados de um estudo abertom multicêntrico, prospectivo, de braço único para avaliar a eficácia e segurança de ruxolitinibe em pacientes com COVID-19 e síndrome respiratória aguda grave

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La COVID-19 no dispone aún de tratamientos específicos dirigidos contra el virus causante (SARS-CoV2). Debido a que el principal mecanismo involucrado en la enfermedad está relacionado con la respuesta inmunitaria, se propone que los fármacos que actúan sobre estos procesos podrían ser de utilidad. El ruxolitinib parece una alternativa segura para reducir la necesidad de emplear respiradores en los pacientes afectados.

What is already known

• COVID-19 SARS has no specific antiviral treatment and there is a current need for such strategies.

• Cytokine storm seems the main pathogenic pathway for COVID-19 SARS

What new knowledge is intended

• Ruxolitinib seems a safe treatment and treated COVID-19 patients did not need mechanical ventilation.

• Mortality rate in UCI COVID-19 patient showed a non-significant trend to be lower

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Abstract:

Introduction: COVID-19 morbimortality is mainly associated with development of severe acute respiratory syndrome (SARS), which has been related to an augmented immune response of the host with elevated circulating cytokines. **Methods:** In this prospective, multicenter, single arm (compared with a historical control), add-on, experimental phase 2 study, ruxolitinib 5 mg BID was added to standard of care in COVID-19 patients. Main objective was to determine efficacy and safety of ruxolitinib in patients with COVID-19-related SARS. **Results:** Even though we could not show a significant reduction of COVID-19 pneumonia patients requiring intensive care unit admission and mechanical ventilation (primary endpoint), a trend to a lower mortality rate in critical ill patients receiving ruxolitinib was reported. Administered ruxolitinib dose had to be increased according to protocol in 32% of patients, without additional toxicity. **Conclusion:** Side effects profile was manageable, and no direct organ injury was caused by the study drug. Ruxolitinib had a fast anti-inflammatory effect, and one-third of patients felt well immediately after starting treatment.

Keywords: coronavirus infections; Janus kinase inhibitors; respiratory distress syndrome, adult.

Resumen:

Introducción: La morbimortalidad por COVID-19 se asocia principalmente con el síndrome respiratorio agudo severo (SARS), relacionado con una respuesta inmunitaria aumentada del huésped con aumento de los niveles circulantes de citoquinas. **Métodos:** En este estudio prospectivo, multicéntrico, de un solo brazo (en comparación con un control histórico), en fase 2, se agregó ruxolitinib 5 mg dos veces al día al estándar de tratamiento en pacientes con COVID-19. El objetivo principal fue determinar la eficacia y seguridad de ruxolitinib en pacientes con SARS relacionado con COVID-19. **Resultados:** aunque no fue posible demostrar una reducción significativa de la proporción de pacientes con neumonía por COVID-19 que requerían ingreso en la unidad de cuidados intensivos y ventilación mecánica (criterio de valoración principal), se observó una tendencia a una menor tasa de mortalidad en los pacientes críticos que recibieron ruxolitinib. La dosis de ruxolitinib administrada tuvo que aumentarse de acuerdo con el protocolo en el 32% de los pacientes, sin toxicidad adicional. **Conclusión:** El perfil de efectos secundarios fue manejable y el fármaco en estudio no causó lesiones orgánicas directas. El ruxolitinib tuvo un efecto antiinflamatorio rápido y un tercio de los pacientes manifestó bienestar inmediatamente después de comenzar el tratamiento.

Palabras clave: infecciones por coronavirus; inhibidores de las cinasas Janus; síndrome de dificultad respiratoria del adulto.

Resumo:

Introdução: A morbidade e mortalidade por COVID-19 estão principalmente associadas à síndrome respiratória aguda grave (SARS), relacionada a um aumento da resposta imune do hospedeiro com aumento dos níveis circulantes de citocinas. **Métodos:** Neste estudo prospectivo, multicêntrico, de braço único (comparado a um controle histórico), na fase 2, ruxolitinibe 5 mg duas vezes ao dia foi adicionado ao padrão de tratamento em pacientes com COVID-19. O objetivo principal foi determinar a eficácia e segurança de ruxolitinibe em pacientes com SARS relacionada ao COVID-19. **Resultados:** Embora não tinha sido possível demonstrar uma redução significativa na proporção de pacientes com pneumonia pela COVID-19 que requereram admissão na unidade de terapia intensiva e ventilação mecânica (desfecho primário), uma tendência a uma taxa de mortalidade mais baixa foi observada em pacientes gravemente enfermos que receberam ruxolitinibe. A dose administrada teve que ser aumentada de acordo com o protocolo em 32% dos pacientes, sem toxicidade adicional. **Conclusão:** O perfil de efeitos colaterais foi controlável e o medicamento do estudo não causou dano orgânico direto. O ruxolitinibe teve um efeito anti-inflamatório rápido e um terço dos pacientes relatou bem-estar imediatamente após o início do tratamento.

Palavras-chave: infecções por coronavirus; inibidores de janus quinases; síndrome do desconforto respiratório do adulto.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was officially declared pandemic by WHO on March 11th 2020[(1)]. By January 2021, the Johns Hopkins University reported that globally infected population reached 92 million, with 2 million deaths[(2)]. Although most patients were asymptomatic, 18% required hospitalization because of pneumonia; in turn, almost 20% of COVID-19 pneumonia patients needed hospitalization in the intensive care unit (ICU) [(2)]. Mortality rates may be as high as 60% in patients requiring mechanical ventilation (MV), depending on several variables[(3)].

COVID-19 morbimortality is mainly associated with development of severe acute respiratory syndrome (SARS), which has been related to an augmented immune response of the host[(4,5)].

Several elevated cytokines have been observed in patients with COVID-19, correlating with adverse clinical outcomes. Most of these molecules act by triggering a distinct intracellular signaling pathway through the activation of the Janus kinases (JAKs). The effectiveness of different immunomodulating drugs has not been well stablished yet. Anti JAK-STAT therapy blocks multiple cytokines, hence JAK-STAT signaling may be considered likely good a therapeutic target[(6,7)].

Herein, our investigation group suggested that the use of the JAK 1/2 inhibitor, ruxolitinib 5 mg every 12 hours (BID) would decrease the proportion of patients with COVID-19 SARS who become critically ill (defined as patients requiring MV and/or a fraction of inspired oxygen [FiO_2] ≥ 50%).

METHODS

Study design
This is a prospective, multicenter, single arm (compared with a historical control), add-on, experimental phase 2 study, registered as NCT04414098[(8)]. Three Argentinean centers (two from Buenos Aires and one from Cordoba) recruited participants according to inclusion and exclusion criteria listed below.

Historical control group (standard of care [SOC] cohort) included patients who met all selected criteria and were hospitalized at the participating center before ruxolitinib availability.

Endpoints
Main objective was to determine the efficacy and safety of ruxolitinib in patients with COVID-19-related SARS. The primary endpoint was to evaluate the proportion of patients with COVID-19 acute respiratory syndrome who become critically ill.

Secondary endpoints were: average duration of hospital stay; clinical status during follow-up at 45 days since ruxolitinib starting; response rate of proinflammatory state by measuring of inflammatory parameters at baseline, at middle and end of treatment; mortality rate; adverse events (AEs) rate and secondary infections rate at day 45 from ruxolitinib treatment starting.

Inclusion and exclusion criteria
Patients with SARS caused by COVID-19 were included in accordance with the following inclusion criteria:
[1] Age ≥ 18 years.

[2] Confirmed SARS-CoV2 diagnosis by detection in nasopharyngeal samples of SARS-CoV2 viral genome by polymerase chain reaction (PCR).
[3] Respiratory rate ≥ 20/min and oxygen saturation ≤ 93% (FiO_2 = 0.21).
[4] Chest X-ray or lung computed tomography showing pulmonary infiltrates.
[5] Signed Informed consent.

Exclusion criteria consisted in:
[1] Pregnancy or breastfeeding.
[2] Thrombocytopenia ≤ 50,000 cells/mm^3.
[3] Neutropenia ≤1000 cells/mm^3.
[4] Hemoglobin < 6 g/dl.
[5] Active infection (human immunodeficiency virus, hepatitis C virus, hepatitis B virus, varicella-zoster virus or *Mycobacterium tuberculosis* (including latent infection detection by Quantiferon® and/or tuberculin skin test).
[6] Current treatment with interferon, tocilizumab or similar drugs during current SARS-CoV2 infection.
[7] History of hypersensitivity to any drugs or metabolites of similar chemical classes as ruxolitinib.
[8] Active onco-hematologic disease.
[9] Mechanical Ventilation.
[10] Aspartate aminotransferase (AST) and/or alanine aminotransferase (AST) > 5 times of upper limit of normal (ULN).
[11] Severely impaired renal function (serum creatinine ≥ 2 mg/dl or estimated creatinine clearance ≤ 30 ml/min).
[12] Any condition that, in the investigator's judgment, may interfere with full participation in the study.

Treatment suspension criteria included:
[1] Voluntary decision of the patient.
[2] Treating physician's decision to discontinue the treatment.
[3] Drug toxicity grade ≥ 3 according to CTCAE 5.0[(9)].

SOC
SOC consisted in dexamethasone 6 mg per day for 10 days or until discharge[(10)], enoxaparin 40 mg/day (or dose-adjusted thromboprophylaxis according to thromboembolic risk factors) [(11)], and supplemental oxygen as needed[(11)]. Convalescent plasma, ampicillin-sulbactam, acetaminophen, codeine and early prone positioning combined with noninvasive ventilation could also be used. No antiviral drug, interferon neither other immunomodulatory medication were used.

Fever patterns
Temperature curves in COVID-19 participants were characterized in seven categories or patterns (table 1), as follows:
[1] Apyrexia.
[2] Fever only at baseline.
[3] Fever up to day 3 ± 1 day.
[4] Fever up to day 6 ± 1 day.
[5] Reappearing of fever, persisting more than one day.
[6] Appearing of fever, persisting more than one day.
[7] Appearing of fever and persisting at least one day.

Table N° 1: Fever patterns

Pattern #	1	2	3	4	5	6	7
Baseline	o	x	x	x	x	o	o
Day +3	o	o	x	x	o	o	o
Day +6	o	o	o	x	o	o	x
Day +9	o	o	o	o	o	x	o
Day +12	o	o	o	o	x	x	o
Day +21	o	o	o	o	x	x	o

(x) = fever ≥ 37.3°C; (o) = no fever

Intervention

Active group participants started ruxolitinib treatment according to protocol (5 mg BID orally). Both groups received SOC and were followed-up for 45 days. World Health Organization (WHO) 8-Points-Scale[12] and NEWS-2 score[13] were assessed in a daily basis, while inflammatory markers (acute phase reactants [APR]: C-reactive protein [CRP], ferritin, D-dimer/fibrinogen) were measured every 72 hours.

Ruxolitinib dose was planned to be increased in case of clinical progression or APR elevation, or both, up to maximum dose of 20 mg BID. No dose change was recommended if APR and NEWS-2/WHO 8-points scores were stable or better. Dose was increased 5 mg BID if APR became worse but with NEWS-2 / WHO 8-points score remaining stable. An increase of 10 mg BID was recommended if both APR and NEWS-2/WHO 8-points became worse. APR worsening was defined as an increase ≥ 20% ULN in at least 2 of 3 parameters. In case of cytopenia, a transient or definitive dose reduction could also be considered. Patients were evaluable only with a minimum of 3 days of follow-up. AEs and severe AEs (SAEs) were screened and registered in a daily basis in the medical records and informed to the Ethical Local Committee and Novartis pharmacovigilance program.

Ethical issues

In all cases, participation in this study was voluntary and certified by an informed consent process. The study was carried out in full accordance with current national and international regulations, including the WHO Declaration of Helsinki in its updated version, the Argentinean Ministry of Health Resolution 1480/2011[14], and Law 25326 on Protection of Personal Data[15]. Informed consents and study data were retrieved in compliance with the contingency plan for the pandemic.

Statistical analysis

Data were anonymized and access was restricted only for authorized personnel with the only purposed of this study, according to local regulations. Due to the nature of our study, sample size calculation was not necessary.

To meet secondary objectives, the Kolmogorov–Smirnov test was performed to estimate the goodness of fit and, according to this result, comparison were evaluated with ANOVA test for quantitative variables and Kruskall-Wallis test for nominal variables. Single 2x2 comparisons for categorical variables were performed through chi-squared or Fisher exact test. IBM SPSS Statistics v.22.0 for Windows was used for statistical analysis. We considered statistically significant a 2-tails value of $p < 0.05$.

RESULTS

Clinical and demographic characteristics

Fifty-four patients with SARS due to COVID-19 were recruited from June 12th to November 10th, 2020. Two patients had to be transferred to another institution and were lost for follow-up. One patient voluntary withdrew the informed consent after 4 days of ruxolitinib treatment and received only SOC. Historical control group was composed by fifty-one patients who met all selected criteria and were hospitalized at the participating center before ruxolitinib availability. A total of 102 patients were evaluable, 51 per each group. Baseline demographic and clinical characteristics of patients and controls are shown in table 2. Median age was 57 years (range: 28–79) and 59 (28–80) with a male predominance (73% vs 69%) in ruxolitinib and SOC groups, respectively. The most frequent comorbidities in both groups were overweight/obesity, arterial hypertension, diabetes mellitus, chronic lung disease (smoking, asthma or chronic obstructive pulmonary disease), prostatic hyperplasia and chronic renal impairment. Characteristics were well balanced in both cohorts, excepting for a significantly higher proportion of hypertensive patients in subjects receiving ruxolitinib. Median time from initial symptoms to confirmed diagnosis was 2 and 4 days in ruxolitinib and SOC group, respectively. Median time to hospitalization was 5 days for both groups.

Table N° 2: Baseline demographic, clinical, and laboratory characteristics of patients and controls

Variable	Control group	Ruxolitinib group
N	51	51
Age, years (median, range)	59 (28–80)	57 (28–79)
Male	35 (69%)	37 (73%)
COVID-19 onset atypical symptoms (chest pain)	0%	1.9%
Time from initial symptoms to diagnosis, days (median, range)	4 (0–11)	2 (0–10)
Time from initial symptoms to hospitalization, days (median, range)	5 (0–12)	5 (0–11)
Clinical characteristics		
Overweight/obesity	18 (35.3%)	23 (45.1%)
Hypertension (*)	12 (23.5%)	24 (47%)
Chronic pulmonary disease	3 (5.9%)	9 (17.6%)
Prostatic hyperplasia	3 (5.9%)	0 0%
Chronic renal failure	2 (3.9%)	0 0%
Diabetes mellitus	13 (25.5%)	17 (33.3%)
Arrhythmia	0 0%	1 (1.9%)
Basocellular skin cancer	0 0%	1 (1.9%)
Lung cancer	1 (1.9%)	0 0%
Congenital brachial paralysis	0 0%	1 (1.9%)
Coronary heart disease	3 (5.9%)	2 (3.9%)
Glaucoma	0 0%	1 (1.9%)
Hypothyroidism	3 (5.9%)	7 (13.7%)
Renal cancer	0 0%	1 (1.9%)
Epilepsy	1 (1.9%)	0 0%
Herpes genital	1 (1.9%)	0 0%
Liver cirrhosis	1 (1.9%)	0 0%
Basal hematological parameters		
Hemoglobin, g/dl (median, range)	13.9 (7.9-17.7)	14.35 (10.4-16.7)
White blood cells, /µl (median, range)	6290 (140-17500)	9050 (3910-20440)
Lymphocytes, /µl (median, range)	1025 (162-2150)	928.5 (357-2182)
Platelets, 10^3 cells/µl (median, range)	216 (56-646)	247 (121-481.5)

All data are n (%), except when specified

No statistic differences was shown between groups, except for (*) p < 0.05 (chi squared test)

All patients (100%) receiving ruxolitinib were alive at the end of follow up, without requirement of supplementary oxygen and/or with functional respiratory recovery, while 95% of SOC-control participants achieved this primary endpoint (p = 0.24, Fisher exact test). Cause of death in five cases in the SOC group was multi-organic failure.

Ruxolitinib dose adjustment was allowed according to protocol amendment (protocol version 3.0, June 19th, 2020) and was implemented in 16 (32%) patients. Maximum allowed dose was 20 mg BID, and it was reached by 4 patients without side effects. No subjects had to reduce ruxolitinib dose because of cytopenia.

Thirty six percent (95%CI: 25-51%; 19 patients) under ruxolitinib treatment and 33% (95%CI: 22-47%; 17 patients) of SOC-control subjects progressed during treatment and required admission in the ICU (p = 0.83). Most frequent comorbidities among these patients in ICU were hypertension (58%), obesity (41%), diabetes mellitus (39%) and chronic lung conditions (14%) (Table 3).

Table N° 3: ICU patients results

	Ruxolitinib group	SoC group	P
	(n = 19)	(n = 17)	
High flow cannula needing	6	3	NS (*)
N (%)	(31.6%)	(17.6%)	
Mechanical ventilation	13	14	NS
	(68.4%)	82.3%	(*)
Hospitalization duration before ICU, days (median, range)	4	5	NS
	(1–17)	(0–14)	(**)
Hospitalization in ICU, days (median, range)	7	8	NS
	(2–41)	(0–37)	(**)
Deaths (n, %)	0 (0%)	5 (29.4%)	0.05 (*)

(*) Fisher exact test

(**) U Mann-Whitney test

Median time from initial COVID-19 symptoms to ruxolitinib starting treatment was 9 days (range 3-22). Respectively, median treatment duration and follow-up to last contact was 9 days (range: 4–14) and 45 days.

Median hospitalization time was 14 days in both groups. At cutoff, 5 patients had been discharged and followed at home by telemedicine, one remained in hospital whereas 96 patients had finished the study. No patients had to be re-hospitalized because of COVID-19 pneumonia progression and there were no relapses after discharging.

APR and laboratory monitoring
D-dimer: sixty eight percent of patients showed levels exceeding upper normal level (UNL) at diagnosis, with the highest value of 4 x UNL. No thrombosis cases were diagnosed during the study period. Fifty percent of patients showed normalization of D-dimer during the first week. No statistically differences were seen between both groups.
CRP: this biomarker seemed the best laboratory parameter for follow-up. Even though no correlation was found between higher levels and responses, all patients normalized CRP levels before discharge.
Ferritin: at treatment starting, 75% of patients showed values over UNL. In the remaining 25% of patients, levels of ferritin increased after few days. A good correlation with clinical response was observed, but ferritin levels returned slowly to normal, usually with non-lineal pattern. Ferritin normalization in SOC-control group was more erratic.
Lymphocyte count: no significant differences were described between ruxolitinib and SOC-controls. Lymphopenia is highly frequent in COVID-19 subjects and a faster recovery is linked to a lower possibility of clinical progression.
Other biomarkers: serum fibrinogen levels > 400 mg closely correlated with D-dimer concentration. However, fibrinogen levels kept high at discharge, while other inflammatory biomarkers returned to normal. Erythrocyte sedimentation rate also stayed high after discharge, but levels reduced during follow-up with a non-lineal pattern. Troponin-1 concentration was not useful as a diagnostic or prognostic biomarker, while hypertriglyceridemia was not found among the study population. Lactate dehydrogenase inconsistently correlated with the inflammatory state.

Imaging
All patients resolved COVID-19 pneumonia imaging during follow-up. Sequalae, mainly pulmonary fibrosis, was observed in 34% of patients of both groups.

Safety
Lymphopenia (<1.5 x 10^3 cells/μl) was described in all subjects at baseline (38% and 48% in SOC-control and ruxolitinib groups, respectively). However, during follow-up, lymphopenia tended to disappear, persisting in 10% in all patients.
Thrombocytosis (> 450 x 10^3 cells/μl) was initially reported in 4% of patients. During follow-up, proportion of thrombocytosis raised to 42% in ruxolitinib cohort versus 16% in the SOC-control group (p < 0.05, exact Fisher test). Maximum reported elevation was 958 x 10^3 cells/μl. No active intervention was needed, and close follow-up was decided. Most cases returned to normal level within one week.
AST/ALT elevation was present in 40% of patients before starting ruxolitinib and the prevalence reached 58% during follow-up. A similar pattern was described in SOC-control cohort. When elevation of AST/ALT was considered grade ≥ 3 (n = 4), ruxolitinib administration were interrupted. The same happened in 1 patient in SOC-controls and no other intervention was necessary.
No patients presented bradycardia (heart rate < 55/min) at baseline. Nevertheless, 22% of subjects in each group developed asymptomatic bradycardia during follow-up. Bradycardia was not associated with other cardiac sign or symptom and only close monitoring was indicated. One patient experienced a QT interval prolongation (520 ms; AE grade 3) with no clinical consequences.
A case of mild pancreatitis was described. The patient presented amylase elevation (3 x ULN), abdominal pain, increased serum lipase and high transaminases. General pancreatitis support measures were taken and ruxolitinib was withdrawn.
According to NEWS-2 and the febrile curve patterns described above, 50% in both groups remained afebrile during follow-up (pattern #1), while 57 febrile episodes were reported in 102 evaluable patients. Thirty-one episodes (54%) occurred in those receiving ruxolitinib. In this group, the most frequent temperature pattern was #2, fever at baseline (32%) that relieved right immediately after treatment initiation and associated with general subjective patients' well-being. Patterns #5 and #6 (reappearing or appearing of fever and persisting ≥1 day, respectively) occurred in 9 patients (18%) and superinfections in this group were confirmed in 10 subjects. In SOC-controls, we identified 26 (46%) febrile episodes with a predominant trend to pattern #3 and #4 (persisting fever for more 3 or 6 days). Superinfections in both groups included secondary pneumonia (n = 8), febrile syndrome of unknown origin (n = 5), urinary tract infection (n = 3) and cellulites (n = 1). Global safety evaluation is summarized in table 4.

Table N° 4: Safety profile

Adverse Events	SoC group (n = 51)		Ruxolitinib group (n = 51)	
	Baseline N (%)	Follow-up N (%)	Baseline N (%)	Follow-up N (%)
Anemia (hemoglobin < 12 g/dl)	2 (4%)	8 (16%)	7 (13%)	2 (4%)
Polycythemia (hemoglobin >18 g/dl)	1 (2%)	0	1 (2%)	0
Leukocytosis (>11.5 x10³ cells/µl)	6 (12%)	8 (16%)	12 (24%)	5 (10%)
Leucopenia (< 4.5 x 10³ cells/µl)	7 (14%)	1 (2%)	4 (8%)	2 (4%)
Thrombocytopenia (< 140 x 10³ cells/µl)	10 (20%)	0	4 (8%)	0
Thrombocytosis (> 450 x 10³ cells/µl)	2 (4%)	8 (16%)	2 (4%)	21 (42%)
AST (< 34 IU/ml) and/or ALT(< 55 IU/ml)	19 (38%)	24 (48%)*	20	29 (58%)*
Creatinine clearance reduction	1 (2%)	7 (14%)	0	4 (8%)
Lymphopenia (<1.5 x 10³ cells/µl)	19 (38%)	5 (10%)	24 (48%)	5 (10%)
Bradycardia (< 55/min)	0	11 (22%)	0	11 (22%)
QT prolongation (> 450 ms)	0	0	0	1 (2%)†
Superinfection	0	7 (14%)	0	10 (20%)**
Facial cellulites	0	0	0	1 (2%)
Acute pancreatitis	0	0	0	1 (2%)
Definitely interruption due to AEs	NA	NA	NA	4 (8%)

Safety data were available for 102 patients

(*) Grade 3 AE (4 patients in the ruxolitinib group, 1 patient in the SoC group)

(†) Grade 3 AE (1 patient)

(**) Febrile curve pattern #5 and #6 were described in 9 cases

DISCUSSION

While many efforts on COVID-19 approach are focusing on an anti-SARS-CoV-2 vaccine or antiviral drug regimen, most of the potential treatments are still under investigation[16]. We could not show a significant reduction of COVID-19 pneumonia patients requiring ICU admission and MV (primary endpoint), but we found a trend to a lower mortality rate in critical ill patients. As shown in table 5, several open-label studies yielded similar endpoints and their findings were described. For example, in a prospective, single blind, multicenter, randomized, controlled, phase II study, Cao et al[7] investigated clinical improvement, defined as the time from randomization to an improvement of 2 points, and showed a faster clinical recovering, a trend to decrease some specific cytokines at initial treatment, and a faster increasing of immunoglobulin M with normal virus clearance time. La Rosee et al[17] in a retrospective, single center study, introduced a COVID Inflammatory Score (CIS) that allowed recognizing the best time to initiate the treatment, a close clinical follow-up and predictive factors of response. Capochiani et al[18] in a retrospective, multicenter study, investigated the rapid reduction of respiratory impairment; they reported that higher initial doses of ruxolitinib were associated with better outcomes and stated that reducing inflammation would be a key to a success treatment. Vannucchi et al[19] published a prospective, observational, compassionate use, add on study; their endpoint was clinical improvement (decrease of ≥ 2 points in an ordinal scale) from a first ruxolitinib dose up to day 28. They also described that interleukin 6 and CRP were good biomarkers, and that elderly patients with severe comorbidities were the most benefited of this treatment. In our study, we showed good tolerability, an acceptable drug-study management with safeties and more benefits to critical ill patients under high flow oxygen demand or MV. Paradoxically, we excluded patients under MV assistance, mainly because there was no previous experience with this indication. The results of our open-label study are in line with a recent press released from Novartis announcing the failure of ruxolitinib therapy to meet the primary endpoint in RUXCOVID Phase III clinical trial[20].

Table N° 5: Ruxolitinib in COVID-19: State of the art

	Cao Y, *et al*[7]	La Rosee F, *et al*[17]	Capochiani E, *et al*[18]	Vannucchi A, *et al*[19]	Iastrebner M, *et al*[(*)]
Design	Prospective, single blind, multicenter, randomized, controlled phase II study.	Retrospective, single center study.	Retrospective, multicenter study.	Prospective, observational, compassionate-use, add-on study.	Prospective, single-arm, add-on, multicenter, control open label, no randomized, compared with historical arm study.
Patients (n)	Soc (21) *vs* Ruxo (20)	Ruxo (14)	Ruxo (18)	Ruxo (34)	Soc (51) *vs* Ruxo (51)
Primary endpoint	Time to clinical improvement (time from randomization to an improvement of 2 points)	CIS improvement (day 7) > 25%	Rapid reduction of respiratory impairment degree	Clinical improvement (decrease ≥2 points in an ordinal scale) from first dose of Ruxo up to day 28	Proportion of patients who become critically ill or required mechanical ventilation
Age, years (median, range)	63 (range 58 - 68)	66 (range 55 - 81)	62 (range 28 - 86)	80 (range 70-85)	57 (range 28 - 79)
Male gender (%)	58%	79%	67%	53%	73%
Ruxo initial dose	5 mg BID	7,5 mg BID	20 mg BID	5 mg BID	5 mg BID
Dose adjustment	No	Yes (maximum 15 mg)	Yes (tapering 10 to 5 mg BID, every 48 h)	Yes, an increase of 10 mg every 48 h (maximum 25 mg) BID	Yes, 5 or 10 mg every 72 h (maximum 20 mg BID)
Mortality rate	0% (Ruxo arm) *vs* 14,3% (Soc arm)	7.14% (1/14 cases)	0%	5.9%	0% (Ruxo group) *vs* 10% (SoC group)
Findings and comments	Faster clinical recovery. Decrease of 7 cytokines IgM first recovery Normal virus clearance time	COVID-19 Inflammation Score (CIS)	Rapid restoration of PaO$_2$/FiO$_2$ in 2 days (2nd endpoint) Ruxo sensibly ameliorate the course of the disease	IL6 and CRP at day +14 Elderly patients with severe comorbidities were the most benefited	Critical ill patients as the most benefited. Febrile patterns associated to superinfections. Dose adjustment model. Thrombocytosis, Lymphocytopenia improvement associated with clinical recovery

(*) Ruxolitinib in Severe Covid-19. Results of a Multi-Center, Single Arm, Control Open-label Clinical Study to Investigate the Efficacy and Safety of Ruxolitinib in Patients with COVID-19 and Severe Acute Respiratory Syndrome [In press]

We chose a 5 mg BID dose on the basis of good results in immune diseases with the goal of being extremely cautious[(21,22)]. Administered dose had to be increased according to protocol in 32% of patients, without additional toxicity. Therefore, a higher initial dose should be taken into account in future studies. The study drug should not be administered after achieving pulmonary functional recovery as it was planned by the protocol, taking into consideration that COVID-19 relapses were not reported after discharging and no second inflammatory wave has been described[(23)].

A trend to clinical recovery was observed with thrombocytosis, and it was more evident in ruxolitinib arm (p = 0.09, Fisher exact test). Among underlying mechanisms, a direct cytokine storm effect stimulating megakaryopoiesis and/or thrombopoiesis has been suggested in COVID-19 patients[(24)]. No medical intervention was taken, and this issue deserves further future research.

Bradycardia and prolonged QTc interval were considered as linked directly to COVID-19; nevertheless, ruxolitinib was suspended as a precautionary measure[(25,26)].

In our clinical series, 5-times elevation above the UNL of transaminases requiring ruxolitinib interruption was recorded in 4 patients. Liver injury seems very common in COVID-19 patients[(27,28)]. Acute pancreatitis was described in one patient, this affection was also probably caused by COVID[(29,30)].

Superinfections were described in both groups and COVID-19 may have a proper predisposition. Most available literature regarding infections refers to chronic hematological diseases[(31)].

CONCLUSION

Ruxolitinib failed to significantly reduce the proportion of COVID-19 pneumonia patients requiring ICU admission and MV, but once admitted, the mortality rate showed a trend to be lower (p = 0.24). Side effects profile was manageable, and no direct organ injury was caused by the study drug.

REFERENCES

1. World Health Organization. Virtual press conference on COVID-19. 2020 Mar. Available at: https://bit.ly/3gg2mrf

2. Johns Hopkins University and Medicine. Coronavirus Resource Center. Available at: https://bit.ly/2JURG57

3. Castaneda C, Ah Rhee CJ, Magh A, Eng C, Mann J, Sanso L, Abe O. Impact of ventilator model on mortality: a retrospective cross-sectional study in 147 mechanically ventilated patients with COVID-19 ARDS. Chest. 2020 Oct;158(4):A617. doi: 10.1016/j.chest.2020.08.58.

4. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017 Jul;39(5):529-539. doi: 10.1007/s00281-017-0629-x.

5. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. Semin Immunopathol. 2017 Jul;39(5):517-528. doi: 10.1007/s00281-017-0639-8.

6. Luo W, Li YX, Jiang LJ, Chen Q, Wang T, Ye DW. Targeting JAK-STAT Signaling to Control Cytokine Release Syndrome in COVID-19. Trends Pharmacol Sci. 2020 Aug;41(8):531-543. doi: 10.1016/j.tips.2020.06.007.

7. Cao Y, Wei J, Zou L, Jiang T, Wang G, Chen L, Huang L, Meng F, Huang L, Wang N, Zhou X, Luo H, Mao Z, Chen X, Xie J, Liu J, Cheng H, Zhao J, Huang G, Wang W, Zhou J. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. J Allergy Clin Immunol. 2020 Jul;146(1):137-146.e3. doi: 10.1016/j.jaci.2020.05.019.

8. Iastrebner M. Ruxolitinib in the Treatment of Covid-19. ClinicalTrials.gov registration number: NCT04414098. 2020 Jun. Available in: https://clinicaltrials.gov/ct2/show/NCT04414098

9. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), V5.0. 2017 Nov. Available at: https://bit.ly/33NS3FN (last accessed Dec 2nd, 2020).

10. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021 Feb 25;384(8):693-704. doi: 10.1056/NEJMoa2021436.

11. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at: https://bit.ly/3oNtWiD

12. World Health Organization. Novel Coronavirus: COVID-19 Therapeutic Trial Synopsis. Switzerland: WHO. R&D Blueprint. 2020 Available at: https://bit.ly/36JbdhV

13. Royal College of Physicians. National Early Warning Score (NEWS) 2. 2017 Dec. Available at: https://bit.ly/3lLYejY

14. Ministerio de Salud de la Nación. Guía para Investigaciones con Seres Humanos. Resolución 1480/2011. Available at: http://www.anmat.gov.ar/webanmat/legislacion/medicamentos/Resolucion_1480-2011.pdf

15. Protección de los Datos Personales. Ley 25326. Ministerio de Justicia y Derechos Humanos. Prom 2000 Oct 30. Available at: http://servicios.infoleg.gob.ar/infolegInternet/anexos/60000-64999/64790/texact.htm

16. Jean SS, Lee PI, Hsueh PR. Treatment options for COVID-19: The reality and challenges. J Microbiol Immunol Infect. 2020 Jun;53(3):436-443. doi: 10.1016/j.jmii.2020.03.034.

17. La Rosée F, Bremer HC, Gehrke I, Kehr A, Hochhaus A, Birndt S, Fellhauer M, Henkes M, Kumle B, Russo SG, La Rosée P. The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation. Leukemia. 2020 Jul;34(7):1805-1815. doi: 10.1038/s41375-020-0891-0.

18. Capochiani E, Frediani B, Iervasi G, Paolicchi A, Sani S, Roncucci P, Cuccaro A, Franchi F, Simonetti F, Carrara D, Bertaggia I, Nasso D, Riccioni R, Scolletta S, Valente S, Conticini E, Gozzetti A, Bocchia M. Ruxolitinib Rapidly Reduces Acute Respiratory Distress Syndrome in COVID-19 Disease. Analysis of Data Collection From RESPIRE Protocol. Front Med (Lausanne). 2020 Aug 4;7:466. doi: 10.3389/fmed.2020.00466.

19. Vannucchi AM, Sordi B, Morettini A, Nozzoli C, Poggesi L, Pieralli F, Bartoloni A, Atanasio A, Miselli F, Paoli C, Loscocco GG, Fanelli A, Para O, Berni A, Tassinari I, Zammarchi L, Maggi L, Mazzoni A, Scotti V, Falchetti G, Malandrino D, Luise F, Millotti G, Bencini S, Capone M, Piccinni MP, Annunziato F, Guglielmelli P; RUXO-COVID Study Group. Compassionate use of JAK1/2 inhibitor ruxolitinib for severe COVID-19: a prospective observational study. Leukemia. 2021 Apr;35(4):1121-1133. doi: 10.1038/s41375-020-01018-y.

20. Novartis Press Release: Novartis provides update on RUXCOVID study of ruxolitinib for hospitalized patients with COVID-19. 2020 Dec 14. Available at: http://bit.ly/39rTH3r

21. Fioranelli M, Roccia MG, Lotti T. Treatment of dermatomyositis with ruxolitinib. Dermatol Ther. 2016 Jul;29(4):285. doi: 10.1111/dth.12308.

22. Aeschlimann FA, Frémond ML, Duffy D, Rice GI, Charuel JL, Bondet V, Saire E, Neven B, Bodemer C, Balu L, Gitiaux C, Crow YJ, Bader-Meunier B. A child with severe juvenile dermatomyositis treated with ruxolitinib. Brain. 2018 Nov 1;141(11):e80. doi: 10.1093/brain/awy255. Erratum in: Brain. 2019 Jan 1;142(1):e3.

23. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708-1720. doi: 10.1056/NEJMoa2002032.

24. Amgalan A, Othman M. Hemostatic laboratory derangements in COVID-19 with a focus on platelet count. Platelets. 2020 Aug 17;31(6):740-745. doi: 10.1080/09537104.2020.1768523.

25. Amaratunga EA, Corwin DS, Moran L, Snyder R. Bradycardia in Patients With COVID-19: A Calm Before the Storm? Cureus. 2020 Jun 13;12(6):e8599. doi: 10.7759/cureus.8599.

26. Merino JL, Martínez-Cossiani M, Iniesta A, Escobar C, Rey JR, Castrejón-Castrejón S. COVID-19 and QT interval prolongation: more than just drug toxicity? Europace. 2020 Oct 1;22(10):1479. doi: 10.1093/europace/euaa145.

27. Agarwal A, Chen A, Ravindran N, To C, Thuluvath PJ. Gastrointestinal and Liver Manifestations of COVID-19. J Clin Exp Hepatol. 2020 May-Jun;10(3):263-265. doi: 10.1016/j.jceh.2020.03.001.

28. Wang Q, Zhao H, Liu LG, Wang YB, Zhang T, Li MH, Xu YL, Gao GJ, Xiong HF, Fan Y, Cao Y, Ding R, Wang JJ, Cheng C, Xie W. Pattern of liver injury in adult patients with COVID-19: a retrospective analysis of 105 patients. Mil Med Res. 2020 Jun 7;7(1):28. doi: 10.1186/s40779-020-00256-6.

29. Aloysius MM, Thatti A, Gupta A, Sharma N, Bansal P, Goyal H. COVID-19 presenting as acute pancreatitis. Pancreatology. 2020 Jul;20(5):1026-1027. doi: 10.1016/j.pan.2020.05.003.

30. Komar HM, Serpa G, Kerscher C, Schwoegl E, Mace TA, Jin M, Yang MC, Chen CS, Bloomston M, Ostrowski MC, Hart PA, Conwell DL, Lesinski GB. Inhibition of Jak/STAT signaling reduces the activation of pancreatic stellate cells in vitro and limits caerulein-induced chronic pancreatitis in vivo. Sci Rep. 2017 May 11;7(1):1787. doi: 10.1038/s41598-017-01973-0.

31. Clancy CJ, Nguyen MH. Coronavirus Disease 2019, Superinfections, and Antimicrobial Development: What Can We Expect? Clin Infect Dis. 2020 Dec 17;71(10):2736-2743. doi: 10.1093/cid/ciaa524.