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ARTICLE

Compassionate use of ruxolitinib in patients with SARS-Cov-2 infection not on mechanical ventilation: Short-term effects on inflammation and ventilation

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Abstract

Ruxolitinib is an anti-inflammatory drug that inhibits the Janus kinase-signal transducer (JAK-STAT) pathway on the surface of immune cells. The potential targeting of this pathway using JAK inhibitors is a promising approach in patients affected by coronavirus disease 2019 (COVID-19). Ruxolitinib was provided as a compassionate use in patients consecutively admitted to our institution for severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection. Inclusion criteria were oxygen saturation less than or equal to 92%, signs of interstitial pneumonia, and no need of mechanical ventilation. Patients received 5 mg b.i.d. of ruxolitinib for 15 days, data were collected at baseline and on days 4, 7, and 15 during treatment. Two main targets were identified, C-reactive protein (CRP) and PaO_2/FiO_2 ratio. In the 31 patients who received ruxolitinib, symptoms improved (dyspnea scale) on day 7 in 25 of 31 patients (80.6%); CRP decreased progressively from baseline (79.1 ± 73.4 mg/dl) to day 15 (18.6 ± 33.2, $p = 0.022$). In parallel with CRP, $PO2/FiO_2$ ratio increased progressively during the 3 steps from 183 ± 95 to 361 ± 144 mmHg ($p < 0.001$). In those patients with a reduction of polymerase chain reaction less than or equal to 80%, delta increase of the $PO2/FiO_2$ ratio was significantly more pronounced (129 ± 118 vs. 45 ± 35 mmHg, $p = 0.02$). No adverse side effects were recorded during treatment. In patients hospitalized for COVID-19, compassionate-use of ruxolitinib determined a significant reduction of biomarkers of inflammation, which was associated with a more effective ventilation and reduced need for oxygen support. Data on ruxolitinib reinforces the hypothesis that targeting the hyperinflammation state, may be of prognostic benefit in patients with SARS-CoV-2 infection.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Some evidence suggest that patients affected by coronavirus disease 2019 (COVID-19) present an exuberant inflammatory response represented by a massive production

of type I interferons and different pro-inflammatory cytokines. Nonetheless, as for the present, there are no proven therapeutic agents for COVID-19, in particular anti-inflammatory and antiviral, with a significant and reproducible positive clinical response.

WHAT QUESTION DID THIS STUDY ADDRESS?

Targeted therapeutic management of pro-inflammatory pathways appears to be a promising strategy against COVID-19, and ruxolitinib, due to its established broad and fast anti-inflammatory effect, appears to be a promising candidate worthy of focused investigations in this field.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Ruxolitinib rapidly reduces the systemic inflammation, which accompanies the disease, thereby improving respiratory function and the need of oxygen support. This effect may contribute to avoid progression of the disease and the use of invasive ventilation.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Data on ruxolitinib contributes the reinforcement of the hypothesis that it is crucial to counteract the early hyperinflammation state, particularly of the lungs, induced by COVID-19 infection.

INTRODUCTION

The respiratory illness syndrome named coronavirus disease 2019 (COVID-19), caused by the novel coronavirus severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), has emerged as a pandemic disease causing a worldwide ongoing health and social emergency.[1,2] The clinical course of the disease is rarely predictable, ranging from asymptomatic or mild forms, to severe respiratory compromise and multiorgan failure,[3,4] but data show that older patients and those with pre-existing cardiovascular or respiratory illnesses are more inclined to develop major complications and death.[5,6] Some evidence suggest that critically ill patients present an exuberant inflammatory response represented by a massive production of type I interferons and different pro-inflammatory cytokines.[7,8] Nonetheless, as for the present, there are no specific therapeutic agents for COVID-19, and many patients have received off-label drugs, in particular anti-inflammatory and antiviral, without a significant and reproducible positive clinical response.[9,10]

Ruxolitinib is a direct oral inhibitor of both JAK1 and JAK2 protein kinases that acts by inhibiting cellular components of both innate and adaptive immunity.[11] Ruxolitinib has a relevant role in the treatment of myeloproliferative diseases,[12] but solid data has been reported even in the treatment of acute and chronic graft-versus-host disease[13] and in different types of autoimmune and inflammatory disease.[14–16] Targeted therapeutic management of pro-inflammatory pathways appears to be a promising strategy against COVID-19, and ruxolitinib, due to its established broad and fast anti-inflammatory effect, appears to be a promising candidate worthy of focused investigations in this field. Here, we report a single-center experience in a cohort of patients hospitalized for COVID-19 who were treated with ruxolitinib on a compassionate use basis.

METHODS

Patients

Novartis has accepted requests from physicians for the compassionate use of ruxolitinib since March 18, 2020. The assessment form for treatment request should include patients with the following major characteristics: (a) inpatients with laboratory confirmed diagnosis of SARS-CoV-2 infection admitted to Policlinico di Monza Hospital, (b) Oxygen saturation less than or equal to 92% on ambient-air at entry, (c) radiologic signs of interstitial pneumoniae, and (d) no need of invasive mechanical ventilation at baseline. Exclusion criteria for the request were severe anemia (Hb level below 8 g/dl), low platelets count (< 50,000 u/l), creatine clearance less than or equal to 30 ml/min, and serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) more than three times the upper limit of the normal range. In approved cases for ruxolitinib use, a fixed dose of 5 mg b.i.d. was given for a period of 15 days. The 10 mg daily dose was chosen following the US Food and Drug Administration (FDA) label for ruxolitinib use in acute graft-versus-host disease, which presents a cytokine storm similar to COVID-19 infection. The same dosage has been selected in the ongoing randomized study with ruxolitinib (NCT04362137). We opted for a follow-up of 15 days considering previous studies with inhibitor of both JAK1 and JAK2 protein kinases, which showed rapid effects of the drug on inflammation.

Data were collected through April 2020. This open-label study did not have a predetermined number of patients.

Design of the study

The study was approved by the local ethics committee and all enrolled subjects signed the consent form for the compassionate use of the drug. The program was designed and conducted with efficacy and safety end points. Laboratory parameters, oxygen-support requirements, and arterial blood gas analysis (ABT) were collected at baseline and on days 4, 7, and 15 after the administration of ruxolitinib. Data was recorded by investigators who also had the responsibility of the statistical analysis. All authors had access to the data and assumed responsibility for the completeness of the reported data.

Considering the characteristics of ruxolitinib, we hypothesized two main effects in patients affected by SARS-CoV-2 infection: (1) reduction of C-reactive protein (CRP) as the response of bloodstream to inflammation, and (2) improvement of ventilation as expressed by the ratio PaO_2/FiO_2. The PaO_2/FiO_2 is the ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen.[17] At sea level, the normal PaO_2/FiO_2 ratio is ~ 300–500 mmHg; lung dysfunction severity is mild when the ratio is from 200 to 300, moderate when 100–200, and severe if less than 100 mmHg. Symptoms and well-being were assessed by the 5-point Likert scale of dyspnea. A patient was defined improved if one or more steps were gained as compared with the baseline.

Patients did not receive other anti-inflammatory agents. No management changes were introduced during the time frame of the study.

Safety of the drug was carefully monitored by two main laboratory parameters: the platelet count and the ALT/AST levels as possible indexes of hepatotoxicity. In case of side-effects, ruxolitinib would be suspended without previous dose reduction.

Statistical analysis

The statistical analysis included all patients with complete collection of clinical data for at least the first two follow-up steps (day 4 and day 7).

The data relating to clinical characteristics, blood chemistry, and respiratory parameters of the population were expanded by descriptive statistics (mean and SD, median and range).

The analysis of variance (ANOVA) method (analysis of variance for repeated measurements) with a 95% confidence interval was used to analyze both the trend of the blood and respiratory parameters during follow-up, and all dual comparisons between the possible combination of hematochemical and respiratory parameters (day 0 vs. day 4; day 0 vs. day 7; day 0 vs. day 15, day 4 vs. day 7, day 4 vs. day 15, and day 7 vs. day 15), reporting in the text a significance for $p < 0.05$. Finally, a correlation analysis was performed between changes of polymerase chain reaction (PCR) as a marker of inflammation and PaO_2/FiO_2 ratio as the index of effective ventilation. For this purpose, the delta changes of the variable CRP from baseline to 7 days were categorized in less than or more than or equal to −80%, and subsequently the 2 groups were relayed with the percentage increase of the PO_2/FiO_2 ratio.

All analyses were conducted with SAS software, version 9.4 (SAS Institute).

RESULTS

In the first 2 weeks of April, 36 patients were evaluated consecutively to receive ruxolitinib. Four were excluded because they were on mechanical ventilation, therefore 32 started the treatment. One patient was excluded after the first dose because he required invasive ventilation. Of the 31 remaining patients included in the analysis, 29 (93.5%) received the full 15-day course of ruxolitinib, and 2 (6.5%) received a 7-day course of treatment.

Baseline demographic and clinical characteristics of the 31 patients are reported in Table 1. A total of 18 patients (58%) were men and the mean age was 69 ± 12 years, median 70.5 (range 42:86 years). One third of the patients had more than one comorbidity, the most prevalent was hypertension. At baseline, the majority were on high flow oxygen support or noninvasive ventilation (NIV). At that time in our institution, all patients received per protocol azithromycin and hydroxychloroquine along with heparin at anticoagulant dosage. Only 8 of 31 patients were on antiviral drugs at baseline (lopinavir + ritonavir, and darunavir + ritonavir) but in 5 of these patients the treatment was discontinued for lack of efficacy when ruxolitinib was started, whereas in 3 patients it was maintained throughout the study. All patients had signs of SARS-CoV-2 pneumonia on chest x-ray, with the involvement of 4 or more lobes in 45%.

An improvement of symptoms (Likert scale) from baseline condition, after 4, 7, and 15 days of treatment with ruxolitinib was observed in 20 (64.5%), 25 (80.6%), and 28 patients (90.3%), respectively (Figure 1).

At baseline, mean CRP was 79.1 ± 73.4 mg/L and progressively decreased to 18.6 ± 33.2 mg/L at 15 days ($p = 0.022$; Table 2). Ruxolitinib was also associated with a significant rapid increase of lymphocyte count at day 4 with a subsequent stabilization. No significant differences were observed in hemoglobin, white blood cells, and platelets counts (Table 2).

After 4 days of treatment, 5 of 13 patients (38%) moved from low-flow oxygen to ambient air, and at day 7 there were 11 of 13 patients (85%). Fifty percent (4/8) of the patients who were on high-flow oxygen at day 4 were on low-flow oxygen, whereas at day 7, two were on ambient air and 4 were on low-flow oxygen support. Among those patients on NIV ($n = 10$), 3 were on high-flow oxygen at day 4, whereas at day 7 two were on low-flow and 4 were on high-flow oxygen. Four patients on NIV at baseline did not improve, and 3 required invasive mechanical ventilation after 7 days ($n = 2$) or 15 days ($n = 1$) of ruxolitinib therapy.

Conversely, all patients in the low and high-flow oxygen therapy were discharged after 15 days without oxygen support.

Arterial blood gas analysis data during treatment are reported in Table 2. Due to different oxygen support no significant changes were observed in arterial oxygen saturation, PaO_2, and $PaCO_2$. On the contrary, the ratio PO_2/FiO_2 positively increased during the 15 days of follow-up from 183.1 ± 94.8 to 361.5 ± 144.3 mmHg with a significant reduction of the respiratory rate (Figure 2).

During ruxolitinib treatment, CRP decreased at day 7 more than 80% from baseline in 17 patients (55%), and only in 4 patients it remained unchanged or slightly increased. In those with a marked decrease of CRP, PO_2/FiO_2 ratio increased significantly more than in the other group (delta% increase 129 ± 118 vs. 45 ± 35 mmHg, $p = 0.02$), thus confirming the association between anti-inflammatory effect and the improvement of ventilation.

The drug was safe and no significant changes of laboratory parameters were noted during the compassionate use of the drug (Table 2). The drug was discontinued in 2 patients after 7 days due to the need of mechanical ventilation, none for side effects. In one patient, we observed a reduction of platelet count, which was transitory and improved after correction of the heparin regimen.

TABLE 1 Baseline characteristics of patients treated with ruxolitinib ($n = 31$)

	Baseline
Age, years, median (range)	70.5 (42:86)
Female, patient (%)	13 (42)
Comorbidities, *n* (%)	
Hypertension	19 (61)
Chronic kidney disease	1 (3)
COPD	3 (10)
Diabetes	6 (19)
Chronic heart failure	5 (16)
Coronary artery disease	3 (10)
More than one comorbidity	10 (32)
Oxygen-support category, *n* (%)	
Ambient air	0
Low-flow oxygen, < 5 L/min	13 (42)
High-flow oxygen, > 5 L/min	8 (26)
NIV	10 (32)
Invasive mechanical ventilation	0
Duration of symptoms before starting ruxolitinib therapy, days, media ± SD	12 ± 7
Ongoing treatments at the start of ruxolitinib therapy, *n* (%)	
Azithromycin	31 (100%)
Hydroxychloroquine	31 (100%)
Antiretroviral	8 (26%)
Low weight heparin	31 (100%)
Abnormal chest on x-ray/CT scan	31 (100%)
> 4 lobes	14 (45%)
3 lobes	15 (48.5%)
2 lobes	2 (6.5%)

Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computer tomography; NIV, noninvasive ventilation.

DISCUSSION

This preliminary report in a limited number of patients affected by SARS-CoV-2 interstitial pneumonia who were

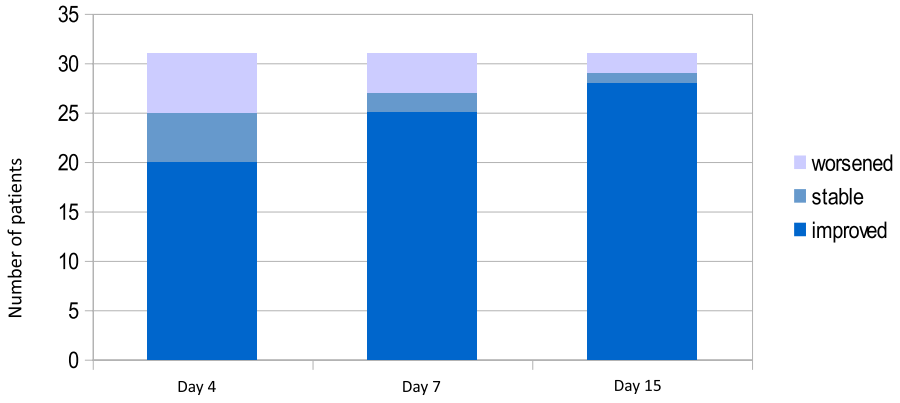

FIGURE 1 Improvement of symptoms (dyspnea) from baseline to days 4, 7, and 15 of ruxolitinib treatment. The 5-point Likert scale of dyspnea was used and a patient was defined improved if one or more steps were earned as compared with baseline

TABLE 2 Effect of ruxolitinib from baseline to day 15 follow-up

	Baseline	Day 4	Day 7	Day 15	*p* value
Complete blood count					
Hemoglobin, g/dl	12.4 ± 1.8	12.1 ± 2.0	12.2 ± 2.0	12.0 ± 1.7	0.92
White blood cells, cells/mcl	8490 ± 3501	8700 ± 3634	8717 ± 4666	9638 ± 5392	0.86
Neutrophils, %	71.5 ± 16..3	66.3 ± 18.9	63.0 ± 18.7	63.4 ± 19.5	0.35
Lymphocytes, %	17.6 ± 11.5	24.4 ± 16.7*	26.6 ± 16.1*	27.6 ± 17.4*	0.07
Platelets, platelets/mcl	287.3 ± 119.1	296.3 ± 113.8	293.9 ± 142,0	329.7 ± 213.6	0.63
CRP, mg/L	79.1 ± 73.4	45.9 ± 69.1	31.7 ± 76.8	18.6 ± 33.2	0.022
Creatinine, mg/dl	0.92 ± 0.66	0.86 ± 0.65	1.25 ± 1.64	0.85 ± 0.19	0.47
ALT, U/L	35.6 ± 25.5	33.8 ± 21.8	44.4 ± 65.1	28.7 ± 31.5	0.62
AST, U/L	49.6 ± 56.1	47.7 ± 34.9	61.6 ± 71.0	53.1 ± 77.9	0.80
Lactic dehydrogenase, mU/ml	565.8 ± 214.6	556.7 ± 280.5	513.9 ± 346.8	381.9 ± 157.9	0.17
D-Dimer, µg/ml	659.1 ± 919.4	574.19 ± 679.7	562.6 ± 835.1	333.6 ± 282.9	0.74
Arterial oxygen saturation, %	95.35 ± 2.51	96.19 ± 2.62	97 ± 1.65	96.15 ± 3.05	0.102
PaO_2, mmHg	89.7 ± 25,7	90.0 ± 32.1	91.4 ± 21.3	108.0 ± 44.2	0.94
$PaCO_2$, mmHg	39.4 ± 5.8	40.2 ± 5.8	37.8 ± 6.6	37.5 ± 4.8	0.354

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive Protein; PaO_2, arterial pressure of oxygen; $PaCO_2$, arterial pressure of carbon dioxide.

*$p < 0.05$ versus baseline.

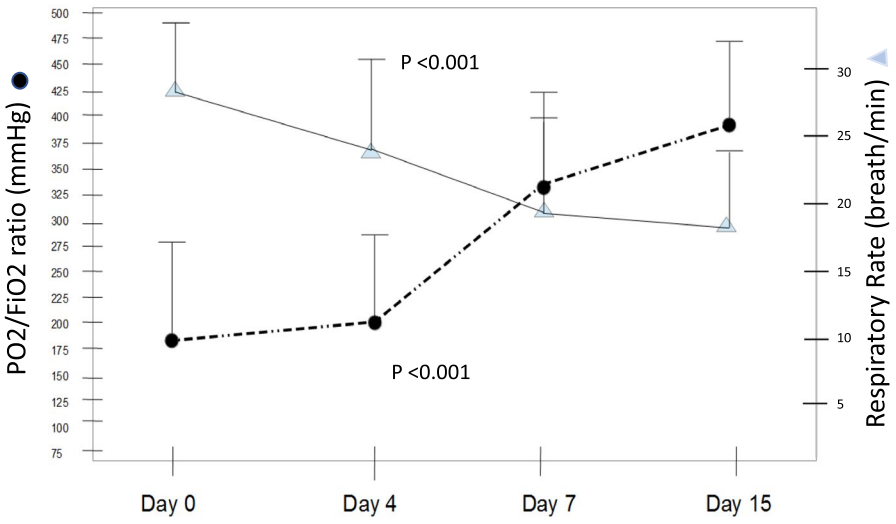

FIGURE 2 Trend of PO_2/FiO_2 ratio (black circles) and of respiratory rate (gray triangles) from baseline to day 15 of treatment. The larger effect of ruxolitinib was observed after 7 days of treatment

not on invasive mechanical ventilation, shows that ruxolitinib rapidly reduces the systemic inflammation that accompanies the disease, thereby improving respiratory function and the need of oxygen support. This effect may contribute to avoid progression of the disease and the use of invasive ventilation.

Ruxolitinib is an oral inhibitor of both JAK1 and JAK2 protein kinases, used to treat myeloproliferative diseases, autoimmune, and inflammatory disorders.[11,18,19] The powerful anti-inflammatory effects of this drugs, whose actions block pro-inflammatory cytokines such as TNF alpha, IL6, and IFN gamma, are likely to have been effective against SARS-CoV-2 infection, which typically presents elevated levels of cytokines.[8,9]

Ruxolitinib was administered orally at 10 mg per day, a dosage much lower than usually used in patients with polycythemia or myelofibrosis. Nevertheless, in more than half of the patients under study it reduced CRP by more than 80% with an associated positive effect on ventilation and respiratory gas exchange. The effect of the drug was rapid and already noticeable after 4 to 7 days of treatment. At the end of the follow-up period of 15 days, most of the treated patients were discharged safely and without oxygen support.

Recently, Cao et al.[20] reported the results of a randomized control study with ruxolitinib in patients with COVID-19. They enrolled 20 patients per arm, and observed a faster clinical improvement, although not significantly different from controls, in patients treated with ruxolitinib. These results

were obtained despite a concomitant large use of glucocorticoids (70%), intravenous immunoglobulin (44%), and antiviral agents (92%). In this study, no data on arterial blood gas analysis are reported, but interestingly, levels of seven cytokines were significantly decreased in the ruxolitinib group as compared with controls.[20] Other three single-arm not randomized studies were published so far about the use of ruxolitinib in COVID-19. All confirm a fast effect of the drug reducing markers on infection and improving signs of respiratory distress.[21–23]

The important role of lung hyperinflammation in COVID-19[19] is again supported by the present study. The network of mediators contributing to inflammatory responses is wide and include, among others, the group of cytokines (interleukin-1 and -6), of interferon (IFN-β and IFN-γ) and of Jak1–2 protein kinases.[9,18,19] Laboratory results in patients hospitalized for COVID-19 showed an increased level of IL-6 suggesting a possible role of the therapy, which may block the effect of IL-6. Tocilizumab is a recombinant humanized monoclonal antibody that has an antagonist effect on the IL-6 receptor. It is used in the treatment of rheumatoid arthritis and has been proposed in patients affected by COVID-19[24]; in a large retrospective study including 100 patients affected by acute respiratory distress syndrome (ARDS) due to COVID-19, Toniati et al.[25] observed that the response to Tocilizumab was rapid, sustained, and associated with significant clinical improvement. However, the randomized controlled trial COVACTA (NCT04320615) failed to meet its primary end point.[26] Nor did tocilizumab improve patient mortality, although tocilizumab-treated patients spent roughly a week less in the hospital compared with those given placebo. Results of the other ongoing randomized trial with this drug are awaited.

Anakinra is a recombinant IL-1 antagonist and is used to treat autoinflammatory disorders, such as macrophage activation syndrome. It was tested by Cavalli et al.[27] to treat patients with COVID-19 with ARDS and hyperinflammation. Authors concluded that anakinra was safe and associated with clinical improvement in 75% of the patients. Two trials have been designed to confirm this preliminary evidence (COV-AID, NCT04330638, and NCT04364009).

Among the inhibitors of the anti-JAK licensed for the treatment of rheumatoid arthritis in addition to ruxolitinib, baricitinib has also been proposed to counteract the hyperinflammation state induced by COVID-19. In a preliminary report in 12 patients affected by COVID-19, baricitinib was safe and significantly improved the clinical and laboratory parameters, none of the patients required intensive care unit (ICU) support, and the majority of the patients were discharged. Interestingly, as we observed for ruxolitinib, the action of baricitinib was rapid with a significant reduction of CRP, and increase of lymphocytes and PO2/FiO_2 ratio.[28]

Reported side effects of the treatment with ruxolitinib include cytopenia, peripheral edema, and new viral or microbial reactivation.[11,12] It is noteworthy that none of our patients reported such adverse effects and only in one case a reduction of platelet count was observed after 10 days of treatment. However, reduction was transitory and changed after modification of the heparin dosage. Differently from a recent report we used a low dose of ruxolitinib, 5–10 time less than reported by Gaspari et al.,[29] and this may have explained the safety of the drug observed in our study.

The major limitations of our pilot study are its open-label design with no randomization and the low number of treated patients. A proper control group was missing and this is indeed required to formally demonstrate the efficacy of the therapy. However, we consecutively enrolled all patients admitted to our institution for COVID-19, not on mechanical ventilation, in the first 2 weeks of April. A control group selected from patients hospitalized in the previous month was not considered a good option due to the different baseline protocol of treatment particularly regarding antithrombotic drugs. Moreover, in an emergency phase of a pandemic disease, randomization of a new drug is a difficult task because, as in the study by Cao et al.,[20] patients received all possible therapies in the attempt to improve prognosis. In our study, other anti-inflammatory drugs were not part of baseline therapy, and only three patients were on antiviral treatment (one on lopinavir + ritonavir, and two on darunavir + ritonavir) but it is very unlikely that they could have affected the results of ruxolitinib therapy.

In conclusion, in this preliminary series of patients affected by COVID-19, but not on severe respiratory distress requiring invasive ventilation, the use of ruxolitinib as compassionate treatment has been shown to rapidly reduce the hyperinflammatory state, thus facilitating a more efficient ventilation and a prompt recovery. We guess that these data are encouraging in terms of clinical impact, reduction of severity progression, and safety. Among others, data on ruxolitinib contributes to reinforce the hypothesis that it is crucial to counteract early the hyperinflammation state, particularly of the lungs, induced by COVID-19 infection.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

A.M., S.M., and G.I. wrote the manuscript. A.M., M.L., G.P., and G.I. designed the research. P.D., C.B., F.C., and P.G. performed the research. D.M. analyzed the data.

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