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Baricitinib in patients with severe pneumonia due to COVID-19 in Veracruz, Mexico

Abstract

Background: Patients affected by COVID-19 pneumonia who present severe symptoms with manifest hypoxemia and cytokine storm have a high mortality rate, which is why therapies focused on reducing inflammation and improving lung function have been used, being one of them Baricitinib

Material and methods: Patients who presented data of severe pneumonia due to COVID-19 with data of severe hypoxemia and cytokine storm were selected, from June to August 2020, to whom the SaO2/FiO2 ratio is measured at the beginning, intermediate and end of treatment.

Results: We included data from 30 patients, 22 (73%) men, with a median age of 58.5 years. 77% had comorbidities: hypertension (43%), obesity (30%), diabetes (27%). The medians of D-Dimer 982ng/mL, Ferritin 1,375ng/mL and CRP 10mg/dL. 97% patients had treatment: azithromycin (77%), ivermectin (53%) and dexamethasone (47%). The initial pulseoximetry (SaO_2) with room air had a median of 80.5% and the median SaO_2/FiO_2 (SAFI) was 134; 90% had moderate ARDS and 10% had severe ARDS. All received Baricitinib 4 mg/day by 14 days. SaO2 at 7 days had a median of 93.0% and the median SAFI was 310; the median SaO2 at 14 days was 95% and the median SAFI was 452. In comparative analysis, baseline SaO_2/SAFI was significantly lower compared to 7 and 14 days ($p = 0.001$ for both comparisons). 90% patients improved and 10% died.

Conclusion: Baricitinib therapy in these patients presented good results by improving clinical status and pulmonary failure, with patients being cared for at home and avoiding mechanical ventilation.

Keywords: Baricitinib; pneumonia; COVID-19

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Introduction

Since the beginning of the pandemic many have been the drugs that have been used in order to give an effective treatment, however, the vast majority have been deprecated for not demonstrating an adequate biosecurity profile and efficacy against COVID-19 infection, mainly in those patients with severe pneumonia who develop cytokine storm and hyper inflammation states that lead to high morbidity, coupled with the absence of randomized controlled clinical trials.[1] After various meta-analysis, the only drugs that appear to be effective are dexamethasone, enoxaparin and a small subgroup of drug s that attempt to decrease hyperinflation states such as anakinra, tocilizumab and jakinibs.[2,3] Anakinra is an IL-1 inhibitor, which has been proposed for critically ill COVID-19 patients who also have acute respiratory insufficiency and cytokine storm and who have failed with other anticytokine drugs like tocilizumab, already supported by various studies although no specific dosage has been established in such situations.[4]

Tocilizumab is an IL-6 receptor blocking drug which, through this effect, decreases the inflammatory response and secondarily the cytokine storm, which extrapolated to the clinic, has shown lower requirements for intensive therapy, vasopressors and need for intubation in critically ill patients although some meta-analysis mentions has had no impact on mortality.[5] Jakinibs are a group of drugs that intracellularly inhibit the pro-inflammatory signal of several cytokines by suppressing Janus kinase (JAK) JAK1/JAK2. A clinical benefit has been shown for patients with rheumatoid arthritis, active systemic lupus erythematosus and atopic dermatitis with good efficacy and safety records. Baricitinib is expected to interrupt the intracellular passage and ablation of SARS-CoV-2 in target cells mediated by the ACE2 receptor and treat the cytokine storm caused by COVID-19. Of these drugs the most commonly used in cases of COVID-19-associated hyperinflation are tofacitinib, ruxolitinib and baricitinib. Among its main advantages in interfering with JAK1/JAK2 signaling are IL-2 blocking, IL-4, IL-5, IL-6, and IL-21 as well as IFNγ which has a greater anticytokine effect than anakinra and tocilizumab, by blocking more pro-inflammatory cytokines, and in theory more effectively to control severe cases with hyperinflation and cytokine storm.[6-8]

There is currently evidence that patients treated with baricitinib have a marked reduction in serum IL-6 levels, IL-1 and tumor necrosis factor (TNF)-A, rapid recovery in the frequencies of circulating T and B cells, and increased production of antibodies against SARS-CoV-2 peak protein, which were clinically associated with a reduction in the need for oxygen flow and a progressive increase in ventilation/infusion, in addition to preventing progression to more aggressive forms of the disease.[9] A recent meta analysis mentions that treatment with Janus kinase inhibitors is significantly associated with positive clinical outcomes in terms of mortality, ICU admission and discharge.[10]

Material and methods

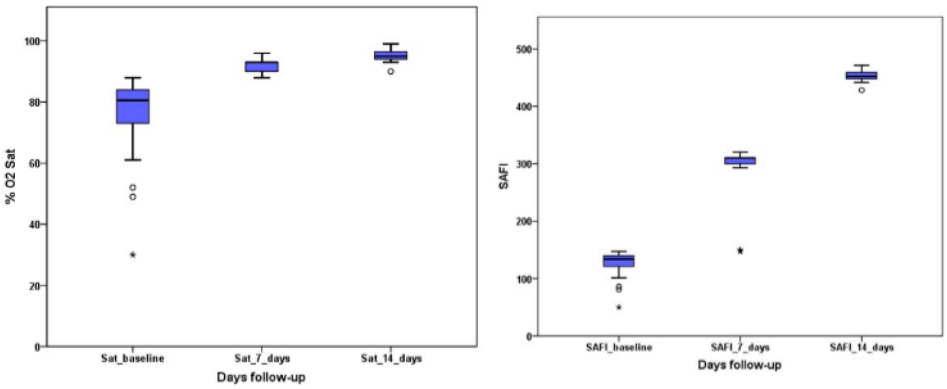
Descriptive and observational study, including adult patients with severe pneumonia confirmed by PCR-RT and pulmonary axial tomography, treated on an outpatient basis who have acute respiratory failure syndrome, secondary hypoxemia and hyperinflation. Medical history, prior medication, oxygen saturation as well as basal SaO_2/

FiO_2 (SAFI) index, mid-treatment and after treatment, characteristics of hematic cytometry, as well as levels of C-reactive protein, D-dimer and serum ferritin are finally analyzed; finally the outcomes after treatment are analyzed.

Results

We include data from 30 patients, 8 (27%) women and 22 (73%) men, with a median age of 58.5 (46.5 – 68.0) years. The number of patients with a history of previous comorbidities was 23 (77%); the most common being high blood pressure (43%), followed by obesity (30%), diabetes mellitus 2 (27%), smoking (7%), dyslipidemia (7%); in addition to cancer, asthma, rheumatoid arthritis, allergic rhinitis, benign prostatic hyperplasia and pulmonary sequelae and tuberculosis, each with a frequency of 3%.

In the basal laboratory we find that the median serum levels of D-dimer [982.0 (734.8 – 2,342.0) ng/mL], Serum Ferritin [1,375.0 (1,019.5 – 2,000.0) ng/mL] and C Reactive Protein [10.0 (7.7 – 12.0) mg/dL], were above the parameters that are considered normal. Median measurements of leukocytes, lymphocytes, neutrophils and platelets were found in normal parameters (Table 1). As for the use of medicinal products prior to the onset of baricitinib, we found that 29 (97%) patients were treated with any medicines, most often using azithromycin (77%), ivermectin (53%) and dexamethasone (47%); the other medicines that patients gave and their frequencies are found in Graph 1. The median medicines received prior to the onset of baricitinib were 3.0 (3.0 – 5.0).



Difference of ranges of SaO2 and SAFI, at baseline (starting day baricitinib), 7 and 14 days (p = 0.001 for both cases; estimated with Wilcoxon range test).

Table 1 Demographic, comorbidities and laboratory

Variable*	Result No. 30
Demographic variables	
Gender	
Women	8 (27)
Mens	22 (73)
Age, years; Median (IQR)	58.5 (46.5 – 68.0)
Previous comorbidities	
Systemic hypertension	13 (43)
Obesity	9 (30)
Diabetes mellitus type 2	8 (27)
Smoking	2 (7)
Dyslipidemia	2 (7)
Chronic kidney disease	1 (3)
Cancer	1 (3)
Asthma	1 (3)
Rheumatoid arthritis	1 (3)
Allergic rhinitis	1 (3)
Benign prostatic hyperplasia	1 (3)
Sequelae of pulmonary tuberculosis	1 (3)
Laboratory variables, median (IQR)	
Leukocytes, cell/mm^3	9,500.0 (6,950,0 – 11,925,0)
Lymphocytes, cell/mm^3	1,310.0 (987.7 – 1,964.2)
Neutrophils, cel/mm^3	6,905.0 (5,046.7 – 9,388.5)
Platelets, cel/mm^3	223,000.0 (180,000.0 – 312,500.0)
D-dimer, ng/mL	982.0 (734.8 – 2,342.0)
Serum ferritin, ng/mL	1,375.0 (1,019.5 – 2,000.0)
C-Reactive Protein, mg/dL	10.0 (7.7 – 12.0)

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With regard to the variables associated with respiratory function that were required in the evaluation in which baricitinib treatment was initiated, we found that the measurement of oxygen saturation by pulse oxymetry with ambient air had a median of 80.5% (73.0 – 84.0) and the median SAFI (SaO_2/FiO_2) was 134.0 (121. 0 – 140.0); as for the type of ARDS, we found that 90% of patients had moderate ARDS and 10% had severe ARDS. The median day of evolution on which baricitinib was started was 10.0 (7.7 – 12.0) days, all patients received doses of 4 mg/day and the median days of baricitinib treatment was 14.0 (13.0 – 14.0) days. In monitoring patients, we found that O2 saturation as measured by pulse oximetry at 7 days had a median of 93.0% (90.0 – 93.0%) and the median SAFI at 7 days was 310.0 (300.0 – 310.0); additionally, the median saturation of O2 measured at 14 days was 95.0% (94.0 – 97.0%) and the median SAFI at 14 days was 452.0 (448.0 – 461.0). In the comparative analysis, we found that the oxygen saturation measured at the start date of baricitinib (basal) was significantly lower compared to measurements made at 7 and 14 days of follow-up ($p = 0.001$ for both comparisons); the SAFI estimate at the start of baricitinib was also significantly lower compared to measurements made at 7 and 14 days of follow-up ($p = 0.001$ for both comparisons) (Graph 2 and Table 2). The outcome was the following, 27 (90%) patients evolved towards improvement and there were 3 (10%) patients who died.

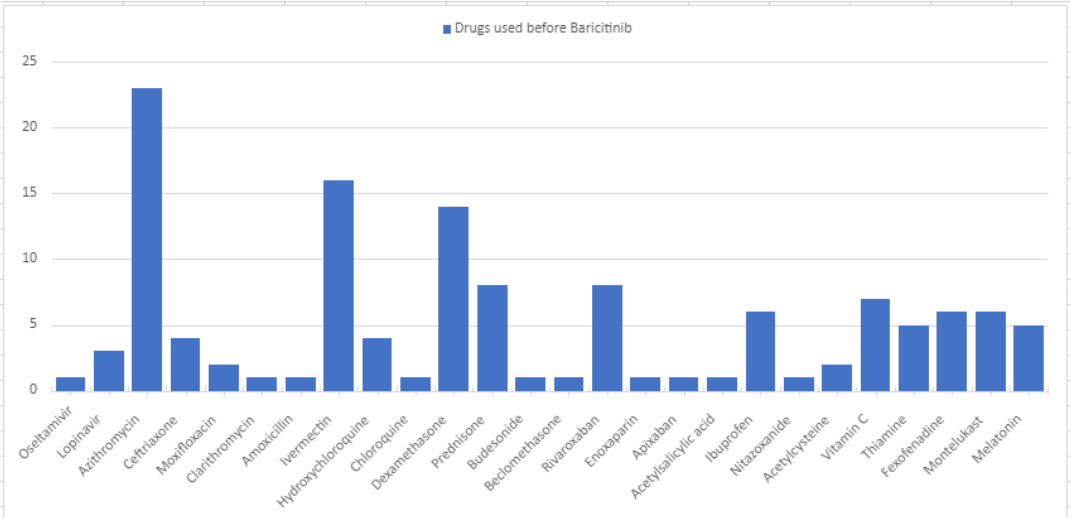

Table 2 Respiratory function and outcome

Variable*	Result No. 30
Respiratory function prior to initiation of baricitinib	
O_2 Sat,%; Median (IQR)	80.5 (73.0 – 84.0)
SAFI (SaO_2/FiO_2), median (IQR)	134.0 (121.0 – 140.0)
ARDS type	
Mild	0 (0)
Moderate	27 (90)
Severe	3 (10))
Variables associated with the use of baricitinib	
Baricitinib Onset Day, Median (IQR)	10.0 (7.7 – 12.0)
Days of treatment, median (IQR)	14.0 (13.0 – 14.0)
Concomitant drugs to baricitinib	
Dexamethasone	3 (10.0)
Enoxaparin	5 (17.0)
Rivaroxaban	22 (73.0)
Apixaban	3 (10.0)
Respiratory function after initiation of baricitinib, median (IQR)	
O_2 saturation at 7 days,%	93.0 (90.0 – 93.0)
SAFI at 7 days	310.0 (300.0 – 310.0)
O_2 saturation at 14 days,%	95.0 (94.0 – 97.0)
SAFI at 14 days	452.0 (448.0 – 461.0)
Outcome	
Improvement	27 (90)
Death	3 (10)

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Discussion

Currently there is an Italian pilot study with baricitinib that has shown clinical utility with improvement within 2 weeks, at a dose of 8mg daily, without adverse events and patients with significant improvement without requiring stay in intensive care, these results are similar to ours in where we only differ from the dose used of 4mg/day.[11] Similarly, there is another Italian multicenter study using baricitinib which has shown to reduce viral load, admission to intensive care and reduce mortality rate, compared to our results, we could not only measure viral load, but the decrease in care admissions Intensive care and decreased mortality are similar to our study, using the drug for two weeks.[12] A study conducted in the United States of America, using baricitinib with hydroxychloroquine, demonstrated efficacy in 12 of 15 patients with moderate to severe pneumonia due to COVID-19; In our experience, the use of baricitinib was mainly accompanied by rivaroxaban (22 patients), enoxaparin (5) and dexamethasone (3), without other concomitant medications.[13]

Some studies recommend the combination of baricitinib with direct antivirals such as lopinavir/ritonavir or remdesivir, in this regard, there is currently a phase III, randomized, double-blind, placebo-controlled study (Adaptive COVID-19 Treatment Trial, ACTT-2) that combines the use of baricitinib with remdesivir, demonstrating to reduce the recovery time of patients hospitalized for severe COVID-19, although final conclusions have yet to be seen. We consider that it is not necessary to add an antiviral, it is more important to evaluate concomitant thrombotic risks.[14,15]

Conclusion

In this series of cases of patients with severe pneumonia and secondary acute respiratory failure after the use of polypharmacy did not have a good evolution, so when having severe hypoxemia, management with baricitinib was chosen with improvement over oxygenation indices, avoiding intubation and favoring survival, randomized controlled studies are necessary to more accurately define the efficacy of baricitinib treatment.

Acknowledgements

None.

Conflicts of interest

None.

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