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Role of Janus Kinase inhibitors in the management of pulmonary involvement due to Long COVID-19 disease: A case control study

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Abstract:

OBJECTIVES: Ongoing symptomatic coronavirus disease 2019 (OSC) is defined as persistent symptoms beyond 4 weeks of acute illness. OSC leads to prolonged hospitalization and oxygen dependence. We aimed to find the outcome of Janus kinase inhibitors (JAKi) as a steroid-sparing agent to treat OSC.

METHODS: In this single-center case-controlled study comparing JAKi and corticosteroids in OSC cases, data of 41 cases out of 86 were included – 21 in the JAKi group and 20 in the corticosteroid group from 4 weeks of acute illness to the next 4 weeks. Clinical parameters and inflammatory markers were recorded. The primary outcome was to compare the proportion of patients who were able to maintain oxygen saturation ≥95% with any oxygen supplementation in the two groups.

RESULTS: The baseline clinical and demographic characteristics were similar in the two groups. The age was 53.65 ± 9.8 years and 51.48 ± 14.0 years in the corticosteroid group and JAKi group, respectively. At the baseline, 85% of patients in the corticosteroid group and 85.8% in the JAKi group were on oxygen support. The most common symptom in both groups was breathlessness followed by cough. Twenty percent of patients in the JAKi group received baricitinib and the remaining were given tofacitinib. At the time of follow-up, the majority of cases had a significant reduction in C-reactive protein (CRP) and D-dimer; however, the change in CRP and D-dimer was similar in both groups. The number of patients off oxygen support at 4 weeks was higher in the JAKi group (85% in the corticosteroid group vs. 95.2% in the JAKi group, $P = 0.269$), and the median time to liberation from oxygen support was significantly lower in JAKi group (19 days in corticosteroid group vs. 9 days in JAKi group, $P < 0.001$). The frequency of any adverse event was also higher in the corticosteroid group (70% vs. 23.8%, $P = 0.003$).

CONCLUSION: JAKi can be used as immunomodulatory drugs in hypoxic OSC cases having evidence of ongoing inflammation.

Keywords:

Baricitinib, Janus kinase inhibitors, long coronavirus disease 2019, postcoronavirus disease, tofacitinib

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Box-ED section

What is already known about the study topic?

- COVID-19 has made a severe impact on the world at every level. It continues to disrupt health care at all levels in different parts of the world. In the acute phase of illness, multiple combinations of drugs were tried to overcome pulmonary involvement. In addition, COVID-19 is associated with several manifestations beyond the acute phase as well, known as long COVID-19 syndrome. Pulmonary involvement due to long COVID-19 disease is of special concern. Steroids are used to overcome this issue, but they come at a significant cost. Steroid-sparing agents like JAK inhibitors (JAKi) have never been used to treat the long COVID-19 syndrome.

What is the conflict on the issue? Has its importance for readers?

- JAK inhibitors are common drugs for multiple rheumatological illnesses such as ulcerative colitis and rheumatoid arthritis. JAKi, such as baricitinib and tofacitinib, were also found to be beneficial in the acute phase of COVID-19 illness
- In the presumption of immune-mediated mechanisms of inflammation contributing to the pulmonary manifestation of the long COVID syndrome and the fact that it responds to corticosteroid therapy, we tried JAKi in the long COVID syndrome.

How is this study structured?

- This was a single-center, retrospective case–control study that included data from patients admitted at a tertiary care institute during the second wave of the COVID-19 pandemic from May 1, 2021, to August 31, 2021.

What does this study tell us?

- The outcome of JAK inhibitors is better compared to corticosteroids in terms of liberation from oxygen therapy. Apart from this, JAKi are safer than corticosteroid therapy and has fewer adverse effects.

Introduction

The world has faced multiple waves of coronavirus disease 2019 (COVID-19) disease with significant disease morbidity and mortality. In addition to the acute illness, COVID-19 has been found to be associated with several manifestations even beyond the acute phase. Such manifestations can be due to persistent inflammation, triggering of autoimmune response, deconditioning, and lung fibrosis. Morbidity associated with long COVID-19 disease has been evaluated in a few studies, and different labels have been given to classify the sequelae of acute COVID-19, such as long-COVID, persistent-COVID, or post-COVID.[1] The incidence of long COVID has been reported to be up to 30%, following an acute illness. With the rising number of total COVID-19 patients, the long COVID-19 pandemic is looming large.[2] To better characterize the illness and to establish uniformity in research on the subject, the National Institute for Health and Care Excellence group from the United Kingdom classified long COVID as signs and symptoms of COVID-19 persisting beyond 4 weeks of illness. Long COVID has been classified into two phases: (a) ongoing symptomatic COVID-19 (OSC) – defined from 4 to 12 weeks of the onset of illness and (b) post-COVID-19 syndrome – defined as signs and symptoms developing or persisting beyond 12 weeks of illness.[3] The most limiting feature is dyspnea, which is usually disproportionate to lung involvement.[4] In an observational study, steroids were found to be well-tolerated and were associated with a significant improvement in symptoms of long COVID-19 illness.[5] Immunosuppression with steroids, despite being associated with clinical benefit, has been associated with several adverse events such as bacterial infections, tuberculosis, invasive fungal infections, and candidiasis, apart from hyperglycemia, avascular necrosis (AVN), and other endocrine disturbances.[6]

Context

Janus kinase signal transducer and activator of transcription (JAK-STAT) protein is involved in multiple pathways, leading to the release of several interleukins and subsequent cytokine release syndrome.[7] JAK inhibitors (JAKi) such as baricitinib and tofacitinib have been found to be beneficial in the clinical management of moderate-to-severe COVID-19 disease.[8-10] Hypothesis and goals of the study: In presumption of immune-mediated mechanisms of inflammation contributing to the manifestation of OSC and the fact that it responds to corticosteroid therapy, we decided to use JAK inhibitors in OSC patients with documented active inflammation and lung involvement. Here, we have presented our experience with the use of JAK inhibitors in patients of OSC with pulmonary involvement.

Methods

Study design and setting

This was a retrospective case–control study conducted in the intensive care unit (ICU) of the department of pulmonary and critical care medicine of a tertiary care public sector teaching university hospital. The ICU is managed by pulmonary intensivists. Data of patients admitted during the second wave of the COVID-19 pandemic from May 1, 2021, to August 31, 2021, were studied.

Selection of participants

As per the evidence, JAKi were used for 14 days[9] only in active illness, following which patients were

continued only on corticosteroids. We selected cases only once they were in the OSC phase of the illness. To overcome selection bias, we included all patients belonging to the category of OSC (defined as persistence of COVID-19 symptoms beyond 4 weeks of illness) under the umbrella of long COVID-19 illness. In the current study, we modified this definition to include patients having persistent hypoxia (oxygen saturation of <95% on room air) with active inflammation (defined by raised C-reactive protein [CRP] levels, greater than twice the upper limit of normal) beyond 4 weeks of illness. We chose the SpO_2 and CRP cutoff based on the national guidelines with previous suggesting linear association between disease severity and CRP levels.[11,12] We used a laboratory-based cutoff value instead of an absolute number to account for the different methods of testing available. We recruited only those patients who had turned negative for SARS-CoV-2 by reverse transcription-polymerase chain reaction during their stay in the hospital. All patients required oxygen or other respiratory support during the active COVID-19 phase. Exclusion criteria include patients having an active (confirmed or suspected) bacterial infection, coexisting fungal infection, or tuberculosis at the time of recruitment. Furthermore, patients currently belonging to the WHO ordinal scale of 7 (requiring extracorporeal membrane oxygenation support or organ support) or those who had been shifted to other centers were excluded. We also included those patients who were not on oxygen support but had a room air saturation of <95%.

Intervention

All eligible cases having features suggestive of lung involvement such as hypoxia and tachypnea with radiological evidence of pulmonary involvement with active inflammation had received corticosteroid (prednisolone or equivalent) therapy at a dose of 0.5–0.75 mg per kg of body weight. Based on the previous experience with JAKi in active COVID, a few cases were also managed with baricitinib (4 mg once daily) or tofacitinib (5 mg twice daily). The choice between either agent was based on cost and availability (baricitinib was the first preference; however, it was costly and had limited availability at the time of the pandemic). All cases who could not be initiated on baricitinib (either due to cost factor or availability) were prescribed tofacitinib. JAKi were started on admission with corticosteroids irrespective of the duration of symptoms. Corticosteroids were rapidly tapered off in patients who were started on JAKi for 7–10 days. In patients who did not receive JAKi, corticosteroids were continued for 3–4 weeks, depending on the clinical improvement. CRP, an inflammatory marker, was assessed weekly and decision of halting JAKi, or corticosteroids was taken in consideration once CRP was less than the upper limit of normal with clinical improvement. All outpatients were assessed weekly for efficacy and safety outcomes, whereas inpatients were assessed daily.

Methods and measurements

Data related to demographics, disease severity, treatment received, and coexisting illness were retrieved. Data available beyond 4 weeks of the onset of illness (the time point at which OSC is diagnosed) were considered the baseline for analysis, and follow-up data for further 4 weeks were used to study the impact of JAKi or corticosteroids on OSC. Among inflammatory makers, data of CRP, ferritin, and D-dimer were collected from both time points (baseline and follow-up). Apart from inflammatory markers, the details of respiratory support and adverse events were also recorded. Follow-up data at 8 weeks were collected from the department for inpatients and from outpatient setting for discharged patients. Data were collected and coded in a digital format (Microsoft® Excel Version 2021) and transferred to the Statistical Package for the Social Sciences (SPSS) version 26 by IBM®, New York, USA for analysis.

Outcomes

Liberation from oxygen is the primary outcome of the study, and for this, we chose the proportion of patients free from any kind of oxygen or respiratory support as well as the time taken for the patients to be liberated from any oxygen support (liberation was defined as the ability to maintain saturation above 95% without any supplemental oxygen). For safety outcomes, we considered four major adverse events – hyperglycemia requiring insulin therapy (blood sugar level above 180 mg/dl was treated with insulin), oral candidiasis (presence of oral thrush), invasive fungal infection (microbiological evidence of fungal elements in otherwise sterile body fluids or organs), and other secondary bacterial infections (pneumonia, bacteremia, pyelonephritis, meningitis, or abscess) excluding skin infections. AVN was also considered; however, none of the patients had developed an AVN till the data cutoff; hence, it was dropped from data analysis.

Statistical analysis

The group of patients who received JAKi was labeled as the intervention group, and the remaining cases who received corticosteroids were grouped as the control group for comparison purposes. Data were presented in a descriptive fashion as means (and standard deviation), numbers (percentages with 95% confidence intervals [CIs]) or medians. The Kaplan–Meier method was used to estimate and compare the time to liberation from oxygen therapy between the two groups. The hazard ratio and associated 95% CI were calculated with the use of a stratified Cox proportional hazards

model. Categorical data were compared between the two groups using Pearson's Chi-square test; whereas the difference between continuous variables was analyzed using the independent Student's *t*-test. For all outcomes, a two-sided $P < 0.05$ was considered to indicate statistical significance. The STROBE case–control reporting guidelines were adhered to during manuscript writing.[13]

Ethical approval

Data were retrieved from the medical records department after due permission from the Ethics Committee. Being a retrospective study, the informed consent process was waivered off vide letter number: 196, dated December 12, 2021.

Results

Over 4 months, data of 86 patients were retrieved. Out of 86 cases, 45 were excluded from the analysis [Figure 1]. From the remaining 41 cases, 21 patients had received JAK inhibitors (JAKi group), and 20 patients were managed with only glucocorticoids. The average duration of follow-up was 59 ± 17 days. Demographic variables of the study population are provided in Table 1. Both groups were age- and gender-matched. All patients were on respiratory or oxygen support during the active COVID-19 phase. All patients admitted in ICU had a significant pulmonary involvement as suggested by the respective computed tomography severity index (CTSI) values in either group. Fever, cough, and breathlessness were the most commonly reported symptoms. All patients were managed as per the institutional COVID-19 management protocol modified from the Ministry of Health and Family Welfare protocol version 3. Twenty-nine percent of the study population received methylprednisolone pulse therapy; whereas only 7.3% received JAKi during the active COVID-19 phase of illness. 36.6% and 17% of patients had type II diabetes mellitus and hypertension, respectively. One patient in each group was suffering from rheumatoid arthritis. Ninety percent of patients complained of breathlessness at the time of diagnosis of OSC; whereas cough was reported in 68.3%.

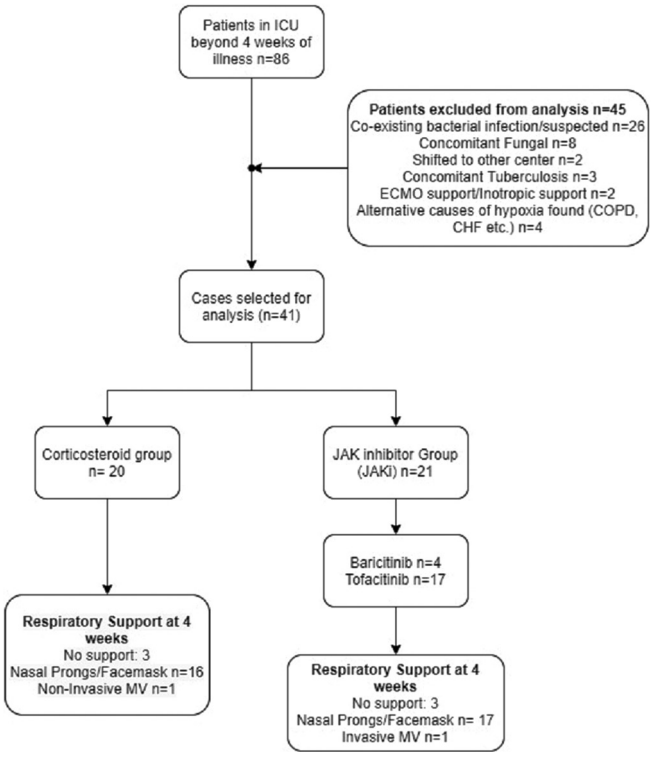

Figure 1: Consortium showing the flow of recruited patients. ICU: Intensive care unit, ECMO: Extracorporeal membrane oxygenation, COPD: Chronic obstructive pulmonary disease, CHF: Congestive heart failure, JAK: Janus Kinase, MV: Mechanical ventilation

Table 1: Baseline characteristics at the time of diagnosis of ongoing symptomatic coronavirus disease 2019 (before Janus kinase inhibitors were started)

Characteristics	Steroid group, *n* (%)	JAK group, *n* (%)
Male	14 (70)	14 (66.7)
Female	6 (30)	7 (33.3)
Age (years)	53.65±9.8	51.48±14.0
CTSI score	17.0±2.3	17.62±3.6
Management in the acute phase		
Methylprednisolone pulse	3 (15)	9 (42.8)
Steroid as per recovery trial	20 (100)	21 (100)
JAKi	0	3 (14.2)
Tocilizumab	0	2 (9.5)
Respiratory support requirement in the acute phase of COVID-19		
Nasal prongs/facemask	14 (70)	14 (66.7)
NIV or HFOT	5 (25)	4 (19.0)
Invasive mechanical ventilation	1 (5)	3 (14.2)
Comorbid illness		
Diabetes mellitus	6 (30)	9 (42.8)
Hypertension	2 (10)	5 (23.8)
Chronic respiratory illness	1 (5)	2 (9.5)
Coronary artery disease	2 (10)	3 (14.2)
Hypothyroidism	3 (15)	1 (4.8)
Rheumatoid arthritis	1 (5)	1 (4.8)
Respiratory support at the time of JAK onset		
No support	3 (15)	3 (14.2)
Nasal prongs/facemask	16 (80)	17 (76.1)
NIV or HFOT	1 (5)	0
Invasive mechanical ventilation	0	1 (4.8)
Symptoms at the time of the diagnosis of OSC		
Breathlessness	19 (95)	18 (85.7)
Fever	5 (25)	10 (47.6)
Cough	15 (75)	13 (61.9)
Fatigue	15 (75)	12 (57.1)
Altered sensorium/insomnia	4 (20)	4 (19.0)
Chest pain	6 (30)	6 (28.5)

COVID-19: Coronavirus disease 2019, CTSI: Computed tomography severity index, NIV: Noninvasive ventilation, HFOT: High-frequency oxygen therapy, OSC: Ongoing symptomatic COVID, JAK: Janus kinase, JAKi: JAK inhibitors

At the baseline, 80.5% of the patients were on the WHO ordinal scale 4 (on nasal prongs or facemasks). Those who were not on oxygen support had oxygen saturation below 95%. The duration of illness was more than 30 days in both groups, before the intervention for OSC. One patient from each group was on mechanical ventilation. At the time of follow-up (after 3–4 weeks), nearly all patients were off oxygen support in both groups. One patient, who was on invasive mechanical ventilation at baseline, was still on supportive oxygen therapy via T-piece through a tracheostomy.

As far as the adverse events are considered [Table 2], 60% of the patients in the corticosteroid group had one or more episodes of hyperglycemia, for which insulin was administered. In the JAKi group, three patients had episodes of hyperglycemia; however, by the end of the 1st week, none of these patients were on insulin therapy. An equal number of patients in both groups suffered from bacterial infections. Two patients in each group suffered from hospital-acquired pneumonia; one patient in the JAK group developed diverticulitis requiring readmission with parenteral antibiotics, and one patient in the corticosteroid group developed urinary tract infection. One patient in the corticosteroid group also developed rhinocerebral mucormycosis requiring amphotericin B and surgical intervention. All cases of oral candidiasis, except one, were found only in the corticosteroid group. All of them were managed with oral fluconazole.

For the analysis of inflammatory markers in either group, we analyzed the values of ferritin, D-dimer, and CRP. In the overall study population, values of both CRP and D-dimer showed a significant fall on follow-up ($P < 0.001$ for both CRP and D-dimer). In contrast, ferritin values showed a statistically significant rise on follow-up ($P = 0.024$). However, there was no difference in the change in CRP, D-dimer, or ferritin when compared between the two groups (P values for ΔCRP, Δferritin, and ΔD-dimer for corticosteroid vs. JAKi group were 0.661, 0.827, and 0.394, respectively) [Figure 2].

At the time of data cutoff, 3 (15%) patients in the corticosteroid group and 1 (4.8%) patient in the JAKi group were still on supplemental oxygen therapy. The median time to liberation from supplemental oxygen was higher in the corticosteroid group compared to the JAKi group, using the Cox proportional hazard model (19 days vs. 9 days ($P < 0.001$, hazard ratio = 0.188; 95% CI, 0.061–0.317). The mean duration of use of corticosteroids in the JAKi group was 8 ± 1 day, and JAKi were continued for 21 ± 6 days.

For the primary end point of efficacy, even though the number of cases on oxygen support was lesser in the JAKi group, a Pearson's Chi-square test suggested that there was no statistically significant difference between the two groups ($\chi^2[1] = 1.22$, $P = 0.269$). However, for the primary end point of safety, a Pearson's Chi-square test suggested that a significantly higher number of patients in the

Table 2: Efficacy and safety parameters at the time of follow-up

Characteristic	Steroid group (*n*=20)	JAK group (*n*=21)	*P*
CRP at baseline (±SD)	32.9 (±9.34)	34.9 (±9.35)	0.733
CRP at follow-up (±SD)	3.52 (±1.05)	7.7 (±1.67)	0.284
Ferritin at baseline (±SD)	571.8 (±207.8)	505.3 (±374.01)	0.488
Ferritin at follow-up (±SD)	650.8 (±176.97)	567.4 (±190.74)	0.155
D-dimer at baseline (±SD)	784.8 (±308.13)	631.9 (±292.47)	0.111
D-dimer at follow-up (±SD)	393.4 (±155.35)	300.2 (±150.33)	0.058
Respiratory support at follow-up, *n* (%)			
Adverse effects	17 (85)	20 (95.2)	0.269
Nasal prongs/facemask	3 (15)	1 (4.7)	
Adverse effects, *n* (%)			
Secondary infection	3 (15)	3 (14.3)	0.948
Hyperglycemia	12 (60)	1 (4.7)	0.002
Invasive fungal infection	1 (5)	0	0.3
Oral candidiasis	12 (60)	1 (4.7)	<0.001
Time to liberation from oxygen therapy (days), median (range)	19 (14–23)	9 (7–12)	<0.001

SD: Standard deviation, CRP: C-reactive protein, JAK: Janus kinase

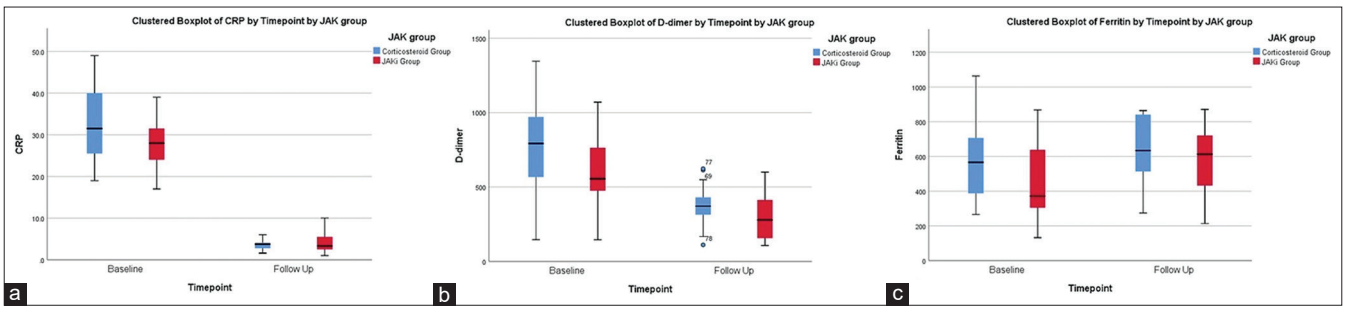

Figure 2: Clustered box plot showing values of (a) CRP; (b) D-dimer; and (c) ferritin, at baseline and 4-week follow-up. JAK: Janus Kinase, JAKi: JAK inhibitor, CRP: C-reactive protein

corticosteroid group had any adverse event compared to the JAKi group (χ^2[1] = 8.789, P = 0.003).

Discussion

In this pragmatic, real world, retrospective analysis of OSC patients with pulmonary involvement, JAKi as steroid-sparing agents were found to have better efficacy in recovery while being associated with a significantly lower number of adverse events compared to corticosteroids. To the best of our knowledge, this is the first study evaluating the role of JAKi or any steroid-sparing agent in the management of long COVID illness.

Both the ACTT-2 and STOP COVID trials, evaluating baricitinib and tofacitinib in COVID, respectively, have been shown to reduce mortality rates and disease progression as assessed using the WHO ordinal scale. These results have been replicated in Indian studies as well.[8] Following the results of these trials, several bodies such as the National Health Service and Centers for Disease Control and Prevention have recommended a therapy for 14 days, during the acute phase only. However, a significant number of cases have persistent symptoms even beyond 4 weeks of illness, leading to prolonged hospitalization, oxygen support, increased burden on the health-care system, immune exhaustion, and risk of hospital-acquired infections, which is more common in cases who have experienced a severe form of acute COVID-19.[14,15] As reflected in the results, 85.4% of the OSC patients were on oxygen support even after 4 weeks of acute illness. The steep surge in the number of new cases and the requirement of prolonged hospitalization led to an acute shortage of hospital beds leading to premature discharges, some of them on home oxygen therapy, and prolonged courses of corticosteroids.[16] Early discharge on supplemental oxygen has its advantages; provided optimal care at home can be ensured, and caregivers are aware and alert about the red flag signs.[17] Such awareness and close follow-up in countries like India, where domiciliary health care is still in its infancy, are a big challenge. In this scenario, anti-inflammatory therapy to reduce the duration of oxygen requirement and hospitalization turns out to be the "need of the hour." Corticosteroids, being one of the most time-tested and easily available medicine, have been used for extended periods in such cases and have been found to be useful in accelerating clinical improvement, but at the cost of several adverse effects such as hyperglycemia and superficial and invasive fungal infections among many others, which has also been demonstrated in our results.[18] Apart from corticosteroids, based on the hypothesis of pulmonary fibrosis in the long-COVID phase, antifibrotic agents have also been tested, but with minimal or no significant benefit.[19]

However, there are several questions that have remained unanswered in our study, which include the duration of use of JAKi, biomarkers that may influence the decision-making process, and the identification of the right candidates. The use of JAKi is not without its own set of adverse events. Prolonged use of JAKi has been associated with the risk of fungal infections, hepatotoxicity as well as increased risk of carcinoma and cardiovascular events.[20]

Even so, JAKi are already proven in multiple rheumatological illnesses such as ulcerative colitis and rheumatoid arthritis. Previous studies in these illnesses have also investigated the optimal dosing and safe duration of tofacitinib as well as baricitinib.[21] Our findings have shown that not only JAKi are safer compared to corticosteroids but also are associated with a significant reduction in the duration of need for oxygen supplementation. As far as efficacy outcomes are considered, JAKi were associated with a higher number of cases being liberated from oxygen therapy although the difference was not statistically significant, without any increase of adverse events. As a summary, we derive that JAKi are safer and noninferior to corticosteroids for their use in OSC with pulmonary involvement and raised inflammatory markers.

Limitations

Through this index study, we have shown the role of JAKi in the OSC phase of COVID-19 illness and present a safer and equally efficacious, if not more, alternative to corticosteroids. This is the first study to evaluate the role of JAKi in the management of long COVID pulmonary involvement and reflects on the fact that postviral syndrome can be a mimicker of predefined rheumatological illnesses both in pathophysiology and presentation.[22,23] In a representative section of high-resolution computed tomography (HRCT) of the chest, Figure 3 shows a significant improvement with the use of JAKi. At best, we anticipate that the index findings are hypothesis-generating.

Our study did carry a few flaws such as being retrospective in nature, the inability to repeat HRCT of all cases which could have suggested the exact change in CTSI scoring, a relatively small sample size, and a lack of pulmonary

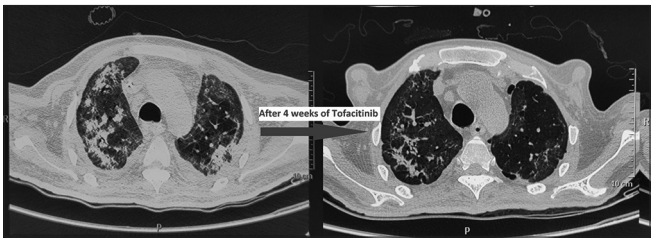

Figure 3: High-resolution computed tomography of the thorax done at a 4-week interval of taking tofacitinib, showing confluent ground-glass opacities with patchy consolidation in the bilateral upper lobes (left) and significant resolution with few residual ground-glass opacities and fibrotic bands (right)

function assessment data. One of the important differences in the baseline characteristics of the two groups was the use of methylprednisolone pulse therapy during the active phase. The long-term impact of methylprednisolone therapy on the OSC aspect of the illness is not known and may have contributed toward the final differences in the outcomes. Small sample size, differences in the baseline characteristics of the two groups, and risk of bias are among the few things which limit the generalization of the study.

Conclusion

JAKi can be used as immunomodulatory drugs in those who are hypoxic in the postacute COVID-19 phase and have evidence of ongoing inflammation. JAKi are safer when compared with corticosteroids and were found to be equally effective.

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Author contributions credit statement
- Conceptualization – PKS, DC, VS
- Data collection – VS, CPS, LKL
- Data curation – PKS, MBG
- Formal analysis – PKS, CPS
- Funding acquisition – Not applicable
- Investigation – Not Applicable
- Methodology – PKS, MBG, VS
- Project administration – DC
- Resources – DC, PKS
- Software – PKS
- Supervision – DC
- Validation – AA, LKL
- Visualization – Not Applicable
- Writing – original draft – PKS, MBG, CPS
- Writing – review and editing – DC, AA, LKL.

Ethical approval
Data were retrieved from the medical records department after due permission from the Ethics Committee. Being a retrospective study, the informed consent process was waivered off vide letter number: 196, dated December 12, 2021.

Conflicts of interest
None declared.

Financial support and sponsorship
None.

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