

A trial of pirfenidone in hospitalized adult patients with severe coronavirus disease 2019

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To the Editor: Coronavirus disease 2019 (COVID-19), which broke out in 2019, has become a global pandemic. Similar to severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003, SARS-CoV-2 could cause acute lung injury and cytokine storms characterized by the increased interleukin (IL)-8, IL-6, and tumor necrosis factor α (TNF- α).^[1] Perspective studies in those survivors from the severe acute respiratory syndrome (SARS) epidemic in 2003 revealed that those SARS patients manifested varying degrees of pulmonary interstitial fibrosis.^[2] Similarly, patients with severe COVID-19 are also featured by the diffuse alveolar damage along with alveolar interstitial fibrosis.^[3]

Pirfenidone (Beijing Contini Pharmaceutical Co., Ltd, Beijing, China) can inhibit the biological activity of fibroblasts and reduce matrix collagen deposition, prevent inflammasome activation and limit oxidative stress responses, supporting a therapeutic potential against idiopathic pulmonary fibrosis (IPF).^[4] Given the presence of alveolar interstitial fibrosis in severe COVID-19 patients and the effect of pirfenidone on anti-inflammatory responses and anti-fibrosis, we hypothesized that pirfenidone can play a positive role in COVID-19 patients, thereby reducing the incidence of complications following SARS-CoV-2 infection. We thus conducted a clinical trial to assess the potential therapeutic effect of pirfenidone on severe COVID-19 patients.

This trial (*ClinicalTrials.gov* number: NCT04282902; Chinese Clinical Trial Register number: ChiCTR2000030333) was conducted from January 31 to March 3, 2020 at Tongji Hospital (Headquarters Campus,

Caidian Campus, Guanggu Campus) and Jingzhou Hospital (Hubei, China), which was approved by the Institutional Review Board of Tongji Hospital and Jingzhou Hospital. Male and non-pregnant female COVID-19 patients (≥ 18 years) with a blood oxygen saturation (SaO₂) of 94% or less, and a ratio (PaO₂:FiO₂) of ambient air or partial oxygen pressure (PaO₂) to inhaled oxygen (FiO₂) of 300 mmHg or less, were eligible for the study. The exclusion criteria were: patient disinterest in the study; the presence of conditions that did not allow for safe compliance, including hypersensitivity to pirfenidone; liver disease (eg, alanine aminotransferase levels >5 times the upper limit of the normal range [ULN] or aspartate aminotransferase levels >5 times ULN; contraindications of pirfenidone and pre-existing interstitial lung disease [ILD]). Consecutive patients, who meet the inclusion criteria, were randomly assigned in a 1:1 ratio to pirfenidone (200 mg, three times daily for the first two days and 400 mg, three times daily thereafter) plus standard therapy or standard therapy alone. Pirfenidone was given through a nasogastric tube in patients who were unable to swallow.

The primary end-point was the absolute changes from baseline in the total score on the King's Brief Interstitial Lung Disease (K-BILD) questionnaire at the 4th week, a change between 4 and 8 points has been suggested to represent a meaningful change. Secondary endpoint was the absolute change in computed tomography (CT) values, the total CT value was the sum of individual lobe values and ranged from 0 (no involvement) to 25 (maximum involvement). Other secondary outcomes included clinical

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laboratory findings (cytokines, biochemical indicators, etc) and the proportion of patients with clinical improvement. Safety outcomes included adverse events that occurred during treatment and premature discontinuation of treatment. Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 [Supplementary methods in Supplementary materials, <http://links.lww.com/CM9/A929>].

A total of 146 COVID-19 patients were recruited, 124 of which were from Tongji Hospital and the rest 22 were from the Central Hospital in Jingzhou. Seventy-three patients were randomly assigned for pirfenidone treatment, and the remaining 73 patients received the standard treatment alone [Supplementary Figure 1, <http://links.lww.com/CM9/A647>]. The median age of patients was 62.0 years (interquartile range [IQR] 53.5–68.5 years), and 64.38% of patients were males. The median interval time between symptom onset and randomization was 40 days (IQR, 25–50 days). At the time of admission, there were no significant differences between the two groups in terms of demographic characteristics, basic laboratory assays, clinical treatment K-BILD scores, and CT scores [Supplementary Table 1, <http://links.lww.com/CM9/A646>].

Although the difference of K-BILD scores did not reach a statistical significance after treatment (75.93 ± 10.07 vs. 76.33 ± 9.15 , $P=0.911$), a trend for the increase from baseline in patients following a 4-week of pirfenidone treatment was noted as compared to that of patients assigned in the standard treatment group (Δ K-BILD, 26.53 ± 11.12 vs. 22.73 ± 8.00 ; 3.80 [95% confidence interval, CI = -4.87 to 12.47]) [Supplementary Table 2, <http://links.lww.com/CM9/A646>]. Similarly, there was no significant difference between two groups in terms of CT images ($P=0.745$) after a 4-week of treatment, but some score changes including consolidation (0.30 ± 0.65 vs. 1.07 ± 1.17 , $P=0.007$), GGO (-12.27 ± 5.72 vs. -11.57 ± 4.07 ; between-group difference = -0.70 , 95% CI = -2.97 to 1.57), and reticulation (-0.90 ± 5.26 vs. -0.30 ± 6.98 ; between-group difference = -0.60 , 95% CI = -3.40 to 2.20) were observed, which reflected the improvement of lung inflammation and interstitial changes [Supplementary Table 3, <http://links.lww.com/CM9/A646> and Supplementary Figure 2, <http://links.lww.com/CM9/A648>].

The levels of pulmonary inflammatory cytokines or coagulopathy biomarker from baseline to the 4th week after receiving treatment were significantly decreased in the pirfenidone group as compared to those from the standard care group, such as IL-2R (-299.00 , 95% CI = -430.50 to -105.00 , $P=0.010$), TNF- α (-3.50 , 95% CI = -5.00 to -0.10 , $P=0.049$), and D-Dimer (-4.57 , 95% CI = -8.98 to -0.16 , $P=0.021$) [Supplementary Table 2, <http://links.lww.com/CM9/A646>].

In addition, the duration of patients in pirfenidone group from randomization to hospital discharge and in intensive care unit was reduced by 2 days (11.21 ± 10.06 vs. 13.21 ± 16.63 days, -2 days, 95% CI = -9.27 to 5.27 ; 19.00 [IQR 15.00–22.00] vs. 22.00 [IQR 16.50–25.50];

-2 days, 95% CI = -3.50 to 8.50) [Supplementary Table 2, <http://links.lww.com/CM9/A646>]. No significant difference was noted for other outcomes such as clinical improvement time, duration of oxygen therapy, and time from randomization to death. However, all patients survived in the pirfenidone treatment group, and two patients were declined to death in the standard care group. The proportional distribution of primary endpoint categories at days 1, 7, 14, and 28 in each patient was presented in Supplementary Figure 3, <http://links.lww.com/CM9/A649> and Supplementary Table 3, <http://links.lww.com/CM9/A646>.

The percentages of patients with any adverse event or serious adverse event were similar between the patients from both groups. Among patients with adverse events, 11% (8/73) of patients reduced the dose of pirfenidone and 3% (2/73) of patients discontinued. Among those eight patients with pirfenidone reduced-dose, four cases were reduced to 600 mg/day due to gastrointestinal discomfort and the remaining four cases were reduced to 600 mg/day due to rash. The most common adverse event was diarrhea, which was reported in 11 out of 73 (15%) patients from the pirfenidone group. Some patients have elevated alanine aminotransferase and alanine aminotransferase level [Supplementary Figure 3 and Supplementary Table 2, <http://links.lww.com/CM9/A646>, <http://links.lww.com/CM9/A649>].

Given that the COVID-19 is a type of infectious disease that could be transmitted through the respiratory tract, lung function test was not included in this study. According to previous studies, patients infected with SARS-CoV-2 are far more likely to form an interstitial change in the lung, while our statistical indicators including K-BILD and CT image ratings reflected improved situation in terms of interstitial changes in pirfenidone treated patients. However, we failed to observe a significant difference between the two groups both for K-BILD and CT scores. Since our observation period only lasted for 4 weeks, our trial did not yield a significantly positive result, and the observation time could be a major factor.

It was noted that pirfenidone did not improve fibrosis, but it did not make the disease worse. Nevertheless, pirfenidone did manifest a strong effect on mitigating the cytokine storm, which seems to be responsible for the complications in severe COVID-19 patients. Indeed, comparative analysis revealed that the levels of IL-2R and TNF- α were decreased significantly following pirfenidone administration. Although the anti-inflammatory effect has not been widely appreciated, pirfenidone has been shown to downregulate inflammatory pathways and the compound may have considerable potential to be deployed as a non-steroidal anti-inflammatory agent.^[5,6]

To our surprise, our study also found that pirfenidone could significantly decrease the level of D-Dimer, which is relevant to the coagulopathy in the blood. There is evidence that COVID-19 renders patients with an increased risk for acute pulmonary embolism, and anticoagulant therapy might be associated with improved outcomes in patients with severe COVID-19.^[7] Therefore,

treatment of COVID-19 with pirfenidone may have the potential to reduce the incidence of thrombosis complications.

The safety and side-effect profile of pirfenidone in patients with severe COVID-19 associated ILD was similar to that observed in patients with IPF.^[8] Despite the presence of certain side effects, but they could be easily managed with supporting therapies and temporary dose reductions or discontinuation. No fatal events were reported in our study, confirming the good safety profile of this drug even in fragile patients.

Our study also has several limitations. First, our sample size is limited. Second, although we have tried to avoid bias as much as possible during the trial, while this possibility cannot be completely excluded. Third, our trial lacks of dynamic clinical and laboratory data such as immune cell subsets and so on. Finally, our trial only lasted a 4-week of observation time, which could be a factor to confirm the antifibrotic effect of pirfenidone. In addition, glucocorticoids could also be a potential factor influencing the results of the study, even though there was no significant difference in the initial dosage, total dosage, and duration of treatment between the two groups.

Although pirfenidone has not been found to significantly improve the interstitial changes in severe COVID-19 patients, the trial, however, confirmed the benefits of pirfenidone therapy in anti-inflammatory responses, and obtained feasible evidence supporting a potential benefit in anti-thrombotic complications. Collectively, our study found that pirfenidone can be considered as a viable drug to treat patients with severe COVID-19, and confirmed that pirfenidone possesses a good tolerability profile without safety alert.

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Conflicts of interest

None.

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