Research Square

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Efficacy of Sivelestat Sodium in the Therapy of Critically ill Patients at high risk of developing ARDS due to SIRS: A Multicenter Prospective Study

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Abstract

Background

Sivelestat sodium has been proposed as a therapeutic strategy to mitigate respiratory dysfunction and reduce the need for mechanical ventilation in critically ill patients. Its clinical usage remains controversial. This multicenter prospective study aimed to evaluate the efficacy of sivelestat sodium in patients presenting high-risk of developing acute respiratory distress syndrome (ARDS) due to systemic inflammatory response syndrome with an oxygenation index (PaO2/FIO2 ratio; P/F ratio) between 100–400 mmHg upon ICU administration.

Methods

Eighty-two patients were divided into two groups: sivelestat group and conventional group. Clinical information, including vital sign, etiology, scoring systems for illness severity, laboratory test data, P/F ratio and chronic comorbidities were collected at the time of administration. The primary end points were invasive mechanical ventilation ratio and ventilator-free days (VFDs). Besides, the severe ARDS ratio, changes of P/F ratio (ΔP/F ratio), levels of inflammatory factors (procalcitonin (PCT), C-reactive protein (CRP) and Interleukin-6 (IL-6)) before and after 7 days therapy were also collected.

Results

Prescribe sivelestat sodium, as compared with conventional therapy, did not have a significant effect on mechanical ventilation ratio or severe ARDS ratio. Notably, sivelestat group exhibited significantly higher VFDs and an improved ΔP/F ratio in mild and moderate ARDS subgroup. Additionally, the ΔP/F ratio was significantly elevated on the fifth day following therapy initiation. Furthermore, there was a reduction in the levels of CRP and PCT, indicating a potential anti-inflammatory effect.

Conclusion

The results facilitate a randomized controlled trial to determine sivelestat sodium may be considered to alleviate inflammation response and protect patients with mild or moderate ARDS.

Introduction

With an in-hospital mortality rate of 34.9–46.1%, ARDS is a life-threatening condition characterized by acute lung injury and inflammation, leading to impaired gas exchange and respiratory failure [1]. The incidence of ARDS has increased over the past decades, primarily due to the incidence of critical illnesses such as sepsis, trauma, and pneumonia [2,3]. High-risk ARDS patients, including those with chronic comorbidities, older age, and severe disease severity, have a higher risk of developing severe ARDS and a

worse prognosis. Current therapy options for ARDS include supportive cares, such as mechanical ventilation and fluid management, which have poor effects on high-risk ARDS patients [4]. Therefore, current studies pay more attention to reduce inflammation and the resulting respiratory failure [5].

Sivelestat sodium, a neutrophil elastase inhibitor, has shown promising results to attenuate ARDS [6]. The mechanism of sivelestat includes inhibition of nuclear factor-kappa B (NF-κB) activation, reduction of reactive oxygen species (ROS) production, and modulation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway [7]. These effects contribute to the suppression of pro-inflammatory cytokines and chemokines which are key mediators of ARDS pathogenesis [8]. In addition, sivelestat sodium appears to reduce clinical neutrophil stiffness, improve postoperative lung permeability and reduce alveolar damage, which happens in the onset phase of ARDS [9,10]. Despite sivelestat sodium has been demonstrated effective in animal models, there is still controversy over its clinical efficacy of improving the oxygenation status of patients, especially those at high-risk of progressing to severe ARDS [11,12].

In this study, we examined the clinical manifestations of patients with different P/F ratio receiving sivelestat sodium therapy at our department and affiliated institutions. The objective of our study was to clarify the clinical significance of administering sivelestat sodium to patients at high risk of developing ARDS due to SIRS.

Methods

Trial design and oversight

The initial study was conducted on 157 patients combined with P/F ratio between 100 to 400mmHg, increased inflammatory factors (IL-6 or CRP) levels and generally decreased transparency in chest X-ray who were admitted to intensive care unit (ICU) of eight centers including Tongji Hospital, Wuchang Hospital, People's Hospital of Dongxihu District, Wuhan Traditional Chinese Medicine Hospital, Xiangyang Central Hospital, The Second Affiliated Hospital of Nantong University, The Third People's Hospital of Hubei Province, and The Sixth Hospital of Wuhan from December 10th 2022 to June 15th 2023. The etiology of 157 patients were ARDS high-risk factors (pneumonia, trauma, sepsis, pancreatitis, etc.).

Patients were excluded if they were younger than 18 years old, had a history of respiratory system diseases (chronic obstructive pulmonary disease or bronchial asthma). Patients with severe liver, renal failure, severe hemodynamic instability, myasthenia gravis, severe cardiac failure, or deemed unsuitable by researchers were also excluded from this trial.

In the end, the subjects of this study were 82 patients who underwent randomization and were divided into sivelestat group or conventional group. All 82 patients were given non-invasive oxygen therapy (nasal cannula, face mask or high-flow nasal cannula). Sivelestat sodium (Shanghai Huilun Pharmaceutical Technology Co., Ltd, China) was continuously administered intravenously at a rate of 0.2mg/kg/h within

48 hours after the onset of SIRS in 41 cases (100%), within 24 hours after the initiation of oxygen therapy in 41 cases (100%) of sivelestat group for a maximum of 14 days. Referring to published clinical trials, daily information, including the vital sign, laboratory test data and adverse events were collected before and 7 days after therapy [13,14].

An oversight of the study procedures was provided in Fig. 1.

The research project was approved by the Ethical Review Committee of Huazhong University of Science and Technology, and each patient or their family member waived informed consent.

Diagnosis of SIRS and ARDS

All patients met the criteria for SIRS, which included at least three of the following clinical features [15]: (1) body temperature > 38°C or < 36°C; (2) heart rate (HR) > 90 bpm; (3) rapid breathing, defined as a respiratory rate > 20 bpm, or hyperventilation, indicated by PaCO2 < 32 mmHg; and (4) white blood cell (WBC) count > 12,000 cells/mm3 or < 4,000 cells/mm3, or the presence of more than 10% immature neutrophils.

The criteria for the diagnosis of ARDS were [16]: (1) PaO2/FiO2 ≤ 300 mmHg (P/F ≤ 300 mmHg); (2) the presence of bilateral pulmonary infiltrates on chest X-ray; (3) pulmonary edema of non-cardiogenic origin, characterized by a pulmonary capillary wedge pressure (PCWP) ≤ 18 mmHg, or in the absence of elevated left heart filling pressures.

Trial end points

The study established three sets of end points for analysis. The primary end point includes invasive mechanical ventilation ratio and VFDs. VFDs were defined as the number of days from day 0 to the day on which a patient received invasive mechanical ventilation assistance. Secondary end point were severe ARDS ratio (P/F ratio < 100mmHg) and number of ΔP/F ratio reduced patients 7 days after therapy. In exploratory end point analysis, we examined number of inflammatory factors (PCT, CRP, IL-6) elevated patients.

Data collection

Baseline data were collected from patients daily recording sheet. Clinical data, including the gender, ages, vital sign, etiology of SIRS, the values of illness severity (APACHE II and SOFA scores) and chronic comorbidities were collected at the time patient was enrolled. Laboratory data, such as WBC count, PLT count, P/F ratio and inflammatory factors levels were collected before and 7 days after therapy.

The safety of sivelestat sodium in the therapy of ARDS has been evaluated in several clinical trials [17, 18]. Any adverse events happened during therapy was recorded by investigators.

Statistical Analysis

Statistical analysis was performed using SPSS 23.0 software. For measurement data that followed a normal distribution, the mean ± standard deviation was used for representation. For statistical analysis, we employed t-tests and analysis of variance (ANOVA) for comparing continuous variables, while chi-square tests were utilized for proportion comparisons. A P-value < 0.05 was considered statistically significant.

To maintain homogeneity, we examined and contrasted the baseline data with t-tests and ANOVA between the randomized groups. To evaluate the clinical efficacy of sivelestat sodium, we analyzed three sets of end points using the Cox proportional hazards model. Cause specific Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each factor. The Kaplan–Meier method was used to estimate VFDs. For comparing ΔP/F, ΔIL-6, ΔCRP and ΔPCT before and after sivelestat or conventional therapy, paired or unpaired Student's t-tests were used as appropriate.

In this study, to further investigate the therapeutic effects of sivelestat sodium on patients with varying degrees of ARDS, we categorized P/F ratio into three grades: (1) P/F ratio 100 to 200 mmHg ($100 \leq P/F < 200$); (2) P/F ratio 200 to 300 mmHg ($200 \leq P/F < 300$); (3) P/F ratio 300 to 400 mmHg ($300 \leq P/F < 400$). The above studies were also conducted among different subgroups.

Results

Trial Patients

157 SIRS patients were randomly assigned to two groups: conventional and sivelestat groups. Of these, we excluded 5 patients who were younger than 18 years, 54 patients required invasive mechanical ventilation, 6 patients with history of chronic pulmonary diseases, 5 patients with severe chronic liver and kidney disease, and 5 patients declined to participate. There left 82 patients (55 men and 27 women) included in the study. The characteristics of 82 patients at the time of administration are presented in Table 1. Baseline data were balanced between the two groups. The mean (± SD) age of the patients was 62.1 ± 9.1 years (64.2 ± 6.4 years in the sivelestat group and 59.8 ± 9.7 years in the conventional group).

Sepsis was the most common cause of SIRS, affecting 33 patients, which accounts for 40.2% of all the cases. It was mainly followed by pneumonia in 28 patients (34.1%), pancreatitis in 7 patients (8.5%), multiple trauma in 6 patients (7.3%), cerebral infarction in 5 patients (6.1%) and some other cases. Besides that, the respiratory function at the beginning of ICU administration were divided into 3 groups. The P/F ratio was between 300 to 400 mmHg in 15 patients (18.3%), 200 to 300 mmHg in 39 patients (47.6%), and 100 to 200 mmHg in 28 patients (34.1%). There was no significant difference between sivelestat group and conventional group regarding sex, age, vital signs, etiology or chronic comorbidities. Measurements of complete blood count, blood biochemistry and inflammatory factors showed no significant differences between the trial groups. Similarly, there were no significant differences in APACHE II and SOFA scores between the two groups.

Invasive Mechanical Ventilation Incidence

Sivelestat therapy, as compared with conventional therapy, did not have a significant effect on total incidence of invasive mechanical ventilation (which occurred in 7 of 41 patients in the sivelestat group and in 7 of 41 patients in the conventional group; hazard ratio, 1.000; 95% confidence interval [CI], 0.822 to 1.217), P/F 100–200 mmHg (in 4 of 17 patients in the sivelestat sodium group and in 2 of 11 patients in the conventional group; hazard ratio, 0.773; 95% CI, 0.169 to 3.528), P/F 200–300 mmHg (in 2 of 17 patients in the sivelestat sodium group and in 3 of 22 patients in the conventional group; hazard ratio, 1.159; 95% CI, 0.217 to 6.179), P/F 300–400 mmHg (in 1 of 7 patients in the sivelestat sodium group and in 2 of 8 patients in the conventional group; hazard ratio, 1.750; 95% CI, 0.199 to 15.413),with similar background of age, sex, etiology and disease severity (Table 2).

ΔP/F reduced patients

Referring to the secondary end points, we noticed sivelestat sodium do not reduce total incidence of ΔP/F reduced patients before and 7 days after therapy (which occurred in 20 of 41 patients in the sivelestat group and in 25 of 41 patients in the conventional group; hazard ratio, 1.25; 95% CI, 0.840 to 1.860), P/F 100–200 mmHg (in 6 of 17 patients in the sivelestat sodium group and in 5 of 11 patients in the conventional group; hazard ratio, 1.288; 95% CI, 0.517 to 3.209), P/F 200–300 mmHg (in 12 of 17 patients in the sivelestat sodium group and in 12 of 22 patients in the conventional group; hazard ratio, 0.773; 95% CI, 0.474 to 1.261). However, sivelestat sodium therapy achieved therapeutic effect on P/F 300–400 mmHg subgroup (2 of 7 patients in the sivelestat sodium group and 8 of 8 patients in the conventional group; hazard ratio, 3.500; 95% CI, 1.085 to 11.292), which demonstrates that sivelestat sodium could improve P/F ratio in patients with SIRS at high risk for ARDS (Table 2).

Severe ARDS Incidence

There was no effect of sivelestat sodium as compared with conventional therapy on incidence of severe ARDS (which occurred in 6 of 41 patients in the sivelestat group and in 8 of 41 patients in the conventional group; hazard ratio, 1.667; 95% CI, 0.668 to 4.161). Further study of different P/F ratio subgroups revealed the same conclusion (Table 2).

Inflammatory Factors Elevated Patients

In exploratory endpoints analyses, there was no significant effect on IL-6 and PCT elevated patients between sivelestat sodium and conventional groups (IL-6: 14 of 41 patients in the sivelestat sodium group and 13 of 41 patients in the conventional group; hazard ratio, 0.929; 95% CI, 0.500 to 1.723; PCT: 7 of 41 patients in the sivelestat sodium group and 10 of 41 patients in the conventional group; hazard ratio, 1.429; 95% CI, 0.602 to 3.338), excluding CRP level. After 7 days of therapy, the number of patients with elevated level of CRP in sivelestat sodium group was significantly lower than that in the conventional group (10 of 41 patients in the sivelestat sodium group and 21 of 41 patients in the conventional group; hazard ratio, 1.818; 95% CI, 1.003 to 3.296).

Ventilation Free Days

For analysis of VFDs, trial groups were compared by t test analysis. The results were presented in Table 3 and Fig. 2. Total VFDs was longer in the sivelestat group than in the conventional group (4.71 ± 0.76 vs 3.00 ± 1.00 days, $p < 0.05$). Findings were also analyzed in different P/F subgroups: P/F 100–200 mmHg (5.00 ± 0.82 vs 3.50 ± 2.12 days, n.s), P/F 200–300 mmHg (4.50 ± 0.71 vs 2.67 ± 0.57 days, $p < 0.05$), while patients in P/F 300–400 mmHg was too small for statistical analysis.

In addition to estimating the survivorship of ventilation free patients, Kaplan-Meier Curves showed a slower drop in the sivelestat group from day 2 to day 5. However, there was no statistical difference in the ventilation free patients between the two groups over 7 days therapy.

Trend of P/F Ratio

To further analyze the therapeutic effect of sivelestat sodium on P/F ratio, we examined the trend of P/F ratio and ΔP/F values before and after 7 days of therapy. The results showed that the use of sivelestat sodium significantly improved ΔP/F values before and after therapy (21.96 ± 119.69 vs -25.58 ± 93.37, $p < 0.05$, Table 4), with statistical significance observed on Day 5 when compared with conventional group (265.56 ± 109.22 vs 192.69 ± 73.65, $p < 0.05$, Fig. 3A). Among different P/F ratio subgroups, improvements of the P/F ratio were seen after therapy with sivelestat sodium (Supplemental table 1, Fig. 3B-D). However, possibly due to the small number of participants, no clear statistical difference was found in all the three subgroups.

Level of Inflammatory factors

As previously described, the decrease of CRP might be an important indicator of the therapeutic efficacy of sivelestat sodium. We analyzed the trends in the levels of CRP, IL-6 and PCT before and after 7 days of therapy. Findings for sivelestat sodium as compared with conventional therapy were similar with respect to exploratory end points, the decrease of CRP and PCT was statistically significant in sivelestat group when compared with conventional group (ΔCRP: -64.91 ± 110.26 vs -43.40 ± 91.62, $p < 0.05$; ΔPCT: -10.68 ± 23.07 vs -1.13 ± 10.27, $p < 0.05$, Table 5). Moreover, when comparing the trends of CRP, IL-6 and PCT changes between the two groups, results did not show any statistically significant differences (Supplemental table 2).

Adverse Events

There were no substantial differences in the incidence of organ insufficiency complications or any side effects related to sivelestat observed between the sivelestat group and conventional group as assessed by the record data and safety monitoring board (Supplemental table 3).

Discussion

Neutrophil activation plays a crucial role in initiating SIRS, which is thought to be an important trigger factor of ALI/ARDS [19]. Sivelestat sodium is a promising anti-inflammatory agent that has shown beneficial effects by improving oxygenation index and reducing the duration of mechanical ventilation in

ARDS patients [20–22]. However, the timing of drug initiation and its therapeutic effect on different severities of ARDS are still controversial.

The complexity of ARDS stems from multiple factors which could trigger inflammatory responses, including trauma, infection, and other systemic inflammatory states [23,24]. Our preliminary clinical observations suggested that sivelestat sodium administration (≤ 48hrs) to patients with mild to moderate ARDS of various etiologies such as drowning, aspiration pneumonia, and chemical lung injury could improve oxygenation index and clinical outcomes [25]. Conversely, sivelestat sodium may have limited therapeutic effect on severe ARDS patients especially those requiring endotracheal intubation and mechanical ventilation, including worldwide pandemic covid-19 virus [26,27]. We speculate sivelestat sodium is not a cure for ARDS but rather a therapeutic option to improve patient outcomes by alleviating SIRS.

In order to confirm the efficacy of sivelestat sodium compared to conventional therapy, we designed a prospective, multicenter randomized cohort clinical study. In this study, sivelestat sodium therapy did not result in a lower risk of invasive mechanical ventilation than conventional therapy (with adjustment for age, sex, etiology, disease severity and clinical examination) among SIRS patients. However, referring to VFDs, we observed a longer time in sivelestat group when compared with conventional group. Among three P/F ratio subgroups, P/F 200 to 300 seems to account for the most significant difference, which suggested that patients with mild ARDS may have a favorable response to therapy with sivelestat sodium. We also noticed a slower drop of the percentage of non-mechanical ventilation patients in the sivelestat group from day 2 to day 5. Although the result was not statistically significant, it may be restricted by the number of patients enrolled and a short observation period.

As research in the field of pathophysiology advances, the understanding of ARDS has led to novel therapeutic treatments (such as granulocyte colony stimulating factor, PD-L1) that could potentially be targeted for therapeutic intervention [28–30]. Moreover, given the complexity of ARDS, it is unlikely that any single agent will be a panacea. Therefore, the decision to administer sivelestat sodium would not be taken arbitrarily. Clinicians should consider factors such as the patient's overall health, comorbidities, especially the severity of ARDS. In the present study, findings were similar for secondary end points. We found no effect of sivelestat sodium as compared with conventional therapy on the numbers of ΔP/F reduced patients or severe ARDS patients. While, sivelestat sodium could decrease ΔP/F reduced patients in P/F ratio 300 to 400 mmHg subgroup. The finding appears to be inconsistent with the results observed in longer VFDs subgroup (P/F 200–300 mmHg). To further confirm the effect of sivelestat sodium on P/F ratio, we analyzed ΔP/F before and after therapy, as well as daily ΔP/F between the two groups. The study found that sivelestat sodium significantly improved ΔP/F ratio compared to conventional therapy. In addition, the most prominent ΔP/F ratio happened on the 5th day. No significant differences were observed in the changes of P/F ratio among the three subgroups. Although there is no statistically significant, sivelestat sodium tended to increase the P/F ratio on day 5 compared to conventional therapy in both P/F 200 to 300 mmHg and P/F 300 to 400 mmHg groups. Compared to the P/F 200 to 300

mmHg group, fewer patients in the P/F 300 to 400 mmHg group progressed to invasive mechanical ventilation, which explains the rarely improved VFDs by sivelestat sodium.

The adoption of precision medicine in the treatment of ARDS aims to identify and target specific biomarkers that could predict patient response to sivelestat sodium therapy. The biomarker could seek for individualize therapy plans, lead to more effective management and ultimately improve patient outcomes. Activated neutrophils in sepsis had reduced deformability and increased stiffness, which negatively affected the rheologic properties of whole blood [31]. Sivelestat also attenuated leukocyte adhesion in pulmonary capillaries and appeared to decrease leukocyte deformability in an animal model of ALI. In our study, we attempted to identify inflammatory markers that could guide the clinical efficacy of sivelestat sodium, and the result suggested that CRP is a potential indicator. Although the decrease of inflammatory factors before and after treatment suggested that PCT has statistical significance, as a predictor of infectious diseases, PCT is often influenced by antibiotic drug usage and its intensity. Therefore, apart from CRP, PCT requires further clinical trials for validation.

Despite its benefits, sivelestat sodium still have potential side effects. The most common adverse reactions include headache, nausea, diarrhea, and hypotension. According to present studies, sivelestat sodium has been increasingly reported to alleviate the progression of chronic diseases such as renal failure. [32, 33]. The vital data and safety monitoring board found no substantial differences in the incidence of adverse reactions between the two groups.

Conclusion

In conclusion, sivelestat sodium is an effective therapeutic agent for improving the clinical course of high-risk patients progressing to ARDS or mild ARDS. Its clinical effects are specifically manifested by an increase in VFDs and a decrease in P/F ratio, which could be predicted by CRP.

Limitation

There were several limitations in our study. The most significant one is that the study population was very small. Furthermore, the influence of these therapeutic interventions on patient outcomes should be meticulously evaluated through ongoing clinical trials and real-world studies. It is imperative to conduct additional research to determine the most effective dosing strategy, the long-term safety profile, and the cost-effectiveness of sivelestat sodium in patients with ARDS. Additionally, the impact of these therapies on patient outcomes and healthcare resource utilization should be carefully assessed through ongoing clinical trials and. further research is needed to establish the optimal dosing regimen, long-term safety profile, and cost-effectiveness of sivelestat sodium in ARDS patients.

Abbreviations

ARDS: acute respiratory distress syndrome; SIRS: systemic inflammatory response syndrome; P/F ratio: PaO2/FIO2 ratio; VFDs: ventilator-free days; PCT: procalcitonin; CRP: C-reactive protein; IL-6: Interleukin-6; NF-κB: nuclear factor-kappa B; ROS: reactive oxygen species; JAK/STATE: Janus kinase/signal transducer and activator of transcription; ICU: intensive care unit; HR: heart rate; WBC: white blood cell; PCWP: pulmonary capillary wedge pressure; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; ANOVA: analysis of variance; HRs: Hazard ratios; CIs: confidence intervals

Declarations

Authors' contributions

Liang Jing drafted the initial manuscript and incorporated feedback from co-authors. Liang Xu and Jian Dai oversaw patient recruitment at Wuhan Wuchang Hospital and managed local data collection. Jun Zhang and Tingting Shu collected and processed data at Wuhan Traditional Chinese Medicine Hospital. Fengsheng Cao and Ting Jiang supervised the trial conducted at Xiangyang Central Hospital and collected data. Feng Li and Min Li led patient recruitment at The Second Affiliated Hospital of Nantong University and managed local data collection. Yan He and Maoqing Wu supervised the trial conducted at The Third People's Hospital of Hubei Province and collected data. Haitao Yuan and Jia Wang oversaw patient recruitment at People's Hospital of Dongxihu District and managed local data collection. Guochao Zhu and Huaping Liu collected and processed data at The Sixth Hospital of Wuhan. Wei Zhu led the overall coordination of the study across all centers, reviewed the final manuscript and provided expert opinions on trial design.

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Consent for publication

The authors consent to data being used for this research and publication.

Competing interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Tables

Tables 1 to 5 are available in the Supplementary Files section.

Figures

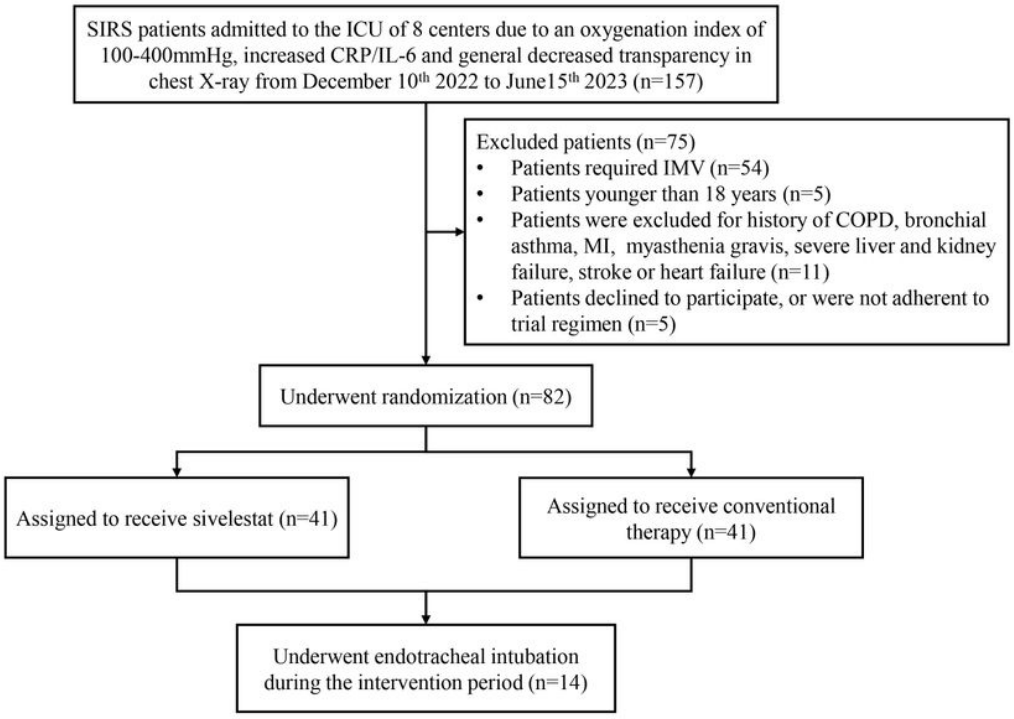

Figure 1. Flow chat of the study. IMV: invasive mechanical ventilation, COPD: chronic obstructive pulmonary disease, MI: myocardial infarction.

Figure 1

See image above for figure legend.

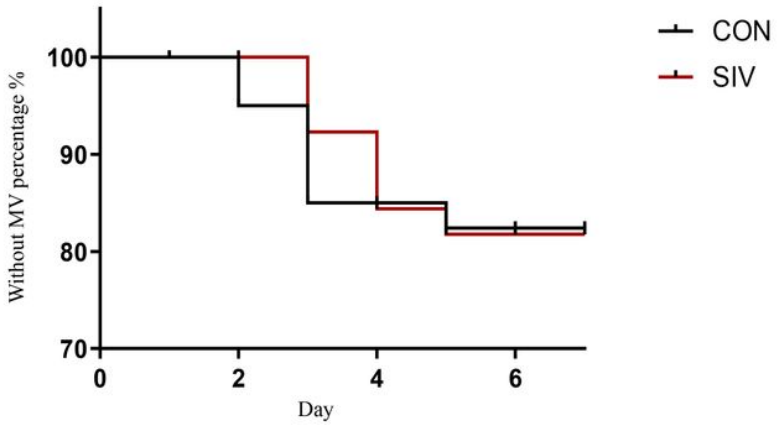

Figure 2. Kaplan-Meier Curves reveal the survivorship of ventilation free patients between sivelestat and conventional groups.

Figure 2

See image above for figure legend.

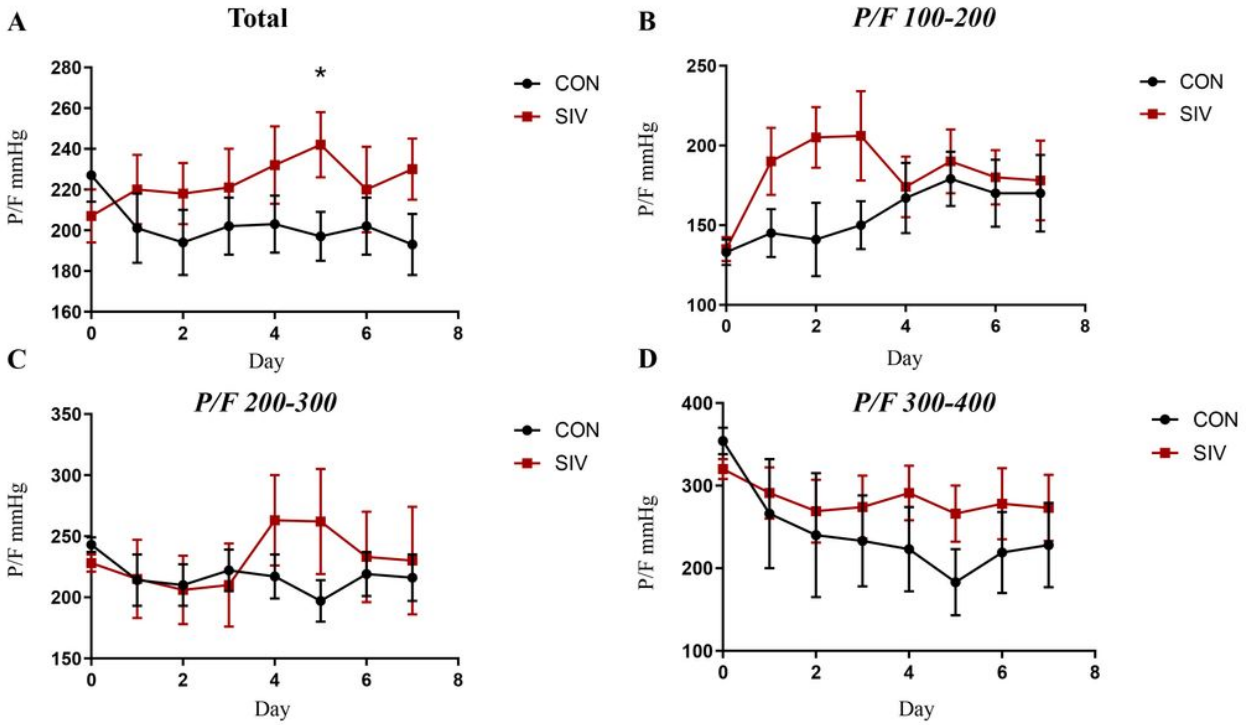

Figure 3. Trend of P/F Ratio before and after 7 days of therapy between sivelestat and conventional groups. A. Total group: P/F ratio 100 to 400 mmHg, B. Subgroup1: P/F ratio 100 to 200 mmHg, C. Subgroup2: P/F ratio 200 to 300 mmHg, D. Subgroup3: P/F ratio 300 to 400 mmHg. *p< 0.05, conventional versus sivelestat group.

Figure 3

See image above for figure legend.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementTable13.pdf
- Table15.pdf