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Clinical effects of a neutrophil elastase inhibitor, sivelestat, in patients with acute respiratory distress syndrome

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Abstract
Purpose. We assessed the effects of a neutrophil elastase inhibitor, sivelestat, on respiratory and organ functions as well as on the mortality of patients with acute respiratory distress syndrome (ARDS) associated with systemic inflammatory response syndrome (SIRS).
Methods. We retrospectively divided 25 patients who fulfilled the diagnostic criteria for SIRS and ARDS into two groups. One group (S group, $n = 12$) received a continuous infusion of sivelestat ($0.2\,mg \cdot kg^{-1} \cdot h^{-1}$), and the other did not (C group, $n = 13$).
Results. Between days 1 and 10, the Pa_{O_2}/FI_{O_2} ratio in the S group significantly improved from 119.1 ± 51.1 to 214.4 ± 88.2 mmHg ($P < 0.05$). Furthermore, the S group spent significantly fewer days on a ventilator than the C group (16.7 ± 5.8 vs 26.6 ± 14.3 days; $P < 0.05$). The length of the intensive care unit stay was also significantly shorter for the S group than for the C group (18.7 ± 4.9 vs 27.5 ± 13.5 days; $P < 0.05$). However, the mortality rate at 29 days did not statistically differ between the two groups.
Conclusion. Our results suggested that sivelestat has a beneficial effect only on the pulmonary function of ARDS patients with SIRS.

Key words Sivelestat · Neutrophil elastase inhibitor · ARDS · ALI · SIRS

Introduction

Serious organ lesions that often develop as complications of acute respiratory distress syndrome (ARDS) usually end in death. Lung lesions such as acute lung injury (ALI) or ARDS are particularly difficult to treat. This is because the diversity of causative factors and the rapidity with which the symptoms develop result in severely impaired oxygenation and a high mortality rate [1]. Systemic inflammatory response syndrome (SIRS), an exaggerated expression of the inflammatory response that is supposed to function primarily as a defense mechanism, represents the first step in a series of responses that progress from sepsis and septic shock to multiple organ failure [2]. Inflammatory mediators generated because of a predisposing condition might induce inflammatory cells to become abnormally sequestered in the pulmonary microvasculature and to secrete proinflammatory mediators that damage the microvascular endothelium [3]. Many of the manifestations of an acute inflammatory response are attributable to neutrophil actions [4]. Neutrophils and neutrophil elastase appear to play key roles in endothelial injury and in the increased vascular permeability that is characteristic of ARDS because excessive neutrophil activity results in lung injury. Thus, inhibiting such activity could prevent the development and progression of ARDS [5,6].

Sivelestat (sodium *N*-{2-[4-(2, 2–dimethylpropionyloxy) phenylsulfonyl-aminobenzoyl] amino-acetate tetrahydrate}) is a reversible, competitive inhibitor of neutrophil elastase that reliably attenuates lung injury in animal models of ALI/ARDS [7–9]. However, the efficacy of sivelestat against human ALI/ARDS remains controversial [10–12].

The present study evaluated the effects of sivelestat on respiratory and organ functions as well as on the mortality of ARDS with associated SIRS. We discuss the controversial effect of the efficacy of sivelestat in clinical trials.

Methods

Patients

A series of patients with ARDS who fulfilled all of the inclusion or exclusion criteria (Table 1) were retro-

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Table 1. Study selection criteria

Age 18 years and over
SIRS criteria: fulfillment of two or more of the following
Body temperature >38°C or <36°C
Heart rate >90 bpm
Respiratory rate >20 bpm or Pa_{CO_2} < 32 mmHg
WBC >12 000 · ml^{-1} or <4000 · ml^{-1} or stab cells >10%
ARDS criteria: fulfillment of all of the following
Pa_{O_2}/FI_{O_2} <200
Acute onset of respiratory failure
Bilateral chest infiltrates on frontal radiograph
Absence of elevated left-heart filling pressure (PCWP < 18 mmHg)
Patients who underwent positive pressure ventilation with ventilator for >10 days in the ICU

SIRS, systemic inflammatory response syndrome; WBC, white blood cell; Pa_{O_2}, arterial oxygen pressure; FI_{O_2}, fraction of inspired oxygen; PCWP, pulmonary capillary wedge pressure; ICU, intensive care unit

spectively examined. Sivelestat (Ono Pharmaceutical, Osaka, Japan) was approved and became commercially available in Japan in June 2002 as a treatment for ALI/ARDS associated with SIRS. We designed our study as follows. The control group (C group) consisted of 13 ARDS patients who were admitted to the intensive care unit (ICU) between June 2001 and May 2002 before sivelestat became commercially available and thus were not administered the drug. The S group consisted of 12 ARDS patients who were admitted to the ICU between June 2002 and May 2003 after sivelestat became commercially available. Patients who remained for less than 10 days in the ICU were excluded from the study.

Procedure

Sivelestat was infused intravenously into patients of the S group at a rate of 0.2 mg·kg^{-1}·h^{-1} for 14 days from the moment the above criteria were fulfilled. All patients underwent mechanical ventilation with a Bennett 840 ventilator (Puritan-Bennett, Carlsbad, CA, USA) or a Siemens Servo 300 ventilator (Siemens, Danvers, MA, USA). To reduce ventilator-associated lung injury from overdistension, the peak airway pressure in both groups was always maintained below 30 cm H_2O in pressure-controlled ventilation or pressure-support ventilation mode (or both) with positive end-expiratory pressure (PEEP) at tidal volumes of 6–7 ml·kg^{-1}. Patients were weaned from mechanical ventilation as much as possible according to the criteria defined by the ARDS Network [13,14]. To evaluate illness severity and organ failure status, Acute Physiology and Chronic Health Evaluation II scores (APACHE II scores) were determined within 24 h of entering the ICU and sequential organ failure assessment (SOFA) scores were assessed daily. From the first day, only ARDS patients with low arterial oxygen pressure (Pa_{O_2})/fraction of inspired oxygen (FI_{O_2}) (P/F) values (<100 mmHg) received one dose of steroid (methylprednisolone 250 mg) and urinastatin (300 000 units/day) for 3 days. Continuous hemodiafiltration (CHDF) was applied to the patients with the acute renal failure, and polymyxin-direct hemoperfusion (PMX-DHP) was applied to the one patient in the S-group with catecholamine-resistant septic shock.

This study was approved by the Ethics Committee of Kagoshima University Hospital. Written informed consent was obtained from the families of the patients.

Statistical analysis

All data are presented as means ± SD. Parametric data were analyzed by an unpaired *t*-test or by one-way analysis of variance (ANOVA) followed by Fisher's protected least significant difference (PLSD) test. Nonparametric data were evaluated by the Mann-Whitney U-test and the chi-squared test. Differences between the two groups were evaluated using the ANOVA for repeated measurements. If this procedure revealed significant differences, each measurement point between the groups was statistically compared by the unpaired *t*-test. Kaplan-Meier estimates of mortality described the relative risk of death. $P < 0.05$ was considered significant.

Results

Table 2 shows that the two groups of patients did not differ in terms of age, body weight, sex, disease, or other parameters. The general conditions of the patients were compared using the APACHE II and SOFA scores (Table 2, Fig. 1). Figure 2 shows the values for the P/F ratio of both groups. The P/F ratios (on day 1) before the administration of sivelestat for the S and C groups did not differ significantly. Between days 1 and 10, the P/F ratio in the S group significantly improved (from 119.1 ± 51.1 to 214.4 ± 88.2 mmHg; $P < 0.05$), whereas

Table 2. Demographic and clinical characteristics

Parameter	S group ($n = 12$)	C group ($n = 13$)	P
Patient information			
Male/female	10/2	11/2	>0.9
Age (years)	73.1 ± 6.95	70.4 ± 7.65	>0.1
Weight (kg)	57.5 ± 7.95	60.4 ± 8.65	>0.1
Disease category			>0.1
Cardiovascular	6	8	
Gastrointestinal tract	4	4	
Respiratory	1	0	
Other	1	1	
APACHE II	21.9 ± 3.4	21.2 ± 3.2	>0.4
Steroid and urinastatin	5	5	>0.8
CHDF (PMX-DHP)	8	6 (1)	>0.5
Mechanical ventilation (days)	16.7 ± 5.8	26.6 ± 14.3	<0.05
Days in ICU	18.7 ± 4.9	27.5 ± 13.5	<0.05
Mortality	4/12 (33.3%)	5/13 (38.5%)	>0.05

Data are expressed as means ± SD
C group, controls; S group, sivelestat; APACHE II, Acute Physiology and Chronic Health Evaluation II; CHDF, continuous hemodiafiltration; PMX-DHP, polymyxin-direct hemoperfusion

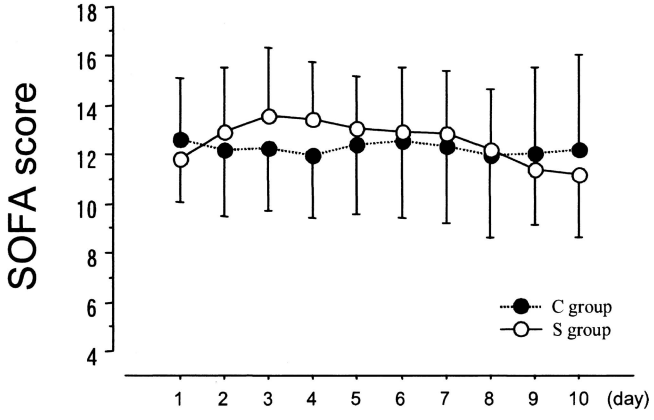

Fig. 1. Time course of changes in the sequential organ failure assessment (SOFA) score. Data are expressed as the mean ± SD

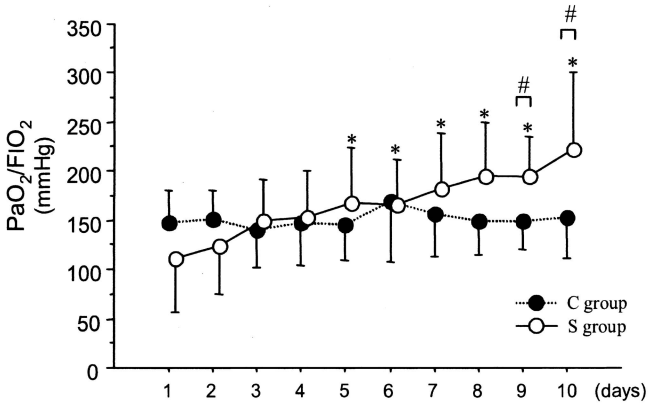

Fig. 2. Time course of changes in the Pa_{O_2}/FI_{O_2} ratio. Data are expressed as means ± SD. *C group*, controls; *S group*, sivelestat. $^{*}P < 0.05$ vs. initial value (day 1) in the same group; $^{\#}P < 0.05$ vs. value obtained at the same time in the C group

that in the C group did not (from 147.8 ± 33.1 to 154.0 ± 42.9 mmHg; not significant). The S and C groups required positive-pressure ventilation for 16.7 ± 5.8 and 26.6 ± 14.3 days, respectively, indicating that the S group spent significantly less time on the ventilator ($P < 0.05$). The S group remained in the ICU for significantly less time than the C group (18.7 ± 4.9 vs. 27.5 ± 13.5 days, respectively; $P < 0.05$) (Table 2).

We compared the serum laboratory values of individual patients before and after treatment and found that abnormalities in renal, hepatic, or hematological variables did not differ. The SOFA scores over 10 days and mortality rates at 29 days for the two groups also did not significantly differ (Fig. 1). The causes of death are summarized in Table 3.

Table 3. Causes of death

Cause of death	S group	C group
Acute respiratory failure	0	1
Multiple organ failure	2	2
Obstruction of stent graft (TAA)	1	0
Bleeding (DIC)		
Gastrointestinal system	0	1
Lung	0	1
Brain	1	0
Total deaths	4	5

TAA, thoracic aortic aneurysm; DIC, disseminated intravascular coagulation

Discussion

Histological studies of lung specimens obtained from patients early in the course of the disease show marked accumulation of neutrophils predominantly in pulmonary edematous and bronchoalveolar lavage fluids. Other studies have shown that many animal models of ALI are neutrophil-dependent [1,15]. Clinical and experimental studies have also provided circumstantial evidence of neutrophil-mediated injury in ALI/ARDS, and substantial evidence from humans and other animals supports a causative role for neutrophil elastase in lung injury [4–6]. Therefore, the inhibition of neutrophil elastase might prevent the development and progression of ALI/ARDS. Furthermore, an inhibitor of neutrophil elastase (sivelestat) attenuates ischemic-perfusion injury of the liver and heart [16–18]. Miyazaki et al. [19] have shown that sivelestat attenuates vascular endothelial injury mediated by activated neutrophils. Furthermore, the production of monocyte chemoattractant protein-1 (MCP-1) by macrophages is stimulated by neutrophil elastase and by oxygen radicals generated by hypoxia, and sivelestat significantly reduces MCP-1 mRNA in the liver after ischemia-reperfusion [17]. These data indicated that sivelestat could protect against not only lung injury but also the failure of other organs.

The present study found that sivelestat (neutrophil elastase inhibitor) significantly improved the P/F ratio of ARDS patients with SIRS after 5 days of administration. Furthermore, patients on sivelestat (S group) were weaned from the ventilator and remained in the ICU for significantly less time than the control group (C group). SOFA scores that assessed multiple organ failure were similar in the two groups, and the 29-day survival rates were similar. Approximately 89% (8/9) of the deaths were the result of diseases other than acute respiratory failure (Table 3), which may be one of the reasons no difference in total survival rate between the two groups was found. Our results suggested that sivelestat has a beneficial effect only on the pulmonary function of ARDS patients with SIRS. However, the present and retrospective studies involved a limited number of patients. Consequently, further clinical investigation is required to assess whether sivelestat protects against not only lung injury but also the failure of other organs. Before a large number of clinical studies are initiated, however, the optimal means to assess the efficacy of sivelestat should be established.

Two large clinical trials have examined the efficacy and safety of sivelestat in ALI/ARDS patients [10–12]. In the phase III clinical study described by Tamakuma et al. [10,11], 230 ALI/ARDS patients with SIRS were randomized to either high-dose ($0.2\,mg \cdot kg^{-1} \cdot h^{-1}$, $n = 113$) or low-dose ($0.004\,mg \cdot kg^{-1} \cdot h^{-1}$, $n = 108$) sivelestat for up to 14 days. The results showed that 71.7% (81/113 patients) were moderately or obviously improved in the high-dose group compared with 55.6% (60/108 patients) in the low-dose group, and that the high-dose group was discharged from the ICU significantly sooner than the low-dose group. However, the overall survival rates did not differ significantly between the two groups [10,11]. Their results suggested that sivelestat might have a beneficial effect only on the pulmonary function of ALI/ARDS patients with SIRS, which is quite similar to our results. However, the Sivelestat Trial of ALI Patients Requiring Mechanical Ventilation (STRIVE) described by Zeiher et al. [12] in which 492 ALI/ARDS patients were randomized in a 1:1 fashion to sivelestat or placebo, uncovered no evidence of an effect on measures of pulmonary function that met the weaning criteria, including the P/F ratio. Furthermore, their final analysis revealed that sivelestat did not affect either the primary endpoints of ventilator-free days (days 1–28) or the 28-day all-cause mortality rates. Although their Kaplan-Meier 180-day survival curves showed no difference between the treated groups ($P = 0.102$), the 180-day all-cause mortality increased in the sivelestat group compared with the placebo group ($P = 0.006$) [12]. Their results suggested that sivelestat might not have a beneficial effect on the pulmonary function of ALI/ARDS patients, and that it might have reduced the survival rate. These data were completely different from ours and those of the phase III clinical study. We considered why the findings differed between the two large clinical trials. One possibility is that the phase III clinical study contained more patients with SIRS and ALI/ARDS (100%) than the STRIVE study (89.3%). In addition, more patients had sepsis defined as SIRS in response to an active infectious process in the host in the phase III clinical study (68.8%) than in the STRIVE study (58.5%). Thus, the resulting plasma concentrations of neutrophil elastase were higher in the former study (low-dose and high-dose groups: 859 ± 1547 and $672 \pm 590\,ng \cdot ml^{-1}$, respectively) than in the latter study (placebo and sivelestat groups: 268 ± 260 and $249 \pm 263\,ng \cdot ml^{-1}$, respectively). Patients with multiple organ failure involving four or more organs were excluded from the phase III clinical study but were not excluded from the STRIVE study [11,12]. These findings indicate obvious differences between patient characteristics in the two large clinical trials. Furthermore, the values for neutrophil elastase activity in the phase III clinical study showed that sivelestat significantly promoted pulmonary function in the ARDS patients. Thus, sivelestat affects respiratory function differently according to illness severity and neutrophil elastase activity, so the timing and duration of sivelestat administration might be crucial to its ultimate success.

Conclusions

The results of the present study suggest that sivelestat has a beneficial effect on the lungs of ARDS patients with SIRS. To assess the efficacy of sivelestat correctly, ARDS patients should be divided into groups with a similar etiology of ALI/ARDS, similar values for neutrophil elastase activity (e.g., sepsis, pneumonia, trauma), and similar severity of illness assessed by APACHE II, SOFA, and multiple organ failure scores. Additional clinical and preclinical studies might be warranted not only to clarify the clinical potential of sivelestat intervention but also to define more clearly the activities of neutrophil elastase in inflammatory disorders such as ALI/ARDS and multiple organ failure.

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