

The effect of an oral leukotriene antagonist, ONO-1078, on allergen-induced immediate bronchoconstriction in asthmatic subjects

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Background: Cysteinyl leukotrienes are potent contractile agonists for airway smooth muscle. To examine the relative role of cysteinyl leukotrienes in immediate airway obstruction in human subjects with asthma after allergen challenge, we investigated the effect of ONO-1078, a potent receptor antagonist of cysteinyl leukotrienes, on the response.

Methods: ONO-1078 and an inactive placebo, in 150-mg capsule form, were administered every 12 hours for 1 week, in a double-blind, cross-over fashion. To examine the effect on the early part of the response, total respiratory resistance (Rrs) was continuously evaluated for 10 minutes after the start of a 1-minute exposure to an appropriate concentration of allergen. Rrs and FEV_{1.0} were estimated every 10 minutes for 60 minutes after the exposure.

Results: ONO-1078 significantly reduced percent changes in Rrs and FEV_{1.0} from 20 to 60 minutes after the exposure, as well as percent maximum changes in these indices, although the treatment did not alter the time from the start of allergen exposure to the beginning of elevation of Rrs, the time from the start to the point at which total respiratory conductance decreased by 35% from its baseline value, or percent changes in Rrs or FEV_{1.0} 10 minutes after the exposure.

Conclusions: Therefore, we conclude that cysteinyl leukotrienes primarily mediate a later part of immediate airway obstruction after allergen exposure. (*J ALLERGY CLIN IMMUNOL* 1993;92:507-12.)

Key words: Cysteinyl leukotrienes, asthma, antagonist, ONO-1078, allergen challenge

Cysteinyl leukotrienes (LTs) are potent contractile agonists for airway smooth muscle.¹⁻³ Some of these mediators have been demonstrated to be present in the bronchoalveolar lavage fluid of subjects with allergic asthma 5 to 10 minutes after allergen instillation into the lung,^{4, 5} although the onset of their release has been reported to be slower than that of histamine.⁶ With the use of specific receptor antagonists, some investigators have suggested the participation of LT D₄ in immediate bronchoconstriction after allergen challenge in subjects with asthma.^{7, 8} However, the relative roles of cysteinyl LTs in the

Abbreviations used

Grs:	Total respiratory conductance
LTs:	Leukotrienes
PT ₃₅ -Grs:	Time from the start of allergen exposure to the point at which Grs decreased by 35% from its baseline value
Rrs:	Total respiratory resistance
SRS-A:	Slow-reacting substance of anaphylaxis
Ta:	Time from the start of allergen exposure to the beginning of elevation of Rrs

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early part of the immediate airway obstruction after allergen challenge has not been well defined. By contrast, in an in vitro study in which a single concentration of antigen was used, it has been demonstrated in sensitized human bronchial strips that the onset of contraction is caused by histamine first released by the antigen and that

TABLE I. Patient characteristics

Subjects	Age (yr)	Sex	Height (cm)	Weight (kg)	PD ₃₅ -Grs (units)	ST-S (wt/vol)	Allergen concentration (wt/vol)
1	26	M	176	75	3.49	-4	1:5
2	23	M	184	85	0.68	-4	1:5
3	26	F	158	52	1.83	-4	1:5
4	23	M	168	54	2.30	-4	1:5
5	23	M	181	72	1.82	-3	1:5
6	20	F	158	51	2.14	-4	1:5
7	23	M	173	80	2.35	-3	1:10
8	33	F	161	52	2.97	-4	1:10
9	21	M	174	61	2.87	-3	1:20
10	21	M	169	61	2.04	-3	1:20

Skin test threshold (ST-S) is expressed by a logarithmic scale.

the later part of the response is primarily mediated by slow-reacting substance of anaphylaxis (SRS-A).⁹

In the present study, therefore, to investigate the relative role played by cysteinyl LTs in immediate airway obstruction induced by allergen challenge in subjects with asthma, we examined the effects of ONO-1078,^{10, 11} a potent receptor antagonist of cysteinyl LTs, on continuous change in total respiratory resistance (Rrs) for 10 minutes after a 1-minute exposure to an appropriate concentration of allergen and on changes in Rrs and FEV_{1.0} every 10 minutes for 60 minutes after the challenge.

METHODS

Subjects

Ten adult subjects with asthma participated in the study. Anthropometric data, airway reactivity to methacholine,¹² skin test threshold, and allergen concentration used in challenges are summarized in Table I. All subjects had positive bronchial response to inhaled house dust allergen, a history of episodic dyspnea with wheezing, and a documented increase in FEV_{1.0} of more than 20%, either spontaneously or after medication. None of the subjects had other pulmonary or cardiovascular diseases. None of the subjects had experienced respiratory tract infection or exacerbation of asthma for at least 4 weeks before the study or during the period of the study.

The present study was approved by the ethics committee of Tohoku University School of Medicine. All patients gave written informed consent before entry into the study.

Protocol

The study was performed in a placebo-controlled, double-blind cross-over fashion. Of 14 subjects who

participated, 10 were able to complete the study. Among these 10, at unblinding, we found that three subjects had received ONO-1078 for the first week and an inactive placebo for the second week and that the remaining seven subjects had received these in reverse order. The four patients who could not complete the last challenge because of airway narrowing had been treated with an inactive placebo during the second week. ONO-1078 and placebo, in 150-mg capsule form, were orally administered every 12 hours, for 1 week. None of the subjects received any other medication for 1 month before or during the period of the study. Each allergen inhalation challenge was done at the same time of day on different days, 2 hours after administration of the last dose of ONO-1078 or inactive placebo.

Allergen inhalation challenge

On day 1, to determine the allergen concentration to be used in actual challenges, subjects inhaled aerosols of doubling concentrations of house dust allergen (from 1:80 to 1:10 wt/vol) for 1 minute, in a stepwise increasing fashion, every 5 minutes until total respiratory conductance (Grs) had decreased by 35% from its baseline value. One week later (day 2), an allergen concentration twice that of the last one on day 1 was inhaled for 1 minute. For pulmonary function tests, we used Rrs estimated with the forced 3-Hz oscillation technique (Astograph; TCK 6100H, CHEST, Tokyo) and FEV_{1.0} measured with a spirometer (OST-80A; CHEST, Tokyo). Rrs was continuously measured for 10 minutes after the start of allergen exposure and FEV_{1.0} was measured before and 10 minutes after the exposure. In addition, Rrs and FEV_{1.0} were measured 20, 30, 40, 50, and 60 minutes after the exposure. Further, 1 week later (day 3), the challenge was repeated in the same manner.

We defined three indices from the Rrs response curves during the first 10 minutes after the start of allergen inhalation as follows: (1) appearance time

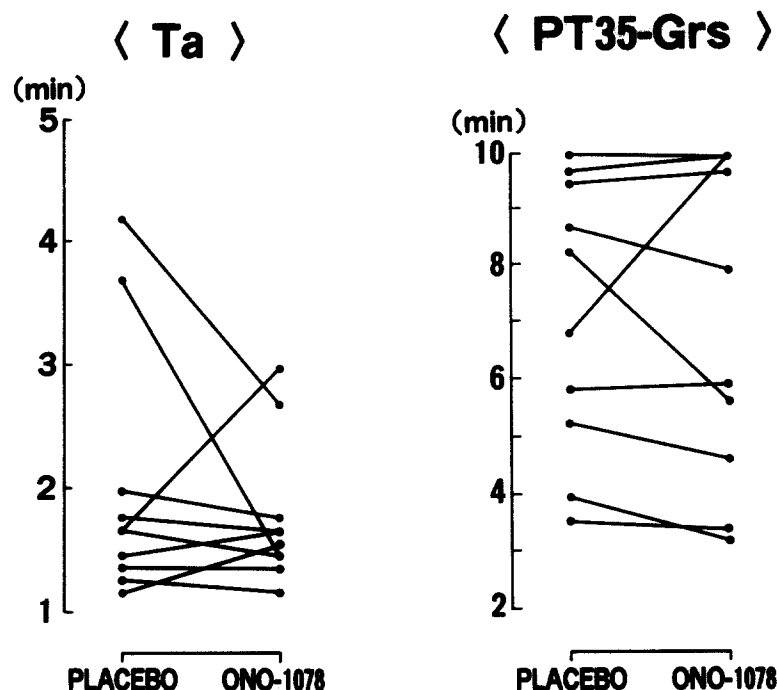


FIG. 1. Values of Ta and PT₃₅-Grs after 1-week treatments with both inactive placebo and ONO-1078 (300 mg/day). Ta was 2.05 ± 0.98 minutes after placebo treatment and 1.81 ± 0.55 minutes after ONO-1078 treatment, and corresponding values of PT₃₅-Grs were 7.19 ± 2.27 minutes and 7.09 ± 2.63 minutes. Thus there was no statistical difference in Ta or PT₃₅-Grs between the two treatments.

TABLE II. Baseline pulmonary functions after each treatment

Subjects	Inactive placebo		ONO-1078	
	FEV _{1.0} (%predicted)	Rrs (cm H ₂ O/L/sec)	FEV _{1.0} (%predicted)	Rrs (cm H ₂ O/L/sec)
1	103	3.6	104	3.2
2	96	4.0	98	3.6
3	107	3.6	106	3.4
4	100	4.0	101	3.8
5	110	4.2	106	4.8
6	98	4.2	97	4.6
7	97	4.8	100	4.6
8	102	4.8	102	4.8
9	107	3.7	110	3.5
10	104	5.8	101	5.8
Mean $\pm$ SD	102.5 $\pm$ 3.3	4.23 $\pm$ 0.77	102.4 $\pm$ 4.8	4.25 $\pm$ 0.67

(Ta), the time from the start of the exposure to the beginning of elevation of Rrs; (2) provocation time (PT₃₅-Grs), the time from the start of the exposure to the point at which Grs decreased by 35% from its baseline value; and (3) percent increase in Rrs 10 minutes after the exposure. In addition, we estimated percent decrease in FEV_{1.0} from its baseline values 10 minutes after the exposure. Moreover, percent increase in Rrs and percent decrease in FEV_{1.0} from their

respective baseline values were evaluated 20, 30, 40, 50, and 60 minutes after the exposure.

Statistical analysis

These data are presented as mean plus or minus the SD. Comparisons between placebo- and active-treatment groups were made by an analysis of variance.

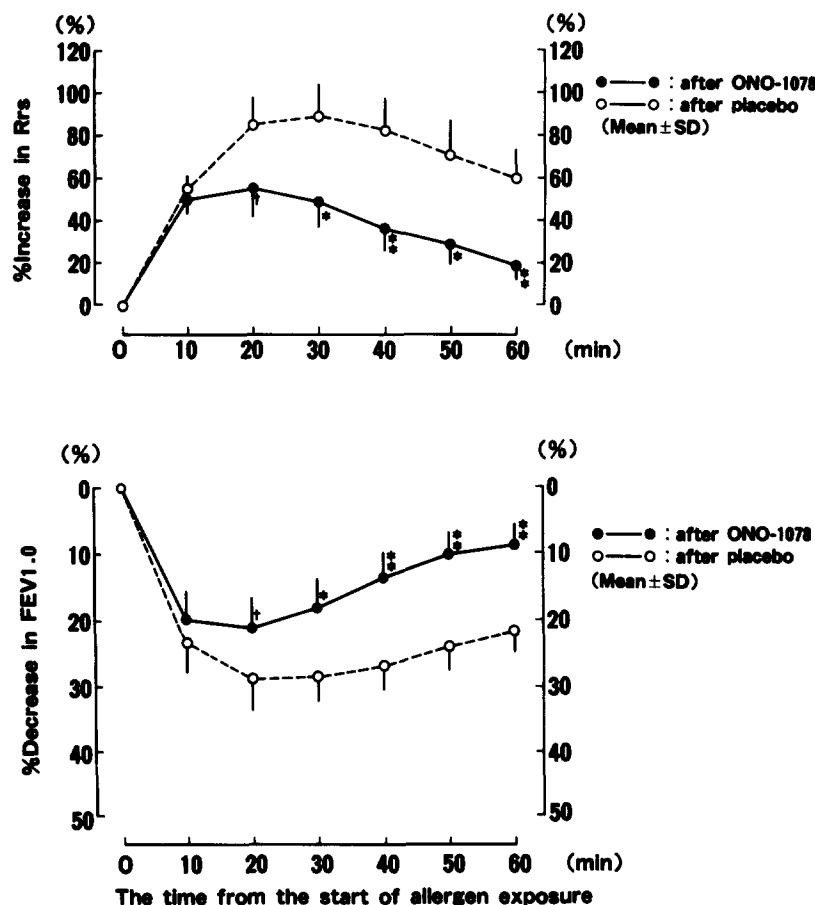


FIG. 2. Percent increase in Rrs and percent decrease in FEV_{1.0} after treatments with both inactive placebo and ONO-1078. ONO-1078 treatment significantly reduced percent change in Rrs and FEV_{1.0} from 20 to 60 minutes after 1-minute exposure to appropriate single concentration of allergen, in comparison with placebo treatment.

RESULTS

Table II summarizes baseline pulmonary function values before both challenges. Percent FEV_{1.0} to predicted values were $102.5\% \pm 3.3\%$ and $102.4\% \pm 4.8\%$ after placebo and ONO-1078 treatment, respectively. The corresponding values of Rrs were 4.23 ± 0.77 cmH₂O/L/sec and 4.25 ± 0.67 cm H₂O/L/sec. Thus there were no statistical differences in baseline pulmonary functions between the two treatments.

As shown in Fig 1, the values of Ta were 2.05 ± 0.98 minutes and 1.81 ± 0.55 minutes after placebo and ONO-1078 treatment, respectively. The corresponding values of PT₃₅-Grs were 7.19 ± 2.27 minutes and 7.09 ± 2.63 minutes. By contrast, from 20 to 60 minutes after the exposure, the percent increase in Rrs and percent decrease in FEV_{1.0} after ONO-1078 treatment were significantly smaller than those after placebo treatment (Fig. 2). In addition, the percent max-

imum increases in Rrs with placebo and active treatment were 92.5 ± 46.1 and 64.5 ± 37.2 , respectively. The corresponding values of percent maximum decreases in FEV_{1.0} were 31.1 ± 14.5 and 22.1 ± 14.1 . We have found neither order effect nor carry-over effect in any of the analyses. Thus ONO-1078 significantly reduced maximum airway obstruction and constriction from 20 to 60 minutes after the challenge, although it did not alter airway obstruction during the first 10 minutes after the exposure.

DISCUSSION

In the present study, we continuously evaluated the early part of immediate airway obstruction after a 1-minute exposure to an appropriate concentration of allergen as the change in Rrs. Consequently, we showed that a 1-week treatment with ONO-1078 did not alter Ta, PT₃₅-Grs, or percent changes in Rrs or FEV_{1.0} 10 minutes after

the exposure. However, we also showed that the treatment significantly reduced percent maximum changes in Rrs and FEV_{1.0}, as well as percent changes in these two indices from 20 to 60 minutes after the exposure, in comparison with placebo treatment. Thus we demonstrated that ONO-1078 selectively inhibited the amplitude of the later part of the immediate bronchocontraction without any delay in the onset or any decrease in the amplitude of the early part of immediate airway obstruction after the challenge.

In an in vitro study, Lewis et al.¹³ reported that histamine release occurs within the first minute, and reaches near maximum a few minutes after allergen exposure and that SRS-A release occurs later in sensitized human lung fragments. In addition, with use of a single concentration of antigen, Adams and Lichtenstein⁹ reported that treatment of sensitized human bronchial strips with FPL 55712 decreases the amplitude and duration of the prolonged phase of the contraction without any delay in the onset or any decrease in the amplitude of the initial phase of the contraction. Thus, in in vitro studies, it has been suggested that SRS-A action is later than that of histamine in antigen-induced contraction of human bronchial strips. However, cysteinyl LTs have been reported to be released within 5 to 10 minutes after allergen instillation into the lung of subjects with allergic asthma.^{4, 5} Therefore we infer that cysteinyl LTs did not physiologically participate in the early part of immediate airway obstruction after allergen exposure.

There is conflicting evidence about the relative role played by cysteinyl LTs in immediate airway narrowing after exposure to allergen in subjects with asthma. Thus Britton et al.¹⁴ have shown that L-649923, a competitive antagonist of LT D₄, causes only a small reduction in the early response to antigen, and Bel et al.¹⁵ have found that L-648051, a competitive inhibitor of LT D₄ and LTC₄, does not protect against early asthmatic response to antigen. By contrast, Fuller et al.⁷ reported that the maximum change during immediate airway obstruction is significantly reduced after treatment with LY171883, an LT antagonist, and Taylor et al.⁸ showed that ICI204219, an LT D₄ receptor antagonist, significantly attenuates the early bronchoconstriction to inhaled allergen. These conflicting reports may be a result of differences in the potency of the agents,^{16, 17} because there are few differences in challenge procedures and subjects among the previous studies. In vitro studies have shown that ONO-1078 is a potent

receptor antagonist of cysteinyl LTs, being approximately four times more potent than FPL-55712.^{10, 11} In addition, as previously reported, in normal volunteers, 7-day medication with ONO-1078 inhibited LTD₄ induced airway obstruction in a dose-dependent fashion and medication with 150 mg/day of ONO-1078 blocked the obstruction observed after inhalation of LTD₄ almost completely.¹⁸ Therefore, we assume that the lack of inhibition of the early part of immediate airway obstruction was not a result of weak potency of the agent.

In conclusion, we showed that ONO-1078 significantly inhibited the later part of immediate airway obstruction induced by inhaled allergen without any improvement in the early part of the obstruction. Therefore we conclude that cysteinyl LTs are the contractile agonists responsible for the later part of immediate airway narrowing observed after allergen challenge in human subjects with asthma.

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