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In Vivo Pharmacologic Profile of YM158, a New Dual Antagonist for Leukotriene D_4 and Thromboxane A_2 Receptors

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ABSTRACT—The antagonistic activity of oral YM158 (3-[(4-*tert*-butylthiazol-2-yl)methoxy]-5′-[3-(4-chlorobenzenesulfonyl)propyl]-2′-(1*H*-tetrazol-5-ylmethoxy)benzanilide monosodium salt monohydrate), a new dual antagonist for leukotriene (LT) D_4 and thromboxane (TX) A_2 receptors, was investigated. Oral YM158 caused dose-dependent inhibition of LTD_4-induced increases in plasma leakage and LTD_4- or U46619-induced increases in airway resistance, with ED_{50} values of 6.6, 8.6 and 14 mg/kg, respectively. The dose-range of YM158's inhibitions was almost the same for both LTD_4 and TXA_2 receptors, and repeated oral doses did not affect its efficacy. Furthermore, oral YM158 inhibited antigen-induced bronchoconstriction. Although the potency of pranlukast for LTD_4 receptor antagonism (ED_{50} = 0.34 mg/kg) is greater than that of YM158 (ED_{50} = 8.6 mg/kg), the doses of both pranlukast and YM158 for significant inhibition of the antigen-evoked airway response were the same, indicating that the TXA_2 receptor antagonism of YM158 plays an important role in its anti-asthmatic effects. In conclusion, YM158 promises to be a novel agent for treating bronchial asthma.

Keywords: YM158, Leukotriene D_4, Thromboxane A_2, Receptor antagonist, Asthma

Arachidonic acid metabolism is thought to contribute to the pathogenesis of various types of inflammation. Arachidonic acid is a 20-carbon essential fatty acid that is stored in the sn-2 position of membrane phospholipids and is cleaved by phospholipase A_2. The free arachidonic acid is then metabolized to both cysteinyl-leukotrienes (cys-LTs; LTC_4, LTD_4 and LTE_4) (1) via the 5-lipoxygenase pathway, and thromboxane (TX) A_2 via the cyclooxygenase pathway (2). Since the 5-lipoxygenase pathway has been reported to be highly expressed in leukocytes, and 5-lipoxygenase is found in lung, pancreas, ileum and thymus (3), cys-LTs are thought to have some roles in bronchial asthma. These 5-lipoxygenase and cyclooxygenase products are important mediators in allergic response in lungs of asthmatic patients and sensitized animals (4 – 7). The pharmacologic manipulation of the effects of cys-LTs and TXA_2 using receptor antagonists or biosynthesis inhibitors could provide novel therapeutic approaches to treat bronchial asthma (8). Potent cys-LTs antagonists, pranlukast (9, 10) and zafirlukast (11 – 13), have already been marketed to treat bronchial asthma. The TXA_2 receptor antagonist, seratrodast (14, 15), and synthetase inhibitor, ozagrel (16), are also sold in Japan.

Previous studies showed that cys-LTs and TXA_2 play important, but mutually complementary roles in the onset of bronchial asthma. For example, LTD_4 induces potent bronchoconstriction (17, 18) and enhances vascular permeability (19, 20) and mucus secretion (21), whereas TXA_2 induces bronchial hyperreactivity (22 – 24) and bronchoconstriction (25, 26). This difference suggests that a multi-pathway inhibitory agent, such as a dual antagonist of both LTD_4 and TXA_2 receptors, would prove a potent therapeutic agent in treating bronchial asthma.

YM158 is a newly synthesized dual antagonist for LTD_4 and TXA_2 receptors, and shows almost the same potency against LTD_4- and TXA_2-induced responses as shown by functional assay systems in vitro (27). In this report, the pharmacologic profile and anti-asthmatic effects of oral YM158 are described.

MATERIALS AND METHODS

The following experiments were performed in compliance with the regulations of the Animal Ethical Committee of Yamanouchi Pharmaceutical company.

Animals

Two groups of male Hartley guinea pigs (Japan Charles

River, Yokohama) weighing 240 to 340 g and 420 to 810 g were used in experiments on plasma leakage and the agonist- or antigen-induced increase in airway resistance, respectively. Animals were given free access to food and water until the day before the experiment and were then fasted from the evening of the day before being used in experiments on the effects of orally administered compounds. In the study of efficacy after repeated oral administration of YM158, food and water were given ad libitum during the period of administration, and the animals were fasted from the evening of the day before the induction of increase in airway resistance, with water given ad libitum.

Chemicals

The following drugs and chemicals were used: YM158 (3-[(4-*tert*-butylthiazol-2-yl)methoxy]-5′-[3-(4-chlorobenzenesulfonyl)propyl]-2′-(1*H*-tetrazol-5-ylmethoxy)benzanilide monosodium salt monohydrate) (27, 28), zafirlukast (4-(5-cyclopentyloxycarbonylamino-1-methylindol-3-ylmethyl)-3-ylmethyl)-3-methoxy-*N*-*o*-tolylsulfonylbenzamide) (11) and montelukast (1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl)(3-2-(1-hydroxy-1-methylethyl)phenyl)propyl) thio)methyl)cyclopropane) acetic acid sodium salt) (29) were synthesized by Yamanouchi Pharmaceutical Co., Ltd. (Tsukuba). Pranlukast (4-oxo-8-[4-(4-phenylbutoxy)benzoylamino]-2-(tetrazol-5-yl)-4*H*-1-benzopyran hemihydrate) (30) and seratrodast (7-(3,5,6-trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoic acid) (31) were purified from the commercially available formulations ONON® (Ono Pharmaceutical Co., Osaka) and BRONICA® (Takeda Chemical Industries, Osaka). The other compounds purchased were as follows: LTD_4, U46619 (Cayman Chemical Co., Arbor, MI, USA); ovalbumin (OA, grade VI), indomethacin, pyrilamine maleate salt, propranolol hydrochloride, urethane (Sigma Chemical Co., St. Louis, MO, USA); Evans blue (Tokyo Kasei Co., Tokyo); gallamine triethioide (Flaxedil®; Rhone-Poulenc Rorer, Paris, France); hydroxypropyl-methylcellulose 2910 (HPMC2910, TC-5E), polyoxyethylene hydrogenated castor oil 60 (HCO-60) (Shin-etsu Chemical Co., Tokyo).

For experiments on antigen-challenged airway lung resistance, the free base of YM158 was dissolved in DMSO containing TC-5E (15 mg/ml) and HCO-60 (2.5 mg/ml). For experiments on plasma leakage and lipid mediator-stimulated airway lung resistance, YM158, zafirlukast, montelukast and seratrodast were suspended or dissolved in 0.5% carboxymethylcellulose (MC) solutions. Pranlukast was dissolved in DMSO containing TC-5E (15 mg/ml) and HCO-60 (2.5 mg/ml). LTD_4 and U46619 were dissolved in absolute EtOH and stored at −80°C and −30°C, respectively. For experiments on cutaneous microvascular leakage and airway lung resistance, the stock LTD_4 EtOH solution was diluted with 0.9% saline (final concentration of EtOH was under 1%). For experiments on airway resistance, the stock U46619 EtOH solution was diluted with 0.9% saline (final EtOH concentration was 3%) supplemented with Na_2CO_3 (final molar concentration of Na_2CO_3 was equal to that of U46619). Pyrilamine maleate, propranolol, OA and Evans blue were dissolved in 0.9% saline. Indomethacin was dissolved in 0.9% saline with a few drops of 1 N NaOH added to improve solubility.

Mediator-induced airway resistance increase

Male Hartley guinea pigs were anesthetized by intraperitoneal injection of 1.2 g/kg urethane. A tracheal cannula was then inserted. Spontaneous respiration was stopped with gallamine (1 mg/kg, i.v.), and artificial respiration was carried out at a rate of 60 strokes/min and volume of 1 ml/100 g body weight per cycle. After intravenous administration of LTD_4 (300 ng/kg) or U46619 (3 μg/kg), airway resistance was measured using a respiratory function measuring apparatus (Model 6; Buxco Electronics, Inc., Sharon, CT, USA). The airway resistance was measured as a mean every 5 s and expressed as the percent change compared with the basal resistance level. The agent was orally administered 1 h before intravenous injection of agonists. The effects of each agent were evaluated using the peak change percentage of lung resistance.

Antigen-induced asthmatic responses in actively immunized guinea pigs

Male Hartley guinea pigs were actively immunized by three intraperitoneal administration of 5 μg OA containing 1 mg of Alum ($Al(OH)_3$) every 2 weeks. These immunizations were performed according to the modified method previously described (32, 33). One week after the last intraperitoneal antigen administration, the animals were anesthetized with urethane (1.2 g/kg, i.p.) and a tracheal cannula attached to the constant volume respirator was inserted. Artificial respiration was carried out at a rate of 60 strokes/min, at a volume of 1 ml/100 g body weight per cycle. The animals were pretreated with gallamine (1 mg/kg, i.v.), indomethacin (2 mg/kg, i.v.), pyrilamine (2 mg/kg, i.v.) and propranolol (0.3 mg/kg, i.v.) at 10, 3, 2 and 2 min prior to antigen challenge. After intravenous administration of antigen (OA 0.5 mg/kg), increases in airway resistance were measured by a respiratory function measuring apparatus for 15 min. The value of lung resistance was measured as a mean every 5 s. YM158 and pranlukast were orally administered 1 h before OA challenge. Since antigen-induced increases in lung resistances lasted more than 15 min, the inhibitory effects of agents on antigen-induced increase in lung resistance were evaluated by using the decrease in the area under the time-response curve (AUC).

LTD_4-induced acceleration of plasma leakage in guinea pig skin

Tests on LTD_4-induced skin reaction were examined according to the modified method previously described (20). Briefly, male Hartley guinea pigs, whose back fur had been shaved with an electric clipper on the day before the experiment, were given an intravenous administration of saline (1 ml per animal) containing 1% Evans blue. Two minutes later, 5 ng LTD_4 and the vehicle solution was administered intracutaneously on the back of the guinea pig (at 2 points for LTD_4 and 2 points for vehicle). The guinea pig was sacrificed by decapitation 30 min later. The skin was removed, and the visible blood in this isolated skin was also removed as much as possible. Then, the pigment retained within the skin was extracted by the addition of extraction buffer ([7 : 3] acetone : 0.5% Na_2SO_4 solution). The amount of LTD_4-induced pigment leakage was measured using the 620 nm absorbance of the extract (UV-visible recording spectrophotometer, model UV-160A; Shimadzu, Kyoto). LTD_4-induced dye leakage was defined after subtracting dye content in the vehicle-injected site from that in the LTD_4-injected site, so these calculated dye contents were corrected for Evans blue dye that remains within the vasculature. This dye amount was used as an index of plasma leakage, although there was a potential uncontrolled hydrostatic pressure effects in this system. Test compounds were orally administered 1 h before the intracutaneous administration of LTD_4.

Effect of repeated dosing of oral YM158 on LTD_4- or U46619-induced increase in airway resistance

Animals were orally administered 30 mg/kg of YM158 or 0.5% MC twice a day for 28 days. On day 29, the effect of YM158 on airway resistance induced by LTD_4 or U46619 was compared to MC-treated groups. The inhibitory effects of orally administered YM158 (3 to 30 mg/kg) 1 h before the intravenous administration of LTD_4 or U46619 were measured and shown as the percent change of lung resistance compared to the basal resistance level. The effects of the agents were evaluated using the peak change percentage of lung resistance.

Statistical analyses

All data are shown as the means ± S.E.M. or the mean with 95% confidence limits (CL). Statistical significance was determined by Dunnett's multiple range test using SAS (statistical analysis system). In order to compare all repeated dosing test groups, statistical significance was determined by Bonferroni's multiple range test using SAS.

RESULTS

Oral YM158 inhibits increased airway resistance induced by LTD_4 or U46619

As shown in Figs. 1–4, intravenous administration of 300 ng/kg LTD_4 or 3 μg/kg U46619 consistently induced increases in airway resistance. When orally administered 1 h before LTD_4 or U46619 injection, YM158 at a dose of 30 mg/kg strongly inhibited these responses (Figs. 1 and 3). The percent change of the peak increase in induced airway resistance was dose-dependently inhibited by YM158, with ED_{50} values of 8.6 (2.7–21) for the LTD_4 receptor (Fig. 1B) and 14 (6.1–78) mg/kg for the TXA_2 receptor (Fig.

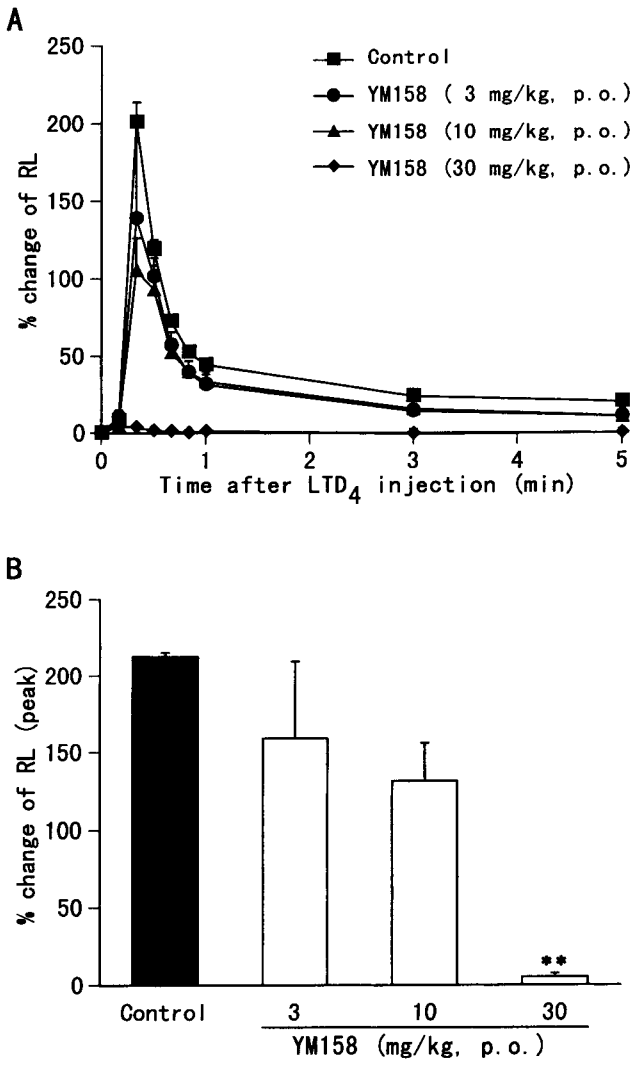

Fig. 1. Effect of YM158 on increase in the lung resistance (RL) induced by LTD_4. Results are expressed as a time course of the change percentage of resistance (A) and as a change percentage of the peak increase in resistance (B) to the basal resistance level. Data represent the mean ± S.E.M. of three animals. **P<0.01: significant difference compared to the control using Dunnett's multiple range test.

3B), respectively. In these experiments, pranlukast inhibited the LTD_4-induced response with an ED_{50} value of 0.34 mg/kg (Fig. 2), and seratrodast inhibited the U46619-induced response with an ED_{50} value of 0.13 mg/kg (Fig. 4).

YM158 inhibits the antigen-induced immediate airway response

The anti-asthmatic effects of YM158 and pranlukast were examined by measuring the increase in airway resistance induced by the intravenous injection of antigen in actively sensitized guinea pigs. The increase in airway resistance reached a peak 5 to 6 min after the intravenous injection of antigen. YM158 at doses of 3 to 30 mg/kg, p.o. dose-dependently inhibited increases in airway resistance (Fig. 5A). Since the antigen-induced increase in airway resistance was lasted more than 15 min after the antigen challenge, the inhibitory effect was evaluated by using AUC for this 15 min. The inhibitory effect was statistically significant at 10 and 30 mg/kg of YM158 when evaluated by $AUC_{0-15\,min}$ (Fig. 5B). Pranlukast at doses of 1 to 10 mg/kg, p.o. also inhibited increases in airway resistance (Fig. 6A), its effect reaching statistical significance at 10 mg/kg of pranlukast when evaluated by $AUC_{0-15\,min}$ (Fig. 6B).

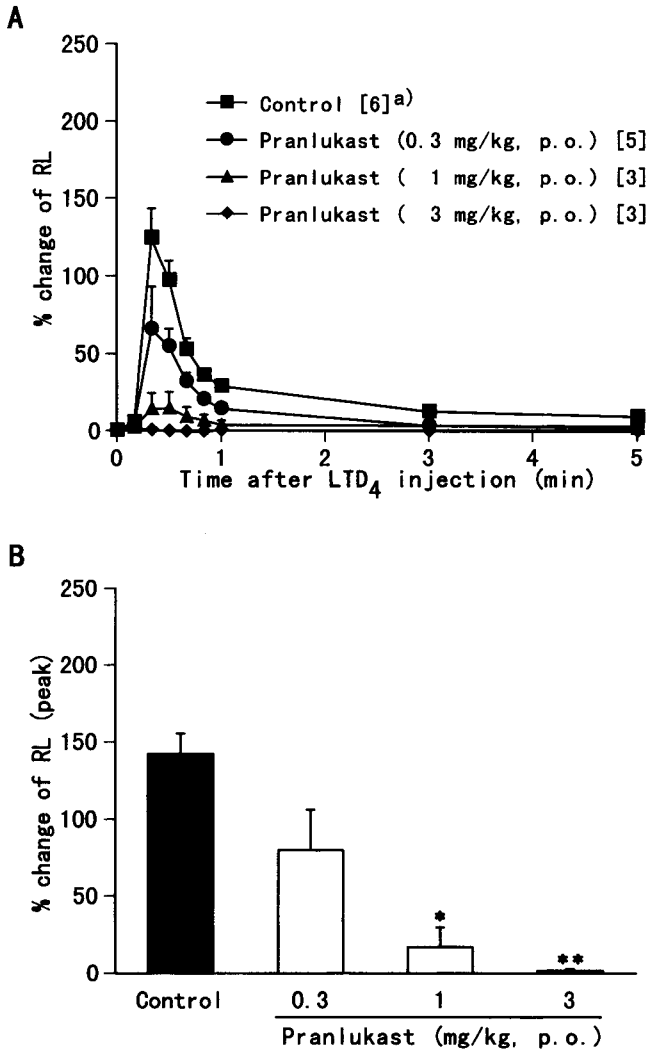

Fig. 2. Effect of pranlukast on increase in the lung resistance (RL) induced by LTD_4. Results are expressed as the time course of the change percentage of resistance (A) and as a change percentage of the peak increase in resistance (B) to the basal resistance level. Data represent the mean ± S.E.M. of three to six animals. a)Figures in parenthesis represent the number of animals. *P<0.05, **P<0.01: significant difference compared to the control using Dunnett's multiple range test.

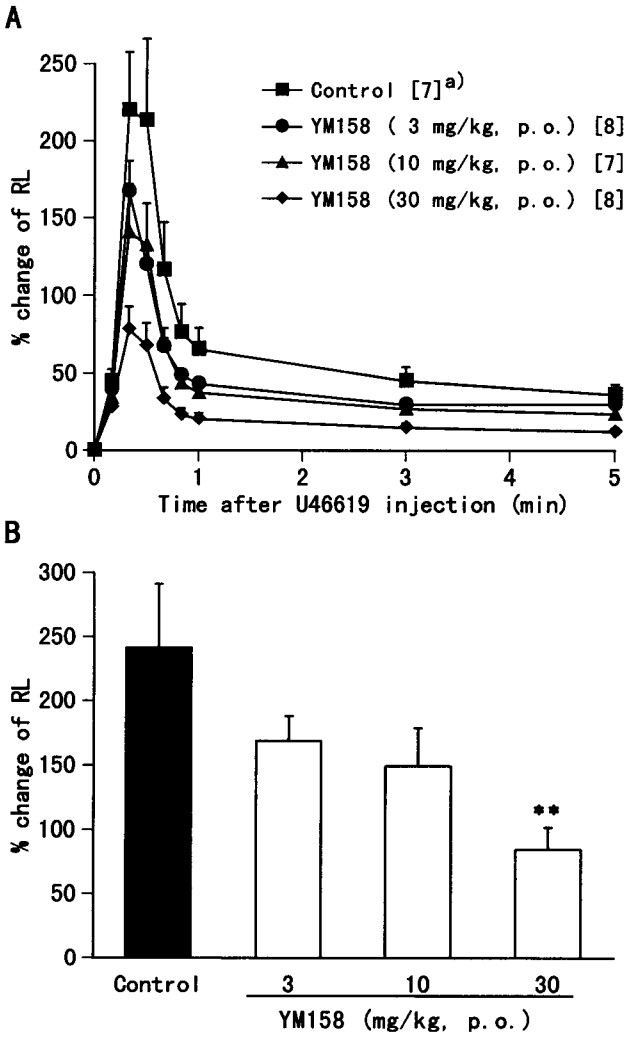

Fig. 3. Effect of YM158 on increase in the lung resistance (RL) induced by U46619. Results are expressed as a time course of the change percentage of resistance (A) and as a change percentage of the peak increase in lung resistance (B) to the basal resistance level. Data represent the mean ± S.E.M. of seven to eight animals. a)Figures in parenthesis represent the number of animals. **P<0.01: significant difference compared to the control using Dunnett's multiple range test.

Oral YM158 inhibits LTD_4-induced skin reaction in guinea pigs

An intradermal injection of LTD_4 induced an inflammatory skin reaction, that is an increase in plasma leakage. YM158 at doses of 10 and 30 mg/kg, p.o. significantly inhibited the skin reaction with an ED_{50} value of 6.6 mg/kg (95% CL: 4.8–9.3), p.o. dose-dependently (Fig. 7A). Previously described potent LTD_4 antagonists, pranlukast (1 mg/kg, p.o.), zafirlukast (1, 3 and 10 mg/kg, p.o.) and montelukast (0.01 and 0.03 mg/kg, p.o.), also significantly inhibited the skin reaction, with ED_{50} values of 0.52, 1.3 and 0.0072 mg/kg, p.o., respectively (Fig. 7: B, C and D).

Effects of repeated dosing of oral YM158 on LTD_4- or U46619-induced increased airway resistance

The mean values of YM158's concentrations in guinea pig plasma 1 h after the oral administration of 30 mg/kg YM158 in MC- or YM158-repeated dosing groups were 52.7–75.8 ng/ml and were not statistically different from each other. The inhibitory effects of YM158 orally administered 1 h before the intravenous injection of LTD_4 were statistically significant at doses of 3 mg/kg or more in MC-treated guinea pigs and 10 mg/kg or more in YM158-treated guinea pigs. In comparison, the same dose of

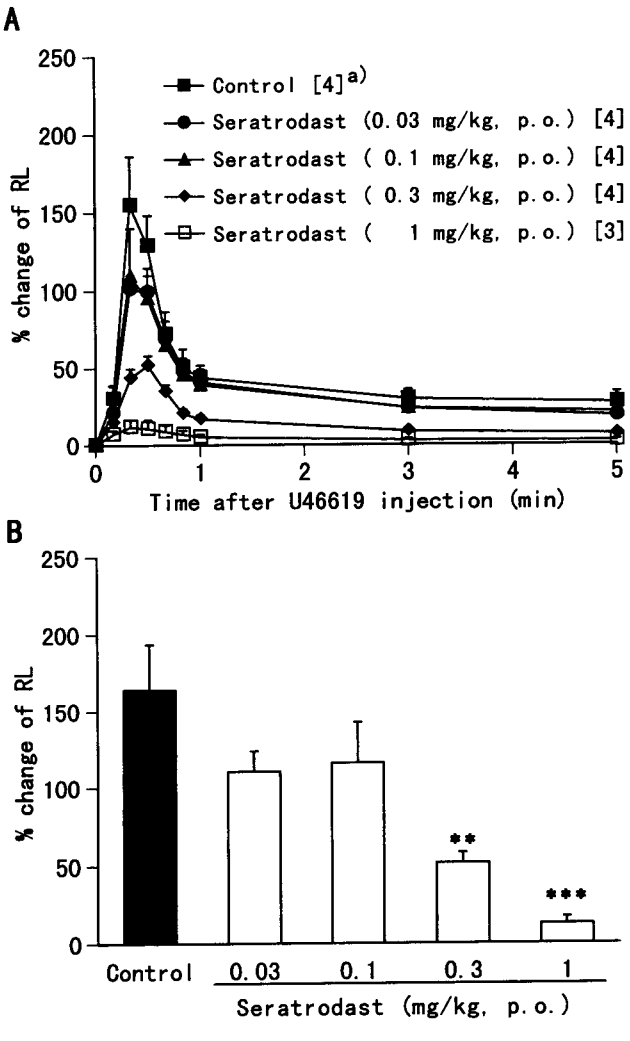

Fig. 4. Effect of seratrodast on increase in the lung resistance (RL) induced by U46619. Results are expressed as a time course of the change percentage of resistance (A) and as a change percentage of the peak increase in lung resistance (B) to the basal resistance level. Data represent the mean ± S.E.M. of three to four animals. a)Figures in parenthesis represent the number of animals. **P<0.01, ***P<0.001: significant difference compared to the control using Dunnett's multiple range test.

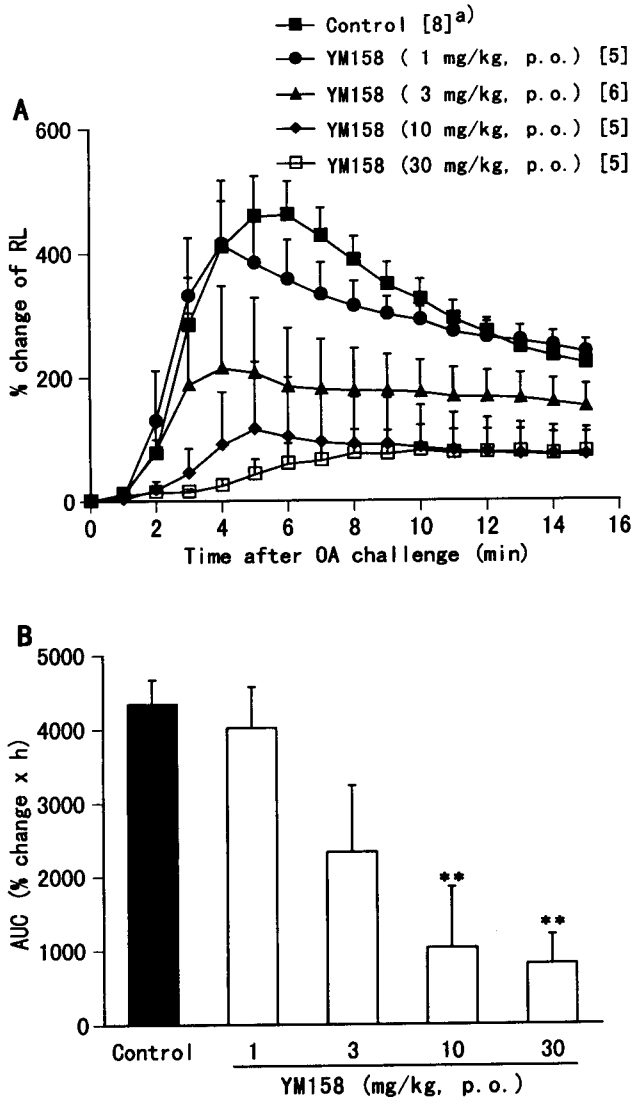

Fig. 5. Effect of YM158 on the airway resistance increase in actively sensitized guinea pigs. Results are expressed as a time course of the change percentage of resistance (A) and as an area under the time-response curve (AUC) (B). Data represent the mean ± S.E.M. of five to eight animals. a)Figures in parenthesis represent the number of animals. **P<0.01: significant difference compared to the control using Dunnett's multiple range test.

YM158 between MC- and YM158-treated groups produced no significant difference (Fig. 8A).

U46619-induced enhancement of airway resistance was inhibited by YM158 at a dose of 30 mg/kg in MC-treated guinea pigs and 10 and 30 mg/kg in YM158-treated guinea pigs. In the comparison at the same dose of YM158 between MC- and YM158-treated groups, there was no significant difference (Fig. 8B).

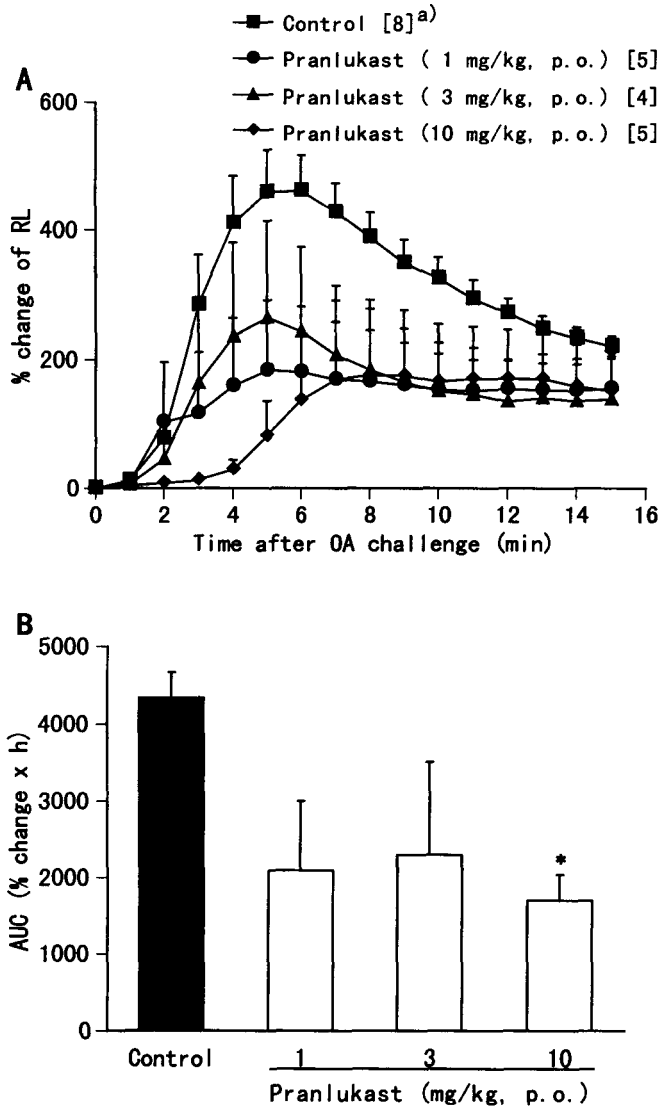

Fig. 6. Effect of pranlukast on the airway resistance increase in actively sensitized guinea pigs. Results are expressed as a time course of the change percentage of resistance (A) and as an area under the time-response curve (AUC) (B). Data represent the mean ± S.E.M. of four to eight animals. a)Figures in parenthesis represent the number of animals. *P<0.05: significant difference compared to the control using Dunnett's multiple range test.

DISCUSSION

YM158 is a compound reported to exhibit competitive dual antagonism of LTD_4 and TXA_2 receptor-mediated contraction of isolated guinea pig tracheae, with pA_2 values of 8.87 and 8.81, respectively (27). In this study, we mainly evaluated the effects of oral YM158 on lipid mediator related microvascular leakage and airway resistance. Drug vehicles that we used for oral administration were confirmed to have no significant effects on these responses. The present study showed that YM158 is an orally active antagonist for LTD_4 and TXA_2 receptors. YM158 inhibited increased airway resistance induced by LTD_4 or U46619 dose-dependently when orally administered 1 h before LTD_4 or U46619 injection, with ED_{50} values of 8.6 and 14 mg/kg, respectively. These results indicate that the antagonistic activities of oral YM158 for LTD_4 and TXA_2 receptors are exhibited at the same dose range. Furthermore, oral YM158 also inhibited the LTD_4-induced skin reaction, that is an increase in plasma leakage, with an ED_{50} value of 6.6 mg/kg. These results demonstrate that YM158 is an orally active dual antagonist for LTD_4 and TXA_2 receptors.

Cys-LTs have been reported as lipid mediators that increase microvascular leakage in airways and the skin (19, 20). Airway microvascular leakage is a primary feature of inflammation and leads to the formation of mucosal edema, followed by bronchial narrowing. Since, it is difficult to evaluate the effects on intravascular volumes or hydrostatic pressures in our system, the dye content in isolated skin was used as an index of plasma leakage. Also, we have preliminary evidence showing that intravenously injected YM158 (0.1 – 3 mg/kg) exhibited no remarkable effect on blood pressure in anesthetized dogs. From the result that orally administered YM158 showed the significant inhibition of microvascular leakage induced by LTD_4, YM158's may also play an important role in improving antigen-induced bronchoconstriction.

Although, the effects of oral YM158 on histamine-, LTC_4- or carbachol-induced responses were not evaluated, the YM158 concentration in guinea pig plasma 1 h after the oral administration of 30 mg/kg YM158 was not enough to exhibit the antagonism for these stimulants. Because 1×10^{-6} M of YM158, equal to 721 ng/ml, was reported to have no effects on histamine-, LTC_4- or carbachol-induced tracheal contractions (27). Thus the antagonism of oral administration of 30 mg/kg of YM158 is thought to be specific in vivo. The effect of YM158 on antigen-induced bronchoconstriction was examined in actively sensitized guinea pigs in the presence of indomethacin, pyrilamine and propranolol. Two milligrams of intravenous indomethacin predominantly induced cys-LTs production (9). Pyrilamine and propranolol were used to eliminate the role

of endogenous histamine and β-agonistic activity in this response. Since a 5-lipoxygenase inhibitor and an LTD_4 receptor antagonist inhibit the immediate asthmatic response in guinea pigs pretreated with indomethacin and pyrilamine, cys-LTs are one of the main mediators of anaphylactic bronchoconstriction in this asthmatic model (9). Under these conditions, oral YM158 showed dose-dependent and statistically significant inhibition of antigen-induced bronchoconstriction when evaluated by AUC. Although the LTD_4 receptor antagonistic activity of YM158 was less potent than that of pranlukast, antigen-induced asthmatic responses were inhibited by the same dose range of pranlukast and YM158. We have preliminary evidence that the treatment with 2 mg/kg indomethacin may not be enough to completely block cyclooxygenase pathway in this model. Briefly, the predominant lipid mediator is controlled by intravenous injection of 0, 1 and 5 mg/kg indomethacin and a predominant mediator related antagonist is effective in passively sensitized guinea pigs; that is, the predominant lipid mediator in indomethacin non-treated guinea pigs is TXA_2, 5 mg/kg indomethacin induces a LTD_4 predominant condition, and 1 mg/kg indomethacin induces a condition in which both LTD_4 and TXA_2 equally participate (34). Thus, under this indomethacin (2 mg/kg)-treated condition, TXA_2, in addition to cys-LTs, may play a certain role in antigen-induced bronchoconstriction, and TXA_2 antagonism of YM158 might contribute in part to anti-asthmatic effects. In passively sensitized guinea pigs, pranlukast exhibited only weak suppression in indomethacin non-treated guinea pigs, and this effect of pranlukast was potent in a condition where the cyclooxygenase pathway is completely inhibited (34). Therefore, a dual antago-

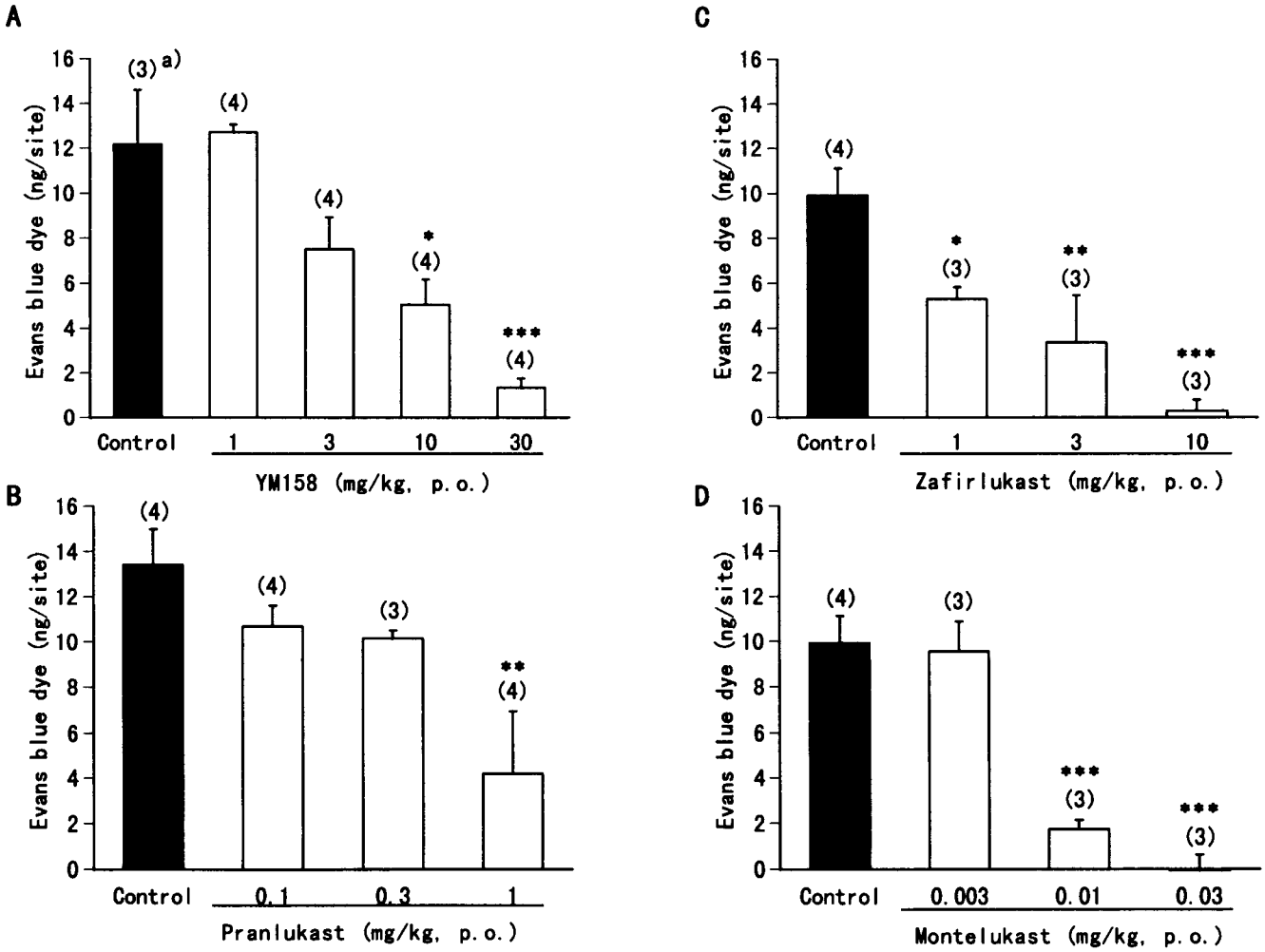

Fig. 7. Effects of YM158 (A), pranlukast (B), zafirlukast (C) and montelukast (D) on LTD_4-induced skin reaction in guinea pigs. Data are expressed as contents of Evans blue dye at the skin where there was intradermal injection of LTD_4 and represent the mean ± S.E.M. of three to four animals. [a] Figures in parenthesis represent the number of animals. *P<0.05, **P<0.01, ***P<0.001: significant difference compared to the control using Dunnett's multiple range test.

nist for LTD_4 and TXA_2 receptors may have advantages in treating bronchial asthma resulting from both cys-LTs and TXA_2 participation, such as the present asthma model. It was reported that many different mediators, such as cys-LTs, TXA_2 and platelet activating factor (PAF), and the interactions of these mediators are involved in the pathogenesis of asthma. For example, a TXA_2-receptor antagonist was reported as a reagent that had inhibitory effects on LTD_4- or PAF-induced smooth muscle contractions (35–37). However, these mediators-evoked asthmatic responses were not all mediated via TXA_2, namely, these mediators induce tracheal contractions both directly and indirectly. Thus, a multi-pathway inhibitory agent could prove very effective in treating bronchial asthma considering the strength of its therapeutic effect. Thus if it is possible to roughly classify asthmatic patients into specific mediator predominant types, a multi-pathway inhibitor would be expected to have different effects on various types of asthmatic patients. Therefore, a multi-pathway inhibitory agent like YM158 could prove very effective in treating bronchial asthma considering both the strength of its therapeutic effect and the number of patients who would respond to the drug.

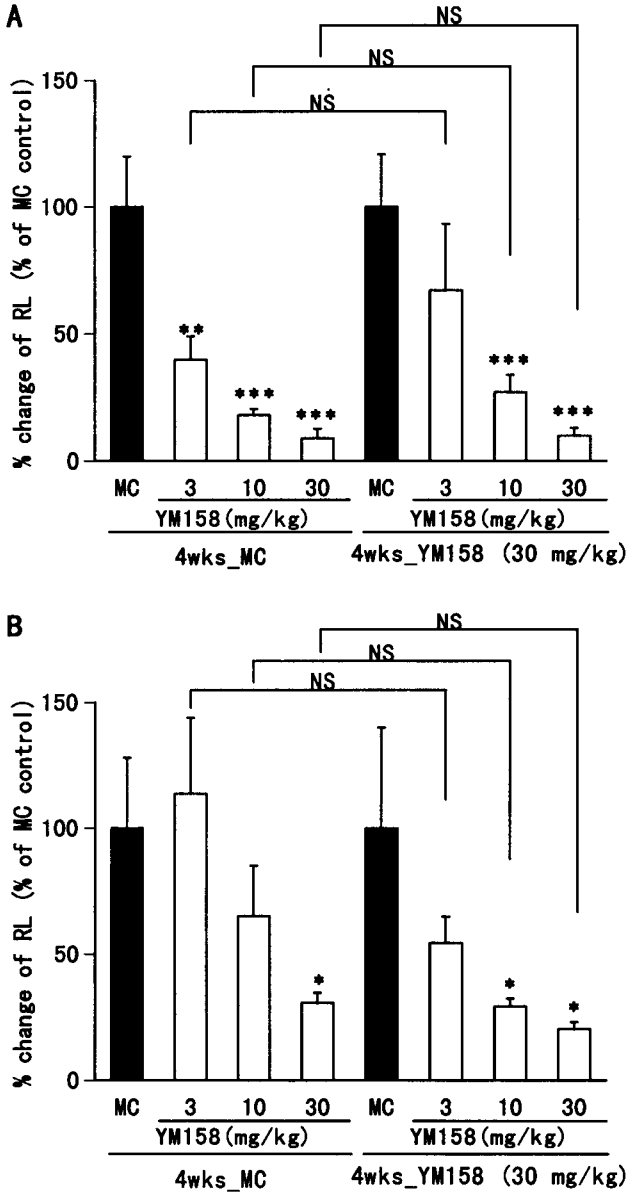

Fig. 8. Effect of repeated oral administration of YM158 on the antagonistic activity for LTD_4 (A) and TXA_2 (B) receptors. Animals were challenged by intravenous injection of 300 ng/kg LTD_4 (A) or 3 μg/kg U46619 (B). Results are expressed as a change percentage of the peak increase in lung resistance (RL) to the corresponding MC control and represent the mean ± S.E.M. of six animals. *P<0.05, **P<0.01, ***P<0.001: significant difference compared to the corresponding MC control and NS: no significance compared at the same dose between MC-repeated and YM158-repeated groups, by using Bonferroni's multiple range test.

Clinically, an anti-asthmatic agent is often repeatedly administered to patients. Therefore, the effect of repeated oral doing of YM158 twice a day for 28 days on its efficacy was examined. Since TXA_2 receptor density in domestic swine was reported to be increased during chronic exposure to TXA_2 receptor antagonist (38), we were concerned about whether the potency of YM158 for TXA_2 receptor antagonism was diminished by repeated oral dosing of YM158. However, from the results shown in Fig. 8, repeated dosing of YM158 showed no effect on its antagonistic activity, suggesting that repeated administration of YM158 does not cause saturation, hyperreactivity or hyperexpression of the receptors.

In conclusion, YM158 is an orally active dual antagonist for LTD_4 and TXA_2 receptors. Oral YM158 showed dual antagonism and inhibited increased airway resistance induced by not only lipid-mediators but also antigens. Therefore, YM158 shows promise as a new type of anti-asthmatic agent with high therapeutic potential for patients with bronchial asthma.

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