

Mast cell inhibitor R112 is well tolerated and affects prostaglandin D₂ but not other mediators, symptoms, or nasal volumes in a nasal challenge model of allergic rhinitis

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ABSTRACT

Understanding of the role played by mast cells in allergic rhinitis (AR) has led to the development of novel therapies. The aim of this study was to determine the safety and tolerability of R112, an inhibitor of the tyrosine kinase Syk, in an allergen challenge model of AR. We also examined the effects of R112 on symptoms, mediator release, and nasal airway volumes. This double-blinded, randomized, placebo-controlled, crossover trial enrolled 20 out-of-season volunteers with AR. One intranasal dose of R112 or vehicle was administered and followed by an allergen challenge. In addition to safety monitoring, symptoms; changes in histamine, tryptase, and prostaglandin D₂ (PGD₂) content of nasal secretions; and acoustic rhinometry were determined over a 15-minute period. R112 was well tolerated. Adverse events were similar between treatments. Five minutes after allergen instillation, PGD₂ was decreased when subjects received R112 compared with vehicle (93.4 ± 23.0 pg/mL versus 171.6 ± 23.0 pg/mL; $p = 0.03$), and this correlated with rhinorrhea ($p = 0.05$). However, at 10 minutes, changes in PGD₂, tryptase, and histamine were not significant (46.8 ± 9.2 pg/mL versus 68.6 ± 9.2 pg/mL, $p = 0.1$; 9.5 ± 2.7 ng/mL versus 16.6 ± 2.9 ng/mL, $p = 0.09$; and 1.5 ± 1.6 ng/mL versus 3.5 ± 1.6 ng/mL, $p = 0.4$). No differences were found in symptoms or in acoustic rhinometry between treatment groups. Single-dose R112 appears safe and significantly reduces PGD₂ but not histamine or tryptase release in response to allergen challenge in subjects with AR.

(Allergy Asthma Proc 27:208–213, 2006; doi: 10.2500/aap.2006.27.2861)

Improved understanding of the pathophysiology of allergic disorders has led to the development of new therapeutic agents. It is now recognized that mast cells play a central role in the development of allergic rhinitis (AR). Allergen-specific immunoglobulin E (IgE) binds to the high-affinity immunoglobulin receptor Fcε receptor I (FcεRI) on airway mast cells. When these receptors are cross-linked by allergen, the intracellular protein tyrosine kinases Syk and Lyn that are associated with FcεRI are activated. The signaling pathway thus initiated leads to the release of histamine and tryptase, rapid generation of prostaglandin D₂ (PGD₂), and other mediators and cytokines responsible for both the early and the late allergic response.¹

Among the new treatment agents under development based on this understanding of the pathophysiology of allergic disorders is R112, a novel small molecule inhibi-

tor of the tyrosine kinase Syk critical for mast cell signal transduction. Preclinical data show that R112 is a potent and selective inhibitor of mast cell activation, and clinical phase I data show it is well tolerated (data on file, Rigel, Inc., http://www.rigel.com/rigel/pr_1078949993; last accessed May 10, 2006).

In this phase 1b double-blind, randomized, placebo-controlled, crossover study, we evaluated the safety and efficacy of a single dose of R112 compared with the vehicle control in out-of-season adult volunteers with seasonal AR who were subjected to a nasal allergen challenge. The primary outcome evaluated was the safety and tolerability of the drug in this patient group. Mean changes in early and late-phase symptom scores, tryptase, histamine, PGD₂, and acoustic rhinometry were secondary efficacy outcomes.

METHODS

Subjects

The study enrolled 20 subjects, ≥18 years of age, with at least a 2-year history of grass- or ragweed-induced seasonal AR. At the time of enrollment, all subjects were asymptomatic and were not receiving therapy for AR. Other eligibility criteria included a positive skin-prick test (>3-mm wheal diameter) with standardized grass or ragweed pollen extract and a positive nasal allergen challenge (Bousquet score ≥5).

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Presented in abstract form at the annual scientific meeting of the American Academy of Allergy, Asthma, and Immunology, San Francisco, CA, March 20, 2004
Funded by Rigel, Inc., San Francisco, California

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For these qualifying challenges, subjects were first challenged with intranasal saline to exclude nonspecific reactivity (Bousquet score ≥ 5 reached with saline alone), and then threefold serially increasing doses of standardized ragweed or grass pollen extract every 10 minutes until achieving a Bousquet score of ≥ 5 . The Bousquet score assigns points (maximum total score, 12) for sneezing, rhinorrhea, nasal blockage, nasal itching, palate or ear itching, and conjunctivitis.² Allergen extract dilutions were prepared each Monday and subsequent challenges were performed on the same day of the week to ensure equal potency across testing days. Extracts were brought to room temperature before administration. Extracts were nonglycerinated, from the same lot, and used 0.03% human serum albumin and phenol 0.4% as preservatives.

Subjects were excluded if they had nasal pathology other than seasonal AR, persistent asthma, upper respiratory infection in the 2 weeks before the trial, or had received immunotherapy during the previous 2 years. Medications excluded for the stated period before and for the duration of the study included oral steroids; tricyclic antidepressants; intranasal preparations of corticosteroids, azelastine, cromolyn, nedocromil, or ipratropium bromide (within 4 weeks); antihistamines (within 7 days); oral decongestants (within 48 hours); or aspirin or nonsteroidal anti-inflammatory drugs (within 5 days). Study subjects were not on leukotriene antagonists. Caffeine and alcohol were not permitted in the 24 hours before a nasal allergen challenge.

Measures of safety included monitoring and recording of adverse events, nasal symptoms, interval medical history, and concomitant medication use by review of participant's diaries at each study visit. Physical examination, ECG, and monitoring of peak expiratory flow rate occurred during visits that included nasal allergen challenges. Laboratory testing, including serum chemistry panels for renal and hepatic assessments, urinalysis, and CBC with differential were performed at baseline, the day after each nasal challenge visit, and at the final study visit 2 weeks after the last nasal allergen challenge was performed. The Institutional Review Board of the National Jewish Medical and Research Center approved the protocol and each subject gave written informed consent.

Study Design

This was a phase 1b randomized, double-blind, placebo-controlled, crossover nasal allergen challenge trial. Before administration of study medication, each nostril was lavaged three times with 10 mL of normal saline to wash away any preformed mediators before dosing. Baseline nasal symptom score on a visual analog scale (0–100) for each of four symptoms (sneezing, rhinorrhea, congestion, and itching), acoustic rhinometry,

and nasal secretions were collected 10 minutes later. Both nostrils were then sprayed with R112 or placebo (0.1 mL of 15 mg/mL or 0.1 mL of vehicle). This dose was selected based on animal toxicology studies and a study in healthy volunteers that showed the safety and tolerability of this dose (data on file; Rigel, Inc.). After 15 minutes, a nasal challenge with the dose of allergen extract established at qualification was administered. One hundred forty percent of the extract concentration that produced a Bousquet score of 5 at qualification was used to account for the cumulative challenge dose administered at that nasal challenge. Nasal secretions were collected 5, 10, and 15 minutes after the nasal challenge. Acoustic rhinometry was then repeated. Symptoms were scored at baseline, after administration of study drug, and 15 minutes and 4–6 hours after nasal allergen challenge. There was a 2-week washout and subjects returned for the alternate treatment.

Mediators

Nasal secretions were collected with cellulose sponges (Rhinosorb; Rhino Diagnostics, Inc., San Diego, CA) and analyzed for PGD₂, tryptase, and histamine content. Each sponge was weighed and placed on the anterior one-third of the nasal septum of both nostrils and allowed to absorb nasal secretions for 5 minutes. After collection, saturated sponges were immediately weighed and eluted for 45 minutes with phosphate buffered saline (PBS) for PGD₂ and histamine analysis or with buffer containing 1% bovine hemoglobin for tryptase analysis. One aliquot of eluted secretions was mixed with acetone per the PGD₂ enzyme-linked immunosorbent assay (ELISA) kit protocol (Cayman Chemical Co., Ann Arbor, MI). Another aliquot was acylated using the protocol and reagents provided with the ELISA kit for acylated histamine (Beckman Coulter Co., Fullerton, CA). Processed secretions were then immediately frozen at -80°C . Samples were batch analyzed by ELISA for PGD₂ and histamine content of the samples that were collected at baseline and 5 and 10 minutes after nasal allergen challenge. Tryptase content was determined by Unicap fluoroimmunoassay (Pharmacia and Upjohn, Uppsala, Sweden) of the samples collected at baseline and 10 minutes after nasal allergen challenge. Mediator content was corrected for the volume of nasal secretions absorbed by the sponge and volume of elution buffer used for each subject. Therefore, mediator content per milliliter was multiplied by the sum of the nasal secretions absorbed and the volume of elution buffer used to process a single sponge. Each sponge absorbed $38 \pm 52 \mu\text{L}$ ($n = 24$) of nasal secretions at baseline, and, for samples used to assay histamine and PGD₂, $216 \pm 102 \mu\text{L}$ ($n = 24$) and $83 \pm 64 \mu\text{L}$ ($n = 24$) at 5 and 10 minutes after challenge. The sponges used for tryptase analysis were collected at baseline and at 10

minutes from the other nostril. These absorbed 36 ± 43 μL ($n = 24$) of nasal secretions at baseline and 87 ± 58 μL ($n = 24$) at 10 minutes. The volume of nasal secretions absorbed by the sponges was not determined for the 16 samples that were collected before weighing the sponges became part of the study procedure. For these samples, average volume of nasal secretions absorbed by sponges subsequently weighed in the study were used to correct the mediators absorbed by these sponges for volume.

Preliminary work indicated that maximum sponge saturation took place by 5 minutes and that the sponges, PBS, and bovine hemoglobin did not interfere with mediator assays. We recovered $100 \pm 8\%$ of a known quantity of PGD_2 (14 and 140 ng/mL) and $105 \pm 9\%$ of a known quantity of histamine (8,16, and 24 ng/mL) that was diluted with PBS and human serum albumin and added to the sponges ($n = 4$). Bonafide tryptase was not available to test recovery in this manner.

Acoustic Rhinometry

Bilateral minimal cross-sectional area (MCA) and total nasal volumes were determined by acoustic rhinometry at baseline and 15–20 minutes after nasal allergen challenge. This technique uses sound echoes to measure nasal cavity geometry. Studies have established its accuracy, reproducibility, and correlation with nasal obstruction after nasal allergen challenge.^{3–6} Bilateral nasal volumes from 0–5 cm^3 into nasal cavity and MCA were measured at the stated time points.

Statistical Analysis

All 20 subjects were included in the analysis. For both the primary and the secondary efficacy parameters, an analysis of variance (ANOVA) model was used for analysis, and the least squares estimate of the mean difference between the two treatments and its 95% confidence interval (CI) were presented. All statistical tests used for evaluation of efficacy parameters were performed at the α of 0.05 significance level and all tests were two-sided.

RESULTS

Safety

Primary Outcome. The treatment was well tolerated, with no serious adverse events in either treatment group. Mild adverse events were comparable between the two groups, with 12 (60%) patients in each treatment arm experiencing at least one adverse event (Table 1).

Efficacy

Secondary Outcomes. No significant difference was found in the mean change in nasal symptom score between the two treatment groups, although patients treated with R112 tended to have improved symptoms

Table 1 Adverse events

	Treatment	
	R112	Placebo
Number (%) of subjects	20 (100%)	20 (100%)
Ear pain	0	1 (5.0%)
Dyspepsia	0	1 (5.0%)
Oral pruritus	0	1 (5.0%)
Vomiting	1 (5.0%)	0
Nasopharyngitis	1 (5.0%)	2 (10.0%)
Influenza	1 (5.0%)	0
Upper respiratory tract infection	0	1 (5.0%)
Urinary tract infection	0	1 (5.0%)
Excoriation	1 (5.0%)	0
Aspartate aminotransferase increased	2 (10.0%)	1 (5.0%)
Alanine aminotransferase increased	1 (5.0%)	1 (5.0%)
Headache	4 (20.0%)	3 (15.0%)
Sinus headache	2 (10.0%)	1 (5.0%)
Dizziness	2 (10.0%)	0
Mental impairment	1 (5.0%)	0
Syncope vasovagal	0	1 (5.0%)
Tremor	1 (5.0%)	0
Nasal congestion	2 (10.0%)	1 (5.0%)
Hypertension	1 (5.0%)	0

over placebo (vehicle) at 15 minutes (Table 2). Symptoms were similar between groups 4–6 hours after nasal allergen challenge (Table 3).

Mediator release after nasal allergen challenge decreased with administration of R112. At 5 minutes, R112 was associated with a significant decrease in PGD_2 compared with vehicle (93.4 ± 23.0 pg/mL versus 171.6 ± 23.0 pg/mL; $p = 0.03$), which correlated with rhinorrhea scores obtained 15 minutes after nasal challenge (correlation coefficient = 0.318; $p = 0.05$). At 10 minutes, PGD_2 was no longer significantly different from vehicle (46.8 ± 9.2 pg/mL versus 68.6 ± 9.2 pg/mL; $p = 0.1$; Fig. 1).

Tryptase tended to decrease with R112 administration at 10 minutes postchallenge compared with vehicle (9.5 ± 2.7 ng/mL versus 16.6 ± 2.9 ng/mL; $p = 0.09$) but was not statistically significant (Table 4). Similarly, the trend in histamine concentrations at 10 minutes postchallenge after R112 was lower than after vehicle but not statistically significant (1.5 ± 1.6 ng/mL versus 3.46 ± 1.6 ng/mL; $p = 0.4$; Table 5). Results of acoustic rhinometry showed no significant differences between R112 and vehicle at 20 minutes postchallenge in MCA of the left or right nose (0.5 ± 0.03 cm^2 versus 0.42 ± 0.03 cm^2 ; $p = \text{NS}$; and 0.4 ± 0.03 cm^2 versus 0.4 ± 0.03 cm^2 ; $p = \text{NS}$, respectively).

Table 2 Total VAS of symptoms based on nasal scoring system at 15 minutes postchallenge

VAS LS Mean (SEM)	R112 (n = 20)	Placebo (n = 20)	Difference (R112-Placebo)	p Value
Total of all symptoms				
Baseline	9.80 (1.76)	6.55 (1.76)	3.25 (2.49)	0.20
Posttreatment	118.10 (14.46)	131.70 (14.46)	-13.60 (20.45)	0.50
Rhinorrhea				
Baseline	2.70 (0.79)	1.75 (0.79)	0.95 (1.11)	0.40
Posttreatment	36.85 (4.84)	43.95 (4.84)	-7.10 (6.85)	0.30
Nasal obstruction/congestion				
Baseline	4.35 (0.74)	2.55 (0.74)	1.80 (1.05)	0.10
Posttreatment	36.65 (4.76)	37.25 (4.76)	-0.60 (6.73)	0.90
Nasal itching				
Baseline	1.75 (2.77)	1.10 (0.37)	0.65 (0.53)	0.20
Posttreatment	15.95 (3.20)	18.25 (3.20)	-2.30 (4.52)	0.60
Sneezing				
Baseline	1.00 (1.52)	1.15 (0.33)	-0.15 (0.46)	0.70
Posttreatment	28.65 (5.26)	32.25 (5.26)	-3.60 (7.44)	0.60

LS mean = least squares mean; SEM = standard error of LS mean; VAS = visual analog scale.

Table 3 Total VAS of symptoms* based on nasal scoring system at 4–6 hours postchallenge

VAS LS Mean (SEM)	R112 (n = 20)	Placebo (n = 20)	Difference (R112-Placebo)	p Value
Total of all symptoms				
Baseline	9.80 (1.76)	6.55 (1.76)	3.25 (2.49)	0.20
Posttreatment	37.70 (6.86)	32.80 (6.86)	4.90 (9.70)	0.60
Change in VAS	27.90 (7.31)	26.25 (7.31)	1.65 (10.34)	0.88

*All four symptoms: rhinorrhea, nasal obstruction/congestion, nasal itching, sneezing.

LS mean = Least Squares mean; SEM = standard error of LS mean; VAS = visual analog scale.

DISCUSSION

AR is a significant problem in the United States that contributes to several other conditions, including asthma.⁷ The majority of current treatments for AR target the cellular infiltrate and inflammatory mediators that are released after IgE receptor signal transduction. However, a subset of patients remains unresponsive to these therapies.^{7–9} Hence, treatments that act early in the signal transduction cascade of allergic reactions may favorably complement available treatments.

With the more recent understanding of the mechanisms of allergic disorders and the pivotal role played by mast cells in releasing a number of key mediators, such as PGD₂ and histamine, new treatments are under investigation. Among these are small-molecule inhibitors of novel targets aimed at blocking the release of these mediators. Targeting Syk is based on the critical role this protein tyrosine kinase plays in signaling the allergic inflammatory response.^{1,10} Syk plays a limited role in platelet function, innate immunity, and tumor suppression and studies indicate the safety of targeting this ki-

nase.¹ Data also support the strong efficacy of inhibiting Syk because of its role in regulating the release and production of mediators that cause inflammatory responses.¹ R112 targets the kinase activity of Syk to block mast cell responses to allergic stimuli and thereby inhibit the rapid release of histamine, tryptase, and other granule contents as well as the proinflammatory activation that causes release of cytokines (TNF- α , IL-4, and IL-13) and lipid-derived mediators (LTC₄).

Currently, several studies are underway to evaluate the effect of different approaches to inhibit Syk.^{1,10,11} Using a rat model, Stenton and colleagues recently reported the efficacy of aerosolized Syk antisense oligodeoxynucleotide in suppressing many major components of inflammation and allergic asthma.¹⁰ Other studies are underway to inhibit Syk activation by using nonpeptidic compounds.¹¹

This phase Ib double-blind, randomized study of R112 was undertaken after phase Ia data showed good tolerability.¹ In this study, we used a nasal allergen challenge model, which has been used by several investigators to

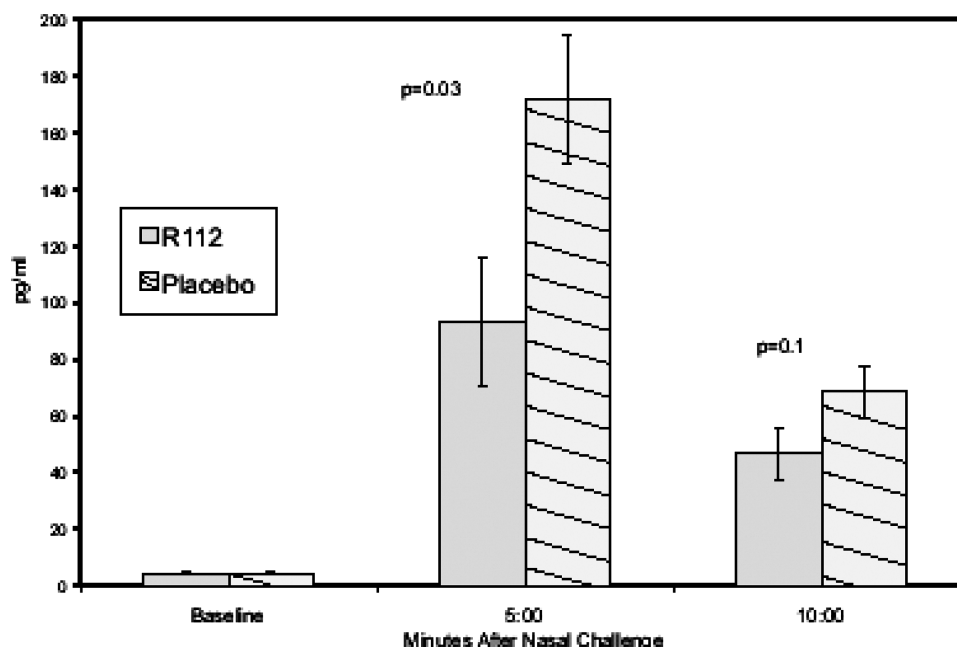


Figure 1. Changes in PGD₂ content of nasal secretions 5 and 10 minutes after nasal allergen challenge in subjects treated with R112 and placebo (vehicle).

Table 4 Tryptase at 10 minutes postchallenge

Tryptase (ng/mL) LS mean (SEM)	R112 (n = 20)	Placebo (n = 20)	Difference (R112-Placebo)	p Value
Tryptase				
Baseline	0.69 (0.03)	0.74 (0.03)	-0.05 (0.04)	0.20
Posttreatment	9.53 (2.70)	16.59 (2.85)	-7.07 (3.93)	0.09
Change in tryptase	8.83 (2.70)	15.85 (2.84)	-7.01 (3.92)	0.09

LS mean = Least Squares mean; SEM = standard error of LS mean.

Table 5 Histamine at 5 and 10 minutes postchallenge

Histamine (ng/mL) LS mean (SEM)	R112 (n = 20)	Placebo (n = 20)	Difference (R112-placebo)	p Value
5 min				
Baseline	0.12 (0.02)	0.12 (0.02)	0.00 (0.03)	NS
Posttreatment	2.58 (0.62)	2.62 (0.62)	-0.04 (0.87)	0.96
Change in histamine	2.46 (0.60)	2.50 (0.60)	-0.04 (0.84)	0.96
10 min				
Baseline	0.12 (0.02)	0.12 (0.02)	0.00 (0.03)	NS
Posttreatment	1.49 (1.55)	3.46 (1.55)	-1.97 (2.19)	0.38
Change in histamine	1.38 (1.54)	3.34 (1.54)	-1.96 (2.18)	0.38

LS mean = least squares mean; SEM = standard error of LS mean.

evaluate the relationship between mediator release and allergic response,¹²⁻¹⁴ to study the safety and efficacy of a single intranasal dose of R112 in asymptomatic seasonal AR patients. Along with the good tolerability of a single dose of R112 in this subject group, we showed that R112

reduced PGD₂ release 5 minutes after a nasal allergen challenge. The reduction correlated significantly with rhinorrhea. Previous studies also have correlated PGD₂ with nasal obstruction and rhinorrhea.¹⁵⁻¹⁷ Favorable trends in the release of histamine and tryptase were observed with

R112 compared with vehicle that did not reach statistical significance. Although the association between the release of these mediators and the development of symptoms has been established in several preclinical and clinical studies,^{4,12–14,18,19} we did not detect a significant difference in symptoms after R112 treatment compared with vehicle.

Limitations of the study could have affected these outcomes. The dose of R112 was based on toxicology studies; however, optimal dose and administration of R112 still have not been established and was not examined in this phase 1b study. The study was undertaken as a safety and proof of concept trial and not optimally powered to detect differences between subjects. However, larger phase II clinical studies of this compound using a different dose protocol have shown significant symptom reduction in patients exposed to a natural pollen season.²⁰ Although each subject served as his or her own control in this crossover trial, there was no control group for the effects of the allergen extract *per se* in our study. Finally, although other studies have shown its reproducibility, we did not find acoustic rhinometry easy to apply in this study. This technique is known to be dependent on operator experience and placement of the ultrasound probe, a factor that may have limited its usefulness in our setting.²¹

Conversely, a strength of this study is its ability to quantitatively express mediators. Collecting nasal secretions by lavage, as has been done in studies similar to ours, does not permit analysis of quantitative mediator content because of the imprecise knowledge of amount of lavage fluid returned and volume of nasal secretions produced by an individual subject. We collected secretions using absorptive cellulose sponges that could be weighed before and after placement to allow quantification of mediators collected. Furthermore, we added prechallenge lavages to the commonly used nasal allergen challenge protocol to prevent collection of preformed mediators from study subjects.

Overall, this study confirms the tolerability of a single dose of R112 and shows its ability to reduce PGD₂ release in subjects exposed to a nasal allergen challenge. Larger studies are now needed to confirm the significant finding and positive trends observed in this study.

ACKNOWLEDGMENTS

We thank Mary Beth Nierengarten and Yu-Kun Chiang for technical and statistical assistance.

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