

Safety of the intranasal toll-like receptor 4 agonist CRX-675 in allergic rhinitis

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Background: CRX-675 is an aqueous formulation of a toll-like receptor 4 agonist and an inducer of T_H1 responses. Studies in allergic dogs showed that pretreatment with CRX-675 reduced nasal congestion induced by allergen challenge.

Objective: To study the safety of intranasal CRX-675 treatment in patients with seasonal allergic rhinitis.

Methods: We conducted a single-center, randomized, double-blind, placebo-controlled, dose-escalating safety trial of single doses of CRX-675 given intranasally before intranasal ragweed challenges. Patients with ragweed-induced seasonal allergic rhinitis received increasing concentrations of ragweed to determine the dose that would result in a 30% reduction in nasal volume (PD_{30}) during screening. Two weeks later, each patient was rechallenged with their assigned PD_{30} ragweed dose. Fourteen days later, patients were treated with either placebo ($n = 16$) or CRX-675 (2, 20, 100, or 200 μg intranasally, $n = 12$ per arm) 24 hours before a subsequent PD_{30} ragweed challenge. Patients were rechallenged with ragweed 14 days thereafter.

Results: No serious or severe adverse events were reported. Most adverse events were mild (grade 1) and either were considered unrelated to CRX-675 or resolved without intervention. The adverse event profile of CRX-675-treated patients was similar to that of placebo-treated patients, and no dose-related toxic effects were observed. There was no clear trend in the ability of CRX-675 to inhibit nasal allergen challenge responses, but improvement in nasal symptom scores was observed at 100 μg .

Conclusions: This preliminary trial suggests that intranasally applied CRX-675 is safe at the doses tested. Appropriate dosing and timing will ultimately define its potential therapeutic role for allergies.

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INTRODUCTION

Despite many therapeutic options, including environmental control, pharmacotherapy, and allergen-specific immunotherapy, many patients with allergic rhinitis have significant clinical symptoms due to the T_H2 -driven allergic inflammatory response.^{1,2} Lipid A, the active component of lipopolysaccharide, is a potent toll-like receptor 4 (TLR4) agonist with immunomodulating activities, including the induction of T_H1 responses.^{3–6} CRX-675 is an aqueous formulation of monophosphoryl lipid A, a TLR4 agonist that exhibits reduced toxicity and pyrogenicity compared with lipopolysaccharide yet retains much of its inherent immunomodulating activity.⁷ Murine models^{4–6} have demonstrated the therapeutic potential of TLR4 agonists to treat allergic diseases. Preclinical studies in allergic dogs showed that pretreatment with single doses of CRX-675 reduced nasal congestion induced by ragweed allergen challenges performed 24 hours later (data on file; Corixa Corp, Seattle, WA). These studies formed the basis for the present study design.

METHODS

To examine the therapeutic potential of CRX-675, we conducted a phase 1 single-center (Creighton University, Omaha, NE), randomized, double-blind, placebo-controlled, dose-es-

calating safety trial of CRX-675 given intranasally before nasal ragweed allergen challenges. This was the first nasal administration in humans, to our knowledge.

Nineteen- to 50-year-old healthy patients with at least a 2-year history of ragweed-induced seasonal allergic rhinitis requiring pharmacotherapy and a positive ragweed skin prick test reaction (≥ 3 mm greater than the diluent) were enrolled after signing informed consent documents approved by the Creighton University institutional review board. Major exclusion criteria included respiratory tract infection within 4 weeks; clinically significant perennial rhinitis or anatomic nasal-obstructing conditions; history of recurrent migraines or epistaxis requiring medical attention within 1 year; rhinitis medicamentosa; asthma or a forced expiratory volume in 1 second less than 80% of predicted; use of medications that could affect nasal allergen challenges; abnormal electrocardiographic, laboratory test, or physical examination findings; immunotherapy within 1 year; smoking; and immunosuppressive disorders.

This study was conducted outside the ragweed season. During screening, patients underwent a ragweed nasal allergen challenge¹⁰ (6 serial 10-fold dilutions of short ragweed, starting at 1:1,000,000) until there was a 30% decrease in nasal volume (PD_{30}) as determined by means of acoustic rhinometry (inclusion criteria) or until the final ragweed dose was achieved (1:10 dilution). Two weeks later, patients underwent a repeated challenge with their individualized calculated cumulative PD_{30} dose of ragweed and must have had at least a 15% decrease in nasal volume to continue in the study.

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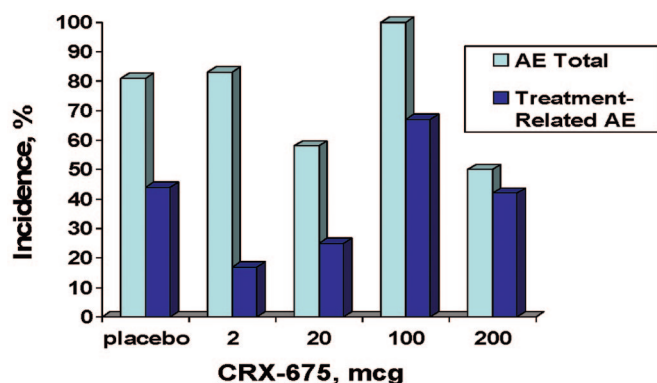


Figure 1. Overall incidence of adverse events (AEs) and treatment-related AEs.

Change in nasal volume from this challenge was considered the baseline value.

Fourteen days later, patients were treated with either placebo or CRX-675 24 hours before a subsequent ragweed challenge with their PD₃₀ dose. Patients were rechallenged with ragweed 14 days thereafter. Four dosing cohorts of 16 patients each were evaluated successively: 2, 20, 100, and 200 μ g. In each cohort, 12 patients received CRX-675 and 4 received placebo (16 total placebo users). All the patients in a cohort received a single dose of CRX-675 or placebo on day 0, equally divided (100 μ L) per nares. Safety assessments included physical examination and vital signs, electrocardiography, spirometry, laboratory tests, and patient diaries and interviews for adverse events recorded for more than 30 days. CRX-675 dose escalation did not occur until the preceding (lower) dose was reviewed for safety issues.

RESULTS

A total of 65 patients were randomized, and 64 received study drug, 16 in each dose cohort. All the patients who received

study drug completed the study. The mean $\pm$ SD age did not differ between cohorts and ranged from 30.1 $\pm$ 7.5 to 35.9 $\pm$ 11.4 years. Fifty-three percent of the patients were women, and 90% were white. The mean $\pm$ SD PD₃₀ ragweed dose ranged from 0.60 $\pm$ 0.85 μ g of antigen E for the 20- μ g CRX-675 cohort to 13.33 $\pm$ 32.33 μ g of antigen E for the 100- μ g CRX-675 cohort.

A total of 134 treatment-emergent adverse events were reported. There were no serious or severe adverse events. One hundred three events (77%) were grade 1 (mild) toxicity, 30 (22%) were grade 2 (moderate) toxicity, and 1 (<1%) was grade 3 (severe) toxicity (back strain). Sixty-five events (49%) were considered to be unrelated to study drug, 65 (49%) possibly related, and 4 (3%) probably related.

Figure 1 and Table 1 show the overall incidence of adverse events and treatment-related adverse events by dosing cohort. The adverse event profile of intranasal CRX-675–treated patients was similar to that of placebo-treated patients, and no dose-related or dose-limiting toxic effects were observed. Indeed, the highest dose of CRX-675 and placebo had similar adverse event profiles.

There also were no differences between predose and post-dose nasal assessments of obstruction, discharge, and edema on day 0 and between day 0 and days 1 and 7 comparing the treatment groups. None of the CRX-675–treated patients had clinically meaningful changes in forced expiratory volume in 1 second subsequent to study drug administration on day 0.

Exploratory responses to CRX-675 were assessed by evaluating percentage change in nasal congestion (as evaluated by means of acoustic rhinometry) and nasal symptom scores after intranasal ragweed challenge. There were no consistent trends for improvement in nasal congestion after ragweed challenge for the CRX-675 treatment groups beyond those observed in the placebo group. There was a consistent decrease in nasal symptom scores in the 100- μ g CRX-675 treatment group compared with the placebo group 1 and 14

Table 1. Incidence of Treatment-Emergent Adverse Events With Onset on Day 0 or 1: Safety Population*

MedDRA preferred term	Placebo group (n = 16)	CRX-675 groups			
		2 μ g (n = 12)	20 μ g (n = 12)	100 μ g (n = 12)	200 μ g (n = 12)
Blood alkaline phosphatase increased	0	0	0	0	1 (8)
Blood bilirubin increased	1 (6)	0	0	0	0
Blood creatinine increased	0	0	0	2 (17)	0
Headache NOS	1 (6)	0	1 (8)	1 (8)	1 (8)
Hemoglobin decreased	1 (6)	0	0	0	1 (8)
Nasal dryness	1 (6)	0	0	0	0
Nasal septum disorder NOS	2 (12)	0	1 (8)	1 (8)	0
Pulmonary function test NOS decreased	0	0	0	1 (8)	0
Sore throat	0	0	0	0	1 (8)
Sinusitis NOS	1 (6)	0	0	0	0
White blood cell count increased	1 (6)	0	0	0	0

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; NOS, not otherwise specified.

* Day 0 is the day of and day 1 is the day after study drug administration. Data are given as number (percentage).

days after CRX-675 treatment when challenged with ragweed. The total nasal symptom scores were too low after ragweed challenge in the 20- and 200- μ g CRX-675 treatment groups to adequately evaluate an effect at those dose levels. Thus, no dose-response relationship was detected.

DISCUSSION

Toll-like receptors are an important family of innate immune response elements with the potential to modulate inflammation in allergic diseases.¹¹ A recent study¹² showed that lipopolysaccharide can prevent local allergen-induced inflammation in cultured nasal mucosa by down-regulation of T_H2 and up-regulation of T_H1 cytokines in tissue; proliferation and activation of T cells positive for CD4, CD25, and TLR4; and increased expression of interleukin 10 via the TLR4-dependent pathway. This phase I trial suggests that the safety profile of CRX-675 given as a single intranasal dose in this patient population is good and confirms the feasibility of using intranasal TLR4 agonists for the treatment of allergic rhinitis. Meaningful data from additional studies designed to examine the safety (including local inflammation) and efficacy of intranasal drug administered multiple times in a treatment cycle will best define the potential role of CRX-675 or other TLR4 agonists in the treatment of allergic rhinitis.

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