A proof-of-concept study of the effect of a novel H_3-receptor antagonist in allergen-induced nasal congestion

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Background: H_1-receptor inverse agonists are used effectively for treating several symptoms of allergic rhinitis, including nasal itching, rhinorrhea, and sneezing, although most agents are not very effective in treating nasal congestion.
Objective: This study evaluated the relative efficacy of a novel selective H_3-receptor antagonist, JNJ-39220675, in preventing nasal congestion induced by exposing participants with ragweed allergy to ragweed allergen in an environmental exposure chamber model.
Methods: In this single-dose, patient-blind, double-dummy, placebo- and active-controlled, phase IIa cross-over study, 53 participants were randomized to JNJ-39220675 plus placebo, placebo plus pseudoephedrine, or only placebo. The primary efficacy assessment was change in nasal patency assessed by measuring the minimal cross-sectional area of the nasal cavity by using acoustic rhinometry. Secondary assessment included total nasal symptom scores (TNSSs) over the 8-hour environmental exposure chamber exposure period.
Results: Smaller decreases in minimal cross-sectional area were observed after JNJ-39220675 (least square mean difference, −0.126; $P = .06$) and pseudoephedrine (least square mean difference, −0.195; $P = .004$) treatment compared with placebo. The means for the baseline-adjusted area under the curve of TNSSs were significantly smaller for JNJ-39220675 ($P = .0003$) and pseudoephedrine ($P = .04$) versus placebo. JNJ-39220675 was significantly effective in treating all 4 individual symptoms ($P \leq .05$ for all scores) compared with placebo, whereas pseudoephedrine only showed a trend for improvement in individual symptom scores of the TNSS. Insomnia was the most frequent adverse event (17.3%) associated with JNJ-39220675 treatment.
Conclusion: Prophylactic treatment with the H_3-antagonist JNJ-39220675 relieved allergen-induced nasal congestion by using standard nasal symptom scoring; however, in contrast to pseudoephedrine, it only showed a trend for increasing nasal patency by using objective measures. (J Allergy Clin Immunol 2013;132:838-46.)

Key words: *Allergic rhinitis, acoustic rhinometry, environmental exposure chamber, H_3-receptor antagonist, JNJ-39220675, pseudoephedrine, total nasal symptom scores*

Allergic rhinitis is the most common chronic atopic disease[1] and is associated with considerable cost and comorbidity.[2] Although a variety of mediators are implicated in the pathogenesis of the allergic reaction, histamine is shown to play a central role, and many of the early symptoms of allergic rhinitis are mediated by the action of histamine at the H_1-receptor site.[3] Inverse agonists of the H_1-receptor are hence used effectively as first-line treatment for many of the hallmark symptoms of seasonal allergic rhinitis (SAR), including nasal itching, rhinorrhea, and sneezing; however, they are not very effective in treating nasal congestion.[4]

Although H_1- and H_2-receptors are well-known targets for many drugs used clinically, newer histamine receptors, including the H_3-receptor, have recently been described.[5] The H_3-receptors are presynaptic autoreceptors present on histamine neurons controlling the stimulated release of histamine and presynaptic heteroreceptors on non–histamine-containing neurons, with the greatest densities found in the central nervous system (CNS).[6-9] H_3-receptors are predominantly expressed in the brain[10] and are also localized in the nasal mucosa.[11] Earlier *in vitro* experiments with isolated human turbinate mucosa have shown that the H_3-receptor agonist R-α-methylhistamine inhibited neurogenic sympathetic vasoconstriction, whereas clobenpropit, a selective H_3-receptor antagonist, blocked this effect, probably by reducing norepinephrine release from sympathetic nerve terminals in the nasal mucosa.[12]

Exploratory studies done earlier with H_3-antagonists have shown mixed results in human allergic rhinitis models. The compounds used in these studies were either dual H_1- and H_3-antagonists or were studied in combination with an H_1-antagonist and hence inconclusive regarding the specific contribution of the H_3-antagonism.[13]

JNJ-39220675, also known as (4-cyclobutyl-[1,4]diazepam-1-yl)-(6-[4-flurophenoxy]-pyridin-3-yl)-methanone, is a novel and selective H_3-receptor antagonist (inhibition constant, 1.4 nmol/L),[14-16] which does not have any significant affinity for the H_1-receptor (data on file, Janssen Research & Development). It has been shown to occupy up to 90% of H_3-receptors in the brain after subcutaneous and oral administration in rats and after intravenous and oral administration in anesthetized baboons.[14-16] After subcutaneous

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Supported by Janssen Research & Development, LLC (formerly Johnson and Johnson Research and Development, LLC).
Disclosure of potential conflict of interest: W. T. Barchuk is employed by and owns stock/stock options in Janssen Research & Development. A. M. Salapatek and P. D'Angelo have been supported by one or more grants from Cetero Research at the time of the study, which was sponsored by Janssen Research & Development. T. Ge and X. Liu are employed by Janssen Research & Development.
Presented at the European Histamine Research Society, Durham, United Kingdom, July 13-17, 2010; the Japan Histamine Society Meeting, Morioka, Japan, October 20-21, 2011; and the American Society for Pharmacology and Experimental Therapeutics meeting, April 22, 2012.
Received for publication September 27, 2012; revised April 29, 2013; accepted for publication May 8, 2013.
Available online June 20, 2013.
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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2013.05.001

Abbreviations used
AcR: Acoustic rhinometry
AUC: Area under the curve
CNS: Central nervous system
ECP: Eosinophil cationic protein
EEC: Environmental exposure chamber
LSM: Least square mean
MCA: Minimal cross-sectional area
SAR: Seasonal allergic rhinitis
TEAE: Treatment-emergent adverse event
TNSS: Total nasal symptom score

administration, JNJ-39220675 is shown to significantly increase histamine levels in the frontal cortex and wake duration in rats.[14]

In this exploratory study we evaluated the relative efficacy of JNJ-39220675 in preventing nasal congestion induced by exposure of participants with ragweed allergy to ragweed allergen in an environmental exposure chamber (EEC) model by using acoustic rhinometry (AcR), an objective method to assess nasal patency,[17] as well as traditional subjective symptom measures. The effect of JNJ-39220675 on T_H2 cytokines and other biomarkers was also explored.

METHODS

Study population

Men and women aged 18 to 65 years (inclusive) with a body mass index of between 18 and 32 kg/m^2 (inclusive) and a body weight of 50 kg or greater and in good health were enrolled. Participants were required to have a clinical history of SAR with a seasonal onset and offset of nasal allergy symptoms during each of the last 2 ragweed allergy seasons and a positive skin prick test response to ragweed allergen (defined as a wheal diameter ≥3 mm larger than that elicited by the negative control) or a positive intradermal skin test response to ragweed allergen (defined as a wheal ≥7 mm larger than that elicited by the negative control) within 12 months before screening.

The study protocol was approved by the institutional review board (IRB Services, Aurora, Canada), and the study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and applicable regulatory requirements and in compliance with the respective protocols. All participants provided written informed consent before participation.

Study design

In this phase IIa, single-dose, patient-blind, double-dummy, placebo- and active-controlled 3-way crossover study, participants were randomized to one of 6 predetermined treatment sequences: ABC, BCA, CAB, ACB, BAC, or CBA (treatment A, 1 mL of 10 mg/mL JNJ-39220675 oral solution plus placebo tablet; treatment B, 1 mL of placebo oral solution plus 60-mg pseudoephedrine tablet; and treatment C, 1 mL of placebo oral solution plus placebo tablet). Each treatment period consisted of 1 EEC session with a minimum 6-day washout period (see Fig E1 in this article's Online Repository at www.jacionline.org). During each EEC treatment session, participants were exposed to airborne ragweed for 8 hours with a mean pollen concentration of approximately 3500 particles/m^3 (SD, 500 particles/m^3). The 10-mg dose of JNJ-39220675 was the highest dose studied in women in a single, ascending-dose, phase I study in which doses of up to 50 mg were studied in men; the 10-mg dose was well tolerated by both men and women and was therefore selected for this study (data on file, Janssen Research & Development).

This study was conducted in the fall and winter months after the local ragweed season had concluded. Participants attended a 3-hour screening EEC visit to ensure that they would have an adequate symptomatic response to ragweed exposure in the EEC. Participants who had a decrease of 10% or greater in the minimal cross-sectional area (MCA) of either nostril after EEC exposure compared with their pre-EEC MCA and who had a minimum total nasal symptom score (TNSS) of 6 or more of 12, including a score of 2 or greater for congestion, on 1 or more diary cards during the EEC screening period were randomized to treatment period 1 (treatment A, B, or C) after a 6-day washout period (see Fig E1).

During each treatment period, participants fasted for approximately 8 hours before receiving the study drug and were given a light snack 2 hours after study drug administration. Study drug was administered in a blinded manner approximately 2 hours before entering the EEC. Participants recorded nasal symptom scores and underwent AcR assessment before receiving the study drug. On entering the EEC, participants underwent AcR assessments every hour throughout the 8-hour ragweed allergen exposure period and were asked to assess symptoms every 30 minutes throughout the 8-hour period.

Nasal lavage

Nasal lavage specimens were obtained from all participants before and after the screening EEC visit and after each treatment period EEC visit. A 10-mL syringe with a nasal "olive" (Crest Tech, Toronto, Ontario, Ontario) on the hub was used to perform the procedure. Under the instruction and supervision of trained EEC personnel, each participant instilled approximately 5 mL of saline solution into their nasal cavities through the left nostril from a forward-flexed neck position (60° from the upright position) and withdrew the fluid. The procedure was repeated twice and completed within 1 minute. The lavage fluid collected was centrifuged (1500 rpm for 10 minutes at 4°C), and the supernatant obtained was then stored at −80°C for cytokine analysis.

Cytokine analysis

Nasal lavage aliquots were concentrated 10-fold and lyophilized to obtain a final volume of 50 μL. Total protein levels were determined by using the Pierce Bicinchoninic Acid Protein Assay (Thermo Fisher Scientific, Uppsala, Sweden). Human albumin (Bethyl Laboratories, Montgomery, Tex) and human eosinophil cationic protein (ECP; MBL, Nagoya, Japan) levels were measured by using ELISA. Levels of human cytokines, including IL-1β, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12 (p70), IL-13, TNF-α, and IFN-γ, were measured by using a multiplex immunoassay.

Efficacy assessments

Efficacy assessments included AcR and nasal symptom scores.

AcR

Changes in nasal patency were assessed by using AcR to determine the MCA of the nasal cavity. All measurements were done by blinded operators trained in the use of the acoustic rhinometer (Rhinoscan; Interacoustics, Assens, Denmark), and the same operator and the same equipment were used for each measurement to ensure consistency. The MCA was measured along the nasal passage from 0 cm (at the nares) to 5.5 cm. For each nostril, the MCA1 (0-2.2 cm) and MCA2 (2.2-5.5 cm) values were measured simultaneously. Four measures (the left MCA1, right MCA1, left MCA2, and right MCA2 values) were captured to determine the average MCA. Each set of 4 measurements were repeated thrice to obtain 12 data points. The minimum value from the 3 MCA averages was reported as the MCA across both nostrils.

Safety

The safety assessments included monitoring treatment-emergent adverse events (TEAEs), physical examinations, vital signs, electrocardiographic results, and laboratory parameters.

Statistical analysis

The efficacy analyses were based on the intent-to-treat population, which included all participants who received 1 or more doses of the study medication