VTX-1463, a novel TLR8 agonist for the treatment of allergic rhinitis

Friedrich Horak
Department of Vienna Challenge Chamber, Institute for Allergy Research, Allergy Centre Vienna West, Huttedorferstrasse, Vienna, Austria

Introduction: Allergic rhinitis significantly impacts quality of life and current treatments are frequently unsatisfying. VTX-1463 is a potent, selective, Toll-like receptor (TLR) 8 agonist administered weekly via the intranasal route without concomitant administration of allergen for the treatment of allergic rhinitis.

Areas covered: The rationale for TLR8 as a therapeutic target in allergic disease is summarized. The potency of VTX-1463 for TLR8 is outlined, and preclinical efficacy data from a ragweed-sensitized beagle dog model of allergic rhinitis are reviewed. Results of three randomized, double-blind, placebo-controlled trials with VTX-1463 are also reviewed: (i) a first-in-man study in healthy volunteers, (ii) an allergen challenge study in atopic individuals out of pollen seasons and (iii) an allergen challenge study in atopic individuals during season.

Expert opinion: Two or four weekly pretreatments with VTX-1463 in subjects with grass pollen allergies provided statistically significant improvement in nasal symptoms, as measured by total nasal symptom score (TNSS) and active anterior rhinomanometry (AAR), while subjects were exposed to grass pollen in the Vienna Challenge Chamber (VCC). Improvement in nasal secretion weights and ocular symptom scores was also observed. VTX-1463 is a promising new agent for the treatment of seasonal, and potentially perennial, allergic rhinitis.

Keywords: allergic rhinitis treatment, IL-12 production, immunomodulation, nasal spray, TLR8, Toll-like receptor agonist, Vienna challenge chamber, VTX-1463

1. Introduction

1.1 Allergic rhinitis

Allergies are linked to a variety of common and serious chronic respiratory illnesses and symptoms of allergies, in particular nasal congestion and the concomitant nasal airway obstruction, have a negative impact on day-to-day activities and overall quality of life [1,2]. Allergen avoidance, pharmacotherapy (e.g., oral and intranasal antihistamines, intranasal glucocorticosteroids, intranasal and oral decongestants and antileukotrienes) and immunotherapy (subcutaneous allergen-specific immunotherapy, sublingual or intranasal immunotherapies) comprise the standard of care for moderately affected individuals as recommended by the ARIA (Allergic Rhinitis and its Impact on Asthma, 2008) guidelines [3]. However, for some patients, the side effects of treatment for allergic rhinitis can outweigh the benefits. Treatment with pharmacotherapeutics may be associated with undesirable effects such as central nervous system symptoms of sedation, impairment of cognition, dizziness and tremor (antihistamines); cardiovascular symptoms of tachycardia, palpitations and...
### 1.2 TLRs and allergy

A common immune response theme has emerged wherein so-called pattern recognition receptors (PRR) are employed that recognize invariant structures within microbial agents. Among the broad category of PRR, Toll-like receptors (TLRs) are a family of 10 evolutionarily conserved receptors expressed either on the cell surface or in intracellular endocytic vesicles or organelles, and which collectively recognize a diverse range of microbial ligands. Stimulation of an innate immune response via TLRs may provide therapeutic benefit in allergic disease via down-regulation of the adaptive immune response. TLR4 which recognizes lipopolysaccharides (LPS) on the cell wall of Gram-negative bacteria was one of the first of the family of TLRs to be evaluated as a therapeutic target in allergic disease.  

VTX-1463 is formulated as a nasal spray for the treatment of allergic rhinitis (Box 1). VTX-1463 is consistent with the goal of delivering therapeutic concentrations of the molecule to the site of action (the nasal mucosa) while minimizing systemic exposure and the potential for undesirable systemic effects.

### 2. Preclinical data

#### 2.1 In vitro characterization of selectivity, potency and pharmacodynamics

Preclinical studies were performed with VTX-378, the active pharmaceutical ingredient in VTX-1463. The specificity of VTX-378 for human TLR8 relative to other TLRs was assessed in transfected human embryonic kidney 293 (HEK293) cells engineered to express individual TLRs (2 – 9) via transfection, and assessed using an NF-kB (nuclear factor-kappa B cells)-driven reporter system. VTX-378 was a potent activator of TLR8 with a half maximal effective concentration (EC$_{50}$) of ~100 nM and a weak activator of TLR7 with an EC$_{50}$ of ~2000 nM in this test system.
VTX-378 had no detectable activity on TLR2, TLR3, TLR5, TLR6 or TLR9 and minimal to no activity on TLR4 (manuscript in preparation). The pharmacologic effects of VTX-378 were characterized in vitro using isolated human peripheral blood mononuclear cells (PBMCs). Incubation with VTX-378 stimulated PBMCs to produce a number of Th-1 cytokines and chemokines including IL-12, IFN, MCP-1 and MIP-1β. VTX-378 also stimulated production of IL-10 (manuscript in preparation). The overall pattern of cytokine induction, notably including the production of IL-12, is distinct for TLR8 stimulation compared with other human TLRs.

2.2 Efficacy in a dog model of allergic rhinitis
The therapeutic activity of VTX-378 was assessed in a well-characterized model of allergic rhinitis in ragweed-sensitized beagle dogs. Acoustic rhinometry (AcR) can be used to measure the direct effect on the nasal mucosa following nasal instillation of ragweed antigen [25]. In multiple experiments using ragweed-sensitized beagle dogs, intranasal administration of 100 – 1000 µg of VTX-378 produced a reproducible, dose-dependent, statistically significant reduction in the allergic response to antigen challenge [26]. Interestingly, the responses to VTX-378 were rapid, occurring after a single dose administered 24 h before the intranasal ragweed challenge. Studies in this model have also found that two VTX-378 doses are more effective than a single dose. Specifically, a single dose of 1000 µg of VTX-378 attenuated nasal congestion 56.5 ± 10.0% while two doses separated by 4 or 7 days improved congestion 65.4 ± 10.3% and 71.9 ± 7.7%, respectively. These findings suggest that weekly intranasal administration of a TLR8 agonist may have a unique pharmacologic profile in the treatment of allergic rhinitis.

3. VTX-1463 clinical results

3.1 Overview of the clinical trials performed
VTX-1463 has been evaluated in three randomized, double-blind, placebo-controlled trials. Each clinical protocol was reviewed and approved by an independent ethics committee and all subjects were required to provide written informed consent before study participation.

Study VRXP-B101 was a first-in-man dose escalation study that evaluated the safety, tolerability and pharmacokinetics of VTX-1463 in 37 healthy volunteers. Studies VRXP-B102 and VRXP-B103 were designed to assess the safety and efficacy of VTX-1463 in attenuating allergic rhinitis symptoms in atopic subjects exposed to grass allergen. Study VRXP-B102 evaluated 2 weekly doses of VTX-1463 out of allergy season and study VRXP-B103 evaluated 4 weekly doses of VTX-1463 during allergy season. Both studies were conducted in the Vienna Challenge Chamber (VCC, Vienna, Austria). The VCC offers a controlled and controllable paradigm to reproducibly evaluate the effects of medications on allergic rhinitis. This model allows the control of environmental conditions and can, therefore, eliminate some of the confounding factors encountered in normal outdoor studies such as the variability of the general environmental allergen load, variability with respect to the time patients spend indoors and occurrence of concomitant respiratory tract infections [27,28]. The efficacy assessments performed in the VCC include: total nasal symptom score (TNSS; the sum of scores for nasal congestion, nasal itching, sneezing and rhinorrhea), nasal airflow resistance as measured by active anterior rhinomanometry (AAR), total ocular symptom score (TOSS; the sum of scores for watery eyes, itchy eyes and red eyes), miscellaneous allergy symptom score (MASS; the sum of scores for cough, itchy throat, itchy ears and palate) and nasal secretion weight.

3.2 VRXP-B101: Phase I trial in healthy volunteers
VRXP-B101 was a randomized, double-blind, placebo-controlled, two-part study to evaluate the safety, tolerability and pharmacokinetics of intranasal administration of VTX-1463 to healthy volunteers (n = 37). The first part of the study assessed cohorts exposed to increasing single doses of VTX-1463 ranging from 32 to 500 µg. The second part of the study evaluated different cohorts exposed to two doses of 250 and 500 µg separated by 7 days. Pharmacokinetic analysis demonstrated a mean T_max occurring between 0.3 and 0.5 h and a mean half-life (t_1/2) ranging between 1.0 and 1.6 h after intranasal dosing. For the 32 and 64 µg dose groups, quantifiable levels of VTX-1463 were below the level of detection (0.1 ng/ml). Measurable levels of VTX-1463 were present in the plasma for an average of 1.8, 2.4 and 4.0 h following administration of 125, 250 and 500 µg doses, respectively.

Overall, VTX-1463 was generally safe and well tolerated. The majority of adverse events were mild (Grade 1), local (nasal) and resolved spontaneously. Local findings included runny nose, nasal irritation, nasal congestion and throat irritation.

3.3 VRXP-B102: allergen challenge in atopic individuals
VRXP-B102 was a randomized, double-blind, placebo-controlled multiple dose level study conducted in the VCC. The primary goal of the study was to assess the safety and efficacy of VTX-1463 in attenuating allergic rhinitis symptoms in atopic subjects exposed to grass allergen. Seventy asymptomatic or minimally symptomatic subjects with confirmed atopy to grass pollen were randomized to receive 2 weekly intranasal doses of 100, 250 or 500 µg of VTX-1463 or placebo out of pollen season. Twenty-four hours after the second dose, subjects had baseline evaluations performed and then underwent a grass allergen challenge in the exposure chamber for 6 h. While in the allergen exposure chamber, subjects
VTX-1463 underwent serial evaluations for symptom scores (TNSS, MASS, TOSS), AAR and nasal secretion weight. VTX-1463 at the doses and dose regimen studied showed improvement over placebo in attenuating allergic rhinitis symptoms. The clinical benefit of VTX-1463 appeared greatest in the 250 µg group, where there was ~25% improvement based on TNSS measurements relative to placebo (4.7 ± 0.6 change from baseline for VTX-1463 treated subjects compared with 6.1 ± 0.6 for subjects who received placebo, p = 0.071) and ~50% improvement in nasal airflow (AAR) compared with placebo (-102 ± 33 cm³/s change from baseline for VTX-1463 treated subjects vs -215 ± 33 cm³/s for subjects who received placebo control, p = 0.019). There was no apparent benefit following two doses of 100 µg VTX-1463.

Tolerability of VTX-1463 was less than desirable for the intended patient population, although adverse events were generally local, mild and transient in nature. Local findings included runny nose, nasal irritation, nasal congestion and throat irritation. Adverse events appeared to be dose related and less severe with the second dose as compared with the first.

3.4 VRXP-B103: allergen challenge in atopic individuals in season
Study VRXP-B103 was a randomized, double-blind, placebo-controlled trial in atopic individuals performed in the VCC. VRXP-B103 differed from VRXP-B102 in that the individual doses administered were much lower and that it was designed to assess the efficacy of VTX-1463 during allergy season while environmental grass pollen counts were elevated. Study VRXP-B103, compared a total dose of 250 µg VTX-1463 administered weekly over 4 weeks as either an ascending dose (25, 50, 75, 100 µg) or a fixed dose (62.5 µg/week) to placebo. These dose regimens were selected with the goal of improving the tolerability of VTX-1463 and based on the observations in study VRXP-B102 that the 250 µg dose level of VTX-1463 was efficacious and that the second dose was better tolerated than the first dose. Eighty asymptomatic or minimally symptomatic subjects with confirmed atopy to grass pollen were enrolled in the study and underwent a 6 h grass allergen challenge in the VCC 48 h after the fourth dose. Subjects who were treated with VTX-1463 and underwent allergen challenge had significantly improved TNSS compared with placebo (p = 0.012). This benefit was observed with both the ascending dose (5.1 ± 0.5 change from baseline for VTX-1463 treated subjects compared with 6.9 ± 0.5 for subjects who received placebo, p = 0.008) and fixed dose regimens (5.2 ± 0.5 change from baseline for VTX-1463 treated subjects compared with 6.9 ± 0.5 for subjects who received placebo, p = 0.012). Mean percent change from baseline in airflow response to allergen challenge as measured by AAR improved by 20.4% in subjects who received VTX-1463 compared with subjects who received placebo. Clinical benefit was also observed for reduction in allergen-induced secretion weights compared with placebo (p = 0.001), and trended favorably for the TOSS and MASS end points (29).

The tolerability of VTX-1463 was also improved in study VRXP-B103. The overall incidence of adverse events was approximately 5.8% higher in subjects treated with VTX-1463 than those treated with placebo. Most adverse events were local and transient and the frequency and severity of AEs did not appear to increase with cumulative number of doses or dose level.

4. Expert opinion
VTX-1463 is a novel, selective, TLR8 agonist administered intranasally on a weekly basis for the treatment of allergic rhinitis. This product is given as a stand-alone agent and is not co-administered with allergen. Data from two, independent double-blind, placebo-controlled studies in subjects with grass pollen allergy performed in the VCC demonstrated clinic benefit. VTX-1463 provides near-term symptom relief, and has the potential (based on the activation of TLR8 on dendritic cells and monocytes in the nasal mucosa) to provide longer-term immunomodulation to seasonal (and/or perennial) allergens.

Several key issues remain to be addressed as this compound advances in clinical development. It will be important to better understand the immunologic mechanism(s) underlying the clinical benefit seen. An intriguing possibility is that the locally administered TLR8 agonist provides immediate/early benefit via modulation of mast cell responses, perhaps via local IL-10 production (consistent with the preclinical data and the observation of clinical improvement in human clinical trials after two or four doses) and that additional doses (potentially via the recurrent production of IL-12) will modulate local T cell responses and decrease Th-2 tone. In this regard, the optimization of the timing of VTX-1463 relative to environmental allergen exposure and the appropriate number of doses required for maximal benefit should be addressed in the next studies of the agent. It will be of great interest to understand how any potential longer-term immunomodulatory benefits compare with conventional immunotherapy or sublingual immunotherapy. Further, it will be important to ascertain whether the clinical benefit seen in the context of seasonal allergy treatment with VTX-1463 extend to perennial allergen responses.

In addition, it remains to be determined where in the sequence of allergic treatments VTX-1463 would be used. The weekly dosing regimen is a potential convenience compared with existing daily or twice daily treatment schemes for antihistamines and intranasal steroids. While the onset of action of VTX-1463 appears rapid based on preclinical animal data, it is not known whether the agent will provide immediate relief in symptomatic patients. In addition, the immune-based mechanism of VTX-1463 as a TLR8 agonist will likely preclude combination with intranasal steroids (but not antihistamines). Finally, while there are no apparent
safety issues from the three studies of VTX-1463 to date, it may be necessary to optimize the local adverse event profile if this agent is to be used in earlier stage disease and/or in the prophylactic setting.

In summary, VTX-1463 has shown promising activity in two, independent studies of allergic subjects, both in and out of allergy season. The target for this agent, TLR8, appears to have distinct immunological properties (including IL-12 production) compared with other TLRs studied in the setting of allergy. It will be critical to optimize the number of doses required, the dosing relative to environmental allergen exposure and the local tolerability. VTX-1463 has the potential to provide a new option for allergy subjects with rapid onset of symptom control and longer-term immunomodulation.

Declaration of interest

Both of the clinical trials in the VCC referred in the paper were sponsored by: VentiRx Pharmaceuticals, Inc., 1700 Seventh Avenue, Suite 1900, Seattle, WA 98101, USA. There are no further conflicts of interest.

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Affiliation
Friedrich Horak
Department of Vienna Challenge Chamber,
Institute for Allergy Research,
Allergy Centre Vienna West,
Hütteldorferstrasse 42-46,
1150 Vienna, Austria
E-mail: f.horak@vcc.at

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