Original Article

Onset of Action of the Fixed Combination Intranasal Azelastine-Fluticasone Propionate in an Allergen Exposure Chamber

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What is already known about this topic? Randomized controlled trials are insufficient to assess the onset of action of rhinitis medications. The 2 most common treatment strategies for uncontrolled rhinitis were not compared for efficacy or onset of action.

What does this article add to our knowledge? In a chamber study, single-device azelastine-fluticasone formulation is effective within 5 minutes and the effect persists over the 4-hour study period. A free combination of intranasal fluticasone propionate and oral loratadine is effective after 2 hours.

How does this study impact current management guidelines? Patients with allergic rhinitis want an effective rapid-onset treatment that is not reflected in the guidelines, which need to become closer to patients' preferences. The study may help physicians to decide which treatment to use.

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This clinical study was funded by MEDA Pharma GmbH & Co KG (Bad Homburg, Germany). Graphical support for the development of figures for this article was provided by Ashfield Healthcare Communications (Middletown, Conn) and funded by Mylan, Inc (Canonsburg, Pa).

Conflicts of interest: J. Bousquet has received personal fees and other fees from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach; and has received other fees from Kyomed, outside the submitted work. E. Meltzer has received provision of writing assistance, medicines, equipment, or administrative support from Ashfield Healthcare; has received consultancy fees from ALK, AstraZeneca, Boehringer Ingelheim, Circassia, GlaxoSmithKline, Glenmark, and Greer/Stallergenes; has received payment for lectures including service on speakers bureaus for ALK, GlaxoSmithKline, Glenmark, Mylan, Teva, and Greer/Stallergenes; and has received payment for developing educational presentations for ALK. A. Koltun is employed by Mylan. U. Munzell, H. C. Kuhl, and F. Kopietz are employed by MEDA Pharma GmbH & Co KG. A. M. Salapatek is employed by and has received fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like from Inflamax Research in a clinical contract research organization; Inflamax Research performed the clinical research and the statistical analyses for the research presented for this trial and money was sent to the institution. (Inflamax Research is a clinical contract research organization that was paid for the full conduct of the clinical research presented here including study design development, clinical conduct, data management, analysis, and reporting of the clinical outcomes.) D. Price has received other support from Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Merck, Mylan, Mundipharma, Napp, Novartis, Teva Pharmaceuticals, Almirall, GlaxoSmithKline, Kyorin, Pfizer, Skyepharma, Teva, Theravance, and Zentiva; has received grants from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp, Novartis, Pfizer, Respiratory Effectiveness Group, Teva Pharmaceuticals, Theravance, UK National Health Service, and Zentiva; has received nonfinancial support from Efficacy and Mechanism Evaluation program and Health Technology Assessment Commissioning Board, outside the submitted work; has stock/stock options from AKL Research and Development Ltd, which produces phytopharmaceuticals; and owns 74% of the social enterprise Optimum Patient Care Ltd (Australia, Singapore, and United Kingdom) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore). The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication November 10, 2017; revised January 14, 2018; accepted for publication January 19, 2018.
Available online ■■

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2213-2198

https://doi.org/10.1016/j.jaip.2018.01.031

Abbreviations used

AEC- Allergen exposure chamber
AR- Allergic rhinitis
EEC- Environmental exposure chamber
ePDAT- electronic Patient Data Acquisition Tablet
FAS- Full analysis set
INCS- Intranasal corticosteroid
INFF- Intranasal fluticasone furoate
INFP- Intranasal fluticasone propionate
LORA- Oral loratadine
MCID- Minimal clinically important difference
MP-AzeFlu- Intranasal azelastine with intranasal fluticasone propionate
RCT- Randomized controlled trial
SPT- Skin prick test
T7SS- Total score of the 7 nasal and ocular symptoms (including TNSS and TOSS)
TNSS- Total nasal symptom score
TOSS- Total ocular symptom score
V1, V2, …, V7- Visit 1, visit 2, …, visit 7
VAS- Visual analog scale

BACKGROUND: A fixed-dose combination of intranasal azelastine hydrochloride and fluticasone propionate (MP-AzeFlu) is the most effective treatment of allergic rhinitis, but its onset of action requires further investigation.
OBJECTIVE: To compare the onset of action of MP-AzeFlu with the free combination of oral loratadine (LORA) and intranasal fluticasone propionate (INFP).
METHODS: In this single-center, randomized, placebo-controlled, double-blind, double-dummy, 3-period crossover trial, allergic rhinitis symptoms were induced in asymptomatic patients by ragweed pollen challenge in an allergen environmental exposure chamber. Patients received single-dose MP-AzeFlu, LORA/INFP, or placebo and were monitored for 4 hours. The primary outcome was onset of action measured by total nasal symptom score (TNSS). Secondary measures were total ocular symptom score (TOSS), total score of the 7 nasal and ocular symptoms (T7SS), and the global visual analog scale (VAS).
RESULTS: The full analysis set included 82 patients, of which 78 completed all treatments. TNSS was significantly reduced versus placebo from 5 minutes for MP-AzeFlu and 150 minutes for LORA/INFP onward (both $P < .05$) till the end of assessment (0-4 hours). MP-AzeFlu reduced TNSS to a greater extent at each time point from 5 to 90 minutes ($P < .05$) and over the entire assessment interval ($P \leq .005$) versus LORA/INFP or placebo. No statistically significant difference between LORA/INFP and placebo was observed over the assessment interval ($P = .182$). The onset of action of MP-AzeFlu assessed by TOSS, T7SS, and VAS was 10 minutes, 2 hours earlier than with LORA/INFP.
CONCLUSION: MP-AzeFlu had a more rapid onset of action (5 minutes) and was more effective than LORA/INFP. © **2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;■:■-■)**

Key words: *Allergic rhinitis; Azelastine; Environmental exposure chamber; Fluticasone propionate; Loratadine; Onset of action*

INTRODUCTION

Most patients with allergic rhinitis (AR) have moderate/severe disease with persistent symptoms that are often insufficiently recognized by their physicians. Comedication is common, with patients self-medicating and doctors concurrently prescribing, most commonly, oral H_1 antihistamines and intranasal corticosteroids (INCSs) despite lack of evidence for this strategy.[1-4] A large number of patients with AR use their treatment intermittently, and frequently expect a rapid onset of efficacy.

The US Food and Drug Administration (FDA) has proposed 3 study types to assess the onset of action of medications[5,6]: the standard phase 3 double-blind randomized controlled trials (RCTs), park-setting studies, and allergen exposure chamber (AEC) studies.[7] However, RCTs cannot provide a sufficient precision to assess the onset of efficacy because they cannot allow repeated timing over short periods of time (minutes). AECs offer some advantages over RCTs in assessing the onset of efficacy of medications because it can be demonstrated in minutes.[7] AECs allow consistent allergen exposure. An AEC involves a manipulated *in vivo* procedure, whereas a park-setting study mirrors real-life exposure. Park-setting as well as AEC studies have not captured the early time. It appears that a crossover trial would be difficult with a park-setting study because of variations in allergen exposure between days. Nevertheless, an AEC cannot replace real-world allergen exposure but can only complement it. To date, AEC studies conducted have been monocentric and have followed protocols unique to each center. Because there are technical differences among AECs, it is not easy to compare the results obtained in different AECs.[8] The environmental exposure chamber (EEC) used in this study has been used in the same manner for a number of onset of action studies and so provides an opportunity for comparison.[9-17]

The aim of this study was to compare the onset of action of 2 treatment strategies for AR, a fixed drug combination of intranasal azelastine hydrochloride and intranasal fluticasone propionate (MP-AzeFlu) versus the sequential monotherapies of oral loratadine (LORA) and intranasal fluticasone propionate (INFP), in an Ontario EEC in treating the nasal and ocular symptoms of seasonal AR induced by a ragweed pollen challenge.

METHODS

Study design

The study was a single-center, randomized, active- and placebo-controlled, double-blind, double-dummy, and 3-period crossover trial (William's design[18]). It was divided into 3 visit categories: screening (V1), priming (V2, V4, and V6), and treatment (V3, V5, and V7)[7] (see the Methods section in this article's Online Repository at www.jaci-inpractice.org). The primary outcome was the onset of action on nasal symptoms (total nasal symptom score [TNSS]). Secondary outcomes were the onset of action on (1) ocular symptoms (total ocular symptom score [TOSS]), (2) the total 7 nasal and ocular symptoms (T7SS), (3) the 7 individual symptoms, and (4) a global visual analog scale (VAS). Other secondary outcomes included the overall efficacy (0-4 hours after dosing) on (5) TNSS, (6) TOSS, (7) and T7SS, and (8) the comparison of time with relevant response to therapy (30% and 50% reductions in TNSS) to investigate a clinically meaningful response.[19]