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BRIEF RESEARCH REPORT

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In perennial allergic rhinitis, RQLQ is improved similarly by Azelastine 0.15 and mometasone furoate

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ABSTRACT

Some double-blind, placebo-controlled trials have shown that Azelastine (Aze) high dose (0.15%) was effective in seasonal (SAR) and perennial allergic rhinitis (PAR). However, there was no long-term comparison between Aze 0.15% and intranasal corticosteroids (INCS) on safety and quality of life in perennial allergic rhinitis.

An open-label, active-controlled, parallel-group one-year study comparing mometasone furoate and Aze 0.15% in adults assessed safety over 1 year. Efficacy using the 28-item rhino-conjunctivitis quality of life questionnaire (RQLQ) was a secondary end point.

A total of 703 patients were randomized and 687 (97.7%) were included in the intent-to-treat (ITT) population. The present formulation was shown to be safe with long-term use over 12 months, with a mean duration of exposure of 270.7 days.

Over the one-year period, there was no significant difference for any RQLQ domains between Aze and mometasone furoate (MF) for all evaluations (baseline, 6, 9, and 12 months). This study suggests that Aze 0.15% and MF display a similar improvement of RQLQ (2.80 [2.78] for Aze 0.15% vs 2.81 [2.75] for MF).

Clinical trial registry number: NCT00720382.

Keywords: Perennial allergic rhinitis, Azelastine, Mometasone furoate, RQLQ

INTRODUCTION

Intranasal corticosteroids (INCS) are the mainstay for the treatment of moderate-severe allergic rhinitis.[1,2] However, azelastine (Aze) high dose (0.15%) is only considered as a first-line treatment in the US practice parameters,[2] whereas ARIA combined the 3 Aze dosages in its recommendations.[1]

Some double-blind, placebo-controlled trials have shown that Aze 0.15% was effective in seasonal allergic rhinitis (SAR)[3] and perennial allergic rhinitis (PAR).[4] However, there was no long-term comparison of Aze high dose (0.15%) with INCS on quality of life in PAR.

METHODS

This was an open-label, active-controlled, parallel-group one-year study (Study MP436,

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NCT00720382). The main objective of the trial was to assess safety over 1 year. Efficacy assessed the 28-item rhino-conjunctivitis quality of life questionnaire (RQLQ)[5] as a secondary end point. RQLQ was tested in the present study.

The study was conducted at 57 centres in the United States. Subjects 18 years of age and older were included if they had a history (>1 year) of rhinitis due to perennial allergies and serum specific IgE to perennial allergens. Subjects with a seasonal allergic component might also have been included, provided they had significant symptoms outside the allergy seasons (the full protocol with inclusion and exclusion criteria is online).

The study was reviewed and approved by the Sterling Institutional review board (IRB ID is from 2407-001 to 2407-060 for 60 study sites) at participating sites. The study was conducted in accordance with Good Clinical Practice and written informed consent was obtained from the subjects.

Subjects were randomized in a 2:1 ratio to Aze (1644 mcg/day) 2 sprays per nostril twice daily or mometasone furoate (MF [200 mcg/day]) nasal spray 2 sprays per nostril once daily. Subjects recorded the diary daily. RQLQ was assessed at entry before treatment and at each clinical visit (3, 6, 9, and 12 months).[5] Since the primary endpoint was safety, patients did not record their nasal symptoms in the diary during the study but at screening only (to confirm subject eligibility).

The sample size was based on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

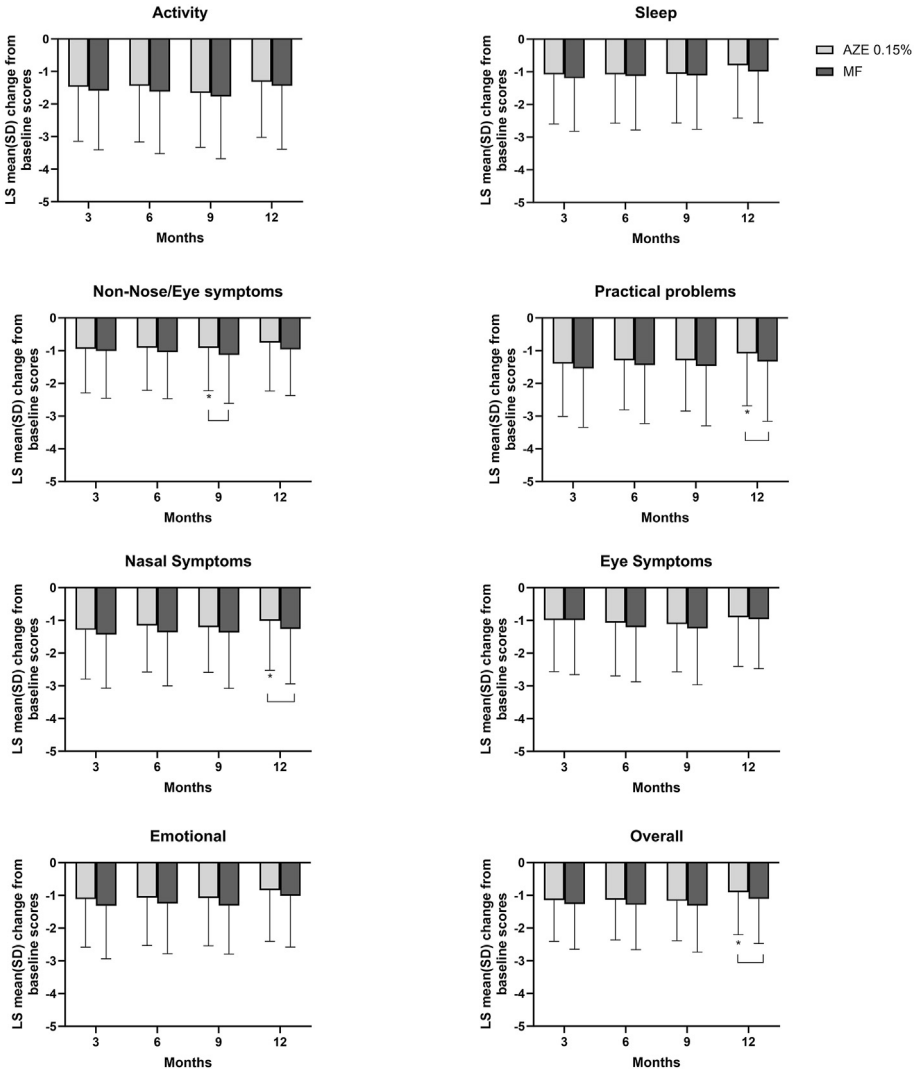

Fig. 1 Adult Rhino-conjunctivitis Quality of Life Questionnaire change from baseline Outcomes (Intent-to-Treat Population), *p < 0.05.

(ICH) guideline – "ICH E1: Population Exposure: The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions". Based on an estimated attrition rate of 25% at the six-month time point, and of 50% by the one-year time point, 400 subjects in the Aze 0.15% group represented an appropriate sample size to ensure an adequate safety database. Change from baseline to each clinical visit for overall score and individual domain was summarized by treatment group. Treatment comparisons were also performed using an analysis of covariance (ANCOVA) model with baseline as a covariate. The model included treatment group and site as fixed effects and was used in estimating least-square (LS) means. Efficacy analyses were performed on the intent-to-treat (ITT) population. The minimal clinically important difference between the 2 treatments was also calculated.[5]

RESULTS

A total of 703 patients were randomized and 687 (97.7%) were included in the ITT population (Sup. Fig. 1). Demographic characteristics are presented in Sup. Table 1. Concomitant medication usage was similar in both groups (86.3% in Aze and 87.3% in MF). However, reported medications did not interfere with study results. From diary data, a total of 412/466 (88.4%) subjects in the Aze group and 215/237 (90.7%) in the MF group were considered to be >75% compliant with study medication.

The present formulation was shown to be safe with long-term use over 12 months, with a mean duration of exposure of 270.7 days. The most common events (>5% and <14%) in the treatment group included dysgeusia, nasal discomfort, sinusitis, upper respiratory tract infection, epistaxis, nasopharyngitis, and headache (Table 1). There were no deaths, severe adverse events (SAEs), or unexpected adverse events related to therapy in the treatment group. No nasal mucosal ulcerations or nasal septal perforations were observed in the treatment groups during this study. Out of the 176 (37.8%) discontinuations in the Aze 0.15% treatment group, 54 were due to adverse events. There were 59 (24.9%) discontinuations in the MF group out of which 17 were due to AE. Most AEs were of mild or moderate severity, and were primarily local effects, in particular dysgeusia. Most findings on the focused head and neck evaluation were mild or moderate, and among subjects with severe findings for mucosal edema and nasal discharge, there were moderate decreases following 12 months of Aze 0.15% treatment (from 23 subjects

Preferred Term	Aze 0.15% (N = 466) No. of Subjects (%)	MF (N = 237) No. of Subjects (%)
Any adverse event	349 (74.9)	163 (68.8)
Dysgeusia	62 (13.3)	3 (1.3)
Nasal discomfort	46 (9.9)	19 (8.0)
Sinusitis	44 (9.4)	19 (8.0)
Upper respiratory tract infection	43 (9.2)	28 (11.8)
Epistaxis	43 (9.2)	24 (10.1)
Nasopharyngitis	43 (9.2)	20 (8.4)
Headache	41 (8.8)	30 (12.7)
Pharyngolaryngeal pain	22 (4.7)	14 (5.9)
Cough	15 (3.2)	12 (5.1)

Table 1. List of adverse events (>5%) in the treatment groups. *Somnolence was reported by 17 (3.6%) subjects in the Aze 0.15% group and by 1 (0.4%) subject in the MF group*

to 15 subjects and from 6 subjects to 4 subjects, respectively).

RQLQ results at baseline are presented in Sup. Table 2. There were no significant differences for any domain between Aze and MF. The overall and all individual domain RQLQ scores were significantly ($P < 0.001$) improved from baseline in both treatment groups at Month 1 through Month 12. Most of the individual scores showed comparable results for Aze and MF (Fig. 1). However, there was a slight difference in favor of MF at Month 12 for the overall RQLQ score ($p = 0.037$) but it did not achieve the minimal clinically important difference of 0.5U.[5]

DISCUSSION

This study is the first to show that Aze 0.15% is safe with long-term use over 12 months and improves RQLQ at 3, 6, 9, and 12 months similarly to MF.

This study does, however, have some limitations. First, it was an open-label, active-controlled, parallel-group one-year study without a placebo group.[6] It would have been difficult for ethics committees to approve a one-year placebo arm in the United States, and a large drop-out rate might have been expected.[7] Moreover, comparisons between medications can be made in such studies. Second, RQLQ was only a secondary end point of an efficacy study, but it is common practice to perform a safety study with secondary end points concerning efficacy.[8]

This study also has strengths such as the large number of patients enrolled and the low drop-out rate. Moreover, the RQLQ baseline values were similar in both groups. Quality-of-life is an important patient reported outcome measure and RQLQ is probably the best validated measure in rhinitis.

When deciding between azelastine (AZE) twice daily (BID) and mometasone once daily (QD) for treating allergic rhinitis, clinicians should consider several factors like efficacy, dosing convenience, side-effects, and patient preferences. Aze is known for its quick onset of action and effectiveness in reducing nasal symptoms such as congestion, itching, and sneezing while mometasone is known for its efficacy in reducing inflammation and providing long-lasting relief from these symptoms.[9] Aze may cause dysgeusia and somnolence in some patients, while mometasone can cause nasal irritation or dryness.[10] Both BID and QD regimens of Aze 0.15% are safe and effective, with the choice often depending on individual patient needs and preferences.[4]

The message is clear. Both medications are equally effective in reducing the RQLQ global score and all domains. There is 1 small difference in a single end point that is not clinically relevant. In this study, Aze high dose is therefore equivalent to MF and is considered to be an effective alternative to INCS.[11]

Abbreviations

ANCOVA, Analysis of covariance; Aze, Azelastine; BID, Twice a day; INCS, Intranasal corticosteroid; ITT, Intent-to-treat; MF, Mometasone furoate; PAR, Perennial allergic rhinitis; QD, Once a day; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SAE, Severe adverse event; SAR, Seasonal allergic rhinitis; TNSS, Total nasal symptom score.

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Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Author contributions

Jean Bousquet, Ludger Klimek, G. Walter Canonica, and Rajesh Kumar Ramalingam were involved in the conceptualization, preparation, and critical review of the manuscript. Duc Tung Nguyen was involved in the planning, clinical oversight, and reporting of the study. Hans-Christian Kuhl was involved in the statistical planning and statistical oversight of the analysis of the study. William E. Berger was involved in patient recruitment, patient care, data collection, and result review. Jean Bousquet wrote the manuscript.

Ethics

This clinical trial was reviewed and approved by Sterling Institutional Review Board. Institutional review boards (IRBs) were appropriately constituted and met all of the requirements and guidelines as described in Part 56, Title 21 of the Code of Federal Regulations (CFR). This study was conducted in accordance with Good Clinical Practice (GCP), the Declaration of Helsinki, and applicable regulatory requirements (21 CFR, Parts 50 and 56). Clinical Trial Registry number: NCT00720382.

Author consent
All authors contributed to the article and approved the submitted version for publication in WAO Journal.

Declaration of competing interest
This study and medical writing support were funded by Viatris. DT, HK and RR are employees of Viatris and were involved in the study design, conduct and interpretation of data. WB is employed by Allergy & Asthma Solutions, Inc. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.101021.

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