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REVIEW

The Use of Azelastine Hydrochloride/Fluticasone Propionate in the Management of Allergic Rhinitis in Asia: A Review

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Abstract: The incidence of allergic rhinitis (AR) in Asia and the world is steadily rising. Patients experience incomplete symptom relief despite existing treatment options, which warrants the need for new therapeutic regimes. Azelastine hydrochloride/fluticasone propionate (MP-AzeFlu), a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate has been indicated in the treatment of AR. The current review discusses the effects of MP-AzeFlu versus conventional therapies in achieving superior clinical improvement with a very rapid onset of action (5 minutes). The superiority of MP-AzeFlu in offering complete symptom control with sustained relief in patients with AR compared to the existing therapeutic options is also discussed. MP-AzeFlu has been shown to improve the quality of life for patients with AR, thereby enhancing patient adherence to therapy and establishing its preference for the treatment of AR. Currently, the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines recommend the use of a combination of intranasal corticosteroids and intranasal antihistamines as first-line treatment in patients with persistent AR with visual analog scores ≥5 or when prior treatment with single agents has been ineffective. Widely published data on the efficacy and safety of its prolonged use in adults and children have validated that effective treatment of AR can be achieved with MP-AzeFlu.

Keywords: fixed-dose combination, intranasal, MP-AzeFlu, corticosteroids, antihistamines

Introduction

Allergic rhinitis (AR), a highly prevalent chronic disease of the upper airways, has been found to affect over 600 million people worldwide with an increasing global incidence.[1–3] In the Asia-Pacific (APAC) region alone, the prevalence of AR ranges from 10%–50%.[4] Furthermore, 71% of patients experience persistent AR whereas 29% of patients have intermittent AR.[1] Allergic rhinitis is often associated with comorbidities such as asthma, sinusitis, otitis media, atopic dermatitis, conjunctivitis, and nasal polyposis.[5,6] While most patients with asthma also have rhinitis, asthma is reported in 10%–40% of patients with AR.[7,8] In patients with asthma and co-morbid AR, underdiagnosis or undertreatment of AR could worsen asthma treatment outcomes.[4] The annual medical costs associated with the management and treatment of AR are high. The indirect costs associated with reduced work productivity have been reported to be higher among AR patients compared to those incurred by patients with asthma.[7,9]

MP-AzeFlu, a fixed-dose combination (FDC) of azelastine hydrochloride (AZE) and fluticasone propionate (FP) delivered via one device, is indicated for control of AR-related nasal and ocular symptoms.[10] MP-AzeFlu has an onset of action of 5 minutes, which is comparatively less than those of standard pharmacotherapeutic agents (oral antihistamines [OAH] or intranasal corticosteroids/[INCS]) used as mono- or multiple therapies.[10] Based on the tolerability and effect

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on AR control, the use of this FDC as an advanced alternative in the treatment of AR has been suggested.[11] Studies have also evaluated MP-AzeFlu in terms of total AR-related treatment costs including medical and pharmacy costs when compared to standard therapeutic agents.[11,12]

In this review, we consolidate and assess evidence regarding the clinical efficacy and safety of MP-Aze Flu in resolving AR symptoms and elaborate on its effects on overall symptom relief in patients. Furthermore, we discuss its effect on QoL and patient satisfaction in comparison with standard-of–care medications approved in Asia. The positioning of MP-AzeFlu as a potential candidate for inclusion in the essential drug list is also evaluated.

Prevalence and Burden of Allergic Rhinitis in Asia

Perennial allergies are common in the Asian population and patients experience symptoms of AR lasting up to 298 days in a year.[13] Compounding the substantially high annual medical expenses involved in the treatment and management of AR, the costs associated with low work productivity and absenteeism/presenteeism together pose a major socio-economic burden.[8,14]

According to the Asia-Pacific Burden of Respiratory Diseases (APBORD) observational study, which evaluated 1000 patients across 4 hospitals in Thailand with respiratory diseases such as asthma, AR, chronic obstructive pulmonary disease (COPD), and rhinosinusitis, work productivity loss was reported to be higher in AR (32%) and rhinosinusitis (43.5%), with presenteeism (loss of productivity when working with ill health) being a major contributor to productivity loss. Work productivity loss and medication costs contributed to a mean annual cost of USD 1495 per patient in the overall group. The major cost burden for patients primarily diagnosed with AR was associated with work productivity loss at 82.8% of the overall costs (USD 1378). Furthermore, the study reported higher healthcare resource utilization in AR patients (n=438). During the 4 weeks before the medical visit, 17.8% of patients visited their general practitioner (GP) and 29.1% of patients visited a specialist.[9] The financial burden associated with decreased work productivity in the working group suffering from AR and urticaria was high to the tune of USD 30.7 to USD 105.4 billion.[13]

Current Treatment Landscape in Allergic Rhinitis

Management of AR in adults involves standard practices; however, specific care and considerations are essential for specific groups such as pediatric, geriatric cases and pregnant woman.[5] The currently available treatment options for AR include nasal saline irrigations, oral and intranasal antihistamines, decongestants, anticholinergics, intranasal corticosteroids (INCS), and allergen immunotherapy.[15] Most of these treatment methods bring about symptomatic relief. Of the several symptoms in AR, nasal congestion and itchy nose were found to be refractive to treatment.[2] The prescribing pattern based on the presence of symptoms, such as sneezing, itching, and rhinorrhea, deliberates the use of intranasal or second-generation oral antihistamines, whereas congestion is mitigated by the anti-inflammatory effects of INCS.[9] However, in cases involving overlapping symptoms with varied presentation over time, incomplete treatment outcomes are often encountered.[5,16] Considering the effectiveness of INCS, several guidelines indicate INCS as the first-line treatment in moderate-to–severe "seasonal" AR (SAR)/intermittent AR.[17,18] However, studies have reported that INCS may not necessarily continue to be considered the only effective treatment regimen in moderate-to–severe SAR.[19]

Unmet Needs in the Management of AR in Asia

The treatment of AR has remained a challenge as many patients do not obtain the desired response to treatment.[1] To achieve symptomatic relief for AR, as many as 28 prescription medications and more than 35 over-the–counter drugs, spanning several classes of pharmacotherapies, such as antihistamines, corticosteroids, leukotriene receptor antagonist (LTRA), and mast-cell stabilizers, are currently available. However, dissatisfaction with treatment outcomes has been reported very often by patients.[16]

Based on the reports of a consensus group from the APAC region (Hong Kong, Malaysia, Philippines, Singapore, Thailand, and Vietnam), underdiagnosis, undertreatment, differences in treatment practices, patient perceptions of available treatment options, and the treating physician's approach to adherence to international guidelines and recommendations are some of the key barriers impeding the appropriate management of AR in this region.[3] A study conducted to capture the consensus of experts from countries in the APAC region documented very low compliance with international guidelines among GPs, who most often treat patients with allergies in the primary setup. Owing to the undesirable central nervous system (CNS) and anticholinergic effects of first-generation antihistamines,[3] second-generation antihistamines are preferred as the

first-line treatment of mild intermittent AR, according to the ARIA and European Academy of Allergology and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum and the World Allergy Organization (EAACI/GA(2)LEN/EDF/WAO) recommendations. However, drug interactions among patients taking concomitant medications for renal or hepatic presentations warrant a flexible dosing regimen with these antihistamines.

Data from the APAC survey have captured inadequate efficacy and undesirable side effects as the key reasons for patient dissatisfaction with AR therapies. Only 42% of patients with AR reported well-controlled symptoms. In addition, the lack of sustained effects and poor tolerability have been related to nonadherence in patients.[3]

MP-AzeFlu for the Management of AR

MP-AzeFlu, an FDC of intranasal H1 antihistamine (INAH) Azelastine hydrochloride (AZE) and INCS fluticasone propionate (FP) is indicated in moderate-to–severe SAR and perennial AR (PAR). The advanced formulation of the nasal spray circumvents the need for individual administration of multiple drugs.

Outcomes of Developmental Studies

Several studies have been conducted to determine the pharmacokinetics (PK), efficacy, and safety of MP-AzeFlu (Table 1).[20–40]

Table 1 Overview of Developmental Studies Involving MP-AzeFlu

Type of Study	No. of Studies	N (Overall)	Age group and AR Phenotype	Duration	Comparators	Key Findings
Pharmacokinetics[20]	2	Study 1:19	Healthy volunteers	NA	i. MP-AzeFlu ii. MP-AzeFlu without AZE iii. Marketed FP nasal spray, BI/Roxane Laboratories	• No drug interactions between AZE and FP • Bioavailability of AZE is similar when administered as monotherapy or in FDC • Increased bioavailability of FP with FDC than generic monotherapy
		Study 2:26	Healthy volunteers	NA	i. MP-AzeFlu ii. MP-AzeFlu without FP iii. Marketed AZE nasal spray, Astelin®/Meda Pharmaceuticals	
RCT-Efficacy[12,21–23]	4	4005	≥12 years/SAR	14 days	In 3 of the 4 studies: i. MP-AzeFlu ii. AZE iii. FP In 1 of the 4 studies: i. MP-AzeFlu ii. Astelin®/Meda Pharmaceuticals iii. Flonase/ GlaxoSmithKline	• MP-AzeFlu offered significant benefits in reducing nasal and ocular symptoms compared with AZE/FP monotherapy
RCT-Safety[24]	1	611	≥12 years /PAR; NAR	52 weeks	i. MP-AzeFlu ii. FP	• MP-AzeFlu was well-tolerated even on long-term use
RCT-Pediatric[25–27]	2	753	Children (4–11 years) /SAR	14 days; 12 weeks	i. MP-AzeFlu i. MP-AzeFlu ii. FP	• MP-AzeFlu was effective in improving individual nasal and ocular symptoms in children • MP-AzeFlu was safe and well-tolerated even on prolonged use
RCT-ITT[28]	1	612	≥12 years Chronic rhinitis (PAR/NAR)	52 weeks	i. MP-AzeFlu ii. FP	With MP-AzeFlu, patients experienced 173 symptom-free days (26 days more than those who received FP)
RWE-NIS[29–35]	5	2988	≥12 years/ Moderate-to–severe AR (SAR/PAR)	14 days	MP-AzeFlu	MP-AzeFlu offered rapid, effective, and sustained symptom relief irrespective of AR phenotype or disease severity

(*Continued*)

Table 1 (Continued).

Type of Study	No. of Studies	N (Overall)	Age group and AR Phenotype	Duration	Comparators	Key Findings
Additional studies						
Mechanism of action[36]	–	–	In vitro model–murine airways	–	i. MP-AzeFlu ii. AZE iii. FP	MP-AzeFlu is effective in dilation of pre-contracted airways, similar in action like the bitter antihistamines
Eosinophil survival[37]	–	–	In vitro nasal mucosal cells from human volunteers	–	i. MP-AzeFlu ii. AZE iii. FP	MP-AzeFlu lowered cytokine secretion and eosinophil survival. The effects were more potent than AZE or FP monotherapy.
Permeability[38]	–	–	In vitro 3D model of airway tissue	–	i. MP-AzeFlu ii. FP	Penetration of FP is better in MP-AzeFlu than in monotherapy
Deposition characteristics[39]	–	–	In vitro model of the human nasal cavity	–	i. MP-AzeFlu ii. AZE iii. FP	With MP-AzeFlu, there was no run-off (front or backflow) from the nasal cavity
Onset of action-EEC[40]		82	18–55 years/SAR	–	i. MP-AzeFlu ii. LORA/INFP	The onset of action of MP-AzeFlu is 5 minutes

Abbreviations: AR, Allergic rhinitis; AZE, Azelastine hydrochloride; EEC, Environmental exposure chamber; FDC, Fixed-dose combination; FP, Fluticasone propionate; ITT, Intent to treat; INFP, Intranasal fluticasone propionate; LORA, Loratadine hydrochloride; N, population; NA, Not applicable; NAR, Non-allergic rhinitis; NIS, Non-interventional studies; PAR, Perennial allergic rhinitis; RCT, Randomized controlled trial; RWE, Real-world evidence; SAR, Seasonal allergic rhinitis.

Preclinical Evidence

As a part of the clinical development of the combination medication of intranasal AZE and FP (MP-AzeFlu), two PK studies were carried out to evaluate the possible drug interactions between AZE and FP in the context of altering their individual bioavailability when combined in a single formulation. Both these single-centric studies enrolled 30 healthy subjects, with a three-period, six-sequence, three-treatment crossover design. In the respective studies, patients received either MP-AzeFlu or MP-AzeFlu devoid of FP/AZE (manufactured for this study) or commercially available FP(FP-Boehringer-Ingelheim)/AZE (Astelin®) monotherapy. Apart from PK, the safety and tolerability of all the study medications were also documented. These studies reported good tolerability with all the study medications tested and demonstrated no likely drug–drug interactions between the two active components, AZE and FP. Additionally, a higher peak and total exposure of FP was documented in the MP-AzeFlu formulation in comparison with the commercial FP-BI. Improvement in spray volume and droplet size distribution and lower viscosity of MP-AzeFlu have been indicated as possible factors for the enhanced bioavailability of FP in MP-AzeFlu formulation compared with the FP-mono and FP-BI tested in this study.[20] In vitro studies conducted to further investigate the PK findings have also shown that FP penetration was significantly higher ($p<0.05$) with the MP-AzeFlu formulation than with the FP formulation, ranging between 0 and 6 hours. This study noted a quicker FP permeation with MP-AzeFlu than with FP alone, indicating that MP-AzeFlu rather than FP alone can facilitate faster local effects in the nasal cavity. There were no observable indications of the compromise of tissue integrity in any of the cells tested.[38]

MP-AzeFlu has been reported to function as a potent dilator of pre-contracted airways, mediated by the AZE component, via activation of bitter-taste receptors.[36] Studies have reported the involvement of small or large airway constriction in patients with AR.[41] Therefore, a dilatory effect on pre-constricted airways is likely to bring about an improvement in patient symptomatology in AR. The effects of MP-AzeFlu on inflammatory markers such as cytokines and eosinophil survival have been studied through an in vitro model. MP-AzeFlu brought about a significantly greater inhibition of IL-6 secretion as compared to either FP or AZE at the same drug dilution.[37] MP-AzeFlu also exhibited a significantly superior time-dependent inhibition of eosinophil survival, compared to FP or AZE, at days 3 and 4 at the same drug dilution.[37] These reports are suggestive of a possible synergistic effect of the combination.

Clinical Evidence

Patients treated with MP-AzeFlu reported a two-fold better nasal and ocular (rT7SS) symptom relief compared to monotherapy with FP/AZE as well as three and five times better improvement in nasal congestion than those receiving monotherapy with FP ($p<0.0018$) and AZE ($p<0.0001$), respectively. While clinical studies have confirmed the superiority of MP-AzeFlu vs monotherapy with AZE/FP in bringing about quicker relief in patients with AR,[42] real-world evidence has clearly documented the effectiveness and rapid symptom reduction of MP-AzeFlu in patients with SAR and PAR.[29–35] Results of several randomized studies have documented a superior efficacy of MP-AzeFlu compared to AZE or FP alone. Moreover, MP-AzeFlu has been reported to be well-tolerated by patients in both RCTs as well as real-world evidences (RWEs) (Table 1).

Randomized Controlled Trials

Tables 2 and 3 summarize the four major clinical studies that were performed to evaluate the efficacy of the combination of intranasal AZE and FP during the development phase. While MP4001 studied the safety and effectiveness of the formulation vs commercially available intranasal active comparators Astelin® (Meda Pharmaceuticals Inc,) and Flonase

Table 2 Effects of Combination Therapy Vs Commercially Available Single Agents

Study ID	Study Population	Treatment Arms				
MP4001[21,22]	(N=607) ≥12 years	Arms	MP-AzeFlu (N=153)	AZE (N=152)	FP (N=151)	Placebo (N=151)
		TNSS Mean CFB (SD)	−5.31 (5.08)	−3.25 (4.16)	−3.84 (4.76)	−2.2
	Overall finding	Significantly greater improvement in TNSS with MP-AzeFlu vs placebo and mono components FP and AZE				

Notes: TNSS improvement (percentage) from baseline. MP-AzeFlu>placebo ($p<0.01$); Mp-AzeFlu (28.4%)>AZE (16.4%) ($p<0.01$); MP-AzeFlu (28.4%)>FP (20.4%) ($p<0.01$); RQLQ score: MP-AzeFlu>placebo ($p<0.001$); MP-AzeFlu>AZE ($p<0.005$); MP-AzeFlu>FP ($p<0.29$).
Abbreviations: CFB, Change from baseline; RQLQ, Rhinoconjunctivitis quality of life questionnaire; SD, Standard deviation; TNSS, Total nasal symptom score.

Table 3 Effects of Combination Therapy Vs Single-Agent Comparators Delivered Through the Same Device

Study ID	Study Population*	Treatment Arms				
MP4002[23]	(N=832) ≥18 years	Arms	MP-AzeFlu (N=207)	AZE (N=208)	FP (N=207)	Placebo (N=209)
		rTNSS Mean CFB (SD)	−5.5 (5.2)	−4.1 (4.6)	−5.0 (4.7)	−2.6 (3.9)
MP4004 (Meltzer et al, 2012, Carr et al, 2012)[12,23]	(N=779) ≥12 years	Arms	MP-AzeFlu (N=193)	AZE (N=194)	FP (N=189)	Placebo (N=200)
		rTNSS Mean CFB (SD)	−5.6 (5.2)	−4.4 (4.6)	−5.0 (5.2)	−2.8 (3.9)
MP4006 (Carr et al, 2012)[23]	(N=1791) ≥12 years	Arms	MP-AzeFlu (N=448)	AZE (N=445)	FP (N=450)	Placebo (N=448)
		rTNSS Mean CFB (SD)	−5.6 (5.2)	−4.5 (4.8)	−5.1 (4.7)	−3.2 (4.3)
Meta-analysis (MP4002, MP4004, and MP4006)[23]	(N=3398)	Arms	MP-AzeFlu (N=848)	AZE (N=847)	FP (N=846)	Placebo (N=857)
		rTNSS Mean CFB (SD)	−5.7 (5.3)	−4.4 (4.8)	−5.1 (4.9)	−3.0 (4.2)

Notes: Improvement in TNSS with MP-AzeFlu: Study MP4002: MP-AzeFlu > Placebo ($p<0.001$); MP-AzeFlu > FP ($p<0.034$); MP-AzeFlu > AZE ($p<0.002$). Study MP4004: MP-AzeFlu > Placebo ($p<0.001$); MP-AzeFlu > AZE ($p<0.032$); MP-AzeFlu > FP ($p<0.038$). Study MP4006: MP-AzeFlu > Placebo ($p<0.001$); MP-AzeFlu > AZE ($p<0.016$); MP-AzeFlu > FP ($p<0.029$). Meta-analysis of the 3 studies: MP-AzeFlu > Placebo ($p<0.001$); MP-AzeFlu > AZE ($p<0.001$); MP-AzeFlu > FP ($p<0.001$).
Abbreviations: *ITT, Intent to treat population; CFB, Change from baseline; RQLQ, Rhinoconjunctivitis quality of life questionnaire; SD, Standard deviation; rTNSS, Reflective total nasal symptom score.

(GlaxoSmithKline) in patients allergic to Texas mountain cedar pollen, MP4002, MP4004, and MP4006 studied the effects of the combination vs monotherapy with FP and AZE in the same formulation and rendered through the same device in patients across varied seasons, including spring, fall, and spring to fall, respectively.[5,21–23] The above-mentioned studies reported a significant improvement in TNSS in the combination group vs the placebo, and superior effects compared to monotherapy, thus confirming better therapeutic outcomes with the combination compared to using either agent individually.

According to a meta-analysis of the aforementioned studies (Table 3), the combination therapy brought about a superior reduction in rTNSS and reflective total ocular symptom score (rTOSS) as early as day 1 of assessment, including improvement in each individual nasal symptom score, even in severe cases (MP-AzeFlu vs AZE/FP/placebo). The onset of action with the combination therapy was 30 minutes in a clinical field setting, and the effects persisted over the entire treatment period. The rhinoconjunctivitis quality of life (RQLQ) scores indicated a significant improvement over baseline in all the treatment groups, compared to placebo ($p<0.001$). As 1 in 8 patients with severe AR experienced complete or near-complete resolution of symptoms, an extrapolated view of this effect correlates to the proportion of patients in whom AR would no longer have, or possibly have, minimal functional impairment at school or work.[23]

Real-World Evidence (RWE) With MP-AzeFlu

A pan-European, multinational, multicenter, prospective, non-interventional study involving 2988 patients with moderate-to–severe AR (≥12 years of age) in whom monotherapy with INAH or INCS produced insufficient treatment outcomes assessed the effectiveness of MP-AzeFlu in routine clinical practice. The study included patients from Germany, Sweden, Romania, UK, Denmark, and Norway.[29–35] The pooled data analysis from this study reported a significantly effective control (visual analog scale [VAS] score ≤38 mm) and rapid symptom reduction from baseline (reduction in VAS score; $p<0.001$), even from day 1 of the study. There were sustained effects of MP-AzeFlu till the end of treatment in a real-life setting of patients across Europe. The average reduction in VAS scores at the end of treatment compared to baseline was significant at 50.4±26.1 mm ($p<0.001$). While 26.4% (N=688) of patients achieved clinically relevant symptom reduction (change in VAS scores by ≥23 mm from baseline) by day 1, 58.4% (N=1495) and 79.3% (N=2017) of patients achieved this by day 3 and day 7 of treatment, respectively. However, delayed response (by day 7) was observed in about 20% of patients and the proportion of patients with partly controlled/uncontrolled AR by day 14 was about 24%. Of the overall number of patients enrolled (N=2988), only 11 patients discontinued treatment citing adverse events (AEs), including nausea, nasal discharge, rhinorrhea, sneezing, or altered taste, thereby confirming the good tolerability and acceptance of MP-AzeFlu in the European population. MP-AzeFlu was associated with consistent efficacy, irrespective of age, disease/symptom severity, and varying phenotypes.[29] These individual studies performed in real-world settings confirmed the results previously concluded from RCTs. Interestingly, the responder rates in these studies were higher in comparison to RCTs[31–33] and supportive of its effective use in a heterogenous patient pool (varying AR phenotypes), as against the restricted patient cohorts in RCTs. This supports the use of MP-AzeFlu as the drug of choice in treating patients with moderate-to–severe AR in routine practice.[29]

In addition to the aforementioned studies on the European population, MP-AzeFlu conferred sustained symptomatic relief lasting for 42 days (6 weeks) (assessed by VAS) and was associated with improvement in the mucosal appearance of patients after 28 days (4 weeks) of use (as assessed by endoscopy), according to a study conducted in Ireland. Symptomatic improvement has been reported from day 1 of the application of MP-AzeFlu, thereby confirming its superior efficacy in Irish patients with persistent AR, as assessed by VAS (overall reduction of 45.3 mm from baseline). The efficacy of MP-AzeFlu was found to be consistent irrespective of age (range: 12–65 years), disease severity (baselined VAS score of 50–100 mm), or AR phenotype (only PAR; or SAR and PAR). In addition, patients experienced an improvement in sleep quality assessed over 42 days from baseline. A greater percentage of patients (78.4%) reported very good or good sleep quality on day 28 of the study compared with baseline (25.0%).[43]

Long-term Use of MP-AzeFlu

The safety of MP-AzeFlu has been well established through large clinical studies involving more than 4000 patients and about 3000 patients in a real-world setting. The long-term use of MP-AzeFlu was studied in 612 patients with chronic

rhinitis over a period of 52 weeks. Patients were randomized to receive either the combination of intranasal AZE+FP (MP-AzeFlu) or FP nasal spray for continual use over 52 weeks. A significantly superior reduction in rTNSS from baseline was observed even on day 1 in the combination group as compared to FP monotherapy. The treatment difference between the groups was maintained for the entire 52 weeks of the study, indicating a potential synergistic mechanism of effect in Aze+Flu compared to FP alone. After 30 days of treatment with combination therapy, 71.1% of patients reported 100% reduction in rTNSS, earlier by a median of 9 days ($p<0.0024$) vs a 60.3% reduction in the FP group. This study confirmed the safe use of the combination therapy of intranasal AZE+FP for up to 52 weeks. Headache (4.3%) and dysgeusia (2.5%) were the most common AEs in the FP and MP-AzeFlu groups, respectively. The mean (fasting) serum cortisol levels over 12 months of continuous use of MP-AzeFlu (–0.08 [5.5] mcg/dL) or FP (–1.04 [SD 5.0] mcg/dL) from baseline were not appreciably reduced; moreover, no nasal mucosal ulcerations or perforations were noted over this period. No marked ocular findings, new or clinically significant, potentially classifiable as an AE were observed. All these results are suggestive of the long-term, safe use of MP-AzeFlu.[28]

Efficacy and Safety of MP-AzeFlu in the Pediatric Population

The efficacy of MP-AzeFlu was evaluated in a randomized, double-blind, placebo-controlled study in 348 children, who were between 4 and 11 years of age and had moderate-to–severe SAR. The pediatric rhinitis quality of life questionnaire (PRQLQ) scores, assessed over 14 days, indicated a statistically superior and clinically relevant improvement with MP-AzeFlu when compared with placebo (–0.29, 95% CI –0.55, –0.03; $p<0.027$). In the MP-AzeFlu group, when children self-rated (>90% of the time) their symptoms, a significant improvement in rTNSS ($p<0.002$) and rTOSS ($p<0.009$) was noted as compared with the placebo.[25]

The efficacy and safety of MP-AzeFlu were evaluated when used continuously for 3 months in children between 4 and 11 years of age across 42 investigational sites in USA. The patients were randomly assigned in a 3:1 ratio to MP-AzeFlu (1 spray/nostril bi-daily (bd) or FP (1 spray/nostril bd), respectively. The study recorded a significant reduction ($p<0.0410$) in the total symptom score in the MP-AzeFlu (–0.68 point) vs FP (–0.54 point) group. MP-AzeFlu showed superior effects even on day 1 of assessment, which sustained for up to 90 days. Eight out of 10 children treated with MP-AzeFlu achieved symptom-free AR control in the first month of treatment, and this was faster by up to 16 days compared to the effects observed with FP. During the 3-month study period, 73.5% of the children on MP-AzeFlu experienced none or mild symptoms of AR compared to those on FP (66.0%).[26,27] This study most importantly documented the safety of continued use of MP-AzeFlu over a duration of 3 months in children with AR of age 4 to 11 years. MP-AzeFlu was reported to be well-tolerated in both very young (≥4 to <6 years) and older children. The incidence of treatment-related adverse events (TRAEs) was very low with presentations such as epistaxis, cough, and headache of mild severity, and self-resolving occurrence. The incidence of drowsiness associated with MP-AzeFlu was <1%.[27]

Considering the safety of prolonged use, MP-AzeFlu has been approved by the Food and Drug Administration (FDA) at a dosing of one spray per nostril bi-daily in children aged 6–11 years.[44]

MP-AzeFlu Relieves Asthma Symptoms and Improves QoL in Comorbid AR Patients

A multicenter, non-interventional, real-life, prospective study carried out in 1103 patients with moderate-to–severe AR, including 267 patients presenting with comorbid asthma, evaluated the effects of MP-AzeFlu in relieving symptoms of asthma, in addition to its therapeutic effects on alleviating AR symptoms. There was a considerable reduction in the frequency of use of asthma reliever medication in about 57.6% (N=139) of patients using MP-AzeFlu. A 33.7-mm reduction ($p<0.0001$) in VAS scores was recorded at day 14 from baseline as a measure of reduced troublesomeness with sleep quality. There was a significant reduction in VAS scores of 35.2 mm ($p<0.0001$). Additionally, the troublesomeness in executing daily social and outdoor activities was significantly lower (VAS scores of –33.2 mm: $p<0.0001$; 40.0 mm: $p<0.0001$, respectively) with MP-AzeFlu. These effects on QoL were comparable in patients with and without comorbid asthma. Overall, this study reported improved AR and asthma symptoms with the use of MP-AzeFlu and registered an improved QoL in AR patients with comorbid asthma.[45] MP-AzeFlu usage significantly reduced acute respiratory events

(effect size: 5.8%; p<0.0129) and daily use of reliever medication, with fewer patients requiring >2 puffs/week of short-acting β2-agonists (SABA) (7.7%; p<0.0001). It also reduced the use of inhaled corticosteroids (4.8%; p<0.0078) and asthma was well controlled after 1 year of MP-AzeFlu initiation (4.1%; p<0.0037).[46]

Improvement of Olfaction in AR Patients with MP-AzeFlu

MP-AzeFlu was found to improve olfaction in patients, irrespective of severity level. The improvement was higher in patients with severe PAR. MP-AzeFlu was associated with complete olfactory recovery with an odor threshold, discrimination, and identification (TDI) score >30.5 points after 1 month of treatment with normosmia observed in 100% of the patients (N=47) at the third-month visit.[47]

Effects of MP-AzeFlu on Nasal Hyperreactivity

Nasal hyperreactivity (NHR) involving increased sensitivity to certain non-specific stimuli is prevalent in about two-thirds of patients suffering from AR. It is also present in up to 69% of patients with asthma.[48] Additionally, the risk of exacerbations is higher with increasing outdoor and indoor air pollution in Thailand.[49,50] MP-AzeFlu can be useful in such scenarios as it helps reduce NHR and inflammatory mediators in AR. The reduction in NHR by MP-AzeFlu was significant when compared with the placebo (p<0.0001 vs p<0.21). In addition, MP-AzeFlu brought about a superior reduction, compared with placebo, in the levels of inflammatory mediators such as substance P (p<0.026 vs p<0.941) and β-hexosaminidase (p<0.036 vs p<0.632) as tested in the nasal secretions of these patients. Further, in vivo studies on these anti-inflammatory effects of MP-AzeFlu revealed a possible synergistic effect of AZE and FP in reducing airway inflammation.[51]

Reports from all these RCTs and RWEs conclude that MP-AzeFlu is beneficial in alleviating AR symptoms, in addition to its well-tolerated safety profile, rendering it an appropriate choice of treatment in moderate-to–severe SAR and PAR.

Efficacy, Onset of Action, and Formulation Advantages of MP-AzeFlu for AR

Rapid-acting medications are more desirable to patients with AR, as has been discussed earlier in this review. As RCTs are designed to evaluate efficacy/safety, it is difficult to capture specific features of investigational products, such as the onset of action. Therefore, allergen-exposure chamber (AEC) studies are relied upon to estimate the onset of action of drugs to the exact minute possible.[52] However, several AEC studies have been conducted at single centers following unique protocols, thereby rendering it challenging for comparative evaluations. Alternately, the environmental exposure chamber (EEC) has also been used for this purpose.[40] Table 4 summarizes the onset of action of various AR therapies.

As depicted in Table 4, the onset of action of intranasal AZE+FP is 5 minutes, the most rapid of all therapeutic molecules listed for AR. AZE has been reported to exert perceivable symptomatic relief within 15 minutes of intranasal application and within 3 minutes of topical application to the eyes. The onset of action of INCS is very slow and this is likely to cause barriers to treatment adherence, especially when patients prefer rapid symptomatic relief in AR.

A single-center study following a randomized, double-blind, double-dummy, placebo-controlled cross-over design was conducted by Bousquet et al on 82 patients to study the onset of action of MP-AzeFlu. The effects of single-dose MP-AzeFlu in reducing TNSS were compared with a free combination of loratadine (LORA)-oral and intranasal fluticasone propionate (INFP) and placebo, monitored over a period of 4 hours. With MP-AzeFlu, the TNSS was significantly reduced from 5 minutes of administration, whereas LORA/INFP took 150 minutes to produce an effect. Furthermore, with MP-AzeFlu, a greater extent of reduction in TNSS was observed from 5 to 90 minutes, spanning the overall assessment period (p≤0.005), in comparison to the LORA/INFP and placebo groups. In this study, LORA/INFP did not produce effects superior to the placebo (p<0.182). With MP-AzeFlu, nasal symptoms improved within 5 minutes and ocular symptoms improved within 10 minutes, which are not just statistically significant results but also clinically relevant to patients. Even symptoms that are often refractory to treatment, such as nasal congestion, nasal itch, and itchy eyes, were relieved faster with MP-AzeFlu.[40]

Table 4 Onset of Action and Relative Efficacy of Common AR Therapeutics

Class	Agent	Onset
Combination (INAH+INCS)	**MP-AzeFlu (AZE+FP)**	5 mins[53]
Combination (INCS+OAH)	**FP + LOR**	150 min[53]
INCS	**MF**	150 mins[54]
	BUD	8 h[55]
	CIC	60 min[56]
Combination	**FP + LOR**	150 min[53]
INAH	**AZE**	15 mins[57]
	OLO	30 mins[54]
OAH	**CET**	60 mins[58]
	LevoCET	60 mins[59]
	FEX	45 mins[60]
	DesLOR	180 mins[59]
LTRA	**Montelukast**	120 mins[61]

Abbreviations: AZE, Azelastine; BUD, Budesonide; CET, Cetirizine; CIC, Ciclesonide; DesLOR, Desloratadine; FEX, Fexofenadine; FF, Fluticasone furoate; FP, Fluticasone propionate; INAH, Intranasal antihistamine; INCS, Intranasal corticosteroid; LOR, Loratadine; LTRA, Leukotriene receptor antagonist; LevoCET, Levocetirizine; MF, Mometasone furoate; OAH, Oral anti-histamine; OLO, Olopatadine; SAR, Seasonal allergic rhinitis; VMR, Vasomotor rhinitis.

ARIA 2020 Guideline Recommendations for Managing AR

As per the Allergic Rhinitis and its Impact on Asthma (ARIA) 2020 recommendations, INCS + AZE could be used as first-line treatment in persistent allergic rhinitis (PR) (VAS≥5) when previous treatment with single agents has been ineffective, in previously treated symptomatic patients (VAS <5), in untreated patients having intermediate AR (VAS ≥5), and when congestion is reported. Additionally, in patients with intermittent AR (IAR) and PR with VAS <5, INCS + AZE could be administered at initiation and when moderate to severe nasal congestion is reported. The recommendations were made in consideration of the patient's preference and have been based on evidence from several published studies. The combination of INCS + INAH was found to be more effective than INCS alone; INAH medications, especially those containing AZE, had the fastest onset of action based on the Ontario and Vienna chamber studies.[59]

Unmet Needs in the Management of AR in Asia

The prevalence of allergic diseases in Asian countries is increasing, which is associated with urbanization and rapid economic development in these regions. Alarmingly, the presence of perennial allergens in the APAC region is linked to a longer duration of symptoms, ranging from mild to severe, in patients with AR (34%–41% prevalence of perennial AR) that lasts almost throughout the year. According to a study in APAC (Hong Kong, Malaysia, Philippines, Singapore, Thailand, and Vietnam), patients with AR experienced significant discomfort with nasal allergies associated with nasal obstruction, causing sleep disturbances in 42% of patients and impairment of daily activities in 38% of patients.[62]

Based on the reports of a consensus group from the APAC region, underdiagnosis, undertreatment, differences in treatment practices, patient perceptions of available treatment options, and the treating physician's approach to adherence to international guidelines and recommendations are some of the key barriers impeding the appropriate management of AR in this region.[3] A study conducted to capture the consensus of experts from countries in the APAC region documented very low compliance with international guidelines among GPs, who most often treat patients with allergies in the primary setup. Owing

to the undesirable central nervous system (CNS) and anticholinergic effects of first-generation antihistamines,[3] second-generation antihistamines have been considered for the first-line treatment of AR. In Thailand and the Philippines, low-cost generic antihistamines are widely available and easily accessible; however, there have been reported to have quality concerns.[62] An appropriate choice of treatment considering factors such as efficacy, safety, impact on psycho-motor activities, affordability, and other side effects such as sedation, if any, is warranted.[62]

Data from the APAC survey have captured inadequate efficacy and undesirable side effects as the key reasons for patient dissatisfaction with AR therapies. Only 42% of patients with AR reported well-controlled symptomatology. In addition, the lack of sustained effects and poor tolerability have been related to nonadherence in patients.[3] A survey conducted in the APAC region determined the rapid onset of action (30%), complete symptomatic relief, and sustained effect (25%) as the key attributes that are desirable in allergy medication. Patients reported a preference for nasal sprays (30%) over oral medications (24%) and considered combination therapy better than monotherapy.[63] Moreover, they were willing to spend more for complete symptom relief, rather than attaining mild relief with the current options.[10] All these factors clearly point to an unmet need in the treatment/management of AR, endorsing the necessity for a rapid-acting drug with good efficacy and tolerability, which could help improve the QoL in patients, thereby improving patient experiences/satisfaction in the APAC region.[3]

Drug Listing and Considerations in Asia

A combination of INCS with INAH as discussed in this review has proven to be highly efficacious and safe.

The International Consensus in Allergic Rhinitis (ICAR) documents the rapid onset of action and greater effectiveness of INCS + INAH in the relief of multiple symptoms in AR, in comparison with monotherapy, and its consistently superior efficacy versus placebo. Despite acknowledging the level 1 evidence of the effects of this combination, ICAR has held affordability (higher cost) and access (needing a prescription) as factors limiting the value of this combination as routine first-line therapy in AR.[64] Compared to conventional therapeutic drugs, MP-AzeFlu has significantly reduced total AR-related treatment expenses, including medical and pharmaceutical costs.[11] Therefore, the cost-effectiveness of MP-Azeflu may need to be considered when choosing first-line therapy for AR.

Conclusion

MP-AzeFlu, a novel, intranasal FDC of AZE and FP delivered as a single spray from a single device, has emerged as a promising advancement in the treatment of AR. As it can bring about symptom relief within 5 minutes of application, MP-AzeFlu has been extensively studied for its effectiveness in offering considerable symptom relief coupled with a good safety profile even on prolonged use. Studies performed in real-world settings confirmed higher responder rates and support its effective use in a heterogenous patient pool (varying AR phenotypes). MP-AzeFlu has been widely recommended by several governing bodies in treating AR, especially moderate-to–severe forms of SAR. In Asia, the prevalence of AR has been rising with a greater number of studies documenting the upward trend. Considering the burden of cost, social impact, work productivity, and associated comorbidities such as asthma, an effective treatment of AR is the need of the hour, and it can be achieved with the use of MP-AzeFlu as a first-line treatment in managing moderate-to–severe seasonal and persistent AR.

Clinical Pearls

MP-AzeFlu has been shown to be effective with no serious adverse events through several studies. MP-AzeFlu can be considered a first-line drug in patients with moderate-to–severe AR. Additionally, it could be indicated for patients with uncontrolled symptoms despite treatment with INCS in Asia.

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Author Contributions

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