MP-AzeFlu in Moderate-to-Severe Allergic Rhinitis: A Literature Review

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Keywords

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Abstract

Allergic rhinitis (AR) is prevalent, and many patients present with moderate-to-severe symptomatic disease. The majority of patients are not satisfied with their AR treatment, despite the use of concurrent medications. These gaps underscore the need for treatment with more effective options for moderate-to-severe AR. The authors' objective was to review systematically the efficacy and safety of MP-AzeFlu for the treatment of AR. The primary outcomes studied were nasal, ocular, and total symptoms. Other outcomes included time to onset and of AR control, quality of life, and safety. Searches of PubMed and Cochrane databases were conducted on May 14, 2020, with no date restrictions, to identify publications reporting data

on MP-AzeFlu. Clinical studies of any phase were included. Studies were excluded if they were not in English, were review articles, did not discuss the safety and efficacy of MP-AzeFlu for AR symptoms. Treatment of AR with MP-AzeFlu results in effective, sustained relief of nasal and ocular symptoms, and faster onset and time to control compared with intranasal azelastine or fluticasone propionate. Long-term use of MP-AzeFlu was safe, with benefits in children, adults, and adults aged ≥ 65 years. Other treatment options, including fluticasone propionate and azelastine alone or the combination of intranasal corticosteroids and oral antihistamine, do not provide the same level of efficacy as MP-AzeFlu in terms of rapid and sustained relief of the entire AR symptom complex. Furthermore, MP-AzeFlu significantly improves patient quality of life. MP-AzeFlu is a currently available combination that may satisfy all these patient needs and expectations.

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Introduction

Allergic Rhinitis

Allergic rhinitis (AR) is prevalent, and many patients present with moderate-to-severe symptomatic disease [1]. Moderate-to-severe AR can be classified based on the presence of at least one of the following symptoms: sleep disturbance; impairment of daily activities, leisure, and/or sport; impairment of school or work; and troublesome symptoms [1]. Patients with AR often have comorbidities such as rhinosinusitis, sleep disturbance, otitis media, and asthma [1–3]. The symptom complex of AR, which includes nasal and ocular symptoms, can have a profound impact on quality of life, work productivity, and school performance [1, 4].

Therapy options for AR depend on many factors, including symptom severity and control. Pharmacologic approaches should strive for immediate and sustained symptom relief. Among patients receiving treatment, 43% expect allergy symptom suppression, 12% expect to be cured, and 20% expect both symptom suppression and allergy cure [5]. Patients are willing to pay more to achieve more complete and faster AR symptom relief [6].

Most patients with moderate-to-severe AR are not satisfied with their current treatment, despite the use of concurrent medications [7]. Many patients use on-demand treatment when symptoms are suboptimally controlled, which may lead to daily medication changes [8]. Oral antihistamines are most often used, although they are not the most effective treatment [9]. Poor medication choices lead to undermanaged disease and may contribute to morbidity [10].

AR affects up to 40% of children, whose parents may be unaware of symptom presence or severity (“nasal neglect”) [1]. These issues are compounded by adverse effects of medications used, including sedating antihistamines or medications, which are only licensed for adults [11]. Effective treatments are needed for patients of all ages with AR.

MP-AzeFlu

MP-AzeFlu is a fixed-dose combination product containing an H₁-receptor antagonist (azelastine hydrochloride; AZE) and a corticosteroid (fluticasone propionate; FP) that is administered intranasally [12]. AZE and FP have demonstrated synergistic effects regarding improvement of AR symptoms, with inhibition of the synthesis or release of chemical mediators involved in early- and late-stage allergic reactions (AZE) as well as potent anti-inflammatory activities (FP). The nasal spray delivers 137

mcg of AZE and 50 mcg of FP (137/50 mcg) in each 0.137 mL spray. The recommended MP-AzeFlu dosage is 1 spray/nostril twice daily. The indicated age for MP-AzeFlu varies by country. MP-AzeFlu is recommended by the US Joint Task Force on Practice Parameters as a first-line option for patients with moderate-to-severe AR, and the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines recommend MP-AzeFlu for all patients with AR, independent of disease type or severity [8, 13, 14].

MP-AzeFlu allows for better deposition compared with sequential administration of its components and improved absorption of FP versus the generic formulation, likely because of the decreased volume required for MP-AzeFlu dosing [15]. MP-AzeFlu also has a larger spray volume, lower viscosity, and a finer droplet size distribution profile, resulting in a larger spray pattern diameter, superior dispersion, and larger total area versus FP-Boehringer-Ingelheim [16]. Finally, the pH of MP-AzeFlu is 6.0, which is more neutral than other formulations [11]. These biopharmaceutical characteristics may contribute to improved clinical efficacy of MP-AzeFlu via more active ingredients remaining at the targeted tissue, which leads to enhanced symptom reduction. This review was designed to systematically evaluate the current literature to determine the safety and efficacy of MP-AzeFlu for the treatment of AR.

Materials and Methods

Searches of the PubMed and Cochrane databases were conducted on May 14, 2020, with no date restrictions, to identify publications reporting data on MP-AzeFlu. The primary outcomes studied were nasal symptoms, ocular symptoms, and total symptoms. Other outcomes studied included time to onset of effect, time to AR control, effects on disease-specific quality of life, and safety. In brief, the search strategy included the terms “MP-AzeFlu,” “MP 29-02,” “Dymista,” “formulation of azelastine hydrochloride and fluticasone propionate,” and “azelastine and fluticasone in a single spray.” Research studies of any phase were included; in vitro studies were excluded. Studies were excluded if they were not published in English; if they were review articles or conference abstracts; or if they did not discuss data related to the safety and efficacy of MP-AzeFlu treatment for AR symptoms. Country-specific data from multicenter studies were excluded, except Kaulsay and colleagues [17], because additional endpoints related to nasal mucosal examination were assessed. Because a combination of clinical trials and real-world studies with various primary endpoints were included, a meta-analysis was not suitable.

A single reviewer conducted preliminary screening of all publications identified to assess titles and abstracts according to the eligibility criteria. Consensus to include screened studies was reached with a second reviewer. Any discrepancies were resolved by a third reviewer. After inclusion confirmation, a reviewer extracted relevant data and a second reviewer provided validation of the findings.

Table 1. MP-AzeFlu studies [17–31]

Publication	N	Patient age, years	Study type	Study duration	Primary endpoint
Hampel et al. [18]	610	12+	Randomized, placebo-controlled	14 days	rTNSS
Meltzer et al. [19]			Post-hoc analysis		
Carr et al. [20]	3,398	12+	Randomized, placebo-controlled	14 days	rTNSS
Price et al. [21]	612	12+	Open-label	1 year	rTNSS
Berger et al. [22]	612	12–80	Open-label	1 year	Safety
Klimek et al. [23]	1,781	12+	Real-world	14 days	VAS
Berger et al. [24]	353	6 to <12	Open-label	3 months	TSS
Berger et al. [25]	304	6–11	Randomized, placebo-controlled	14 days	rTNSS
Klimek et al. [26]	2,988	12+	Real-world study	14 days	VAS
Klimek et al. [27]	47	18–67	Observational	3 months	Olfactory function; VAS
Berger et al. [28]	405	4–11	Open-label	3 months	Safety
Bousquet et al. [29]	82	20–55	Environmental chamber	4 h	TNSS
Kaulsay et al. [17]	53	12+	Real-world	42 days	VAS
Kortekaas Krohn et al. [30]	28	18–60	Randomized, placebo-controlled	4 weeks	NHR
Patel et al. [31]	180	18–65	Environmental chamber	14 days	iTNSS

iTNSS, instantaneous total nasal symptom score; NHR, nasal hyperreactivity; TNSS, total nasal symptom score; rTNSS, reflective total nasal symptom score; TSS, total symptom score; VAS, visual analog scale.

Results

Of 103 publications screened (see online suppl. Table 1 at www.karger.com/doi/10.1159/000516417), 16 met the inclusion criteria and were evaluated. Excluded were 52 duplicate publications, 29 unrelated or review articles, and 6 articles publishing data from individual countries when a pooled analysis was available. Among these, studies described effects on nasal symptoms, ocular symptoms, time to AR control, quality of life, safety, and in special populations, as well as time to onset of effect, as described in the remainder of this review (Table 1).

Nasal Symptoms: Efficacy and Time to Control

The presence of nasal symptoms is associated with poor AR control and decreased health-related quality of life and can occur among patients using intranasal corticosteroids and/or oral or intranasal antihistamines [32]. Therefore, disease severity may be underestimated and inadequately treated, with many patients experiencing severe symptoms despite monotherapy use [8]. Real-world evidence supports the recommendation to use a more effective combination of intranasal H₁-antihistamines with intranasal corticosteroids versus intranasal corticosteroids alone among patients with AR [8, 32].

MP-AzeFlu achieved a 44–64% greater nasal symptom improvement versus its component comparators (FP and

AZE) in key pivotal trials [20]. In a pooled analysis of 3,398 patients aged ≥12 years with moderate-to-severe seasonal AR (SAR) enrolled in 3 multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group trials, Carr and colleagues [20] investigated the efficacy of MP-AzeFlu (MP29-02) versus AZE, FP, and placebo; all treatments were administered in the same device with the same vehicle formulation. Over the 14-days treatment period, MP-AzeFlu led to a significantly greater reduction of mean reflective total nasal symptom score versus FP, AZE, or placebo (–5.7 vs. –5.1, –4.4, or –3.0, respectively; all $p < 0.001$). The superiority of MP-AzeFlu to FP and AZE was seen for all individual nasal symptoms. Among patients who experienced a clinically meaningful reduction in nasal symptoms (≥50% reduction in reflective total nasal symptom score, as defined in this study), those treated with MP-AzeFlu reached this threshold up to 3 days earlier versus FP and up to 5 days earlier versus AZE. Complete or near-complete elimination of symptoms (i.e., reduction in all nasal symptom scores to ≤1) was observed in patients treated with MP-AzeFlu up to 5 days faster than in those treated with FP ($p = 0.033$) and up to 7 days faster than in those treated with AZE ($p < 0.001$).

Hampel and colleagues [18] investigated the effects of 14 days of treatment with MP-AzeFlu, AZE, or FP for relieving AR symptoms in a randomized, double-blind study of 610 patients aged ≥12 years with a minimum 2-year history of confirmed allergy to Texas mountain

cedar pollen. Compared with placebo, all treatments led to significantly improved reflective total nasal symptom score ($p < 0.001$), with MP-AzeFlu being significantly superior to either agent alone ($p < 0.01$). Individual nasal symptoms of nasal congestion, itchy nose, and sneezing were also significantly improved with MP-AzeFlu ($p \leq 0.02$) [18].

In a post hoc analysis of the study by Hampel and colleagues [18], Meltzer and colleagues [19] assessed the efficacy of MP-AzeFlu versus AZE and FP for controlling nasal and ocular symptoms, irrespective of baseline severity, to understand the clinical relevance. Only MP-AzeFlu was consistently statistically superior to placebo in reducing reflective total nasal symptom score for all patient types, independent of the most severe symptom. More patients treated with MP-AzeFlu achieved a ≥ 30 , ≥ 50 , ≥ 60 , ≥ 75 , and $\geq 90\%$ reflective total nasal symptom score reduction, which occurred days faster than with either active comparator. Approximately 71% of patients treated with MP-AzeFlu achieved a $\geq 30\%$ reduction in total nasal symptom score, and half achieved a $\geq 50\%$ reduction; 1 in 6 achieved complete/near-complete response. MP-AzeFlu significantly decreased nasal congestion, the most bothersome symptom, versus FP and AZE [19]. When comparing this analysis with results from the 3 parallel-group trials using non-commercially available active comparators, the treatment differences were more pronounced, suggesting a formulation effect [18, 19].

In a randomized, open-label, active-controlled, parallel-group study, Price and colleagues [21] compared the efficacy of MP-AzeFlu with intranasal FP in 464 patients with persistent rhinitis (chronic allergic or nonallergic rhinitis) over 52 weeks. The study included a 7-days screening period and a 52-weeks treatment period. After 1 month, 73.4% of patients treated with MP-AzeFlu achieved a 100% reduction in reflective total nasal symptom score from baseline, a median 8 days faster than the FP group. MP-AzeFlu was more effective than FP, with superior efficacy lasting the whole year, resulting in nearly 30 more symptom-free days (172.8 symptom-free days with MP-AzeFlu vs. 146.9 symptom-free days with FP). Overall, MP-AzeFlu led to a 75% reduction in symptom score compared with FP [21].

In a pan-European, multicenter, observational study, Klimek and colleagues [26] assessed the effectiveness of MP-AzeFlu in 2,988 patients with AR in routine clinical practice, using a visual analog scale. MP-AzeFlu was associated with an effective and rapid symptom reduction from baseline to 23.4 ± 20.3 mm by treatment end, a reduction of 50.4 ± 26.1 mm, which was significant ($p <$

0.001) from day one and sustained until the last day [26]. Notably, previous studies have defined a ≥ 23 mm reduction in visual analog scale score as a clinically meaningful difference [33]. Patients treated with MP-AzeFlu rapidly achieved a clinically meaningful response in this study; 26.4% achieved this reduction at day one, 58.4% at day 3, and 79.3% following 1 week of treatment [26]. Overall, $>93\%$ of patients treated with MP-AzeFlu reported well or partially controlled symptoms by day 3. In comparison, the clinically meaningful response in phase 3 clinical studies, defined as a $\geq 30\%$ reduction in reflective total nasal symptom score [34], was achieved by 71.2% of patients treated with MP-AzeFlu at day 14 [19].

Kaulsay and colleagues [17] assessed the effectiveness of 6 weeks of MP-AzeFlu treatment for relieving AR symptom severity in 53 Irish patients with persistent AR, demonstrating a rapid visual analog scale score reduction from 73.4 mm at baseline to 31.5 mm at day 28 ($p < 0.0001$) and to 28.1 mm at day 42 ($p < 0.0001$), which corresponds to a 57 and 62% change from baseline, respectively. More than half of patients exhibited a clinically significant improvement (~ 23 mm) on day 3 and approximately 75% on the last day of treatment [17]. Using the ARIA-defined cutoff of 50 mm for controlled symptoms, patients achieved this reduction prior to day 7, on average. Endoscopy was used to assess edema, discharge, and redness of the nasal mucosa. After treatment with MP-AzeFlu, the total endoscopy score significantly decreased, from 7.5 at baseline to 3.5 at day 28 ($p < 0.0001$). Reductions were observed in the proportion of patients with severe edema (53.1 vs. 3.8%), thick mucus discharge (28.3 vs. 4.8%), and severe redness (34.9 vs. 0%). These results can be compared with findings from a long-term, randomized controlled trial that demonstrated increases in the proportion of patients with no edema (20.0 vs. 84.1%), no nasal discharge (12.1 vs. 82.6%), and no mucosal redness (42.3 vs. 79.3%) after 1 year of MP-AzeFlu treatment [22].

Gathering data from both randomized controlled trials and real-world studies is needed to produce a complete evidence base for pharmacologic interventions. This is supported by the inclusion of evidence from randomized controlled trials and real-world data in the development of the recent ARIA guidelines [8]. Because real-world studies have a broad, heterogeneous patient population, the results can be generalized to the entire population of patients with AR, which is not possible with randomized controlled trials [26]. In addition, real-world studies provide results that are more reflective of the level of clinical care delivered in everyday practice. However,

because the real-world data presented have no active comparator, the effect size is difficult to interpret against natural improvement of seasonal disease.

In summary, data from randomized controlled trials described above showed that treatment with MP-AzeFlu led to a 44–64% greater nasal symptom improvement versus comparators (FP and AZE) [20], and a 75% reduction in symptom score compared with FP in randomized controlled trials [21]. Data from clinical trials further indicate that 71.2% of patients treated with MP-AzeFlu achieve a clinically meaningful response at day 14 [19], while real-world studies show that 79.3% of patients achieve a clinically meaningful response following 1 week of treatment [26]. These results support the clinical effects of MP-AzeFlu in the real world.

Olfactory Function and Nasal Hyperreactivity

Patients with AR experience olfactory dysfunction, which appears to be more frequent with increasing AR severity and duration [35], and a positive correlation exists between quality of life and olfaction [36]. Nasal hyperreactivity has been reported by two-thirds of patients with AR, and is defined as increased nasal mucosa sensitivity to nonspecific environmental stimuli, leading to nasal symptoms [37]. Antihistamines and topical steroids exert beneficial effects on olfaction; therefore, studies investigating MP-AzeFlu also assessed the impact of treatment.

MP-AzeFlu treatment was associated with significantly improved olfactory threshold, discrimination, and identification scores and symptoms in a multicenter, observational study of 47 patients with persistent AR over time [27]. In addition, a significant interaction among AR severity and olfactory function and visual analog scale was observed. With increasing AR severity, olfactory function decreased; however, greater olfactory improvement was observed in patients diagnosed with more severe AR [27].

In a 4-week, double-blind study of 28 patients with house dust mite AR, MP-AzeFlu significantly reduced nasal hyperreactivity, assessed using a cold dry air provocation protocol, and inflammatory mediators versus placebo [30].

These experimental endpoints for assessing olfactory function and nasal hyperreactivity have been used in previous studies, supporting their use for assessing the effects of treatment. In a prospective clinical trial comparing mometasone furoate and fluticasone furoate, olfactory function was assessed in 24 patients with persistent AR and hyposmia using the extended test battery “Sniffin”

Sticks,” and a visual analog scale was used to assess hyposmia and nasal discharge [38]. Similar effects were reported on hyposmia and nasal symptoms between the 2 treatments and the final nasal symptoms score correlated with visual analog scale improvements. The cold dry air provocation protocol was previously validated in a study of 12 patients with AR, 12 patients with idiopathic rhinitis, and 12 healthy patients [39]. This study demonstrated that cold dry air exposure induced nasal obstruction and led to significantly decreased peak nasal inspiratory flow rates, with a high specificity and sensitivity for diagnosis of nasal hyperreactivity of 100 and 66.7%, respectively, highlighting that this method is reliable for the diagnosis of hyperreactivity in patients with rhinitis [39].

Ocular Symptoms

Ocular symptoms occur in up to 95% of patients with AR when blinking, squinting, frontal headache, and eyelid dermatitis are considered in combination with itch, redness, watering, and swelling, which make up the total ocular symptom score [40, 41]. These can substantially impair daily functioning and quality of life [3]. Among patients with ocular symptoms, 53% recognized they had allergic conjunctivitis, whereas the remaining 40% exhibited ocular neglect [41]. Intranasal corticosteroids reduce ocular symptoms because of a class effect, whereby intranasal corticosteroids bind to the glucocorticoid receptor leading to increased expression of anti-inflammatory molecules and β -adrenergic receptors and decreased expression of pro-inflammatory cells and molecules, with further benefits from the addition of an antihistamine [42]. Therefore, the inclusion of an intranasal corticosteroid and an antihistamine in MP-AzeFlu could contribute to decreased ocular symptoms and the use of fewer medications.

In the meta-analysis by Carr and colleagues [20] described previously, MP-AzeFlu led to a significantly reduced average reflective total ocular symptom score from baseline versus FP (−3.2 vs. −2.8; $p = 0.003$) or placebo (−3.2 vs. −1.8; $p < 0.001$). This corresponds with differences of 27, 23, and 15% with MP-AzeFlu, FP, and placebo, respectively [20]. Of note, this effect was also confirmed in the study comparing MP-AzeFlu with commercially available FP and AZE monotherapies [43]. In the study by Hampel and colleagues [18] described above, MP-AzeFlu treatment significantly improved the overall total ocular symptom score compared with placebo and FP ($p < 0.01$). MP-AzeFlu resulted in a 27% improvement compared with a 21% improvement with AZE, 18% for FP, and 11% for placebo. MP-AzeFlu also improved all

individual ocular symptoms comparatively ($p < 0.05$) except versus AZE for watery eyes [18].

In the post hoc analysis by Meltzer and colleagues [19], MP-AzeFlu led to a significantly superior change in reflective total ocular symptom score from baseline compared with both FP and AZE, with a relative difference of 63% versus FP and 42% versus AZE, despite moderate-to-severe ocular symptoms at baseline. Considering reflective total ocular symptom score plus reflective total nasal symptom score, patients treated with MP-AzeFlu exhibited a greater improvement, of 52 and 56%, versus patients treated with FP ($p = 0.0013$) or AZE ($p < 0.0004$), respectively [19]. With MP-AzeFlu, significant improvements in ocular itching and redness were reported versus FP, AZE, and placebo, and in ocular watering versus FP and placebo [19]. The treatment effects in this study were consistently higher than in the meta-analysis by Carr and colleagues [19, 20], and may be attributable to formulation and device effects.

Time to Onset of Effect

Other treatments, including single-agent FP and AZE and the combination of an intranasal corticosteroid and oral antihistamine, do not provide the same level of efficacy as MP-AzeFlu for rapid and sustained relief of all AR symptoms. A previous study demonstrated an onset of action for the combination of intranasal FP and oral loratadine of 150 versus 5 min for MP-AzeFlu – a difference of nearly two and a half hours [6].

Environmental exposure chambers offer advantages for assessing onset of action that can be demonstrated in minutes [8]. The chamber allows for consistent allergen exposure, whereas in a typical phase 3 study, the first dose and early assessment are conducted under an indoor, low-pollen exposure condition [8]. In a single-center, randomized, placebo-controlled crossover trial of 78 asymptomatic patients, AR symptoms were induced by ragweed pollen challenge in an environmental exposure chamber [29]. Bousquet and colleagues [29] reported a clinically relevant (defined as a 30–50% symptom reduction) and significant effect of MP-AzeFlu versus placebo at 5 min until assessment end (4 h; $p \leq 0.04$). Meltzer and colleagues [44] reported a similar rapid onset of action of MP-AzeFlu in a trial setting, with significantly greater total nasal symptom score improvement versus placebo after 30 min and at all subsequent evaluations.

In a single-center, single-dose, randomized, double-blind trial, 425 patients were exposed to ragweed in an environmental exposure chamber [45]. Patients treated

with mometasone experienced significant symptom reduction compared with placebo at 150 min postdose [45].

A randomized study of 450 adults exposed to ragweed pollen in an environmental exposure chamber showed that treatment with AZE nasal spray led to a significant 45% reduction of total nasal symptom score from baseline, starting 15 min after administration and lasting throughout the 8-h allergen exposure [46].

Effects on Quality of Life

AR can profoundly impact quality of life and contribute to a greater impairment of work productivity than type 2 diabetes and hypertension [1, 4]. Therefore, studies were designed to investigate associations between patient-reported changes in quality of life and MP-AzeFlu treatment.

MP-AzeFlu significantly improved the overall Rhinoconjunctivitis Quality of Life Questionnaire score versus placebo among 779 patients with moderate-to-severe seasonal AR [44]. In the analysis by Carr and colleagues [20], 14 days of treatment with MP-AzeFlu, FP, or AZE led to significantly improved quality of life. In the Hampel and colleagues [18] study previously described, MP-AzeFlu treatment significantly improved nasal congestion; runny nose; itchy nose; sneezing; and itchy, watery, and red eyes, leading to significant improvements in the overall score and each domain of the Rhinoconjunctivitis Quality of Life Questionnaire compared with placebo ($p < 0.001$) and AZE ($p = 0.005$). In a noninterventional study of patients with moderate-to-severe AR treated with MP-AzeFlu for ~14 days, patients reported improvements in mean visual analog scale scores for impairment in sleep quality, work or school daily activity, social activity, and outdoor activity (Van Weissenbruch, et al. Unpublished data). Of importance, these results were similar across all populations, regardless of Immunoglobulin E-mediated disease phenotype, comorbidity, sex, and age. Finally, in noninterventional studies of patients with AR conducted in Ireland, increased rates of patients with very good or good sleep quality from baseline (25%) through day 28 (78.4%) were seen with MP-AzeFlu treatment [17].

These experimental endpoints for assessing quality of life and sleep quality have been used in previous studies of AZE and FP, supporting their use for assessing the effects of treatment. Results from a 14-days study of patients with moderate-to-severe seasonal AR demonstrated significant improvements from baseline in the Rhinoconjunctivitis Quality of Life Questionnaire score among

patients treated with AZE compared with placebo [47]. Among 24 subjects treated with AZE or placebo for 8 weeks, AZE-treated patients reported significant improvements in sleep after treatment that were superior to those reported by the placebo-treated group [48]. Among patients aged ≥ 12 years with seasonal AR, once-daily treatment for 2 weeks with fluticasone furoate nasal spray led to clinically significantly improved Rhinoconjunctivitis Quality of Life Questionnaire score [49]. Of note, this clinical difference was achieved in the individual domain of sleep problems [49]. In a study of 19 patients aged ≥ 18 years with physician-diagnosed asthma and mild AR, 6 weeks of treatment with fluticasone propionate led to a significant increase in the Rhinoconjunctivitis Quality of Life Questionnaire index compared with placebo; however, no significant changes in sleep from baseline were observed [50]. Results from a randomized study of patients with seasonal AR demonstrated that fluticasone furoate nasal spray was more effective than placebo in terms of nighttime sleep disturbances caused by seasonal AR symptoms [51].

Overall, the use of MP-AzeFlu improves the severity of AR symptoms and patient quality of life by reducing the impact on sleep and daily activities, regardless of phenotype or comorbidity. With its rapid time to onset, MP-AzeFlu quickly improves symptoms and lessens the profound impact of AR on patient quality of life.

Safety

When developing combination therapies, potential drug-drug interactions between active components or formulation-based alterations of bioavailability must be investigated [52]. The initial efficacy of MP-AzeFlu warranted assessment of its safety and tolerability. No evidence of pharmacokinetic interactions between AZE and FP in MP-AzeFlu has been reported [12].

In randomized, crossover studies of healthy subjects, no interactions were found between AZE and FP with MP-AzeFlu [16]. Furthermore, AZE bioavailability was similar between MP-AzeFlu and the MP-AzeFlu-based product containing only AZE. FP exposure was higher for MP-AzeFlu-based products versus FP alone; however, FP concentrations were very low among all products, suggesting no clinically meaningful differences in systemic safety [16].

In a 1-year randomized, open-label, active-controlled, parallel-group study of 612 patients with chronic AR or nonallergic rhinitis, patients received one spray per nostril of MP-AzeFlu twice daily or 2 sprays per nostril of FP once daily [22]. The incidences of treatment-related ad-

verse events were low with both MP-AzeFlu (9.4%) and FP (11.1%), with no evidence of late-occurring adverse events. No findings would preclude the long-term (52-weeks) use of MP-AzeFlu in the treatment of AR. The most common treatment-related adverse events were headache (4.3%) with FP and dysgeusia (2.5%) with MP-AzeFlu. No appreciable reduction in serum cortisol was seen from baseline after 12 months of continuous treatment with either MP-AzeFlu (-0.08 ± 5.5 mcg/dL) or FP (-1.04 ± 5.0 mcg/dL) [22].

In the real-life, pan-European study by Klimek and colleagues [26], treatment with MP-AzeFlu was well tolerated, with $<1\%$ of nearly 3,000 treated patients reporting adverse events. The most commonly reported adverse events were dysgeusia ($n = 4$), nausea ($n = 3$), sneezing ($n = 3$), and nasal discomfort ($n = 3$). Rhinorrhea, application-site pain, and epistaxis were also reported by 2 patients each [26]. In Kaulsay and colleagues' [17] noninterventional study of 53 patients, 1 patient reported fatigue and 1 patient reported sedation.

Special Populations

In a multicenter, prospective, noninterventional study of patients with moderate-to-severe seasonal or perennial AR treated with MP-AzeFlu for ~ 14 days, mean visual analog scale scores similarly decreased for impairment of sleep quality among participants aged 12–17 years, 18–65 years, and >65 years. (Van Weissenbruch, et al. Unpublished data). Similar results were reported across age groups for visual analog score improvement in impairment of daily work or school, social, and outdoor activities (Van Weissenbruch, et al. Unpublished data).

In an open-label trial of 405 children aged 4 to <12 years with a history of AR randomized to receive MP-AzeFlu or FP for 3 months, MP-AzeFlu led to a significantly greater reduction in total symptom score [24]. This difference was noted from the first assessment and was sustained for 90 days. In the first month, 80% of children treated with MP-AzeFlu reported no symptoms or mild symptom severity, which was achieved up to 16 days quicker than with FP. More children who received MP-AzeFlu experienced mild or no symptoms throughout the study period versus FP (73.4 vs. 66.0%) [24].

In a 14-days, randomized study of 304 children aged 6–11 years with moderate-to-severe AR, a significant improvement in Paediatric Rhinoconjunctivitis Quality of Life Questionnaire overall score was reported with MP-AzeFlu versus placebo [25]. When children mostly rated their own symptoms, MP-AzeFlu led to significantly im-

proved relief versus placebo for reflective total nasal symptom score, reflective total ocular symptom score, and individual nasal and ocular symptoms [25].

In a 3-month, open-label study of children aged 4–11 years with AR, the incidence of treatment-related adverse events was low with MP-AzeFlu or FP alone (16 vs. 12%) [28]. The most frequent adverse event was epistaxis, which was reported in 9% of patients in both groups. No mucosal ulceration or nasal septal perforation was reported and there were no unusual changes in vital signs or laboratory parameters, demonstrating the safety and tolerability of MP-AzeFlu in children [28].

Competitor Landscape

In a phase 3, double-blind, randomized study of 1,180 patients, 14 days of GSP301, an investigational, fixed-dose combination of olopatadine hydrochloride and mometasone furoate delivered in a nasal spray device, significantly improved the reflective total nasal symptom score versus placebo and olopatadine alone, but not mometasone furoate alone; the instantaneous total nasal symptom score was significantly improved versus placebo and both monotherapies [53]. GSP301 significantly improved individual nasal symptoms, reflective total ocular symptom score, instantaneous total ocular symptom score, and quality of life versus placebo, with an onset of action within 15 min. Overall, 12.9% of GSP301-treated patients reported treatment-emergent adverse events, including dysgeusia (3.3%), which was similar to olopatadine alone (3.0%) [53].

Although the efficacy and safety of MP-AzeFlu and GSP301 are similar, the dosing of GSP301 is 2 sprays per nostril twice daily, whereas MP-AzeFlu requires only one spray per nostril twice daily [12, 53], which may be associated with increased adherence. Compared with mometasone, GSP301 was not significantly superior, whereas MP-AzeFlu treatment led to significant symptom improvements, suggesting GSP301 may be less effective than MP-AzeFlu.

In a randomized, double-blind, double-dummy study of 180 participants, treatment with twice-daily GSP301 led to a significant difference in instantaneous total nasal symptom score change from baseline after 10 min versus placebo [31]. No significant difference in instantaneous total nasal symptom score change was seen with MP-AzeFlu. However, MP-AzeFlu was administered with one spray of placebo in this study, which reduced its effectiveness and impacted time to onset because of a washout effect. Additional direct comparisons are needed to determine any true differences.

Conclusion

This body of literature suggests that treatment options, such as single-agent FP or AZE and the combination of an intranasal corticosteroid and an oral antihistamine do not provide the same level of efficacy as MP-AzeFlu in terms of rapid and sustained relief of the entire AR symptom complex. Taken together, these studies further demonstrate that MP-AzeFlu treatment also improves quality of life. MP-AzeFlu is the only currently available combination that satisfies patient needs and expectations, such as prompt relief, effects on both nasal and ocular symptoms in all patient types, and preference for an intranasal, combination treatment. The use of MP-AzeFlu as first-line therapy for AR is supported by evidence-based medical guidelines. Following the example of combination therapy in asthma control [54], first-line combination therapy for AR may improve symptom control, patient adherence, disease management, and overall quality of life.

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Conflict of Interest Statement

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Author Contributions

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Availability of Data and Material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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