REVIEW

УДК 616.211-002-021.5-085.218.3-085.276:615.451.35 *DOI: 10.26565/2313-6693-2022-45-06*

AN ALGORITHM RECOMMENDATION FOR THE PHARMACOLOGICAL MANAGEMENT OF ALLERGIC RHINITIS IN UKRAINE: A CONSENSUS STATEMENT FROM AN EXPERT PANEL

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Summary. Allergic rhinitis (AR) is increasing at an alarming rate in Ukraine. The clinical picture of AR in modern conditions is changing towards more severe and mixed forms. Allergic rhinitis, especially moderate to-severe, has a negative impact on patient quality of life, productivity, direct, and indirect costs. Achieving adequate symptom control is essential for successful AR management, and relies mostly on pharmacotherapy. Most patients use multiple medications to control symptoms faster and better, but symptoms may persist. With the advent of new combination therapies, such as the intranasal formulation of azelastine hydrochloride and fluticasone propionate in a single device (MP-AzeFlu) like Dymista®, most AR symptoms can be treated effectively. MP-AzeFlu acts synergistically and blocks two important pathophysiological pathways involved in the early- and late-phase reactions of the disease, providing rapid relief from all AR-associated symptoms. A total of 13 experts from Ukraine, Germany, and India participated in the development of this consensus statement. The lead author drafted the questions pertaining to diagnosis, management, treatment adherence, and real-life evidence of AR in Ukraine, and was agreed with the co-authors and expert panel. This consensus is obtained through guiding statements and recommendations based on literature evidences (recent research outcomes, randomized, and comparative studies), clinical practices and personal experience of using MP-AzeFlu in AR by allergist/ immunologists/ otolaryngologists from Ukraine. This consensus statement aimed to assist practitioners in selecting the appropriate treatment strategies, facilitate optimum use of MP-AzeFlu and provide symptomatic relief for patients with AR in the in Ukraine.

KEY WORDS: *allergic rhinitis, azelastine hydrochloride, fluticasone propionate, disease management, Ukraine*

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For citation:

Bil B, Chopyk, Deeva Yu, Dytiatkovska Ye, Gogunska I, Popovych V, Romaniuk L, Umanets T, Zabolotna D, Zaikov S. AN ALGORITHM RECOMMENDATION FOR THE PHARMACOLOGICAL MANAGEMENT OF

ALLERGIC RHINITIS IN UKRAINE: A CONSENSUS STATEMENT FROM AN EXPERT PANEL. The Journal of V. N. Karazin. Kharkiv National University. Series «Medicine». 2022; 45: 51–65. **DOI: 10.26565/2313-6693-2022-45-06**

INTRODUCTION

Allergic rhinitis (AR) is an immunoglobulin E (IgE)-mediated inflammatory disorder of the nasal mucosa, induced by airborne allergens [1, 2]. Prevalence is high globally and affects > 400 million people worldwide [3], and is increasing at an alarming pace in Ukraine, ranging from 6 % to 24.7 % [4, 5]. Despite a substantial psycho-socio-economic burden, AR remains underdiagnosed, underestimated and undertreated in Ukraine [3]. Patients often tend to ignore the disease till it progresses to moderate-to-severe form, while those with mild AR might not report at all. Patients also prefer to self-manage the disease with over-the-counter drugs and depend on internet and advice from neighbors and family doctors. Even if they reach the specialty clinic, a low physician to patient ratio (107 physicians per one million patients), keeps the need unmet. Condition is worsened with polypharmacy and discredit of topical corticosteroids, with no symptomatic relief. About 80 % of the patients in Ukraine develop polysensitization and progress to moderate-to-severe AR, upon missing timely monotherapy [6]. Therefore, optimization of treatment modalities is critical as suboptimal management increases morbidity and impairs patient's functional capacity. The local data presented in this section is solely based on expert opinions in the backdrop of lack of official statistical records.

The key unmet needs in AR are poor efficacy, lack of 24 h coverage for symptommatic relief, breakthrough symptoms, lack both nasal and ocular symptom control, and side effects [7–9].

MP-AzeFlu (Dymista®), is a new addition to the AR therapeutic armamentarium, comprising an intranasal formulation of antihistamine (INAH; azelastine hydrochloride [AZE], 137 µg/spray) and an intranasal corticosteroid (INCS; fluticasone propionate [FP], 50 µg/spray) in a single device [10]. It offers broad pathophysiological coverage by incorporating two different drug classes with different yet complementary modes of action. The combination antagonizes both early- and late-phase allergic responses, is convenient to use, and has the potential to be considered as the drug of choice for the management of patients with AR in Ukraine. MP-AzeFlu is indicated for symptomatic relief from moderate and severe seasonal AR (SAR) and perennial AR (PAR) in patients aged ≥ 12 years), considering monotherapy with either INAHs or INCS is not sufficient [11].

With a steadily increasing disease prevalence coupled with lack of awareness around disease and treatments, a patient-centered approach to AR management is warranted. Therefore, a consensus guideline was developed to optimize the usage of MP–AzeFlu for the management of patients with AR in Ukraine.

METHODS: CONSENSUS PROCESS

The current consensus reviews the recent evidence on AR and presents evidence-based recommendations on the use of MP-AzeFlu for the management of AR in Ukraine. An expert panel of 13 authors from Ukraine, Germany, and India with prior national and international publications in AR participated in this consensus statement development. In order to impart the highest possible evidence base for the use of MP-AzeFlu in the management of AR, a systematic review of the literature was initiated. Existing guide-lines, meta-analyses, systematic reviews, randomized controlled trials (RCTs), non-RCTs, and key cited articles relating to management of AR were identified by conducting a literature search from electronic database using PubMed, The Cochrane Library, Google, Google Scholar, and trial registers at Clinical Trials (http://www.clinicaltrials.gov/). These articles were screened, publications considered relevant to the topic were included, and inputs from all the participants were sought. The lead author drafted the questions pertaining to diagnosis, management, treatment adherence, and real-life evidence of AR in Ukraine and was agreed with the co-authors and expert panel. All the co-authors also provided their perspectives on unmet needs in surgical treatment of patients with AR. The lead author collated all the responses and disagreement were resolved via e-mail correspondence. Thereafter, the panel and the

authors met virtually on December 03, 2020, and the data was reviewed and discussed. The lead author then drafted and finalized the consensus statement following discussion with the co-authors and shared with the expert panel for the final review. In case of little or no evidence, the expert panel relied on logical empiricism and consensus to make their recommendations.

DIAGNOSIS

The definition, etiology and classification of AR presented in Table 1 [12–15]. The diagnosis of AR is mainly clinical, although symptoms do not establish either the cause or type of AR. Therefore, clinical examination combined with diagnostic tests are necessary for a complete disease characterization. The diagnosis is confirmed on the basis of family history, social history (exposure to animal dander, pollens and dust, pets, and possible triggers) and visual examination [15]. In-vivo diagnostic test includes the skin prick test (SPT) and in-vitro include serum IgE assay. Serum IgE testing is done either when SPT is not available or it is not feasible due to eczema, dermatographism, urticaria, or if the patients are taking antihistamine (AH) or other medications that interferes with test results [16].

Table 1

Definition, etiology, classification, triggers, history and physical examination of allergic rhinitis

Definition of AR	**Defining symptoms**	**Characteristics**
IgE-mediated inflammation of the nasal mucosa, induced by exposure to airborne allergens	Rhinorrhea, sneezing, nasal itching, and nasal congestion	Symptoms are reversible spontaneously or with treatment
Etiology	**Early-phase reaction**	**Late-phase reaction**
Th2-mediated inflammation	• Rapid IgE-mediated degranulation of mast cell and mediator release • Occurs in sensitized individuals within minutes of exposure to the allergen	• Predominantly inflammatory in nature, characterized by inflammatory cellular influx comprising of T-lymphocytes, basophils and eosinophils • Prolongation of symptoms (e.g., sneezing, rhinorrhea), nasal congestion lasts for 18–24 h
Classifications of AR		
Seasonal: In response to a seasonal allergen (e.g., tree pollen)	*Perennial:* In response to an allergen present all year round (e.g., house dust mite)	
According to duration		
Intermittent: Symptoms are present for <4 days/week OR for <4 consecutive weeks	*Persistent:* Symptoms are present for >4 days/week AND for >4 consecutive weeks	
According to severity		
Mild: All of the following • Normal sleep • Normal daily activities • Normal work and school • No trouble symptoms	*Moderate/severe:* One or more factors are present	Factors • Abnormal sleep • Impairment of daily activities, leisure, sport • Impairment of school/work • Troublesome symptoms
Common triggers		
Trigger type	*Origin/specific example of trigger*	*Types of AR caused*
Mites	House dust mite, storage mites, allergen in mite fecal pellets	Perennial
Pollens	Trees, grasses, shrubs, weeds	Seasonal
Animals	Cats, dogs, horses, mice rats	Perennial
Fungi (moulds)	*Alternaria*, *Cladosporium*, *Aspergillus*	Seasonal and/or perennial
Occupational induced	Flour, latex, laboratory animals, wood dust, chlorine, chloramine, enzymes, other airborne proteins	Reversible with early diagnosis and avoidance but becomes chronic and irreversible if exposure is prolonged; may progress to asthma

Continued of table 1

Occupation aggravated	Smoke, cold air, formaldehyde, sulphur dioxide, ammonia, glues, solvents	Pre-existing rhinitis can be aggravated by work-place irritants
Components of complete history and physical examination		
History	*Physical examination*	
Personal: congestion, nasal itch, rhinorrhea, sneezing, eye involvement, seasonality, triggers	**Outward signs:** mouth breathing, rubbing the nose/transverse nasal crease, frequent sniffling and/or throat clearing, allergic shiners (dark circles under eyes)	
Family: allergy, asthma	**Nose:** mucosal swelling, bleeding, pale, thin secretions, polyps or other structural abnormalities	
Environmental: pollens, animals, mould, humidity, tobacco use	**Ears:** generally normal, pneumatic otoscopy to assess for Eustachian tube dysfunction, Valsalva's maneuver to assess for fluid behind the ear drum	
Medication/drug use: beta-blockers, ASA, NSAIDs, ACE inhibitors, hormone therapy	**Sinuses:** palpation of sinuses for signs of Tenderness, maxillary tooth sensitivity	
Comorbidities: asthma, otitis media, nasal polyps, sinus involvement, conjunctivitis	**Posterior oropharynx:** postnasal drip, lymphoid hyperplasia («cobblestoning»), tonsillar hypertrophy	
Response to previous interventions: avoidance measures, saline nasal rinses, second-generation oral antihistamines, intranasal corticosteroids	**Chest and skin:** atopic disease, wheezing	
Abbreviations: *ACE, angiotensin-converting enzyme; AR, allergic rhinitis; ASA, acetylsalicylic acid; Ig, immunoglobin; NSAIDs, non-steroidal anti-inflammatory drugs* Adapted from Scadding et al. [10]; Bousquet et al. [11]; Pawankar et al. [12]; Small et al. [13]		

UNMET NEEDS IN THE MANAGEMENT OF AR

Allergens avoidance

The first-line treatment of AR involves the avoidance of allergens including house dust mites, animal dander, molds, pets, pollens, and other triggers. Allergen-impermeable bedding covers, removing pets from the home and the use of high-efficiency particulate air (HEPA) filters may also reduce symptoms [13].

Education

Patients or parents of children should be educated on the nature of allergens, allergen avoidance, potential side effects of available agents, alternative treatment options, and be apprised with realistic expectations of the results of therapy [10,17,18]. Patients should be informed about the negative effects of AR on their quality of life (QoL) and benefits of complying with therapeutic recommendations. Patients should also be motivated to attend AR educational programs in order to become active partners in managing their disease. Appropriate training is essential regarding the importance of the correct use of intranasal sprays and drops to ensure maximum adherence to the therapy [19]. AR education program needs to be better targeted to otolaryngologist's, family doctors, pharmacists and healthcare professionals for better management of AR symptoms [10, 20]. Standardized allergy education of healthcare professionals has shown to improve disease-specific QoL in patients with PAR [21].

Mobile health

Mobile health (mHealth), including apps running on smart devices (i. e., smartphones and tablets) has the potential to profoundly impact health-related services, screening of undiagnosed patients, data and information flow, and self-management of AR patients

[22–24]. mHealth technologies may assist physicians in making well-informed diagnostic and therapeutic decisions. The recent position papers from European Academy of Allergy and Clinical Immu-nology (EAACI) [22] and the American College of Allergy and Immunology (ACAAI) [25] recommends the use of mHealth apps for high-quality care to patients with AR. In Ukraine, there is an unmet need for well-informed decision making and hence warrants the implementtation of mHealth for better management of patients with AR. Several e-diaries are also available for management of allergic diseases in other European countries, and some leveraged in clinical studies or observational studies [23, 26–28].

Pharmacological treatment

If symptoms persist despite avoidance strategies, second generation oral AHs (OAHs) are the first-line therapies for management of AR, have been used commonly and demonstrated acceptable safety and efficacy profile. Compared with first generation OHAs, second-generation OAHs are less sedating, with the additional benefit of a faster onset of action within minutes and longer duration of action [29]. The therapeutic effect of INAH is superior to that of OHAs, with faster onset of action within < 30 mins [30]. INAHs ensure drug delivery directly to the nasal mucosa, thus enhancing its local anti-allergic and anti-inflammatory effects while minimizing systemic exposure to therapy [31]. Responsive patients may be recommended to continue INAH therapy during periods of allergen exposure, while those symptomatic after two weeks of therapy should be stepped-up.

INCSs are also recommended as first-line therapy, with better efficacy than AHs, but slower onset of action as their maximum efficacy is only reached after two weeks of treatment [29, 32–34]. The combination of INCSs and OAHs offer no advantage over INCSs alone [35]. In case of INCSs intolerance or in case of non-preference, adding a leukotriene receptor antagonists (LTRAs) to an oral AH may be considered [36–38]. To achieve quicker and more profound symptom relief, MP-AzeFlu can be administered immediately in patients with AR.

Combination treatment with INAHs and INCSs may provide greater relief for patients with SAR [39]. Indeed, the sequential use of INCS and INAH has shown benefits over monotherapy in patients with moderate-to-severe SAR [39]. However, there are some disadvantages, including a negative impact on concordance [40], increased run-off both posteriorly and anteriorly [41], and nonhomogeneous distribution of active agents on the nasal mucosa [42]. Besides, it is also inconvenient for a patient to use two sprays in turn, within an interval of 20 minutes, which calls for a better administration, i. e., a single spray with both the agents.

MP-AzeFlu, is currently the only combination therapy, is available for the treatment of AR and has the potential for broad disease coverage and symptom control. This combination treatment extends an additive advantage culminating from the different primary mechanisms of action of the two active agents (AZE and FP), and adherence is enhanced as both the agents are delivered in a single spray packaged in a single device [41]. Single spray enhances the delivery by providing a more uniform distribution, larger spray pattern diameter and area coverage, greater retention in the nasal cavity and no runoff versus sequential dosing of AZE and FP [42–44]. A summary of guidelines recommending MP-AzeFlu in combination therapy for the management of AR is depicted in Table 2 [17, 45–47].

Two pharmacokinetic (PK) studies (randomized, three-period, six-sequence three-treatment crossover design) were conducted to determine if there were any drug-drug interactions between the active components of MP-AzeFlu, and to evaluate the bioavailability of these components versus commercially available formulations of AZE and FP [43]. Results from the PK assessment showed no drug-drug interactions between AZE and FP in the MP-AzeFlu formulation. The bioavailability of AZE was comparable to the MP-AzeFlu formulation and marketed AZE (Astelin®) but FP bioavailability differed between the marketed and MP-AzeFlu-FP-mono formulations. Maximum and total FP exposure was higher for the MP-AzeFlu formulation than marketed FP, indicating differences in how it is constituted (formulation) and how it is delivered (device) [43]. This unique PK profile of the FP component within the MP-AzeFlu formulation suggests that MP-AzeFlu is more than just two drugs in the same

device [43]. Four MP-AzeFlu efficacy and safety studies were conducted over two weeks in ≥ 4000 patients (USA), ≥ 12 years of age with moderate-to-severe SAR [48–51]. The design of all four of these 2-week SAR studies was similar. However, for three of the studies (MP 4002, MP 4004, and MP 4006) [50, 51], MP-AzeFlu was compared with noncommercially available formulations of AZE and FP which were reformulated and prepared in the same vehicle and delivery device as MP-AzeFlu, in order to observe the pure pharmacological differences between active groups, without the contribution of formulation and device. For the fourth study (MP 4001) [48, 49], MP-AzeFlu was compared with commercially available AZE (i. e., Allergodil®) and a generic FP nasal spray (i. e., Flixonase®).

Table 2

Summary of guidelines recommending MP-AzeFlu for management of allergic rhinitis

Guideline	Summary
MACVIA [45]	• Combination of intranasal AZE and intranasal FP in a single intranasal formulation (MP-AzeFlu) is recommended more effective than monotherapy, and as a first-line option for moderate-to-severe AR
EUFOREA AR Pocket Guide 2020 guidelines [17]	• Recommends fixed combination of INCSs and INAHs (MP-AzeFlu) as the first-line treatment option for those with difficult to treat AR • MP-AzeFlu is the only step up option recommended by EUFOREA for patients already on INCS with VAS score ≥5/10 cm • Recommends symptom-targeted add-on treatments to MP-AzeFlu
The American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) guidelines [46]	• Recommends combination pharmacologic therapy in patients with AR uncontrolled with monotherapy
2020 ARIA NEXT generation guidelines [47]	• The specific recommendation is given in tiers, tier 1: AH, LTRA or cromones; tier 2: INCS; tier 3: MP-AzeFlu; tier 4: oral corticosteroid (short course); tier 5: allergen immunotherapy • In treatment initiation, MP-AzeFlu is recommended as a first-line treatment option in patients with moderate-to-severe, intermittent AR, and in patients with persistent AR regardless of its severity • It is necessary to consider the patient's preferences in order to improve compliance, because adherence to treatment is the main unresolved issue in AR • Before intensifying therapy (step-up), it is necessary to check again the diagnosis, adherence to treatment, the impact of comorbidities, the presence or absence of anatomical abnormalities of the nasal cavity • MP-AzeFlu is recommended as a first-line step-up treatment option in all scenarios of AR. • Strengthening of pharmacotherapy with the transition to a fixed-dose combination is appropriate a) for all patients who are already receiving AR treatment with VAS score ≥5; b) for those who are already taking a fixed-dose combination of AZE and FU and have a VAS score ≥5, it is possible to add oral glucocorticosteroids as a short course; c) if the assessment of AR by VAS remains ≥5/10, the use of ASIT should be considered • When taking a fixed-dose combination of AZE and FP: step down to INCS or INAH, depending on the predominant symptoms (nasal congestion or rhinorrhea) • Switching treatments during step-up and step-down has the potential to reduce compliance, and patients may prefer agents that is more effective and fast acting, like MP-AzeFlu

Abbreviations: *AH, antihistamine; ARIA, allergic rhinitis and its impact on asthma; AR, allergic rhinitis; ASIT, allergen-specific immunotherapy; AZE, azelastine hydrochloride; EUFOREA, European forum for research and education in allergy and airway diseases; INCS, intranasal corticosteroid, INAH, intranasal antihistamine; LTRA, leukotriene receptor antagonist; MACVIA, Contre les MAladies Chroniques pour un VIeillissement Actif; MP-AzeFlu, azelastine–fluticasone propionate combination; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis; VAS, visual analogue scale*

The impact of MP-AzeFlu's formulation/device on clinical efficacy is suggested from the larger treatment differences observed between MP-AzeFlu and commercially available FP (i. e., MP4001 study) [48, 49] versus MP-AzeFlu and reformulated

FP (i. e., MP4002/MP4004/MP4006 studies) [50,51], since in the latter the effect of formulation and device have been eliminated. This greater treatment effect versus a comercial FP occurred for each efficacy parameter assessed, including change from baseline in rTNSS, rTOSS, and each of the individual nasal and ocular symptoms [48–50] (Table 3).

Table 3

Contribution of MP-AzeFlu's formulation to its superior efficacy of over marketed fluticasone propionate

Parameter	MP 4001 (effect of formulation included [48]			MP 4002/MP 4004/ MP 4006 (effect of formulation eliminated) [50]			Formulation effect
	MP-Azeflu (n = 153)	**Marketed FP** (n = 151)	**MP-AzeFlu-FP**	**MP-Azeflu** (n = 848)	**Reformulated-FP** (n = 846)	**MP-AzeFlu-FP**	
LS mean rTNSS (95 % CI)	-5.31	-3.84	-1.47 (-2.44, -0.50), p = 0.0031	-5.7	-5.1	-0.8 (-1.18, -0.34), p=0.001	0.67 points
LS mean rTOSS (95 % CI)	-3.33	-2.17	-1.17 (-1.91, -0.42), p = 0.0022	-3.2	-2.8	-0.47 (-0.78, -0.16), p = 0.003	0.7 points
	Patients at day 14, %		**No. days advantage over FP**	**Patients at day 14, %**		**No. days advantage over FP**	
≥ 50% reduction from baseline rTNSS	49.1	38.2	≤ 6 days, p = 0.0284	~50	~45	≤ 3 days, (significance not reported)	≤ 3 days

Abbreviations: *CI, confidence interval; FP, fluticasone propionate; LS, least squares; MP-AzeFlu, a novel formulation of an intranasal antihistamine, azelastine hydrochloride, and an intranasal corticosteroid, fluticasone propionate, in a single spray; rTNSS, reflective total nasal symptom score; rTOSS, reflective total ocular symptom score*

Percentage of patients exhibiting ≥ 50 % improvement in rTNSS by treatment day showed more patients with MP-AzeFlu achieved rTNSS reductions and did so up to six days faster than either AZE or FP, highlighting the fact that FP contained within MP-AzeFlu has a different clinical efficacy profile to marketed FP. Thus, the time advantage of MP-AzeFlu over re-formulated FP (i.e., ≤ 3 days) was half of that observed versus the time advantage over commercial FP (i.e., ≤ 6days) [50–51]. This rapid improvement could also improve compliance. Taken together, these results confirm MP-AzeFlu as a new product for management of AR. MP-AzeFlu provided superior symptomatic relief to FP and AZE in patients with moderate-to-severe AR, even when the effect of formulation and device had been eliminated. This provides a sound evidence for a purely pharmacological and additive benefit over either monotherapy [50]. MP-AzeFlu also demonstrated a significant and speedy reduction in overall nasal symptoms versus marketed FP in a randomized, open-label, active-controlled, parallel-group, long-term (52-week) study of 612 patients with chronic AR including nonallergic rhinitis (NAR) and PAR [52]. Statistical superiority of MP-AzeFlu over FP was noted from Day 1 with consistent statistical significance maintained for up to 28 weeks (-2.88 vs. -2.53; p = 0.0048), with treatment difference sustained for 52 weeks, representing a > 75 % reduction in symptom score in the MP-AzeFlu group. Approximately, seven of 10 patients achieved symptom relief in the first month of treatment and did so a median of nine days faster than patients treated with FP (p = 0.0024). Over 52 weeks, patients treated with MP-AzeFlu experienced 26 more symptom-free days than FP-treated patients (8.4 % more, p = 0.0005). A similar pattern was observed in the PAR subpopulation [52].

In a highly controlled environmental exposure chamber study, MP-AzeFlu demonstrated significantly faster onset of action versus the combination of INFP and oral loratadine (LORA) (5 vs. 150 min, p < 0.05), with a difference of almost 2.5 h 53]. For the first time, the significant onset of action after 5 min already reached the minimal clinically important difference (MCID, clinically relevant size). MP-AzeFlu

also showed significantly (p = 0.005) greater nasal symptom relief versus the combination of INFP and loratadine, which did not differ from placebo during the 4 h study period (p = 0.182) [53]. Thus, MP-AzeFlu has the potential to be the preferred therapeutic option for patients requiring a rapid symptomatic improvement.

Real-life data

The controlled clinical studies don't represent the real-life scenarios, and hence real-world studies are required to better understand how treatment works and which patient population benefits most in daily in routine care. The efficacy of MP-AzeFlu in real-life setting was assessed in a pan-European noninterventional study conducted in Germany, Scandinavia (Sweden, Norway, and Denmark), the United Kingdom, and Romania using a visual analogue scale (VAS) in line with EAACI and MACVIA-ARIA initiatives [45,54–57]. VAS is a simple, intuitive to use (requiring no training), reproducible, sensitive, has wide score ranging from 0 mm (not at all bothersome) to 100 mm (extremely bothersome). VAS can be used to assess total symptoms score as well as individual nasal or ocular symptoms [58]; however, it is not used widely in Ukraine. Results of a real-life assessment of MP-AzeFlu by using a VAS, in a large pan-European population of 2988 patients (≥ 12 years) with ARIA-defined moderate-severe AR demonstrated a significant reduction of VAS scores (0 mm-100 mm = not at all bothersome-very bothersome) from baseline to Day 14 (73.7 mm vs. 23.4 mm; p < 0.001), a clinically relevant shift of 50.4 mm [59]. A VAS score changes of 23 mm for AR symptoms following treatment was considered as clinically relevant improvement.

MP-AzeFlu-treated patients also experienced rapid and sustained symptom control, with one in two patients (50.3 %) reporting that their AR was well-controlled by Day 3 and achieving the ARIA define control level within 3 days after treatment initiation. Proportion of patients treated with MP-AzeFlu who had «well-controlled» (i. e., VAS score ≤ 38 mm) were 18.2 %, on Day 1, 40.0 % on Day 3, 66.6 % on Day 7, and 75.9 % on Day 14. After This effect was consistent, irrespective of disease severity, phenotype (SAR, PAR, SAR+PAR and unknown phenotype), age (12–17, 18–65 and > 65 years) or previous treatment (with monotherapy or multiple therapies) underline the clinically relevant response that patients expect from a new AR treatment [59].

Kaulsay et al. assessed the effectiveness of 6 weeks of MP-AzeFlu treatment for relieving AR symptom severity in 53 Irish patients with persistent allergic rhinitis (PAR), demonstrating a rapid VAS 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 [60]. Over half of the patients exhibited a clinically significant improvement (~ 23 mm) on Day 3 and approximately 75 % on the last day of treatment. Using the ARIA-defined VAS score cut-off 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 MPAzeFlu, the total endoscopy scores 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 %). Increased proportion of patients with very good or good sleep quality from baseline (25 %) through Day 28 (78.4 %) were seen with MP-AzeFlu treatment, which further increased to 85.7 % on Day 42. Decreasing proportions of patients reported fair, bad, or very bad sleep quality from Day 7 through Day 42. Symptom improvement was seen in all patient subpopulations irrespective of type of AR (PAR only, SAR, and PAR), age (adolescents, adults), baseline symptom severity, or sex. The mucosal appearance also improved after 28 days of treatment with MP-AzeFlu [60].

Overall, the treatment met patients' expectations for a clinically relevant response expected from a new AR treatment. This supports MP-AzeFlu as the drug of choice for the management of moderate-to-severe SAR and/or PAR. A recent multinational, multicenter, prospective, noninterventional study of 1103 participants evaluated the real-life effect of MP-AzeFlu on symptoms of AR and asthma using a VAS for 14 days. In total,

24 % of patients with AR reported comorbid asthma and 81.8 % of patients with comorbid asthma responded to AR therapy (AR-VAS < 50 mm on at least 1 study day). Among patients with AR and comorbid asthma, MP-AzeFlu improved VAS scores across all study parameters, including AR symptoms, sleep quality, daily work or school activities, daily social activities, and daily outdoor activities. Asthma symptom severity improved by 24.8 mm on the VAS along with reduction in usage of asthma reliever medication [61].

Safety and tolerability

In general, MP-AzeFlu was well-tolerated in clinical [52, 62] and real-life studies [9, 61], with no safety findings that would preclude its long-term use. Most of the adverse events (AEs) were mild-to-moderate in severity and unrelated to treatment. The most common AEs with MP-AzeFlu were headache, epitaxis and dysgeusia (bitter taste). No patient discontinued therapy due to serious or unexpected AEs. Furthermore, in a long-term (52-week) study of 4022 patients (≥ 12 years) with chronic rhinitis, the incidence of treatment-related adverse events (TRAEs) was low, with no evidence of accumulation of TRAEs over time. Additionally, nasal mucosal ulceration or perforations were not seen, and ocular examination findings were unremarkable [63].

RECOMMENDATIONS

- MP-AzeFlu is more effective than INAH or INCS alone and is indicated for patients when monotherapy with either an INAH or INCS is considered inadequate with moderate-to-severe AR or for patients who require quick relief of symptoms.
- MP-AzeFlu is has a faster onset of action, as early as Day 1, and could be a drug of choice for the management of moderate-to-severe SAR and/or PAR.
- MP-AzeFlu delivers the two drugs (AZE and FP) in a single spray using a single device, and enhances the administration in terms of spread, coverage, and uniform delivery of the drugs.
- MP-AzeFlu has a comparable safety profile than its mono-components in the usual dosage.

ALLERGEN-SPECIFIC IMMUNOTHERAPY FOR AR UNCONTROLLED BY PHARMACOLOGIC AGENTS

Allergen-specific immunotherapy may be appropriate for those patients with AR in whom symptoms remain uncontrolled by pharmacotherapies [17]. Immunotherapy may be considered in patients with persistent symptoms predominantly due to grass pollen allergen in Europe [64. Although some patients experience symptomatic relief, but some patients still remain symptomatic and show signs of allergic sensitization [65, 66]. These patients should receive symptomatic treatment in addition to immunotherapy for persistent therapeutic benefits. Relapse may occur even after a successful immunotherapy [67], and hence further treatment options including symptomatic treatment may be considered.

SURGICAL MANAGEMENT OF AR

Chronic AR patients may require comprehensive otolaryngologic care for the presence of any anatomical deviations. Often, coordination between allergists/immunologists and otolaryngologists is required to maximize control of nasal congestion. In rare cases, adjunctive surgery may be necessary to alleviate nasal blockage due to architectonic or architectural changes. Hence, conchotomy, septoplasty, and vasectomy might be indicated in affected patients [68–70]. Symptom control using postoperative medications also play an important role for better health outcomes. MP-AzeFlu would be of great help in these patients, as it has the potential to reduce pharmaceutical burden, which has been already high in the operated patients. Also, it can help manage AR effectively by reducing multiple prescriptions, number of doctor visits, referrals to secondary care, and potentially reducing the number of patients referred for allergen-specific immunotherapy. This is in-line with the UK National Health Service (NHS) cost-saving initiatives for managing more chronic conditions in the primary care setting [71].

ADHERENCE TO TREATMENT

Adherence to pharmacotherapy is an essential determinant of optimal AR management as patients need often long-term therapy. Medication non-adherence lowers the effectiveness of treatment and also increases the cost of therapy. The patients expect faster relief, facilitating of nasal breathing immediately, with a sustained

benefit. MP-AzeFlu has shown the both, faster onset of action and sustained benefit, which tends to improve adherence. Although there is lack of data on the impact of health education on adherence in AR, it is believed that physician-patient relationship is essential in improving adherence rates.

CONCLUSIONS

MP-AzeFlu, an intranasal unique formulation of AZE and FP in single device, is easy to use, effective, and safe in patients with moderate-to-severe AR. MP-AzeFlu provides faster and sustained symptom control versus first-line treatments in phase 3 studies and in real-life settings, making it an ideal treatment consideration for AR. It offers a better symptomatic relief versus an INAH and INCS irrespective of disease severity, age, response criteria or phenotype. MP-AzeFlu represents a first-line therapy in patients with moderate-to-severe AR. Real-life data obtained via mHealth technologies should offer new insights into the phenotypes and management of AR. These consensus statements provide clarity on essential practical issues like indications for use of MP-AzeFlu dose, efficacy and safety. These statements are likely to provide guidance to physicians on optimizing the use of MP-AzeFlu for patients with AR in clinical practice **(**Fig. 1).

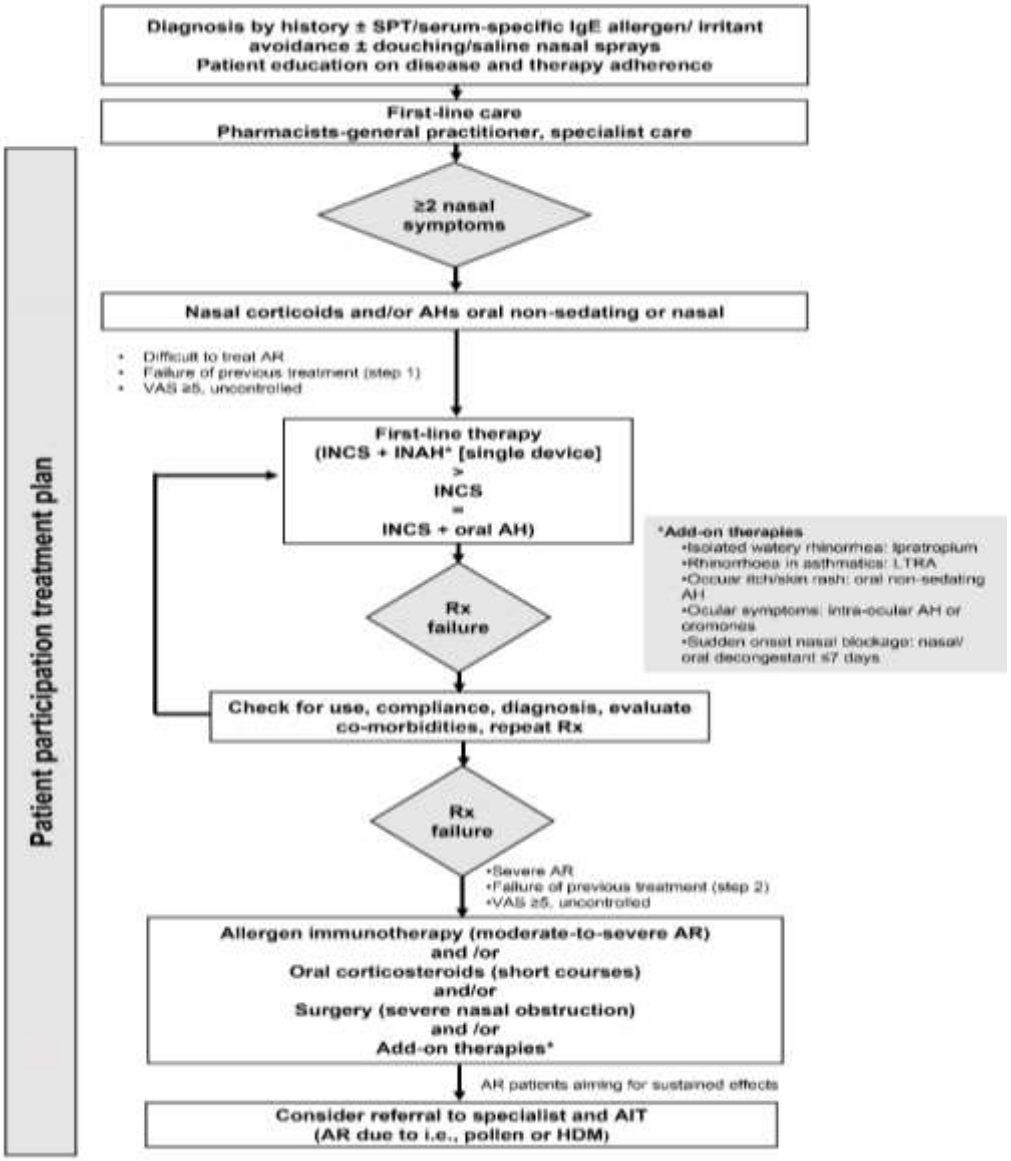

Fig. 1. Treatment algorithm for the management of allergic rhinitis in Ukraine. This figure has been adapted from Hellings et al. [17]

Abbreviations: *AH, anti-histamine; AR, allergic rhinitis; Ig, immunoglobin; INCS, intranasal corticosteroid, INAH, intranasal antihistamine; LTRA, leukotriene receptor antagonist; SPT, skin prick test; VAS, visual analogue scal*

ACKNOWLEDGEMENTS

The authors thank Dr. Palash Kumar Das (Ph.D.) for providing medical writing and Gaurav Anand (both Tata Consultancy Services, India) for additional editorial assistance towards the development of this article, funded by Viatris Inc.

FUNDING

This work was sponsored by Viatris Inc.

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РЕКОМЕНДАЦІЯ З АЛГОРИТМУ ФАРМАКОЛОГІЧНОГО ЛІКУВАННЯ АЛЕРГІЧНОГО РИНІТУ В УКРАЇНІ: КОНСЕНСУСНА ЗАЯВА ЕКСПЕРТА

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Алергічний риніт в Україні зростає загрозливими темпами. Клінічна картина алергічного риніту в сучасних умовах змінюється в бік більш важких і змішаних форм. Алергічний риніт, особливо від середнього до тяжкого, негативно впливає на якість життя пацієнтів. Досягнення адекватного контролю симптомів має важливе значення для успішного лікування алергічного риніту в основному залежить від фармакотерапії. Більшість пацієнтів використовують кілька ліків, щоб швидше та краще контролювати симптоми, але симптоми можуть зберігатися. З появою нових комбінованих методів лікування, таких як інтраназальний препарат азеластину гідрохлориду та флутиказону пропіонату в одному пристрої (MP-AzeFlu), як-от Dymista®, більшість симптомів алергічного риніту можна ефективно лікувати. MP-AzeFlu діє синергетично та блокує два важливі патофізіологічні шляхи, залучені в ранню та пізню фазу реакцій захворювання, забезпечуючи швидке полегшення всіх симптомів, пов'язаних з алергічним ринітом. Загалом у розробці цієї консенсусної заяви взяли участь 13 експертів з України, Німеччини та Індії. Провідний автор підготував питання, що стосуються діагностики, лікування, прихильності до лікування та реальних доказів алергічного риніту в Україні, і було узгоджено зі співавторами та групою експертів. Цей консенсус досягнуто через керівні твердження та рекомендації, засновані на літературних доказах (результати останніх досліджень, рандомізованих та порівняльних досліджень), клінічній практиці та особистому досвіді використання MP-AzeFlu при АР алергологами/імунологами/отоларингологами з України. Ця консенсусна заява мала на меті допомогти лікарям-практикам у виборі відповідних стратегій лікування, полегшити оптимальне використання MP-AzeFlu та забезпечити симптоматичне полегшення для пацієнтів з алергічним ринітом в Україні.

КЛЮЧОВІ СЛОВА: *алергічний риніт, азеластину гідрохлорид, флутиказону пропіонат, лікування захворювань, Україна*

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Для цитування:

Біль Б, Чопік В, Дєєва Ю, Дитятковська Є, Гогунська І, Попович В, Романюк Л, Уманець Т, Заболотна Д, Зайков С. РЕКОМЕНДАЦІЯ З АЛГОРИТМУ ФАРМАКОЛОГІЧНОГО ЛІКУВАННЯ АЛЕРГІЧНОГО РИНІТУ В УКРАЇНІ: КОНСЕНСУСНА ЗАЯВА ЕКСПЕРТА. Вісник Харківського національного університету імені В.Н. Каразіна. Серія «Медицина». 2022;45:51–65. **DOI: 0.26565/2313-6693-2022-45-06**

Conflicts of interest: *author has no conflict of interest to declare.*
Конфлікт інтересів: *відсутній.*

Отримано: 03.09.2022
Прийнято до друку: 20.11.2022
Received: 09.03.2022
Accepted: 11.20.2022