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SPECIAL SUPPLEMENT

FUTURE OF ALLERGIC RHINITIS MANAGEMENT: A SYNOPSIS

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FUTURE OF ALLERGIC RHINITIS MANAGEMENT: A SYNOPISIS

Introduction:
Allergic rhinitis (AR) is an inflammatory condition affecting the nasal mucosa mediated by immunoglobulin-E (IgE).[1] It impacts an estimated 25% of Canadians, of whom most report inadequate symptom control despite treatment as well as high rates of asthma comorbidity.[2] First line pharmacologic options include non-sedating, 2nd generation oral H1-antihistamine (OAH) and/or intranasal corticosteroid (INCS) therapeutic agents. Allergen immunotherapy (AIT) is a possible treatment option for moderate-to-severe disease which is uncontrolled with the use of first-line therapies or for those patients wishing to avoid pharmacologic intervention. However, patient education, engagement, and empowerment are central to optimal clinical outcomes. This supplement summarizes the literature to present the future of AR management.

Mobile Health (mHealth):
The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines provide specific recommendations for the pharmacotherapeutic management of AR. In 2020, the guidelines were updated using a Grading of Recommendations, Assessments, Development and Evaluation (GRADE)-based approach coupled with real-world evidence (RWE).[3] This RWE was obtained using the Mobile Airways Sentinel Network (MASK), a mHealth tool that is available on both the Apple and Google Play App stores and is designed for AR patients and health care providers to monitor disease symptomology and medication utilization.[4] Data from two large-scale MASK studies (> 9000 users) included patient behaviours related to adherence and treatment efficacy. The results demonstrated low treatment adherence among subjects and that MPAzeFlu, an azelastine–fluticasone propionate combination, was deemed the most effective, while

OAHs were deemed to be the least effective category of medication.[5,6] According to the World Health Organization, mHealth tools can transform the delivery of health services, and AR is no exception.[7] Still, there are limitations to mHealth apps like MASK, such as potential biases and the inability to precisely characterize patients and impact treatment adherence; however, the novel information these tools provide and their ability to collect large-scale data is unprecedented.[3]

Pharmacotherapy:
Combination formulations of intranasal H1 antihistamines (IAH) and INCS are a new drug class representing AR management's future. Specifically, MP-AzeFlu (DYMISTA®) is an azelastine–fluticasone propionate combination formulated as a nasal spray. It is indicated for moderate-to-severe seasonal AR (SAR) in adults and children. MP-AzeFlu is more efficacious than INCS and IAH monotherapy and has a fast onset lof action.[8,9] Several European non-interventional studies have evaluated the effectiveness of MP-AzeFlu in patients with ARIA-defined moderate-to-severe AR.[10–14] Results from one pan-European study (n = 2988, aged ≥ 12 years) demonstrated a significant reduction ($p < 0.001$) in Visual Analogue Scale (VAS) scores compared with baseline from day 1 until the last day of the study (day 14).[13] Studies in Sweden, Denmark, and Romania mirror these findings supporting the efficacy of MP-AzeFlu across differing geographies, age, phenotype, and severity of disease.[10–12] A similar multinational study also examined patients with comorbid asthma (n=267) and found improved VAS scores across all outcome measures, including asthma symptom severity (MP-AzeFlu is not indicated for the treatment of asthma in Canada), sleep quality, daily work or school activities, daily social activities, and daily outdoor activities.[14] Finally, a 2-year, pre-post, historical cohort study used data from the Optimum Patient Care Research Database to assess the effect of MP-AzeFlu on asthma outcomes in 1,188 patients with AR and asthma. More patients had well-controlled asthma after 1-year of MP-AzeFlu utilization ($p = 0.0037$), regardless of reduced INCS use.[15] Together, these real-world studies demonstrate the beneficial clinical effects of MP-AzeFlu for moderate-to-severe AR. Canadian data on MP-AzeFlu is limited, except for a small representation (users, n=17) in the MASK study,[6] and should be the focus of future research.

GSP301 is a fixed-dose combination nasal spray containing olopatadine hydrochloride and mometasone furoate monohydrate that was submitted to Health Canada in 2020. In 2019, the safety and efficacy of GSP301 were assessed using a pooled analysis from three natural-allergen exposure studies and an environmental exposure chamber study. GSP301 twice-daily treatments resulted in significantly and clinically meaningful nasal symptom improvements vs. placebo ($p < 0.001$), olopatadine ($p < 0.01$), and mometasone ($p \leq 0.001$) and was well-tolerated.[16]

Allergen Immunotherapy:
AIT is a preventative, disease-modifying therapy indicated for moderate-to-severe AR. It consists of giving multiple doses of an allergen to achieve clinical tolerance, thereby reducing clinical symptoms. In Canada, AIT is approved to be administered as subcutaneous immunotherapy (SCIT) by injection or as sublingual immunotherapy (SLIT) in oral form. SLIT tablets for several allergens have been developed to manage AR, and in 2020, Health Canada approved the once-daily SQ Tree SLIT tablets (ITULATEK™) for the treatment of tree pollen allergy. It is indicated for the treatment of moderate-to-severe AR induced by birch tree, alder, and/or hazel pollen. The results from a randomized, double-blind, placebo-controlled phase III trial (n=634, age 12-65) demonstrated that treatment with SQ Tree SLIT tablets significantly reduced the daily combined score compared to placebo ($p < 0.0001$) and was well-tolerated by patients.[17]

In 2021, our group performed a cost-minimization analysis to estimate the economic impact of SQ Tree SLIT-tablets compared with other AIT options, such as SCIT, which is available in Canada. The direct costs for three years of treatment (drug and physician services costs) were similar for both SQ Tree SLIT tablets vs. Tree Pollen SCIT. However, treatment with SQ Tree SLIT tablets costs less when the indirect costs (including patient's travel expenses and lost working hours) are included in the model and, therefore should be considered a cost-minimizing alternative to Tree Pollen SCIT.[18] This result mirrors our group's earlier finding on the cost-minimizing potential of house dust mite SLIT.[19]

Dual treatment with grass (GRASTEK®) and ragweed (RAGWITEK®) SLIT tablets is another important consideration for the future management of AR. One open-label, multicenter trial (NCT02256553) assessed a 4-week sequential SLIT tablet dosing schedule followed by a simultaneous intake of grass and ragweed tablets and found it was safe and well-tolerated.[20] Future research should focus on combining allergens for SLIT.

Peptide Immunotherapy:
An area of continued research interest for AR management is synthetic peptide immunotherapy epitopes (SPIREs) – short synthetic peptides derived from specific allergens. Although not approved in Canada, treatment with grass allergen peptides has been shown to improve AR symptoms after 3 intervening grass pollen seasons, corresponding to up to 2 years off treatment.[21] However, future large and adequately powered real-world studies are required.

Biologics:
Dupilumab (DUPIXENT®) is a monoclonal antibody (mAb) that targets interleukin (IL)-4Rα, a common receptor for IL-4 and IL-13, and thus inhibits the actions of both of these Type 2 cytokines. It is indicated in Canada for the treatment of asthma, atopic dermatitis, and chronic rhinosinusitis. Recently, two trials have investigated its use in perennial AR (PAR), specifically on asthma patients with comorbid PAR (n > 1000). Both studies demonstrated improved symptom scores after treatment with dupilumab (200 or 300 mg every 2 weeks), suggesting that dupilumab as an adjunctive therapy to systemic asthma therapy may improve treatment outcomes in these patients.[22,23]

Omalizumab (XOLAIR®) is a recombinant, humanized, monoclonal antibody against IgE indicated for adults and pediatric patients with moderate-to-severe persistent asthma with PAR whose symptoms are inadequately controlled with inhaled corticosteroids. A systematic review and meta-analysis of clinical trials of omalizumab for uncontrolled AR has demonstrated a significant reduction in daily nasal symptom severity score ($p < 0.0001$) and a statistically significant reduction in daily nasal rescue medication score $p = 0.01$). There are clinical trials underway investigating the use of omalizumab for AR, including pre-seasonal treatment effects (NCT0448912151)[24] and the use of omalizumab in patients with severe-to-most-severe seasonal AR aged ≥ 12 years and < 18 years (NCT04648930).[25]

Due to the cost of biologics, AR is unlikely to become a primary indication for these therapeutic agents. However, the knowledge of established benefit for AR patients with on-label comorbidities can help shape AR management.

Conclusion:
Advances in disease management for AR patients are focused on mHealth tools, combination pharmacotherapies, and new SLIT tablets. However, emerging trial data on peptide immunotherapies and RWE on the impact of biologic treatment options are occurring rapidly for AR. These approaches, combined with patient education remain pivotal to successful integrated care.

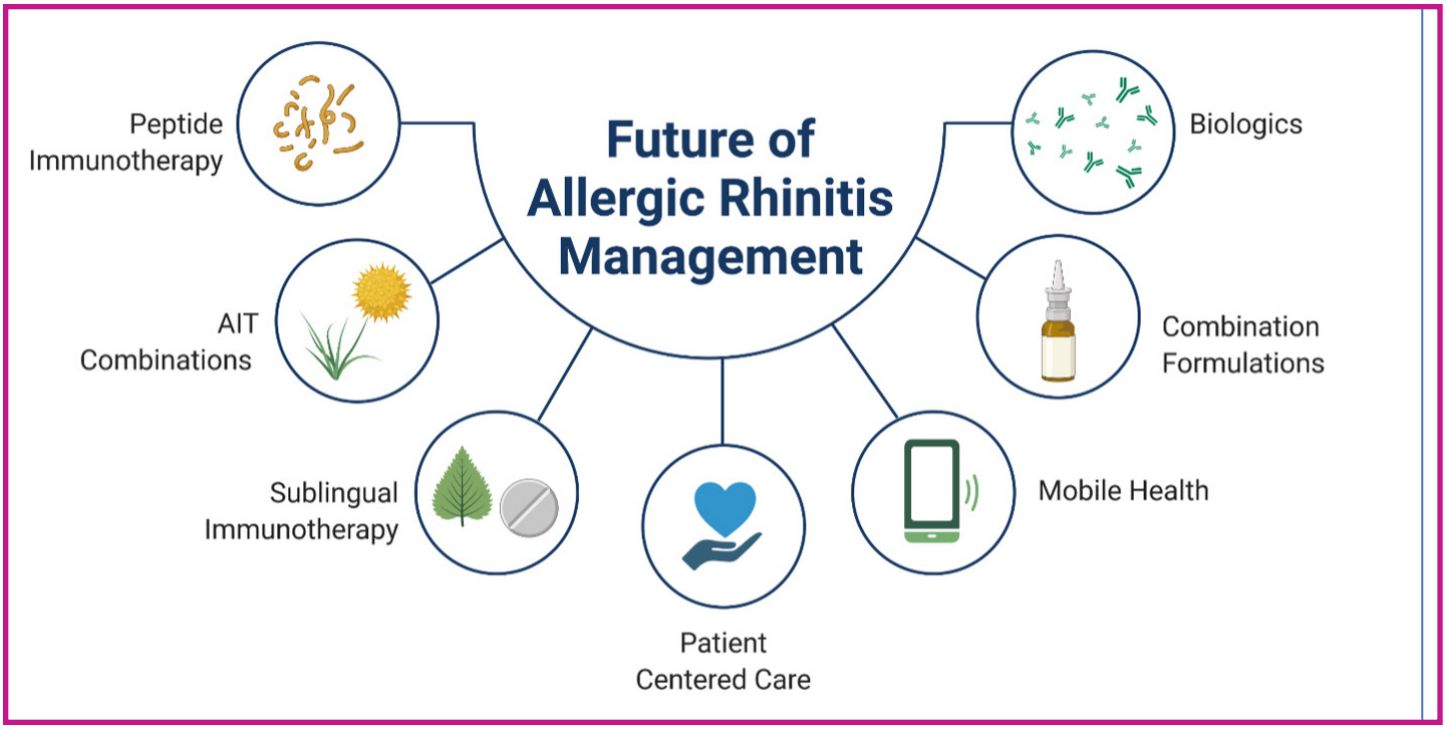

Figure 1. *Future of Allergic Rhinitis Management Diagram*

Product Name	Active Ingredient(s)	Indication	Dosage form(s)	Reference
DYMISTA® (MPAzeFlu)	• Azelastine Hydrochloride • Fluticasone Propionate	• Moderate to severe SAR • Adults, adolescents, and children aged 6 years and older	37 mcg/50 mcg per metered spray	6, 8-15
GSP301	• Olopatadine Hydrochloride • Mometasone Furoate Monohydrate	• This product is not approved in Canada	665 mcg/25 mcg per metered spray	16
ITULATEK™ (SQ Tree SLIT tablets)	• Standardized Allergen Extract, White Birch (*B.* verrucosa)	• Moderate to severe SAR induced by pollen from birch, alder and/or hazel • Adults aged 18 to 65 years	12 SQ-Bet tablet	17,18
GRASTEK®	• Standardized Timothy Grass Pollen (*P. pratense*)	• Moderate to severe SAR induced by Timothy and related grass pollen • Adults and children aged 5 years and older	2800 bioequivalent allergy units /tablet	20
RAGWITEK®	• Standardized Short Ragweed Pollen Allergenic Extract (*A. artemisiifolia*)	• Moderate to severe SAR induced by short ragweed pollen • Adults and children aged 5 years and older	12 Amb a 1-U/ tablet	20
N/A	• Grass peptides	• This product is not approved in Canada	6-12 nmol/intradermal injection	21
DUPIXENT®	• Dupilumab	• Moderate to severe atopic dermatitis in adults and children aged 6 years and older. • Severe asthma in adults and children aged 6 years and older • Severe chronic rhinosinusitis with nasal polyposis in adults	• 300 mg single-use syringe (300 mg/2 mL) • 300 mg single-use pen (300 mg/2 mL) • 200 mg single-use syringe (200 mg/1.14 mL) • 200 mg single-use pen (200 mg/1.14 mL) • 100 mg single-use syringe (100 mg/0.67 mL)	22,23
XOLAIR®	• Omalizumab	• Moderate to severe asthma with PAR • Adults and children aged 6 years and older	• 75 mg and 150mg pre-filled syringe	24,25

Table 1. *Summary of the Aforementioned Therapies Involved in the Management of AR*

Abbreviations:

AIT	Allergen immunotherapy	MASK	Mobile Airways Sentinel Network
AR	Allergic rhinitis	OAH	Oral H1-antihistamine
ARIA	Allergic Rhinitis and its Impact on Asthma	PAR	Perennial AR
GRADE	Grading of Recommendations, Assessments, Development and Evaluation	RWE	Real-world evidence
IgE	Immunoglobulin-E	SAR	Seasonal AR
IL	Interleukin	SCIT	Subcutaneous immunotherapy
INCS	Intranasal corticosteroid	SLIT	Sublingual immunotherapy
IAH	Intranasal H1 antihistamines	SPIREs	Synthetic peptide immunotherapy epitopes
mAb	Monoclonal antibody		

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