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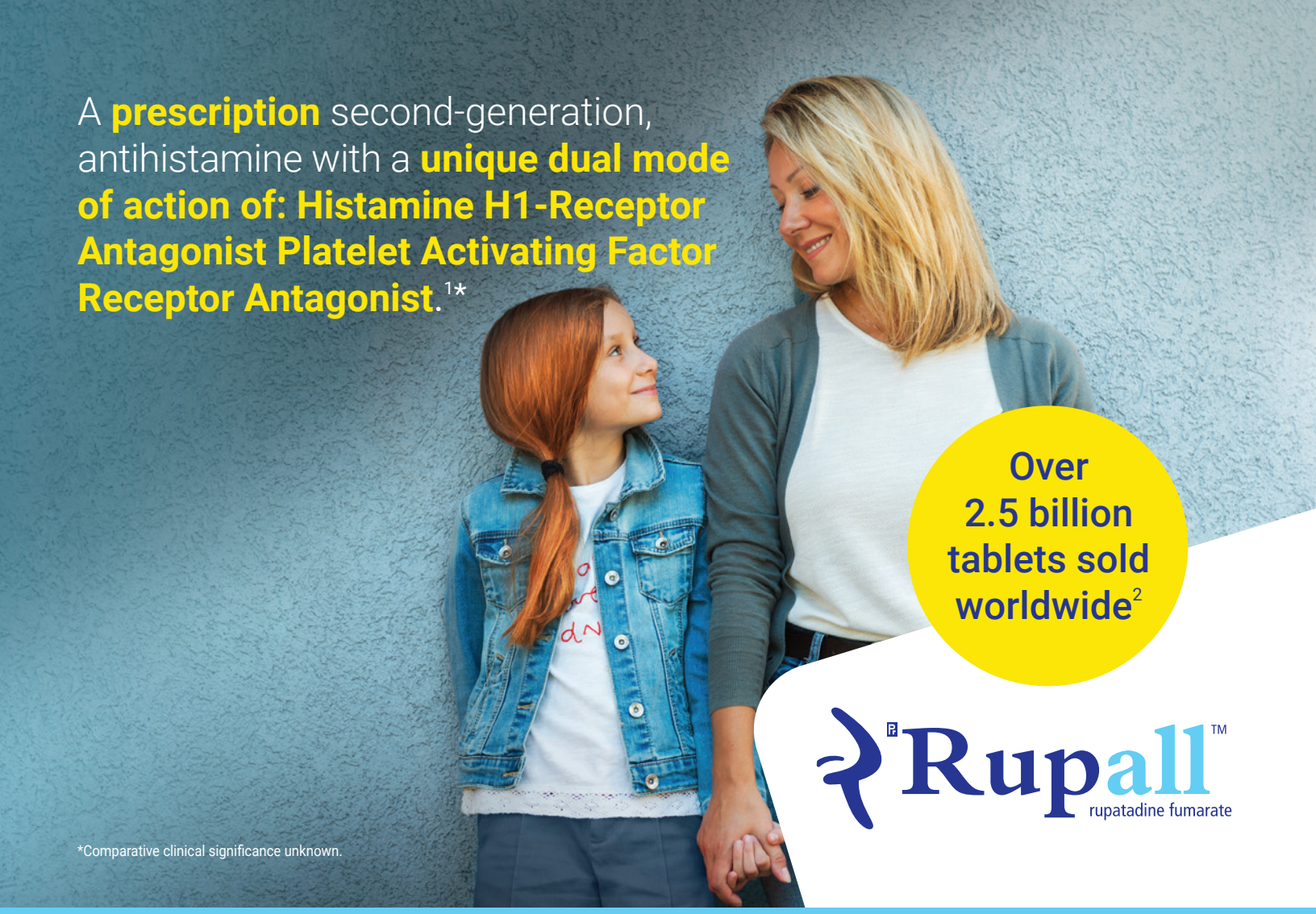

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AN ALLERGIST'S APPROACH TO EOSINOPHILIC ESOPHAGITIS

Background

Eosinophilic esophagitis (EoE) is a chronic, inflammatory disease of the esophagus that produces a range of symptoms in both adults and children, from acid reflux to food bolus impaction. The diagnosis is confirmed by endoscopic biopsies showing 15 or more eosinophils per high-power field.[1] The pathophysiology of EoE is believed to be either immune-mediated or antigen-mediated, ultimately resulting in a T helper 2 (TH2) immune response, eosinophilic inflammation, barrier dysfunction, and tissue remodelling.[2,3]

Since its recognition, EoE has been fundamentally linked to atopy, with early case reports drawing attention to this relationship.[4] Patients with EoE tend to be highly atopic, demonstrating a higher incidence of allergic rhinitis, asthma and atopic dermatitis compared to healthy controls.[5] There is also a high prevalence of IgE-mediated food allergies among these patients. A U.S.-based cross-sectional study reported that 32.4% of children and 37.3% of adults with EoE had an IgE-mediated food allergy to at least one food.[6] More recent research has shown that 87% of a cohort of 92 EoE patients had comorbid atopic conditions.[7] A review of 1,218 patients with EoE found that these patients have a 67-fold increased risk of anaphylaxis compared to that of the general population.[8] With this in mind, allergists play a key role in controlling esophageal inflammation and addressing atopic comorbidities.

Allergy testing for foods to identify triggers for EoE has gradually fallen out of favour in the literature. For the 2020 AGA (American Gastroenterological Association) and Joint Task Force (AAAAI/ACAAI) EoE management guidelines, the weakest recommendation ("conditional") and lowest quality of evidence ("very low quality") was assigned to the role of allergy-based testing for identification of specific food triggers when compared to no treatment (i.e. testing was similar to not doing anything), due to limited accuracy.[9] More recently, the 2022 British EoE guidelines explicitly recommending against all forms of food allergy testing (skin prick, specific IgE, specific IgG4, and atopy patch testing) to guide dietary elimination.[1] This evolution is due to multiple revelations in the pathophysiology of EoE and clinical experience. The failure of omalizumab to effectively treat EoE suggests a non-IgE-mediated pathophysiology.[10] Moreover, elimination diets guided by allergy testing have been shown to be no more effective than empiric dietary elimination.[11,12] However, allergy testing for aeroallergens is a key part of EoE management to maintain control of comorbid atopic disorders.[13] While IgE-based testing methods for food allergies cannot reliably predict triggering foods for EoE, such testing can guide the reintroduction of previously avoided foods to which patients may have developed new IgE sensitization, when used in conjunction with oral food challenges. Allergists have special training and expertise in the proper selection and interpretation of skin and serum-specific IgE tests, conducting oral food challenges, and guiding immunotherapy such as aeroallergen or food immunotherapy.

In our first case, we will describe a pediatric patient with EoE and multiple IgE-mediated food allergies, and the potential role of oral immunotherapy (OIT). Our second case will focus on the management of a young adult with EoE and severe allergic rhinitis with consideration for sublingual immunotherapy (SLIT). Our third case, a woman with severe EoE and multiple atopic comorbidities, will allow us to discuss the potential role of dupilumab. All three cases require the unique skill set of an allergist.

Case 1

A 2-year-old female has a known history of EoE and IgE-mediated food allergies to hen's egg, peanut, cashew, and sesame. While she had a clear history of anaphylaxis to egg, cashew and sesame, there was an unclear history for peanut and skin testing was intermediate in size (5 mm wheal) with peanut sIgE of 2.05 kU/L, therefore the diagnosis of peanut allergy was confirmed by an oral challenge. Her EoE is well-controlled with the elimination of cow's milk. However, the family has found food allergen avoidance burdensome and has expressed interest in OIT for the foods of concern. On further review, the patient had an immediate-onset urticaria after accidentally ingesting milk, which had been avoided for approximately six months. Prior to initiating OIT, allergen skin prick testing to cow's milk was performed and was positive. Similar to this patient's history, previous reports have shown EoE patients developing IgE-mediated food allergies after a period of avoidance.[14]

The overall prevalence of EoE after OIT is estimated to be 2.7%, with EoE often resolving after discontinuation of therapy.[15,16] Our centre participated in a real-world Canadian preschool peanut OIT safety analysis, which

showed similar results: three of 270 patients reported symptoms of possible EoE, with one having biopsy-proven EoE (0.37%).[17] Based on the available literature, it is apparent that EoE or esophageal eosinophilia may be a transient feature seen in a subset of long-term OIT patients. This issue is further complicated by a Brazilian study showing that at baseline, cow's milk-allergic patients may have asymptomatic esophageal eosinophilia, suggesting that OIT may "unmask" rather than cause EoE in some patients.[18] The relationship between EoE and OIT remains complex, and the question of whether this represents causation, unmasking or coincidence remains unanswered.

Current OIT guidelines from the Canadian Society of Allergy and Clinical Immunology (CSACI) permit the use of grocery store based OIT products outside of the research setting, due to the absence of Health Canada licensed OIT products. The guidelines list EoE as a relative contraindication (not absolute) for initiating therapy. In fact, EoE patients are typically excluded from OIT trials, given the possible relationship between the two that we have described. The available literature sheds new possibilities on whether OIT causes, unmasks or is coincidental with EoE. Furthermore, esophageal eosinophilia tends to resolve once OIT therapy is discontinued.[14,19] In a longitudinal peanut OIT study of 21 patients, at baseline 3 patients (14%) had asymptomatic eosinophil counts of > 15 eosinophils per high-power field, with most patients showing only transient esophageal eosinophilia during OIT (one patient in this study developed symptomatic EoE).[20] In contrast, other reports have shown that EoE diagnosed in the context of OIT may persist, suggesting that the disease may have been unmasked.[21,22] Regardless, EoE diagnosed during the course of OIT can be effectively treated with the use of swallowed steroids or proton pump inhibitors without stopping OIT.[23,24] For patients in the real world who are diagnosed with EoE in the context OIT, a recent publication has suggested adopting a shared decision-making approach with patient families instead of declaring absolute contraindications.[25] In light of the current understanding of EoE pathogenesis, it is the author's personal opinion and proposal that OIT may be carefully started in patients with EoE who desire it, with the understanding that adjustments to OIT or EoE management can be considered should concern for disease worsening arise.

In cases where a patient suffers from EoE and IgE-mediated food allergies, there is a need for shared decision-making between the family and gastroenterology colleagues. When patients experience gastrointestinal (GI) symptoms during OIT, it is recommended to categorize the symptoms based on whether they are immediate or delayed relative to the OIT dose (**Figure 1**).[19] Immediate IgE-mediated symptoms usually improve with ongoing treatment as desensitization occurs. Delayed reactions of more than two hours raise concern for EoE-related symptoms. It is also important to recognize GI symptoms that are unrelated to OIT: common causes include infectious gastroenteritis, functional abdominal pain, constipation, gastroesophageal reflux disease, and celiac disease.

If a patient with EoE on OIT experiences delayed symptoms, it is important to assess the patient with endoscopy and biopsies if a gastroenterologist is readily available. If there is worsening, there are several possible management approaches involving modifications to OIT dosing or addition of EoE medications, as detailed in **Figure 1**. If these approaches are not successful, the risks and benefits of OIT should be reweighed and therapy may be discontinued. Collaborating with gastroenterology colleagues to optimize pharmacotherapy is the best approach.

Case 2

A 21-year-old male has a known history of EoE, as well as allergic rhinoconjunctivitis. His EoE is currently well-managed with swallowed viscous budesonide. However, his allergy symptoms have been increasingly severe during the spring, affecting his daily activities such as sports and school. Skin testing revealed positive results for alder, birch and grass mix. The patient is unable to undergo subcutaneous immunotherapy due to his busy schedule and would prefer SLIT for tree pollen.

The product monographs for SLIT tablets commonly state that EoE is a contraindication to therapy.[26,27,28] Worsening or causation of EoE on SLIT is generally felt to be rare given how many patients are on SLIT, with case reports having documented some patients developing biopsy-confirmed EoE while receiving SLIT,[29] with endoscopic findings returning to normal between four weeks and 16 months following discontinuation of therapy. The possibility that SLIT can induce EoE suggests that aeroallergens may trigger EoE, potentially through a T cell mediated response.[30] Growing evidence supports the role of aeroallergens in influencing EoE disease activity. Retrospective data has revealed a correlation between EoE diagnoses and seasonal patterns, possibly related to pollen counts.[31] Direct esophageal deposition of aeroallergens is also believed to play a role in EoE inflammation.[32,33] Aeroallergen allergy testing can help identify allergens to avoid, which may improve EoE control, and may also help guide the timing of esophageal biopsies

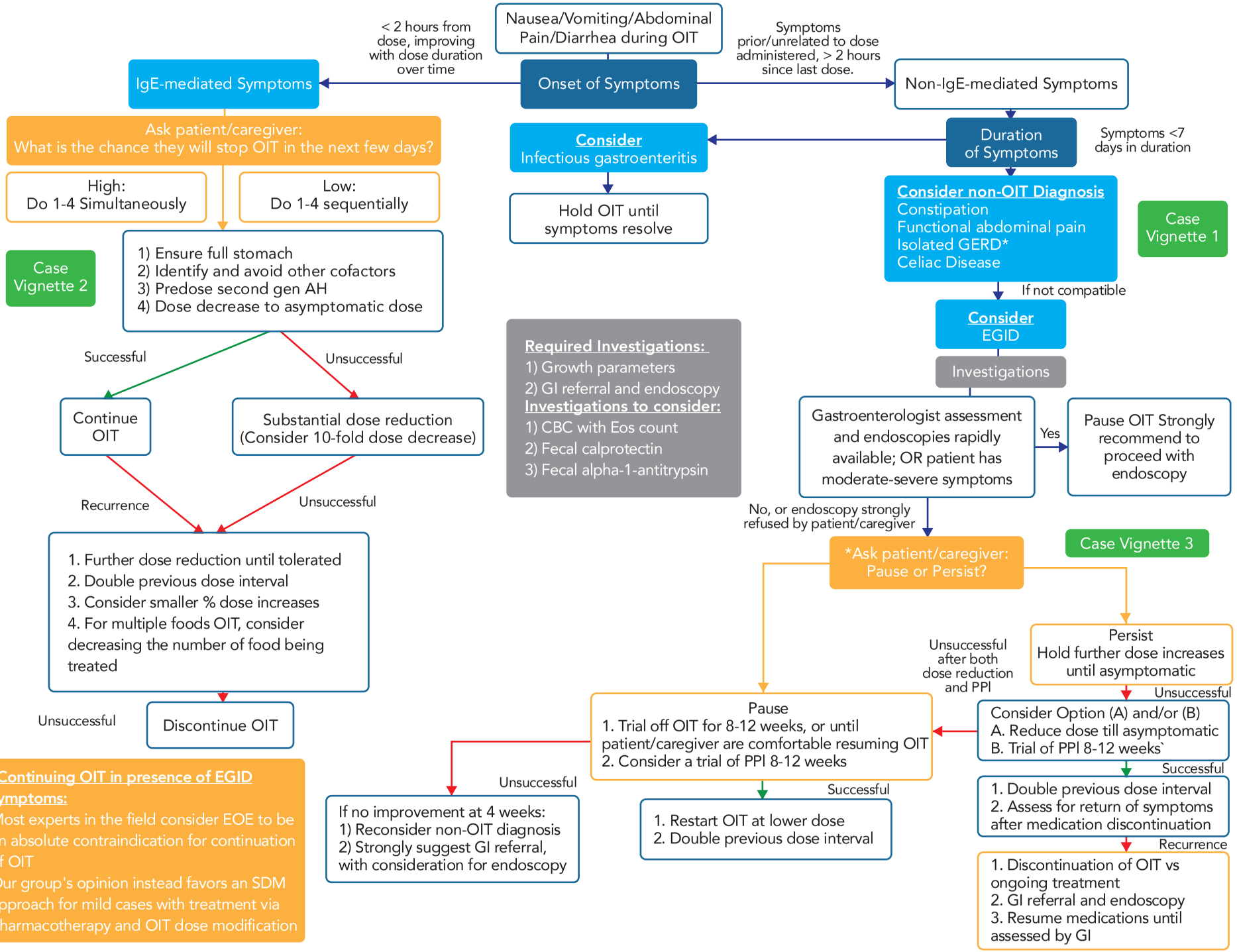

Figure 1: *Flow diagram of diagnosis of gastrointestinal symptoms during oral immunotherapy. CBC, Complete blood count; EoE, eosinophilic esophagitis; EoS, eosinophilic colitis. Reproduced with permission from Chua et al.*[19]

OIT: Oral immunotherapy, Second gen AH: Second generation anti-histamine, PPI: Proton pump inhibitor, GERD: Gastroesophageal reflux disease, EGID: Eosinophilic gastrointestinal disease, GI: Gastroenterology specialist, SDM: Shared decision making

to avoid confounding the interpretation of disease control during periods of seasonal worsening.[13]

While evidence suggests a relationship between local esophageal aeroallergen exposure and esophageal inflammation, SLIT may still have a role in managing underlying atopic disorders in select patients with EoE. In this particular case, SLIT may improve control of the patient's severe allergic rhinoconjunctivitis. Furthermore, clinical studies have linked control of allergic rhinitis to reduced esophageal eosinophilia.[34] Given the literature suggesting that pollen exacerbates EoE, it is possible that immunotherapy could conversely improve seasonal EoE.

After discussing the risks and benefits of aeroallergen SLIT with a patient with EoE, it may be reasonable to initiate this therapy in select patients for whom the benefits of immunotherapy outweigh the risk of exacerbating EoE. It is important to inform the patient's gastroenterologist that this therapy has been initiated, and it may be preferable to document a baseline endoscopy to confirm adequate control of EoE prior to SLIT. These patients should also be instructed to closely monitor for EoE-related symptoms.

Extrapolating from the approach outlined by Chua et al for managing GI symptoms in patients receiving OIT,[19] for a patient who has an established diagnosis of EoE and experiences worsening EoE symptoms while on SLIT, a number of approaches can be considered. If a gastroenterologist is available for assessment, endoscopy with biopsies should be considered. If evidence of worsening EoE is found, several approaches can be taken, such as initiating or adjusting topical swallowed corticosteroid therapy. If the wait time for repeat endoscopy is considered unacceptable, it would be reasonable to proceed with initiating therapy such as a trial of a proton pump inhibitor (PPI). After discontinuation of the medication, the patient should be monitored for symptom recurrence. If these approaches are unsuccessful, the risks and benefits of SLIT should be re-evaluated, and discontinuation of therapy or collaboration with gastroenterology colleagues to optimize pharmacotherapy should be considered.

Case 3

A 35-year-old woman with EoE is seen in follow up in clinic. She is currently managed with swallowed budesonide orodispersible tablets. She reports daily dysphagia. She has a history of emergency department visits for bolus impaction, and her endoscopy shows widespread exudates and edema. Biopsy results showed 65 eosinophils per high-power field and indicate Barrett's esophagus. Additionally, her esophagus was severely narrowed and strictured, precluding passage of a standard endoscope. Her medical history includes severe asthma managed with an inhaled corticosteroid/long-acting beta-agonist inhaler, severe atopic dermatitis managed with betamethasone valerate 0.1% ointment, anaphylactic food allergy to peanut, tree nuts, and fish, and allergic rhinoconjunctivitis.

Dupilumab received Health Canada approval in May 2023 as a primary treatment for eosinophilic esophagitis in patients 12 years and older, weighing at least 40 kg.[35] It is a fully human monoclonal antibody targeting the IL-4Rα chain, which antagonizes both IL-4 and IL-13 signaling. In EoE patients, IL-13 is highly upregulated and plays a key role in promoting an eosinophilic inflammatory response and inducing histologic changes. Meanwhile, IL-4 promotes differentiation of TH2 cells and regulates eosinophil migration.[3]

Specialists caring for EoE patients have raised questions about where this medication fits into the treatment algorithm.[36] It has not been shown to be more effective than swallowed topical corticosteroids. In a phase 3 international, multi-centre, placebo-controlled trial, approximately 60% of patients showed histologic remission after 24 weeks of dupilumab treatment.[37] However, swallowed topical corticosteroids can induce histologic remission in up to 90% of patients, depending on the formulation.[38] Additionally, dupilumab is a costly therapy compared to other available options, and its cost-effectiveness over conventional EoE therapies has not been demonstrated.

Several scenarios have been proposed where dupilumab could be considered as a first-line agent.[39] The drug may be considered for patients with multiple comorbid atopic conditions, including moderate, persistent, or difficult-to-control asthma, atopic dermatitis, and chronic sinusitis with nasal polyps. Patient preference to avoid swallowed topical steroids or dietary restrictions may also be considered. As a step-up therapy, dupilumab can be considered for difficult-to-treat EoE, failure to thrive, poor growth, significant weight loss due to EoE, and frequent use of rescue therapies such as oral systemic corticosteroids or esophageal dilations. Additionally, it may be used for patients with severe diet restriction or those requiring amino acid formulas, clinically significant esophageal strictures or narrow caliber esophagus, and those refractory to current therapies due to continued symptoms, persistent abnormal esophageal inflammation, adverse effects, intolerance, or inability to adhere to existing treatments.

Besides dupilumab, several other biologics have been studied for treatment of EoE and eosinophilic gastrointestinal disorders.[40] Results from clinical trials

of anti-IL-5 agents (reslizumab, mepolizumab, and benralizumab) and the anti-Siglec-8 agent lirentelimab have shown improvement on biopsy but persistence of symptoms, suggesting that eosinophils are only one component of EoE pathology. Omalizumab has not shown efficacy. Clinical trials are ongoing for the S1P receptor modulator etrasimod, anti-IL-13 agents, and anti-IL-15. Additional targets studied in asthma that may have benefit for EoE include anti-IL-33 (itepekimab) and anti-TSLP (tezepelumab).

Identifying severe EoE patients who may benefit from biologic therapy is challenging because there is currently no standardized measure for grading EoE severity. The control of EoE can be assessed by histology and patient symptoms, which may not always align with each other. An "Index of Severity for Eosinophilic Esophagitis" (I-SEE) has been proposed to gauge disease severity in both the research and clinical setting, with a score of ≥ 15 suggesting severe EoE.[41] This index considers symptoms and complications, inflammatory features, and fibrostenotic features and can be easily completed during patient visits.

In this case, our patient has severe EoE (I-SEE score of 25) and is refractory to current therapy with a swallowed topical steroid. Furthermore, she has multiple severe atopic comorbidities, and a history of significant esophageal strictures and narrow caliber esophagus. Given these factors, she may benefit from dupilumab as step-up therapy. Besides controlling her EoE, asthma, and atopic dermatitis, dupilumab could additionally allow her to undergo oral immunotherapy safely to treat her anaphylactic food allergy.[42]

Conclusion

As allergists, we can offer our EoE patients a comprehensive evidence-based approach to controlling esophageal inflammation and addressing atopic comorbidities via our unique skills in proper selection and interpretation of skin or serum-specific IgE tests, oral food challenges, and conducting immunotherapy. Aeroallergen skin testing remains an important facet of EoE management for identifying environmental allergens that may be triggering disease activity. While the role of food allergy testing to identify EoE triggers and guide dietary elimination has fallen out of favour, it plays a role in guiding the reintroduction of previously avoided foods in conjunction with oral food challenges in case of development of potentially anaphylactic IgE-mediated food allergy. The cases we have described illustrate these points, and further touch upon the potential role of immunotherapy in these patients. OIT may be considered for patients with EoE and food allergies, with careful symptom monitoring and a plan for managing GI symptoms. SLIT may also be a consideration for patients with EoE and severe atopic comorbidities. Although approved by Health Canada, the role of dupilumab in the real world needs to be more clearly defined based on its high cost, but it may be most beneficial and cost-effective in treating patients with concurrent severe EoE and multiple atopic comorbidities. Overall, a collaborative approach with our gastroenterology colleagues, and a focus on individualized patient management is essential for the successful management of EoE.

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TAKE ON MODERATE-TO-SEVERE ATOPIC DERMATITIS WITH THE POWER OF CIBINQO®

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CIBINQO is indicated for the treatment of patients 12 years and older with refractory moderate-to-severe atopic dermatitis, including the relief of pruritus, who have had an inadequate response to other systemic drugs (e.g., steroid or biologic), or for whom these treatments are not advisable.

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Clinical use

Can be used with or without medicated topical therapies for atopic dermatitis.

Limitations of use: use in combination with other JAK inhibitors, biologic immunomodulators, or potent immunosuppressants, such as methotrexate and cyclosporine, has not been studied and is not recommended.

Most serious warnings and precautions

Serious infections: patients may be at increased risk for developing serious bacterial, fungal, viral and opportunistic infections that may lead to hospitalization or death; more frequently reported serious infections were predominately viral. If a serious infection develops, interrupt treatment until the infection is controlled. Risks and benefits of treatment should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Monitor for signs and symptoms of infection during and after treatment, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Malignancies: lymphoma and other malignancies were observed in patients taking JAK inhibitors to treat inflammatory conditions and were more frequently observed in patients with rheumatoid arthritis (RA) during a clinical trial with another JAK inhibitor versus TNF inhibitors.

Thrombosis: including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients taking JAK inhibitors to treat inflammatory conditions. Many of these events were serious; some resulted in death. Consider risks and benefits prior to treating patients who may be at increased risk. In a clinical trial in patients ≥50 years of age with RA, a higher rate of all-cause mortality and thrombosis occurred in patients treated with another JAK inhibitor versus TNF inhibitors. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

Major adverse cardiovascular events (MACE): including non-fatal myocardial infarction, were observed more frequently in patients ≥50 years of age with RA during a clinical trial comparing another JAK inhibitor versus TNF inhibitors.

Other relevant warnings and precautions

- Driving or operating machinery
- Dose-dependent increase in blood lipid parameters, lipid monitoring and management
- Hematological abnormalities
- Use with potent immunosuppressants
- Vaccination
- Monitoring and laboratory tests
- Fertility
- Women of childbearing potential
- Pregnancy and breastfeeding
- Geriatrics

For more information

Consult the Product Monograph at http://pfizer.ca/pm/en/CIBINQO.pdf for important information regarding adverse reactions, drug interactions and dosing information, which have not been discussed in this piece. The Product Monograph is also available by calling 1-800-463-6001.

AD=atopic dermatitis; JAK1=Janus kinase 1.
* Clinical significance unknown.

Reference: CIBINQO Product Monograph, Pfizer Canada ULC.

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ANCA-ASSOCIATED VASCULITIS FOR THE ALLERGIST AND IMMUNOLOGIST: A CLINICAL UPDATE

Introduction

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides are a group of multisystemic, relapsing, autoimmune diseases that include eosinophilic granulomatosis with polyangiitis (EGPA), granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA). While rare, with incidences between 1 and 25 per 100,000 individuals/year, these are diagnoses that should not be missed, as unrecognized, they are associated with significant morbidity and mortality.[1] Despite their infrequency, international collaborative research has resulted in multiple new therapeutic strategies across all three diseases.

Sinusitis in ANCA-associated Vasculitis

Sixty to sixty-five percent of patients with EGPA or GPA initially present with sinus symptoms.[2,3] EGPA typically presents with years of difficult-to-control, eosinophilic, polypotic rhinosinusitis with nasal polyposis and asthma, often requiring regular oral glucocorticoids in addition to conventional therapy to maintain disease control. Over time, blood eosinophilia becomes apparent, extra-sinopulmonary manifestations (e.g., eosinophilic pneumonia) often occur, and the disease evolves into EGPA with the emergence of vasculitic features that can include cardiomyopathy, gastrointestinal (GI) involvement, vasculitic skin lesions, and/or neuropathy.[1] Given that symptoms can be common to severe eosinophilic sinopulmonary disease, hypereosinophilic syndromes, and EGPA, it can be difficult to confirm the diagnosis if there are no overt vasculitic findings.[4] The 2022 classification criteria for ANCA-associated vasculitides (AAVs) have assisted in this process but require a vasculitis syndrome to first be diagnosed *before* considering EGPA-specific manifestations, and thus only provides limited inroads to this dilemma.[5] In addition to vasculitic manifestations, profound blood eosinophilia and serum ANCAs (typically to myeloperoxidase) can help differentiate EGPA from other diseases.[6] Recently, sputum ANCAs have demonstrated potential in detecting severe airway disease that is evolving into EGPA.[7]

GPA tends to present more acutely over weeks to months. It can initially manifest as rhinosinusitis (with episcleritis/conjunctivitis that mimics allergic disease in 10% of patients), but is often associated with bloody or purulent discharge suggesting infection that is refractory to antibiotics. As the disease progresses, up to 60% of patients will show tell-tale sinus bony destruction, septal perforation, and neo-osteogenesis on imaging.[8] Systemic manifestations that indicate a diagnosis of GPA includes diffuse alveolar hemorrhage and/or nodular lung disease; hematuria and glomerulonephritis; leukocytoclastic vasculitis; and mononeuritis multiplex.[1] ANCAs are seen in 90% of cases of GPA and are typically reactive to serine protease 3 (PR3). In addition to GPA, several other rheumatic diagnoses to consider based on the presence of erosive sinus disease are drug-induced vasculitis, cocaine-induced midline destructive lesions, IgG4-related disease, and relapsing polychondritis.

Updates in the Treatment of GPA and EGPA

The recent publication of the 2021 American College of Rheumatology guidelines for the management of AAV has consolidated treatment approaches.[9]

EGPA

As a disease with overlap of eosinophilic, allergic and vasculitic pathologies, the treatment for EGPA is varied and influenced by the underlying manifestations. Treatment for vasculitic manifestations of EGPA is often stratified by the five-factor score.[10] Patients with a score of zero, including those with refractory sinus symptoms but relatively mild vasculitis, can be treated with azathioprine or methotrexate; those with a score of one or greater can be treated with cyclophosphamide (followed by azathioprine) or, as suggested by forthcoming data from the REOVAS trial, potentially rituximab as well.[9,11] Vasculitic manifestations of EGPA are often responsive to therapy; the eosinophilic and sinopulmonary components have been more difficult to control with these agents and may require chronic, high-dose oral glucocorticoids.[12]This has changed, however, since the realization of the utility of anti-interleukin-5 (IL-5) agents in treating refractory sinopulmonary EGPA. The MIRRA trial demonstrated the efficacy of high- dose mepolizumab (300 mg subcutaneously every four weeks) to control disease and minimize glucocorticoid use in patients with EGPA; 28% of patients on mepolizumab achieved remission on 4 mg of prednisone per day or less at 52 weeks vs 3% of those taking placebo.[13] There were, however, few patients with true vasculitic manifestations; therefore, the use of mepolizumab for manifestations including cardiomyopathy and glomerulonephritis is not clear. Due to access issues, the conventional dose of 100 mg every four weeks has also been tried with some success, however, many patients do not achieve sufficient control with this dose and require either a switch to another anti-IL-5 agent or dose escalation of mepolizumab, with ongoing trials of alternative dosing strategies and agents.[14]

Despite this success, there continues to be a population of patients who have refractory sinopulmonary disease. This is a large driver of patient frustration and morbidity; assessments of health-related quality of life (HRQOL) indicate that sinus symptoms are the most frustrating for patients with EGPA.[12] Dupilumab, effective in managing other asthma and sinus disease, has similarly been found to be effective as either alternative or adjunctive therapy to anti-IL5 agents. The drug itself, however, may be associated with an increased risk of EGPA in patients with isolated sinopulmonary disease and may unmask it in vulnerable patients.[15] It is also important to note that while these drugs lower chronic oral glucocorticoid requirements for refractory EGPA patients, ongoing inhaled and/or intranasal therapy is often needed to achieve adequate disease

control. These parallel vasculitic and eosinophilic treatment strategies for EGPA, and the persistence of sinopulmonary disease, reinforce the heterogeneity of EGPA and the need to better understand both the disease pathogenesis and treatment options.[4]

GPA & MPA

The CYCLOPS, RITUXVAS and RAVE trials have ushered in the modern era of cyclophosphamide and rituximab as induction therapies for severe GPA and MPA. These agents achieve remission in over 90% of patients with these diseases.[16] The MAINRITSAN series, and RITAZAREM and PEXIVAS trials for maintenance therapy have demonstrated that continued treatment with rituximab can also provide durable remission with relapse rates as low as 5% per year, and that we can treat patients with lower doses of glucocorticoids than previously used.[16] Plasma exchange, long heralded as beneficial for diffuse alveolar hemorrhage, renal disease and mortality in AAV was found to have only some efficacy in acute, severe renal disease within the PEXIVAS trial and has shifted practice away from this intervention. Finally, the introduction of avacopan during the ADVOCATE trial has also helped realize the possibility of glucocorticoid-free treatments for AAV; however, its place in the therapeutic regimen is still being established.

In patients with non-severe disease including sinus involvement, methotrexate continues to be recommended. Sinus disease is, however, a source of impaired QOL; the disease is often refractory, requiring rituximab for effective treatment.[17,18] These findings indicate that our current disease construct of severe or non-severe GPA or MPA is limited. Future treatment regimens explore the possibility of shifting from crude indices of severity to a risk-based approach that allows for optimal strategies based on the patient and their disease. Furthermore, fatigue and sinus disease are identified as the largest drivers of ongoing morbidity and represent an area of unmet need that also requires close follow up.

Immune Consequences of Long-term B-cell Depletion in AAV

The diminished humoral response induced by rituximab is important for disease control in AAV, but it is also associated with increased risk of infection and poor vaccine response. While this was a significant concern during the COVID-19 pandemic, it spurred research that quantified that rituximab is associated with a 65% decrease in the capacity to mount an effective COVID vaccine response, and that B-cell recovery takes more than a year to achieve for 60% of patients.[19] As such, vaccinations should ideally be timed to two-to-three weeks prior to re-administration of rituximab. Furthermore, vaccines should be delayed to at least one year (if safely possible) following completion of rituximab therapy.

A second consideration of long-term rituximab administration is irreversible humoral suppression causing hypogammaglobulinemia. This has been found to occur in approximately 15% of patients, and individuals who demonstrate hypogammaglobulinemia following their first dose of rituximab are at higher risk for it at a later point.[20] While this predisposes a patient to recurrent infections, antibodies may have variable functionality, and antibody replacement with intravenous (IV) or subcutaneous immunoglobulins is indicated only for those with multiple infections, who often have IgG levels below 3 g/L.[9]

Conclusion

Multiple advances have been made in the treatment of AAV that have significantly improved outcomes for patients with these rare but potentially devastating diagnoses, although EGPA treatment continues to be a challenge for many patients. As the disease landscape evolves, research has shifted its focus to finding the optimal balance between disease control and therapeutic toxicity, as well as addressing patient-important outcomes such as sinonasal disease and fatigue. As new therapies are adapted from multiple disciplines, ongoing collaboration will be required to continue to improve the standard of care in AAV.

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Clinical use not mentioned elsewhere in the piece

RINVOQ should not be used in combination with other Janus kinase (JAK) inhibitors, immunomodulating biologics (e.g., biologic DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine.

Pediatrics: The safety and efficacy of RINVOQ in adolescents weighing <40 kg and in children aged 0 to less than 12 years with atopic dermatitis have not yet been established. No data are available; therefore, RINVOQ should not be used in this pediatric patient population.

Geriatrics (≥65 years of age): Caution should be used when treating geriatric patients with RINVOQ.

Most serious warnings and precautions

Serious infections: Patients treated with RINVOQ are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt RINVOQ until the infection is controlled. Reported infections include active tuberculosis (TB), which may present with pulmonary or extrapulmonary disease; invasive fungal infections, including cryptococcosis and pneumocystosis; and bacterial, viral (including herpes zoster), and other infections due to opportunistic pathogens. Test patients for latent TB before RINVOQ use and during therapy. Consider treatment for latent infection prior to RINVOQ use. Do not initiate treatment in patients with active infections including chronic or localized infections. Carefully consider the risks and benefits of treatment prior to initiating therapy in patients with chronic or recurrent infections. Closely monitor patients for signs and symptoms of infection during and after treatment, including the possible development of TB in patients who tested negative for latent infection prior to initiating therapy.

Malignancies: Lymphoma and other malignancies have been observed in patients treated with RINVOQ. An increase in malignancies, including lung cancer, were observed in RA patients ≥50 years with at least one additional cardiovascular (CV) risk factor who were taking a different JAK inhibitor, compared with tumour necrosis factor (TNF) inhibitors. Caution should be applied when using RINVOQ in geriatric patients, patients who are current or past smokers, and patients with other malignancy risk factors.

Thrombosis: Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with JAK inhibitors, including RINVOQ, for inflammatory conditions. Many of these adverse events were serious and some resulted in death. RA patients ≥50 years with ≥1 additional CV risk factor had a higher rate of all-cause mortality and thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis in a clinical trial with a different JAK inhibitor compared to TNF inhibitors. Consider the risks and benefits prior to treating patients who may be at increased risk for thrombosis. Discontinue RINVOQ and promptly evaluate patients with symptoms of thrombosis.

Major adverse cardiovascular events: Major adverse CV events, including non-fatal myocardial infarction, were observed more frequently in RA patients ≥50 years with ≥1 additional CV risk factor in a clinical trial with a different JAK inhibitor compared to TNF inhibitors. Caution should be applied when using RINVOQ in geriatric patients, patients who are current or past smokers, and patients with other CV risk factors.

Other relevant warnings and precautions

- Increases in lipid parameters, including total, low-density lipoprotein, and high-density lipoprotein cholesterol
- Gastrointestinal perforations
- Hematologic events
- Liver enzyme elevation
- Patients with severe hepatic impairment
- Concomitant use with other potent immunosuppressants, biologic DMARDs, or other JAK inhibitors
- Immunizations
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RINVOQ can be used with or without topical corticosteroids.

Not a real patient, for illustrative purposes only.

In the MEASURE UP 1 study:‡

RINVOQ 15 mg demonstrated significant improvement in skin clearance (as measured by proportion of patients with EASI 75; co-primary endpoint & EASI 90; secondary endpoint) **vs.** placebo at Week 16[1,2]

- **EASI 75**: **69.6%** (n/N=196/281) **vs. 16.3%** (n/N=46/281) of patients achieved EASI 75 with **RINVOQ 15 mg vs. placebo** (p<0.0001, multiplicity-controlled).
- **EASI 90**: **53.1%** (n/N=149/281) **vs. 8.1%** (n/N=23/281) of patients achieved EASI 90 with **RINVOQ 15 mg vs. placebo** (p<0.0001, multiplicity-controlled).

A rapid improvement in skin clearance was achieved for RINVOQ 15 mg compared to placebo (defined as EASI 75 by Week 2; secondary endpoint)[1,2]

- **EASI 75**: **38.1%** (n/N=107/281) **vs. 3.6%** (n/N=10/281) of patients achieved EASI 75 at Week 2 with **RINVOQ 15 mg vs. placebo** (p<0.0001, multiplicity-controlled).

A greater proportion of patients treated with RINVOQ 15 mg achieved clinically meaningful itch reduction (≥4-point reduction in Worst Pruritus NRS; secondary endpoint) compared to placebo treatment group at Week 16

- **≥4-point reduction in Worst Pruritus NRS**: **52.2%** (n/N=143/274) **vs. 11.8%** (n/N=32/272) of patients achieved a ≥4-point reduction in Worst Pruritus NRS with **RINVOQ 15 mg vs. placebo** (p<0.0001, multiplicity-controlled).

At Week 16, a greater proportion of patients treated with RINVOQ 15 mg achieved clinically meaningful improvement in emotional state (ADerm-IS emotional state domain score improvement from baseline; secondary endpoint) vs. placebo group (RINVOQ 15 mg [n/N=142/227]: 62.6%; placebo [n/N=42/212]: 19.8%; p<0.0001, RINVOQ vs. placebo, multiplicity-controlled).

RINVOQ is only indicated in patients not adequately controlled with a systemic treatment or when it's inadvisable; majority of the study subjects were treated with systemic therapy or phototherapy before starting RINVOQ.

* Comparative clinical significance has not been established.
† Please see Product Monograph for additional dosing and administration information.
‡ MEASURE UP 1 was a 16-week, randomized, double-blind, multicentre, placebo-controlled study that included adolescent and adult patients with refractory moderate to severe atopic dermatitis not adequately controlled by topical medication(s). At baseline, patients had an vIGA-AD score ≥3 in the overall assessment of AD (erythema, induration/papulation, and oozing/crusting) on an increasing severity scale of 0 to 4, an EASI score ≥16 (composite score assessing extent and severity of erythema, edema/papulation, scratches and lichenification across 4 different body sites), a minimum BSA involvement of ≥10%, and weekly average Worst Pruritus NRS ≥4. Patients received RINVOQ 15 mg or RINVOQ 30 mg once daily, or placebo.

ADerm-IS: Atopic Dermatitis Impact Scale; BSA: body surface area; EASI: Eczema Area and Severity Index; JAK: Janus kinase; NRS: Numerical Rating Scale; vIGA-AD: validated Investigator's Global Assessment for Atopic Dermatitis.

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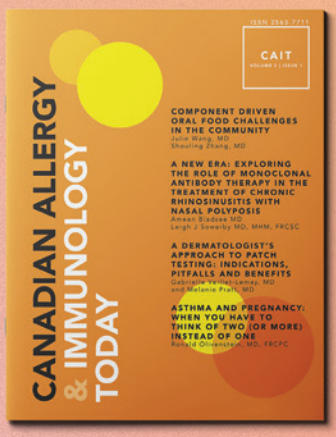

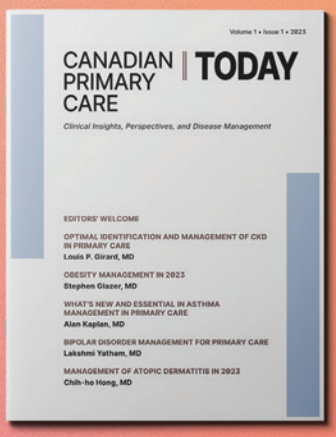

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TARGETED THERAPIES FOR ALLERGIC CONJUNCTIVITIS: AN OPHTHALMOLOGIST'S PERSPECTIVE

Introduction

Allergic eye disease is extremely common as the eye is sensitive to irritants due to its constant exposure to the external environment. Approximately 40% of the general population is affected by ocular allergies.[1] The majority of patients may also suffer with additional associated symptoms of allergic rhinitis, such as nasal congestion, sneeze, etc.; however, 6% may have isolated ocular symptoms.[2] In addition, there are links between ocular allergies and other allergic conditions such as asthma, food allergy and atopic dermatitis.[3] The challenge is that in addition to ocular symptoms, patients experience a substantial negative influence on their quality of life (QOL). The most common symptoms are watery and itchy eyes; redness; soreness; stinging; burning sensations; and swelling.[4] Unfortunately, as these symptoms are quite common, most patients may choose to self-medicate and many cases are undiagnosed or underdiagnosed. As a result of this, patients may not utilize the correct management strategy; this can lead to a further propagation of symptoms and a greater reduction in patients' QOL. Hence, it is crucial for patients to seek professional medical attention, while physicians must gather a comprehensive medical history and conduct relevant investigations. Additionally, the physician ought to propose the correct diagnosis and suitable treatment plan.

Anatomy of the Eye

Each component of the eye can have an impact on the patient's immune response **(Figure 1)**. The eyelids act as a barrier to allergens. The lacrimal gland and its components produce tears which help to lubricate

and protect the ocular surface. The concentration and quality of the tears is affected by any type of inflammatory response.[4] In addition, the conjunctiva and cornea are the external layers that come into contact with allergens. While there are no mast cells within these tissues, these will increase in the setting of an allergic response. The cornea is avascular, therefore it will not be directly involved; however, the influence of the patient's immune response can lead to ocular surface instability and result in blurry vision.[6] The sclera is the next layer under the conjunctiva and is composed primarily of collagen. The uvea is highly vascularized and produces aqueous humour; it is the site involved in uveitis. The retina and optic nerve complete the visual organ.

Allergic Eye Disease

There are numerous components in allergic eye disease, however, the most common consist of seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), which can affect up to 15%-25% of the population. The differentiating factor between these two types of allergic eye disease is typically the periodicity or chronicity of the patient's symptoms. SAC is triggered by transitory allergens (e.g., tree pollen) while PAC is caused usually by indoor allergens (e.g., dust mites or dander).[6] Furthermore, allergic conjunctivitis (AC) can be classified as the following: atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC) and giant papillary conjunctivitis (GPC). The last entity relates primarily to physical friction as opposed to a true allergy. It can be associated with contact lens wear or other types of mechanical rubbing.

Mechanism of Disease

The immunopathophysiology of ocular allergies helps to determine their optimal treatment. Ocular allergies are mediated by both early and late phase reaction, triggered initially by allergens eliciting histamine release. This is followed by a cascade of proinflammatory mediators such as prostaglandins, leukotrienes and cytokines, with eventual eosinophil, neutrophil and macrophage involvement. All of these biochemical molecules contribute to the eventual signs and symptoms of the allergic response.[7]

Treatment Modalities

As mentioned above, in cases of allergic eye disease, the majority of patients self-diagnose and self-medicate with over-the-counter (OTC) products. Prior to this, some patients will simply use water to rinse and wash their eyes to attempt symptomatic relief. This is somewhat effective, as it does help to physically clear away allergens from the ocular surface and dilute them. Another method is allergen avoidance; however, this is sometimes difficult to achieve. Cool compresses offer temporary relief from vasoconstriction.

Antihistamines

Antihistamines are used to target a major factor in the allergic response and they are certainly one of the initial choices for treatment. Of note, clinicians must be aware of the impact of various histamine receptors and their effects. H1 and H4 receptors are primarily responsible for pruritus; H2 relates to vasodilation; and H3 receptors have an immunomodulatory effect as their release actually inhibits histamine release.[8]

A variety of topical applications are on the market, some of which are available on an OTC basis. For example, antazoline (Naphcon-A®) and pheniramine (Opcon-A®) can be easily sourced. They are helpful for the short-term relief of itchiness only and may require repeated instillations to achieve symptomatic relief. They are therefore best used in the acute or early phase of the allergic response.

In addition, oral antihistamines play a role in the treatment of the ocular response. This is due to the fact that ocular symptoms are typically accompanied by symptoms including rhinitis and sneezing, making a systemic approach helpful. In this context, the distinction between first and second generation antihistamines is noteworthy. Second generation antihistamines may be preferred due to their reduced sedative side effect profile resulting from their reduced ability to cross the blood-brain barrier.[9]

Mast cell stabilizers

These agents are best utilized on a prophylactic basis and require a loading period of several weeks prior to antigen exposure. This can lead to decreased compliance as patients do not experience the agents' maximal effect until a later time.[10] Examples of these agents are lodoxamine ([Pr]Alomide®) and sodium cromoglycate 2% ([Pr]Cromolyn®).

Dual-action topical agents

These agents offer the benefits of both antihistamines and mast cell degranulation inhibitors. Therefore, they are effective in the early phase (the antihistamine component) as well as the late phase (prophylactic mast cell stabilization) of allergic eye disease. As they can achieve good overall symptomatic relief, they are generally used as first line. There are few examples of medications in this category. One of these is olopatadine ([Pr]Patanol®) which has been used for many years with good success. It was the first dual-action agent available. In addition to its high H1 receptor affinity, it inhibits leukotriene release, adhesion molecules and cytokines.[9]

Bepotastine ([Pr]Bepreve®) is a relatively new medication, initially used orally for the treatment of allergic rhinitis, urticaria and other dermatological conditions.[11] When used topically, it has been shown to have relatively rapid onset , high affinity for the H1 receptor and a duration of up to 8 hours.[12]

Steroid eye drops

Steroid eye drops treat AC via multiple approaches: They reduce the inflammatory cytokine release, reduce mast cell proliferation and reduce the overall immune response. They are definitely the most effective agent for symptomatic relief; however, due to their potential side effects (e.g, possible increase in intraocular pressure (IOP) and potential for accelerated cataract formation) they are typically used for only a short period of time. Once symptoms have subsided, it is usually recommended that they be replaced with any of the non-steroid approaches mentioned above. In light of this, they are typically utilized in a pulsed fashion to reduce exacerbations. Ester-based steroids such as loteprednol etabonate ([Pr]Alrex® 0.2% or [Pr]Lotemax® 0.5%) are sometimes preferred as they are metabolized more efficiently and therefore produce fewer side effects than other agents.[13]

Stronger steroids, such as ketone-based prednisolone acetate 1% ([Pr]Pred Forte®), prednisolone phosphate 1% and dexamethasone 0.1% ([Pr]Maxidex®), can be used in more severe cases. Naturally, due to their stronger nature, they are also known to cause an increased incidence of side effects.

Topical immunomodulators

Topical immunomodulators are utilized in cases involving the cornea, specifically VKC and atopic keratoconjunctivitis (AKC). The most commonly-used agents are cyclosporine A and tacrolimus; their mechanism of action is T cell inactivation. Cyclosporin A 0.05% ([Pr]Restasis®) has been indicated for dry eye disease (DED) and has traditionally been used in the setting of AC as a steroid-preserving method. However, recently, cyclosporin A 0.1% ([Pr]Verkazia®) has been approved by Health Canada for the treatment of VKC in a pediatric setting (age 4 to adolescence). Cyclosporin A 0.1% contains a unique formulation in which a cationic nanoemulsion is utilized to deliver the cyclosporine onto the corneal surface. As the emulsion is positively charged, the product remains on the negatively charged corneal surface for an extended duration, allowing for improved exposure and more rapid spread of the medicine.[14] Currently available ophthalmic agents for the treatment of AC are described in **Table 1**.

Conclusion

Evolving research within the field of AC has yielded, and will continue to yield, novel and more effective modes of treatment with the objective of optimizing symptomatic relief and reducing potential side effects. In addition to improved efficacy, innovative drug delivery mechanisms will certainly lead the way toward this.

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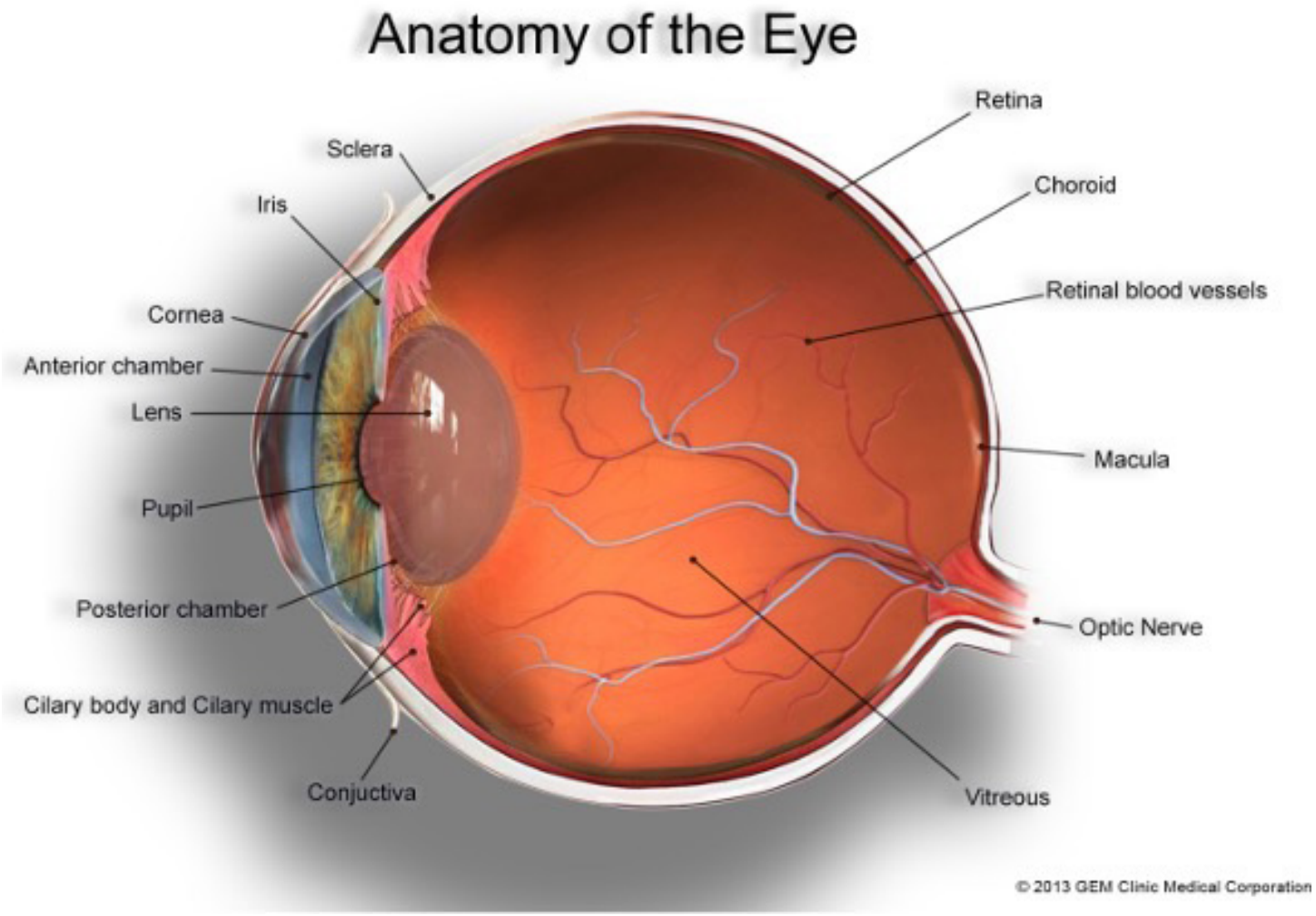

Figure 1: *Anatomy of the Eye.*

Agent (Brand name)	OTC vs. Rx	Dosing
Topical antihistamines	OTC	QID
Antazoline (Naphcon-A)	OTC	QID
Pheniramine (Opcon-A)		
Mast cell stabilizers	Rx	QID
Lodoxamide (Alomide)	Rx	QID
Cromolyn sodium 2%		
Dual activity	Rx	BID
Olopatadine 0.1% (Patanol)	Rx	QD
Olopatadine 0.2% (Pataday)	Rx	QD
Olopatadine 0.7% (Pazeo)	Rx	BID
Ketotifen 0.025% (Zatidor)	Rx	BID
Bepotastine besilate 1.5% (Bepreve)		
Steroids	Rx	BID to QID
Loteprednol etabonate 0.2% (Alrex)	Rx	BID to QID
Loteprednol etabonate 0.5% (Lotemax)	Rx	QD to QID
Fluorometholone acetate 0.1% (FML)	Rx	QD to QID
Prednisolone actetate 1.0% (Pred Forte)	Rx	QD to QID
Dexamethasone 0.1% (Maxidex)		
Topical immunomodulators	Rx	BID
Cyclosporine 0.05% (Restasis)	Rx	QID
Cyclosporine 0.1% (Verkazia)		
Non-medicated	OTC	QD to QID
Soothe allergy + dry eye (0.24% hyaluronic acid and 2% ectoine)	OTC	QD to QID
HYLO-DUAL (0.5 mg/mL hyaluronic acid and 20 mg/mL ectoine)	OTC	QD to QID
HYLO-DUAL Intense (2.0 mg/mL hyaluronic acid and 20 mg/mL ectoine)	OTC	TID to QID
Zaspray (4.5% Per-Lip complex and 0.2% hyaluronic acid)		

Table 1: *Ophthalmic agents for the treatment of AC; courtesy of King Chow, MD, FRCSC*

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AEROALLERGEN AVOIDANCE: UPDATED EVIDENCE AND HOW TO ADVISE PATIENTS

Introduction
Allergic rhinitis (AR) is highly prevalent in Canada, affecting approximately 20–25% of the population. Asthma is estimated to affect approximately three million Canadians, and between 12% and 25% of Canadian children. Approximately two-thirds of individuals with asthma are allergic to aeroallergens, and these allergens act as triggers for asthma exacerbations. Overall, approximately 7.7 million individuals were affected by aeroallergens in Canada in 2016. High concentrations of ambient aeroallergens, including tree pollen and fungal spores have been associated with increased risk of premature birth, myocardial infarction (MI) and asthma-related Emergency Department visits and hospitalizations in cities across Canada. This demonstrates that nation-wide aeroallergen counts are associated with severe signs and symptoms.[1]

Children exposed to various indoor allergens are placed at an increased risk of developing asthma in later life, with sensitization in these individuals being a strong predictor of disease morbidity. Common indoor exposures for infants include house dust mite, pet, cockroach, mould, and rodent allergens.

Sensitization to at least one indoor allergen has been demonstrated to be present in nine of every ten children hospitalized with asthma.[2]

It has been noted that more than 90% of children worldwide breathe polluted air. While the impact of climate change on aeroallergen exposure is not fully understood, there is increasing evidence that it may have an impact on outdoor aeroallergens and, by extension, asthma control in children. Global warming has been projected to influence the duration and intensity of pollen seasons, and may lead to increased pollen production, prolonged pollen seasons, and increased pollen protein allergenicity.

The changing weather patterns including rainfall and wind may cause pollen species to reach environments in which they had not previously been present, contributing to a shift in geographic pollen distributions.

Avoidance and Removal Measures
For indoor allergens, the Global Initiative for Asthma (GINA) strategy does not recommend allergen avoidance as a general strategy, noting limited evidence of clinical benefit particularly with a single-

strategy indoor aeroallergen avoidance approach. A comprehensive approach is most likely to be beneficial, especially in the presence of multiple allergies.

Allergen avoidance and various methods of controlling exposure and allergen concentration have been studied in the setting of AR. Although commonly employed in AR management, most allergen avoidance strategies have demonstrated mixed evidence. Optional physical techniques for allergen exposure control include air filtration, barrier methods, bait traps, insecticides, and acaricides in household cleaners.[3]

There is support for improved AR and asthma control following pet avoidance and removal; however, compliance with pet removal strategies is extremely poor. Pollen avoidance strategies (e.g., air conditioning in buildings and automobiles) are generally well tolerated and are associated with low cost; however, further work is needed to investigate the effectiveness these methods. Overall, pet, pest and pollen allergen avoidance is considered an optional intervention, and occupational avoidance of triggers is considered a recommendation.[3]

House dust mites

Measures to remove house dust mites include mattress and pillow covers (with a pore diameter no more than 10 microns); regular washing of bedding in hot water; removal of stuffed toys, upholstered furniture and carpeting; regular vacuuming; and maintaining low household humidity levels (<50%) **(Figure 1)**. It has been shown that the use of dust mite-eliminating agents, i.e., acaricides (benzyl benzoate, tannic acid), not only cause an insignificant and impermanent reduction in the number of dust mites, but that their population is rapidly restored following acaricide use.[8] Furthermore, the direct effect of these chemical agents on patients' health is uncertain. For this reason, the use of chemical products is not recommended for patients with a house dust mite allergy.

In a systematic review of 20 studies in children and adolescents, multicomponent dust mite interventions reduced the number of asthma symptoms by 0.8 days per two weeks (21.0 symptom days per year) and reduced the number of asthma acute care clinician visits by 0.57 visits per year.[18]

PET allergens

The optimal approach to remove pet allergen from the home is removal of the pet itself from the home. However, even with pet removal it can take months for the pet aeroallergen to reduce to baseline. In a study of 15 homes over a 9-to 43-week period following cat removal, Fel d 1 levels declined gradually in most homes. At 20 to 24 weeks following cat removal, the Fel d 1 levels in 8/15 homes were consistent with those found in control homes without cats.[19] Whether or not the pet is removed from the home, thoroughly cleaning the home and removal of any allergen reservoirs (upholstered furniture and carpeting) may be beneficial. The use of high-efficiency particulate air (HEPA) filters, mattress and pillow covers, and regular washing (in particular for dogs but only if twice a week or more) can be helpful if the pet remains in the home. However, whether or not this reduction in airborne allergen levels impacts asthma disease activity remains controversial. The GINA strategy notes limited evidence of clinical benefit for asthma with pet avoidance strategies. This may be partly because exposure to pet allergens occurs in schools, public buildings and public transportation even if the pet is removed from the home.

Air filters and purifiers fitted with a HEPA system are a frequently recommended method of reducing the quantity of inhalant allergens derived from pets. Based on a current literature review, the most effective of these in terms of effectiveness and cost are free-standing, portable HEPA filters, central air filtration systems and laminar air flow systems. Unfortunately, reports on their efficacy are conflicting. Sulser et al have shown that 12-month usage of laminar flow filters only slightly reduced the quantity of inhalant allergens in the air and did not significantly affect bronchial hypersensitivity.[9] Nevertheless, another study conducted by Sicco van der Heide et al revealed that three-month use of a HEPA air purification system significantly reduced bronchial reactivity and decreased the amplitude of Peak Expiratory Flow (PEF).[9] Despite inconsistencies and doubts regarding the efficacy of this method in animal-produced inhalant allergen reduction, it is worth recommending and can be used as part of a multifaceted approach.

The efficacy of a feline diet with an egg product ingredient containing anti-Fel d 1 IgY antibodies was demonstrated in vitro, ex vivo and in vivo.[17] Data on this topic is scare and further clinical studies to evaluate its efficacy are needed.

Murine and cockroach allergens

Integrated pest management (IPM) strategies have demonstrated efficacy in removing cockroach, mouse and rat allergens from the home. IPM includes sealing all cracks/holes in the home; cleaning surfaces with detergent; vacuuming with HEPA filtration; the use of tracking powder (pesticides) on wall voids/pipe chases; snap traps; and family education about food

storage and kitchen cleaning. Simple interventions such as the use of insecticides can make a significant difference in the removal of these allergens. A recent study of 122 children with moderate-to-severe asthma noted that insecticidal bait in the homes resulted in lower levels of cockroach infestation (P<0.01). Children in control homes without the bait experienced more severe asthma symptoms (P=0.03), greater frequency of unscheduled medical visits (P=0.03); and worsening lung function (P=0.01) vs children in the intervention group.[21] Rodenticide can be considered in this context. For outdoor allergens, the GINA strategy notes that these are impossible to avoid completely.

Pollen allergens

Closing doors and windows and remaining indoors when pollen and/or mould counts are highest play have a role in reducing allergen exposure, although only low-quality evidence is available to support this intervention.

The strategies recommended most frequently include shutting windows and doors; avoiding going outside and, when returning home, washing clothes and taking a bath; wearing glasses to protect the eyes from contact with allergens; and using HEPA filters at home and on car air conditioning systems. Pollen calendars and monitoring of pollen and mould counts may be helpful at the individual and population level, as a correlation has been found between the pattern of pollen load and allergen content, and asthma symptoms. The investigation of novel methods to predict pollen counts, including mobile solutions, is ongoing.[2]

In addition, patients must be aware of the pollens to which they are sensitized. This will allow them to know when to exercise these pollen avoidance measures in order to gain maximum benefit from them.[10] Various methods and smartphone applications to support patients' knowledge regarding pollination periods are available.[11]

Fungi and mould

The basic method of avoiding inhaled allergens produced by moulds is elimination of all mouldy areas.[12] Mould is often found on ceilings, walls, floors, carpets, and toys. These surfaces should be cleaned with agents containing antifungal substances; in addition, they should frequently be dried and vacuumed **(Figure 2)**.

The application of proper drying and mould removal methods may result in as much as a 20-fold decrease in the number of mould spores suspended in the air. If a given area cannot be cleaned in a satisfactory way, the offending substance (e.g., wallpaper, wood panelling, carpet) should be removed. This is often required in old houses or following flooding. Reducing air humidity, ideally to below 50%, is an important measure in reducing the number of fungal allergens. This can be achieved by installing and using ventilators in rooms with high humidity (especially in bathrooms, cellars and attics); sealing and insulating pipes and areas of leakage or water deposition; reducing the number of plants requiring frequent watering; and employing ventilation and air conditioning in months when air humidity is increased.[13] Air conditioning devices in houses and cars are common sites for allergy-causing fungus. They should undergo frequent inspection and filter replacement as, instead of decreasing the number of allergens in the patient's environment, they may actually increase air contamination with spores and fungal allergens **(Figure 3)**.

For outdoor mould, the same recommendations as those mentioned above for pollens apply, including the use of smart phone apps.[14]

Conclusion

Allergen avoidance is one of the pillars in the management of allergic diseases **(Table 1)**. Despite this, the literature involving allergen avoidance in patients with AR is scarce, making it difficult to recommend environmental modifications or measures to reduce allergen exposure. In a 2008 systematic review by Getzsche et al[5] that assessed the effects of reducing exposure to house dust mite antigens with environmental measures in patients with asthma, no statistically significant differences were found in asthma symptom scores or medication usage. This systematic review was published after several randomized, controlled trials produced conflicting results regarding the effectiveness of environmental measures. It remains to be established if the same can be concluded regarding AR.

Several findings have consistently emerged in the controlled trials of allergen avoidance and immunotherapy: the studies are difficult to blind, the number of subjects enrolled is generally modest; and in many cases other treatments have been permitted for use.[15] In some of the successful studies on allergen avoidance, a significant result has been recorded despite small numbers [6,16]

Therefore, a scarcity of data should not alter our recommendations. Allergen avoidance remains a cornerstone of the treatment of allergic patients who present with rhinitis, asthma, or atopic dermatitis. Successful treatment requires defining specific sensitivity (skin tests or serum IgE antibodies), education, and an overall plan to reduce exposure in

the home.[6] Success depends on patient involvement, the relevance of other allergens, and exposure outside the patient's home. In a world in which a large proportion of the population is taking allergy tablets or inhalers on a daily basis, we should take full advantage of a treatment strategy that can be easily maintained without side effects; improves symptoms; consistently decreases bronchial hyperactivity; and decreases reliance on drug treatment.[7]

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Financial Disclosures:

None declared

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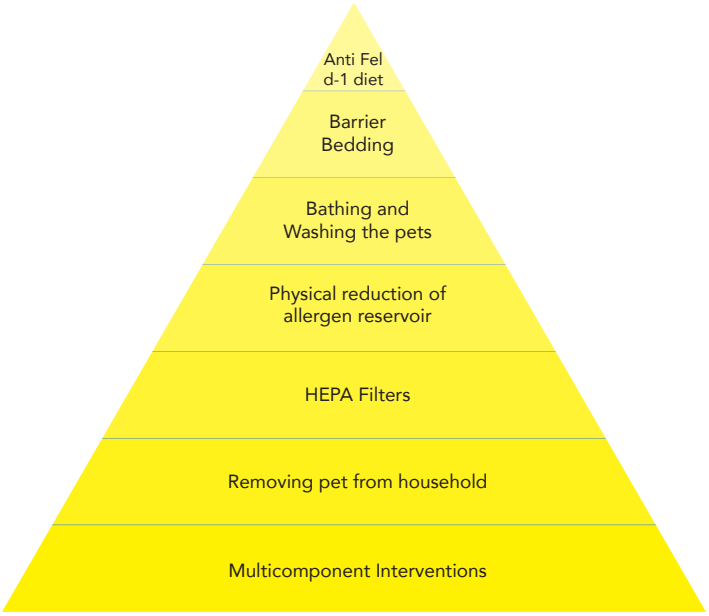

Figure 1: *Pyramid of furry pet allergens avoidance methods. Arrangement based on the clinical effectiveness of each intervention.*[20]

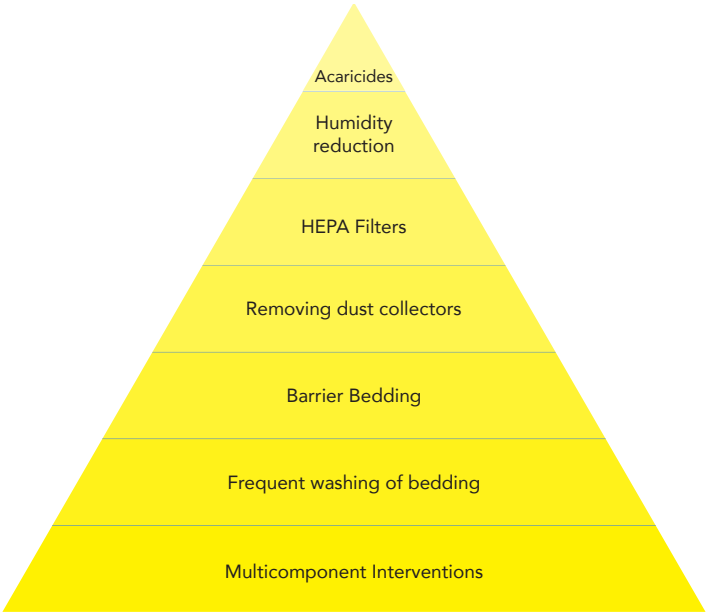

Figure 2: Pyramid of dust mites allergens avoidance methods. Arrangement based on the clinical effectiveness of each intervention.[20]

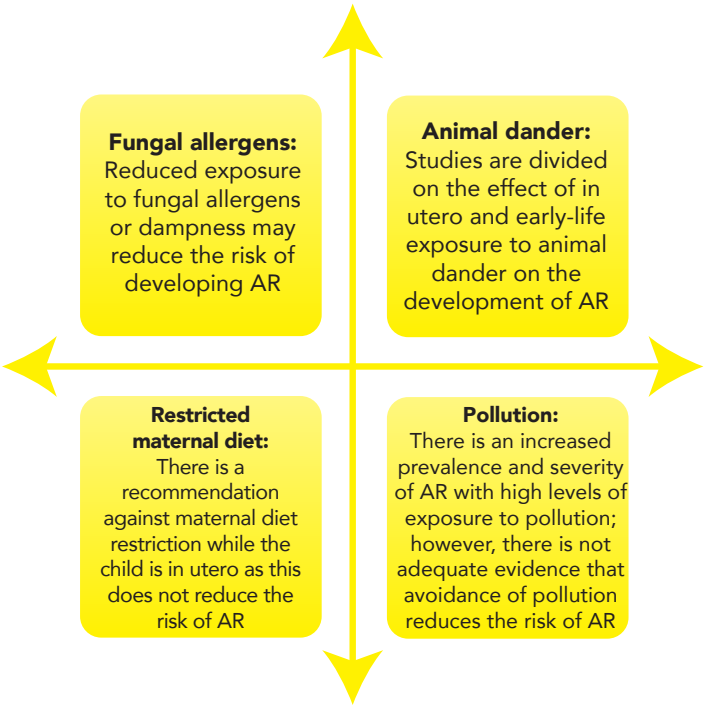

Figure 3: *In utero and/or early-life risk factors for the development of AR: Summary of ICAR:AR-2023* Aeroallergen avoidance and environmental controls: summary of ICAR:AR-2023.*[3]

House dust mites	Data support environmental control strategies with/without use of acaricides
Cockroach	Data support a combination of physical measures and education-based methods
Pets	Highest-level evidence supports environmental controls in patients with Fel d 1 sensitivity
Rodents	Consider work-related exposure and avoidance
Pollen	Option for pollen avoidance and environmental controls. It is recommended to avoid allergens associated with occupational exposures.

Table 1: Effective aeroallergen avoidance strategies per ICAR-AR 2023.[3]

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ADVERSE REACTIONS TO VACCINES: AN ALLERGIST'S APPROACH

Introduction

Vaccination is one of the most impactful and cost-effective interventions for improving global health.[1] Routine immunization has reduced mortality and morbidity resulting from numerous types of infectious diseases.[2]

The widespread use of any reagent is always associated with the risk of adverse reactions, including expected and common side effects, as well as those that are unexpected or idiosyncratic.[3] Mild, local injection site reactions such as redness, tenderness, swelling, or constitutional symptoms such as fever and malaise, are common after vaccination and are not contraindications to further vaccination; they are generally manifestations of the physiologic response to vaccination. Uncommon reactions can vary; they may manifest as delayed hypersensitivity to vaccine components causing injection site nodules or severe, rare anaphylactic reactions.[4] Anaphylaxis occurs at approximately one per million doses administered.[5] The extremely rare Arthus reaction, a type of local Type 3 hypersensitivity reaction, resulting in local immune complex deposition due to the presence of pre-existing IgG antibodies, is typically limited in duration and is not a contraindication to further tetanus vaccination.[6]

Allergists are often seen as stewards of information regarding many of these reactions, although most of these reactions are not allergic in nature. It can be difficult to distinguish between a true allergic reaction to a vaccine and other clinical manifestations that may occur during or acutely after vaccination, such as anxiety, vasovagal responses, and pronounced local reactions.[7] Patients who have had adverse reactions to vaccines may be unnecessarily advised to avoid subsequent immunization, which can put them at risk of morbidity or mortality.[2] The importance of making this clinical distinction has become particularly significant during the ongoing COVID-19 pandemic. The allergist plays an important role in investigating adverse reactions to vaccines and ensuring that patients who are eligible can be safely vaccinated following appropriate investigation. For those patients with true immediate-onset allergic reactions, allergists are able to provide safe revaccination following established protocols.[8]

There are very few true contraindications to vaccination, and they are reviewed in **Table 1**. When reactions are deemed to be allergic or in possible cases of anaphylaxis, patients require assessment by an allergist prior to proceeding with vaccination as some may require confirmatory testing, a more monitored environment, and possibly graded dosing.

Allergist's Approach to Adverse Reactions to Vaccines

This approach is summarized in **Figure 1**.

Allergists are typically confronted with two common scenarios:

1. The patient requires guidance on receiving additional doses of a particular vaccine and/or other related vaccines following an apparent allergic reaction to that vaccine.
2. A patient with a history of known allergy to a vaccine ingredient or component requires guidance on future vaccination containing that component.

In both scenarios, the initial question to ask is, "Were the character and timing of the previous reaction consistent with anaphylaxis or an immediate IgE-meditated allergy to the vaccine, or did the patient have an allergic reaction to a component of concern?" Features consistent with a probable anaphylactic reaction generally occur within the first four hours following vaccine administration, although in practice this is typically much shorter i.e., within the first few minutes to one hour post-vaccination. The criteria for this include typical signs or symptoms for more than one of the following systems.[8–10]

Absolute Contraindications to Specific Vaccines:
Influenza vaccine → GBS within 6 weeks of receiving an influenza vaccination Pertussis containing vaccine → History of encephalopathy soon after a pertussis containing vaccine Rotavirus vaccine → History of GI anatomical issues e.g., malrotation Live vaccines in pregnancy
Contraindications to Routine Vaccination (Require Specialty Consultation):
Live vaccines in immunodeficiency, primary or secondary or immunosuppression→ Require consultation with relevant specialist e.g., Infectious disease, Immunology, Oncology, etc. True allergy to a vaccine or component of a vaccine → Require consultation with Allergist to determine how to vaccinate e.g., one dose, graded dosing, etc.
Note: Contact dermatitis to a component of the vaccine e.g., Neomycin, Thimerosal, PEG is not a contraindication to vaccination with vaccines containing these components Note: Some primary immunodeficiencies are absolute contraindications to use of live vaccine. However, this may not be the case of some non-combined immunodeficiencies.

Table 1: *Contraindications to Vaccination; courtesy of Zainab B. Abdurrahman, MMath, MD, FRCPC, David M. Putman, MD, PhD*

If the patient's history is suggestive of a non-immediate reaction, generally no allergic workup is required.[8,11] For delayed-onset nodules, patch testing may potentially be helpful for investigation of possible contact dermatitis. However, delayed-type hypersensitivity or local formation of nodules are not contraindications to future vaccination.[3] These non-immediate reactions are not contraindications to further vaccination. Subsequent doses of vaccine can be administered following standard recommendations. Of note, certain vaccine adverse reactions are best assessed by other medical specialties, as they can better evaluate the risk of recurrence and use joint decision-making with the patient to guide future vaccination. This includes referral to cardiology for myocarditis after mRNA-based COVID-19 vaccines; neurology for encephalitis, Guillain-Barré syndrome (GBS), or encephalopathy within a few weeks of the administration of any vaccine; and hematology for significant symptomatic thrombocytopenia within a few weeks of the administration of measles, mumps and rubella-(MMR)-containing vaccines.

If there is a suspicion of anaphylaxis or immediate-type allergy, skin prick testing with vaccine, and if clinically indicated, vaccine components, can be conducted **(Figure 1)**. Allergy to the components can be ruled out on history. For example, a history of eating eggs without reaction rules out egg allergy. If there is still a suspicion for a particular component in the vaccine of concern, skin prick testing can be used for that component. It is not recommended to test for unrelated components or components the patient is tolerating on history. Specific vaccine components of concern are reviewed below.

Skin prick testing is done with a full-strength vaccine unless there is a history of severe anaphylaxis, in which case it can be initiated at a 1:10 or 1:100 dilution. Skin prick testing should be completed with both positive and negative controls. If the test is negative, one can proceed to intradermal testing with 0.02 mL of 1:100 dilution of the vaccine. A negative control intradermal test should also be performed. If skin testing is negative and further doses are required, the vaccine can be administered in the usual manner with a 30-minute observation period following vaccine administration. If additional doses of this vaccine are required and skin testing is positive, the vaccine can generally still be safely administered in graded doses in a setting prepared to treat possible anaphylaxis.[8] However, as an alternative approach, if specific IgG levels of the immunization target are already in a range considered to indicate serologic protection from infection, further boosters may be delayed until the levels start to decline.

An example of a graded dosing regimen appears below. It involves 15-minute intervals between completed steps, performed in a setting prepared to treat a systemic allergic reaction with each dose administered via the usual route of the vaccine.[8]

1. 0.05 mL of 1:10 dilution
2. 10% of the target full dose undiluted
3. 20% dose undiluted
4. 30% dose undiluted
5. 40% dose undiluted

Allergy Evaluation of Vaccines Components

Common components associated with reactions to vaccines include gelatin, egg, yeast and latex.[8,12] Egg and yeast extracts for skin prick testing are commercially available. Gelatin for skin prick testing can be prepared by dissolving 5 g of commercially available food-grade gelatin powder in 5 mL of normal saline. Commercial latex preparations for skin prick testing are available. Alternatively, although non-standardized, a latex glove in saline also solubilizes latex for skin testing. Allergen-specific, quantitative IgE in vitro testing is commercially available for latex, gelatin, egg, and yeast.

Latex

Latex is not an ingredient within actual vaccines. Certain multidose vial stoppers or general packaging may contain latex which is leached into the vaccine solution. Therefore, for patients with a history of latex allergy, we recommend avoiding products with latex packaging or stoppers.[13]

Gelatin Allergy

Gelatin is used as a stabilizer and has been identified as an antigen responsible for anaphylactic reactions to MMR, varicella and Japanese encephalitis vaccines.[14] As gelatin has been identified as the etiologic agent in some cases of anaphylaxis, its manufacturers have since changed their formulations to contain either less or no gelatin.[11] In patients with a history of gelatin allergy, the current guidelines recommend referral to an allergist to facilitate vaccination for MMR, varicella or Japanese encephalitis. If a gelatin-free alternative vaccine is available, it should be used instead.[15]

Egg Allergy

Historically, there have been concerns about patients with egg allergy receiving influenza vaccination. However, numerous clinical studies have specifically

evaluated the administration of these vaccines in patients with egg allergy, including those with severe reactions or anaphylaxis.[16,17] Therefore, the most recent guidelines state that no special precautions are required regarding the administration of influenza, MMR or rabies vaccines in patients with egg allergy[3]. Yellow fever vaccine does contain egg protein.[16,18] The current recommendation is that patients with egg allergy have allergy testing with yellow fever vaccine as described above and in **Figure 1**.

Yeast

It is recommended that patients with a history of probable immediate-onset allergic reactions to baker's or brewer's yeast be referred to an allergist prior to vaccination with hepatitis B or quadrivalent human papillomavirus vaccine (HPV4). Both of these are reported to contain residual yeast protein due to their manufacturing processes.[19] Of note, yeast allergy is extremely rare.

Milk

Small amounts of milk protein derivatives are present in the pentavalent and quadrivalent Tdap vaccines. There are rare case reports of this as an etiology for anaphylactic reaction to these vaccines in patients with severe milk allergies.[20]

Polyethylene Glycol (PEG)

In the early evaluation of possible allergic reactions to the mRNA COVID-19 vaccines, polyethylene glycol (PEG) was identified as a possible etiologic agent. However, subsequent studies have suggested that PEG skin testing is of limited to no use either clinically or in the evaluation of possible allergic reactions to mRNA-based COVID-19 vaccines.[21] If true anaphylaxis to an mRNA-based COVID-19 vaccine is suspected, a clinician may consider graded dosing or the use of an alternative platform such as a viral-vector vaccine rather than an mRNA vaccine.[22,23]

Conclusion

The allergist plays an important role in investigating and safely vaccinating patients with a history of possible allergic reactions to vaccines. Through methodical risk stratification guided by the careful collection of patient history data, and the judicious use of skin testing, we can generally safely vaccinate patients even if there is a history suggestive of anaphylaxis.

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Financial Disclosures:

None declared

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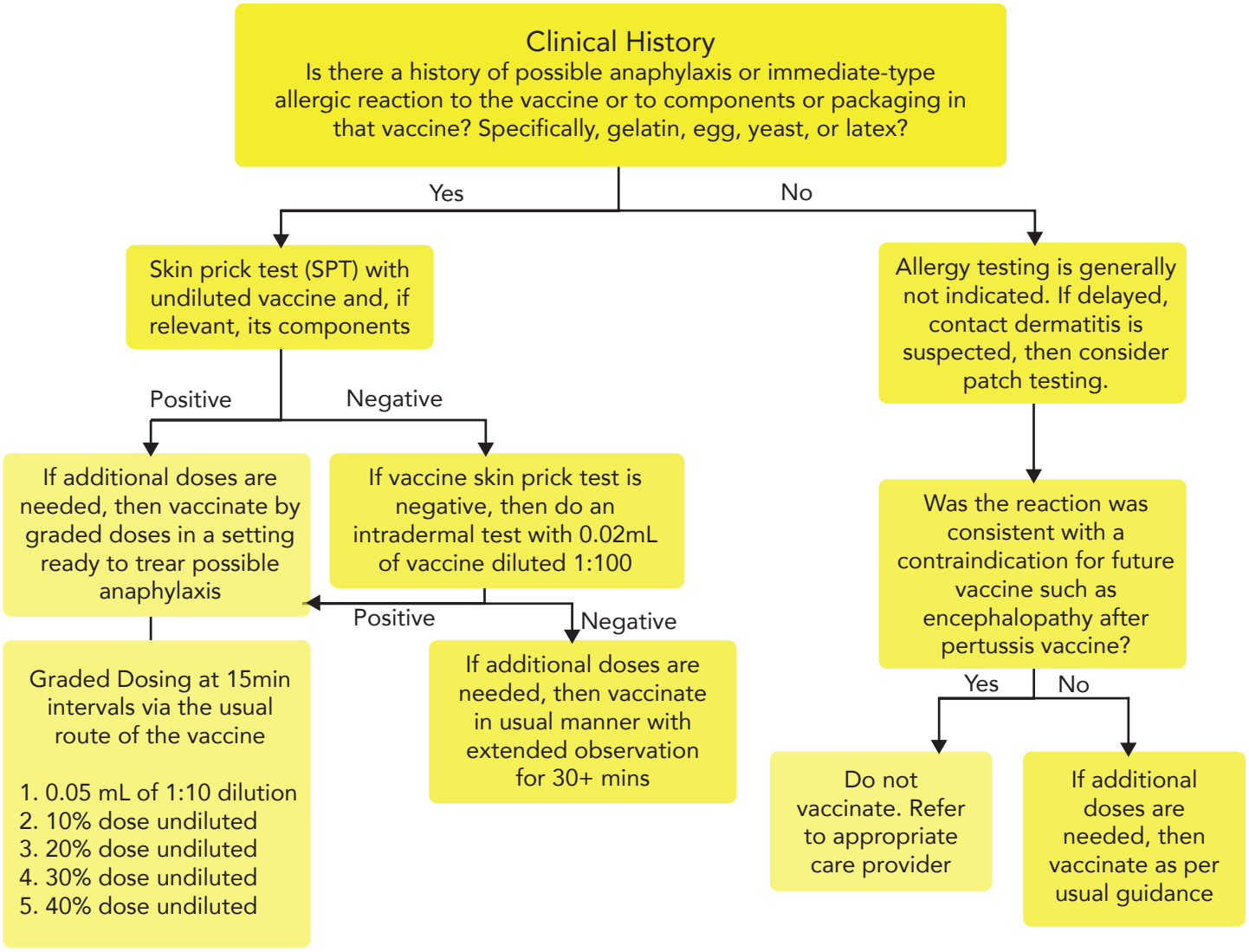

Figure 1: *Allergist's approach to adverse reactions to vaccine or vaccine components; adapted from AAAAI practice parameters (Kelso et al., 2012) and ICON guidelines (Dreskin et al., 2016).*

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