

# Expanding Options in House Dust Mite Allergy Immunotherapy: Optimising Individual Patient Outcomes

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## Meeting Summary

Prof Calderón opened the symposium by noting its overall aim: to improve outcomes in patients with allergic diseases. Currently, patients can wait an average of 8.5 years to see an allergy specialist and this places a significant burden on individuals. Traditional therapeutic management of patients with allergies is suboptimal, and while appropriate use of allergen immunotherapy (AIT) maximises its impact, treatment guidelines are complex.

Prof Zieglmayer explained that house dust mite (HDM) allergy is a global problem. Allergic rhinitis (AR) drives asthma, with the highest risk in children. Symptoms associated with AR and allergic rhino-conjunctivitis can be different in children compared with adults and adolescents. A holistic approach is needed that treats not only the classic symptoms of AR, but also the accompanying physical and mental impairment. It is critical that clinicians gain a greater understanding of the unique burden of AR in order to better treat their patients.

Prof Gevaert emphasised that precision medicine is key to optimising patient outcomes and that advances have been made in this area, particularly with artificial intelligence. For children, the ultimate aim is to achieve an early diagnosis and use precision medicine for early prevention and treatment with AIT. For adults, better help is required with uncontrolled allergic disease. Precision medicine will make use of all available data to help select patients who are most likely to benefit from AIT.

Prof Demoly summarised data from a Phase III randomised, double-blind, placebo-controlled clinical trial that demonstrated the efficacy and safety of a 300IR HDM sublingual immunotherapy (SLIT) tablet in adults and adolescents with HDM-associated AR. Concluding, Prof Casale reiterated that AIT is a crucial tool in the therapeutic armamentarium against HDM allergy and should be used for early prevention and early treatment, without delay.

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### Introduction

#### Professor Moisés Calderón

Prof Calderón emphasised that the aim of the symposium was to improve outcomes for patients with HDM allergy, noting that:

- a) Waiting for effective treatment places a significant burden on individuals. Patients with allergic diseases can wait an average of 8.5 years to see an allergy specialist, with the wait for AIT being even longer.<sup>1,2</sup>
- b) Traditional therapeutic management of patients with allergies is suboptimal. Symptomatic drugs do not slow or halt progression of allergic disease, and many patients continue to display allergy symptoms despite optimal pharmacotherapy.<sup>3-9</sup>
- c) Appropriate use of AIT maximises its impact on allergic diseases, but treatment guidelines are complex, and none propose care pathways. Recently, care pathways for AIT have been proposed by the Allergic Rhinitis and its Impact on Asthma (ARIA) group.<sup>10</sup>

### Burden of House Dust Mite-Allergic Respiratory Diseases

#### Professor Petra Zieglmayer

Mite allergy is of global relevance.<sup>11-20</sup> The proportion of the population affected by mite allergy ranges from 4% in China and Korea to almost 50% in Australia and New Zealand. Approximately 25% of the population in Europe and North America is affected by respiratory allergies. In Europe, this is expected to increase to >50% by 2025. The problem lies in that almost half of all allergy patients in the European Union (EU) are misdiagnosed, resulting in delayed diagnosis and treatment.<sup>21-23</sup>

AR is known to drive the development of asthma.<sup>24</sup> This is more relevant in the paediatric population, as a German study found that AR in children up to the age of 5 years was a predictor for the development of wheezing at school age.<sup>25</sup> An Australian study reported a 7-fold increased risk of developing asthma in children aged 7-12 years displaying AR compared with the healthy population. This risk decreased with increasing age but was still 2-fold greater in adults displaying

AR compared with those who have never displayed AR.<sup>26</sup> This has important implications for the individual.<sup>27</sup>

A total of 70 of 100 million Europeans with AR display asthma.<sup>23</sup> Patients with AR may feel impaired in daily social activities; rhinorrhoea and sneezing may be perceived as socially unacceptable. Nasal obstruction can lead to reduced quality of sleep. Systemic allergic symptoms can lead to tiredness and a general sense of feeling unwell. This, along with the side effects of medication, can result in malaise that can lead to reduced performance at school and work, loss of productivity, and an economic burden to society.<sup>23</sup> Thus, AR and allergic asthma result in significant individual and societal costs.

HDM allergy is not easy to diagnose as patients present with unspecific symptoms such as loss of smell, general tiredness, and recurring sinusitis. In a European survey, patients with severe HDM-induced respiratory allergies reported peaks in their symptoms in spring, autumn, and (to a lesser extent) mid-winter.<sup>28</sup> The same survey reported a 2-year period from the first symptoms until consultation with a specialist. Furthermore, patients consult general practitioners (GP) and specialists several times a year and often consult several healthcare professionals simultaneously.<sup>28</sup> It is evident the extent to which patients are affected. A total of 30% of GP were aware of ARIA guidelines but only 10% implemented them.<sup>29</sup> Thus, it is not surprising that patients who primarily consult their GP for mite allergy are not adequately treated. To further complicate matters, mite allergic patients are not only sensitised to mites but also present with other allergies (e.g., grass pollen and cat dander) and report comorbidities such as headache, conjunctivitis, sinusitis, and otitis.<sup>28</sup>

Sleep disorders, rhinorrhoea, and nasal obstruction were reported to be the most bothersome symptoms in both children and adults with HDM allergy; however, the order of importance was different.<sup>30</sup> Irrespective of age, however, more symptoms resulted in greater impairment. A study of adults and children with AR showed that the severity of rhinitis has more of an effect on quality of life (QoL), school or work productivity, and daily activities than the duration of rhinitis.<sup>31</sup> A further online, questionnaire-based study reported nasal

congestion as the most bothersome symptom.<sup>32</sup> Patients with the most severe symptoms had an impairment in productivity with some unable to work. AR has also been shown to increase the risk of driving accidents, with a quarter falling asleep easily, especially when behind the wheel.<sup>33</sup> Sneezing increases the risk of an accident as one sneeze renders the driver blind for 100 metres. In fact, the degree of impairment is comparable to that seen at a blood alcohol level of 0.05%, the legal limit in many countries.<sup>34</sup> This is not only related to side effects of histamines, as driving ability is even more impaired with untreated AR.

Symptomatic treatment, including antihistamines, nasal steroid sprays, eye drops, and oral steroids, is used by most patients.<sup>5</sup> Immunotherapy may be prescribed to only 2% of patients. Certain medication for AR is reimbursed by the social system of different countries; however, preparations that have been on the market for over 20 years generally need to be paid for by individuals. Costs related to loss of productivity and sick leave also need to be considered. A French study looking at medical resource utilisation and related costs for perennial AR, with or without concomitant allergic asthma, showed a clear increase in costs with severity of AR and poor control of asthma.<sup>35</sup> Concomitant asthma increased medical resource costs at least 2-fold. Household adjustments, such as replacement furniture, humidifiers, or air cleaners, and disposal of soft furnishings, are expensive with little perceived benefit.<sup>5</sup>

Prof Zieglmayer concluded that mite allergy is of global relevance, and that AR drives asthma. The symptoms associated with AR and allergic rhino-conjunctivitis can be different in children compared with adults and adolescents. She emphasised that a holistic approach is needed that treats the classic symptoms of AR in addition to the accompanying physical and mental impairment. It is critical that clinicians gain a greater understanding of the unique burden of AR in order to better treat their patients.

## Precision Medicine to Optimise Patient Outcomes

### Professor Philippe Gevaert

Prof Gevaert mentioned that 20 years ago, he and his colleagues had dreamt that patient samples (blood and nasal secretions) containing a biological marker could be used to personalise treatment with precision medicine. This dream, based on predicted outcome, has altered, and it is now understood that one marker might not be sufficient to achieve this goal.

The case of a 6-year-old boy with a constant cold, blocked nose with open-mouth breathing, rhinorrhoea, and nightly cough all year round was presented. Removal of the adenoids was indicated as a possible treatment option for this patient; however, this child was eventually diagnosed with allergy. Diagnosis in a child is very difficult due to their immature immune systems and the presence of infections and other environmental factors that may lead to rhinitis symptoms. AR patients are classified into two groups: 'sneezers and runners' and 'blockers'. The 'sneezers and runners' often have itching, sneezing, and conjunctivitis. Their symptoms are worse during the day and improve at night. Diagnosis may take some time, but generally after two seasons they are diagnosed with hay fever. 'Blockers', on the other hand, often have severe nasal blockage with little sneezing and no itching. Symptoms are constant but may be worse at night. Diagnosis usually takes a long time. The standard of care is to conduct a skin prick test (SPT) in these patients. Of 2,320 Belgian patients who underwent a SPT, 40% had sensitisation, of which 80% were symptomatic. Almost 30% of the Belgian population had AR symptoms and sensitisation. In those aged 20–40 years, approximately 45% had AR symptoms and sensitisation, implying an increase in allergy with age.<sup>36</sup>

Nowadays, further analyses can be conducted, including measuring specific genes and allergen components. The evolution of sensitisation in children and adolescents to HDM was investigated and was found to begin with Der p 2, Der p 1, and Der p 23.<sup>37</sup> Other allergen components (e.g., Der p 5, Der p 7) were important with increasing age. These data can potentially be used to facilitate

better diagnosis and predict better outcomes. Recent data show that mite-specific IgE testing carried out on nasal secretions by means of allergen microarray might soon become an option in the diagnostic workup of AR.<sup>38</sup>

The severity and frequency of symptoms determines therapy as per the ARIA recommendations for the management of AR. With regards to primary and secondary prevention, data are lacking and recommendations are vague. Breastfeeding is recommended regardless of the atopic background of the infant. No general recommendation can be made regarding early-life exposure to pets and HDM avoidance, and dietary manipulations are not recommended. Environmental tobacco smoke should be avoided in pregnant women and children, and the primary prevention of occupational allergy is recommended. Secondary prevention of asthma remains a matter of debate. Early indoor aeroallergen exposure does not appear to affect development of allergic sensitisation or AR in high-risk children.<sup>39</sup> Once a patient is allergic, prevention entails eliminating HDM from the home. According to ARIA guidelines, there is some evidence that encasing bedding in impermeable covers, washing bedding on a hot cycle (55–60 °C), and replacing carpets with hard flooring has some effect on allergen levels but the clinical benefit is less apparent. There is weak or no evidence, however, for acaricides and/or tannic acid; minimising the number of objects that accumulate dust; using vacuum cleaners with integral high-efficiency particulate air filter and double-thickness bags; and removing, hot washing, or freezing soft toys. A systematic review found no effect of chemical or physical methods to reduce exposure to HDM antigens in the homes of people with mite-sensitive asthma.<sup>40</sup>

Prof Gevaert returned to the case of the 6-year-old boy. The child had been prescribed numerous courses of antibiotics and vaccination with Broncho-Vaxom; however, a SPT revealed AR and HDM allergy. Antihistamine and nasal steroids were given following diagnosis. The atopic march, which occurs when the individual develops multiple atopic (allergic) conditions with increasing age, typically starts early with food allergies and eczema, finally ending in asthma and/or AR.<sup>41</sup> At present, AIT is only given once a clinical diagnosis of AR has been made.

Early treatment would be recommended in this young child to prevent disease progression. Prof Gevaert emphasised the need to consider preventative AIT and combine all patient data in order to use precision medicine to select a high-risk child for early AIT.

Prof Gevaert also presented the case of a 46-year-old man with a blocked nose, rhinorrhoea, post-nasal drip, disturbed sleep, snoring, nightly cough, and all-day tiredness. His symptoms lasted all year round. He had a nasal endoscopy and septal deviation was evident. A septoplasty alone however would not cure this patient as further tests showed he also had HDM allergy, emphasising the importance of multidisciplinary efforts to ensure a complete diagnosis. This man took antihistamines and nasal corticoids with no effect. He also had a history of long-term overuse of decongestants. After seeing his GP, he was prescribed a shot of depot systemic corticoids. His HDM allergy remained uncontrolled with medication. Severe chronic upper airways disease defines those patients whose symptoms are inadequately controlled despite adequate (i.e., effective, safe, and acceptable) pharmacological treatment based on guidelines.<sup>8</sup> These patients have impaired QoL, social functioning, sleep, and school or work performance. With optimal treatment, >20% of patients with rhinitis are totally uncontrolled. This could be explained by disease-related (e.g., exogenous, endogenous, or genetic), diagnosis-related (e.g., incorrect diagnosis), patient-related (e.g., poor adherence), or treatment-related (e.g., inadequate treatment) factors.<sup>42</sup>

A Belgian study investigated the control of persistent rhinitis in a real-life community pharmacy setting. Uncontrolled symptoms were reported in 60% of presenters despite medication. Dissatisfaction with the way their rhinitis symptoms were controlled at present was reported by 40%. The nasal spray technique was subsequently evaluated in 1,276 patients. The results indicated a suboptimal spray technique in >80%, with patients not always shaking the medication, tilting the head forward, or spraying away from the septum. Adherence was also a problem, with 54.8% under-adherent (i.e., <80.0% adherence). Decongestant overuse has been reported in 50% of people with persistent rhinitis.<sup>43</sup> Surprisingly, only 3% of presenters use systemic glucocorticosteroids to control AR.

However, use of depot-steroid injections has been shown to increase the risk of osteoporosis and diabetes.<sup>44</sup> Thus, AR should not be treated with systemic corticosteroids long term.

Precision medicine is increasingly recognised as the way forward for improving patient outcomes. A consensus on the position and gradual implementation of the principles of precision medicine within existing adult treatment algorithms for AR and chronic rhinosinusitis has been published.<sup>45</sup> Prediction of success of the initiated treatment and patient participation in the treatment plan can be implemented at the time of diagnosis. Strategies to prevent progression of disease, in addition to prediction of therapy success and patient participation in the long-term therapeutic strategy, are included in the second-level approach. Personalised care should be positioned at the tertiary level. Prof Gevaert returned to the case of the 46-year-old man and suggested that this patient would be a candidate for AIT.

The technological revolution means that nowadays all patient data are digitalised. When computers begin to read patient letters and connect data on a large scale (big data), artificial intelligence techniques may facilitate better diagnosis and precision medicine. The goal is to achieve an early diagnosis in children and use it for early prevention and early treatment with AIT. In adults, better help is needed for uncontrolled allergic disease. Prof Gevaert emphasised that precision medicine will help select patients who are most likely to benefit from AIT.

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## The 300IR 'Solution' and Future Trends

Professor Pascal Demoly

HDM SLIT drops have been shown to alleviate the burden of HDM allergies in children and adults with HDM-associated AR and/or asthma.<sup>46</sup> The drop format offers dose flexibility which is important for tailored individual treatment and the development of tablets with the same composition would offer simplicity.

New drugs are developed in accordance with regulatory guidelines.<sup>47</sup> Clinical significance

and clinical relevance should be demonstrated. In AR, the primary trial outcome must reflect both symptom severity and intake of rescue medication (total combined score [TCS]). Secondary outcomes, defined *a priori*, contribute supplementary information on the effect size and safety. The estimation of the effect size must be precise enough to be able to reasonably eliminate the possibility that the effect may be too small to have benefit (positive benefit/risk balance). Prof Demoly emphasised that clinical relevance is not synonymous with statistical significance. Clinical relevance can be quantified with different metrics including effect size, relative clinical impact, numbers of patients needed to treat, and minimal important difference.<sup>48</sup> However, one can also focus on symptoms which are known to be bothersome (e.g., severe blocked nose), factors of which impact is more relevant (e.g., QoL), or specific groups of patients who may be more responsive (e.g., more symptomatic patients).

Prof Demoly reported the results of a confirmatory Phase III, randomised, double blind, placebo-controlled clinical trial which aimed to evaluate the efficacy and safety of the 300IR HDM SLIT tablet when administered for 12 months to adults and adolescents with HDM-associated AR.<sup>49-52</sup> The trial was conducted at 231 centres in Canada, USA, EU, Russian Federation, and Israel. The study included male and female outpatients aged 12-65 years with HDM-associated AR (with or without concomitant asthma) for at least 1 year, sensitised to Der p and/or Der f, and with an average TCS of  $\geq 5$  over the baseline evaluation period. A 4-week run-in period was included prior to randomisation with the 300IR tablet (n=802) or placebo (n=805) to allow for the selection of patients with more severe symptoms. The primary evaluation period was the same duration as the run-in period and comprised the last 4 weeks of the treatment period. The primary endpoint of the trial was the average TCS calculated as the average daily TCS during the 4-week evaluation period. The TCS is the sum of two patient daily scores: rhinitis total symptom score and rescue medication score. Additional key outcomes used to assess clinical benefit included efficacy (individual rhinitis symptom scores, QoL, days with AR symptoms under control) and safety.

The average TCS over time showed symptom improvement and reduction in rescue medication use. The relative least squares mean difference (95% confidence interval) versus placebo was -16.9%.<sup>49</sup> Improvements versus placebo in the secondary endpoints rhinitis total symptom score and rescue medication score were also significantly reduced in the 300IR group versus placebo. AIT with 300IR HDM sublingual tablet among adults and adolescents with HDM AR significantly improved nasal symptoms compared to patients receiving placebo despite a higher consumption of rescue medication in the latter group. This treatment was particularly efficient at relieving blocked nose which is a troublesome symptom with a significant socioeconomic burden.<sup>50</sup> QoL scores, as measured by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), were taken at the end of the treatment period. Significant improvements in QoL score were seen; this was observed across the seven domains of the RQLQ including sleep and daytime activities.<sup>51</sup> Adults and adolescents with HDM-associated allergic rhinitis benefited from treatment with 300IR HDM SLIT tablet by having more days with their AR symptoms under control compared to patients on placebo.<sup>52</sup> The SLIT tablet was generally well-tolerated, with no reports of severe anaphylactic reaction and no deaths. The most common adverse events were application-site reactions. The safety profile was similar in adults and adolescents, and consistent with previous studies.

Prof Demoly concluded that different solutions are available for different patients. HDM AIT SLIT drops offer dose flexibility for children and adults with AR and/or asthma. The 300IR HDM SLIT tablet is effective and safe in adolescents and adults displaying persistent AR due to HDM.

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## Final Remarks

### Professor Thomas Casale

Prof Casale confirmed that a significant amount of morbidity is associated with HDM AR. He emphasised that a clinician's job is to improve patient outcomes by gaining a greater understanding of the unique burden of AR and providing better treatment. Early prevention and early treatment with AIT are crucial, especially in children, and AIT should therefore be used now without delay.

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