



Allergen-specific immunotherapy with storage mites

A neglected indication

Ludger Klimek · Randolph Brehler · Karl-Christian Bergmann

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Abstract As a result of the German Therapy Allergen Ordinance and justified demands for large, double-blind, placebo-controlled studies on allergen-specific immunotherapy, rare therapy allergens as immunotherapeutic agents have moved out of the scientific and allergological spotlight. Allergen-specific immunotherapy with house dust mite extracts is well established, but beside house dust mites, storage mites may cause similar allergic symptoms that also require a causal treatment. Especially in Asia storage mites are the most important inhalative allergens, but they are important allergens as well for some patients in Germany. The cross-reactivity between house dust mites and storage mites but also cross-reactivity between different kinds of storage mites is low. Therefore, storage mites should be included in diagnostic procedures to prevent misdiagnosis in patients suffering from perennial rhinitis. Thus, manufacturer should guarantee the availability of storage mite extracts for diagnostics and allergen-specific immunotherapy. Clinical trials documenting the efficacy of these extracts are necessary.

Keywords Allergen specific immunotherapy · Storage mites · Rare allergens · Therapy allergen ordinance

Introduction

Since the introduction of the Therapy Allergen Ordinance (*Therapieallergene-Verordnung*, TAV) in Germany, research has largely been restricted to TAV allergens (pollen from trees and grasses, bee and wasp venom, and house dust mites)—other therapy allergens play virtually no role in research and treatment reality [1]. However, rarer inhalant allergens, such as storage mites (Table 1), are also of considerable relevance for a smaller number patients and are equally capable of triggering persistent allergic rhinitis.

Identical symptoms

Persistent allergic rhinitis is particularly frequently associated with comorbidities such as bronchial asthma, atopic dermatitis, sleeping disorders, chronic sinusitis, and eustachian tube dysfunction.

Patients with house dust mite rhinitis generally report persistent nasal obstruction, recurrent periods of sneezing and rhinorrhea, as well as an impaired sense of smell—the same symptoms are also seen in rhinitis due to storage mites. Symptoms of sinusitis (e. g., feeling of pressure in the forehead area or frontal headaches) are also frequently observed. However, its designation as “perennial rhinitis” does not always tally with the actual period of symptoms: symptom duration ranges from perennial to symptom-free periods, probably due to indoor mite allergen exposure that modulates over the course of the year [2].

In addition to symptoms of allergic rhinitis involving impaired nasal breathing and rhinorrhea or rhinitis sicca, patients also suffer from ocular symptoms, e. g., in the context of usual allergic or vernal conjunctivitis. Symptoms of bronchial asthma, such as recurrent dyspnea and a dry cough at night, are also observed and are signs that an allergic march has oc-

Prof. Dr. L. Klimek (✉)
 Center for Rhinology and Allergology, An den
 Quellen 10, 65183 Wiesbaden, Germany
ludger.klimek@allergiezentrum.org

R. Brehler
 Department of Dermatology, University of Muenster,
 Muenster, Germany

K.-C. Bergmann
 Department of Dermatology and Allergy, Allergy Centre
 Charité, Charité—Universitätsmedizin Berlin, Berlin,
 Germany

Table 1 Allergy-relevant storage mites. (All pictures reproduced with permission from Leti)

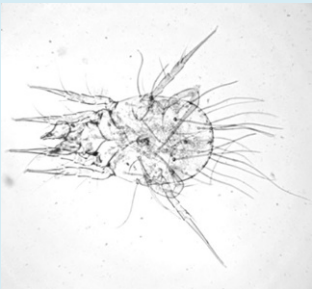
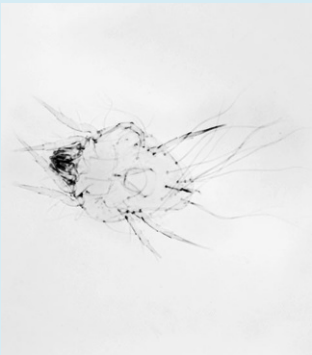
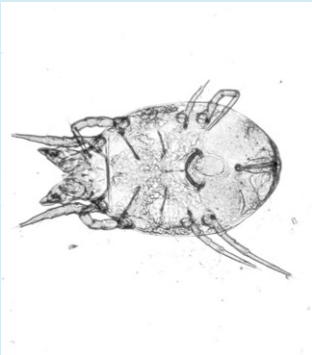
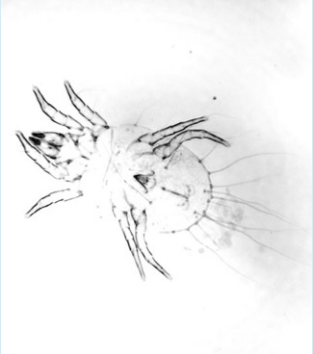
Storage mites	Allergens	Cross-reactivity
<i>Glycyphagus domesticus</i> (house or furniture mite)  	Number of sequenced allergens: 8 Relevant allergens: Gly d 2	High with <i>Lepidoglyphus destructor</i>, moderate with <i>Tyrophagus putrescentiae</i>, low to moderate with Pyroglyphidae
<i>Lepidoglyphus destructor</i> (hay mite)  	Number of sequenced allergens: 9 Relevant allergens: Lep d 2, Lep d 7	High with <i>Glycyphagus domesticus</i>, moderate with <i>Tyrophagus putrescentiae</i>, low to moderate with Pyroglyphidae
<i>Blomia tropicalis</i>  	Number of sequenced allergens: 20 Relevant allergens: Blo t 3, Blo t 11, Blo t 21	Low with <i>Dermatophagoides farinae</i> and other Pyroglyphidae, low to moderate with storage mites
<i>Chortoglyphus arcuatus</i>  	Number of sequenced allergens: 1 Relevant allergens: Cho a 10 tropomyosin	Precise information not available as yet

Table 1 (Continued)

Storage mites		Allergens	Cross-reactivity
<i>Tyrophagus putrescentiae</i> (mold mite)		Number of sequenced allergens: 9 Relevant allergens: Tyr p 2, Tyr p 35, Tyr p 36	Moderate with <i>Lepidoglyphus destructor</i> and <i>Glycyphagus domesticus</i> , low with Pyroglyphidae
			
<i>Acarus siro</i> (flour mite)		Number of sequenced allergens: 7 Relevant allergens: Aca s 2, Aca s 13	Low with <i>Dermatophagoides farinae</i> and other Pyroglyphidae, low to moderate with storage mites
			

curred. Sleep disorders are also reported. These often impair patients in their everyday professional and domestic lives, as well as children in their ability to learn.

In mite-allergic individuals, oral allergy syndrome to seafood, crustaceans, and shellfish can be caused by the cross-reactivity of tropomyosins that are also found as slightly modified fibrillar structural proteins in mites and cockroaches.

A challenging diagnosis

The diagnosis of mite allergy is hampered by its often nonspecific symptoms, which frequently develop insidiously and by no means always include attacks of paroxysmal sneezing and itching.

House dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*) are the allergologically most important mites; however, storage mites also play a significant role—primarily among farmers, but also in municipal areas—and should be made provision for in an extended test battery for persistent rhinitis [3].

Therefore, the German S2 guideline on skin testing for inhalant allergies [4] recommends—in addition to *Euroglyphus maynei* and the two house dust mites—also testing for the species summarized in Germany under the term storage mites (*Acarus siro*, *Lepidoglyphus destructor*, *Tyrophagus putrescentiae*, and *Glycyphagus domesticus*) in the case of suspected mite allergy. Other relevant storage mites include *Aleuroglyphus ovatus*, *Acarus farris*, *Blomia tjobodas*,

Blomia tropicalis, *Blomia kulagini*, *Chortoglyphus arcuatus*, *Cheyletus eruditus*, *Suidasia medanensis*, and *Thyreophagus entomophagus* [5].

Description of the storage mite

Like house dust mites, storage mites belong to the arachnids (Arachnida) [5]. They are found wherever living conditions are optimal for them, which applies in particular to microclimatic environmental conditions in terms of temperature and relative humidity. Under conditions that are ideal for their rapid development (25 °C ambient temperature, 90% relative air humidity), up to 30 generations can be produced annually. They are virtually unable to develop at below 60% relative air humidity. Storage mites feed on “stocks” such as grain, flour, and plant residues, as well as on molds. Although the life cycle of the storage mite is shorter than that of the house dust mite, the speed at which they propagate is three- to seven-fold faster. In parts of Asia, storage mites are in actual fact the most common inhalant allergens [6].

Crossreactivities

Cases are known in which storage mites as food allergens have triggered allergic symptoms and even anaphylactic reactions (e. g., *Acarus siro* and *Lepidoglyphus destructor*). Particularly storage mite allergens in cereal flour and oilseed are causal here. Local allergic

Table 2 Storage mite preparations available for AIT in Germany

Allergen	Manufacturer	Preparation	Availability
<i>Acarus siro</i>	Allergopharma	NOVO-HELISEN® DEPOT	In approximately 6 months
<i>Acarus siro</i>	Leti	Depigoid®	Available without restrictions
<i>Lepidoglyphus destructor</i>	ALK Abelló	Pangramin® ULTRA	From November 2017
<i>Lepidoglyphus destructor</i>	Allergopharma	NOVO-HELISEN® DEPOT	Expected end of 2017
<i>Lepidoglyphus destructor</i>	Leti	Depigoid®	Available without restrictions
<i>Tyrophagus putrescentiae</i>	Allergopharma	NOVO-HELISEN® DEPOT	In approximately 6 months
<i>Tyrophagus putrescentiae</i>	Leti	Depigoid®	Available without restrictions
<i>Blomia tropicalis</i>	Leti	Depigoid®	Available without restrictions
<i>Chortoglyphus arcuatus</i>	Leti	Depigoid®	Available without restrictions
<i>Euroglyphus maynei</i>	Leti	Depigoid®	Available without restrictions
<i>Glycyphagus domesticus</i>	Leti	Depigoid®	Available without restrictions
AIT allergen-specific immunotherapy As of: August 2017			

rhinitis (LAR) to storage mites has also been reported [7].

Due to the fact that some belong to different families, the major storage mite allergens (classes 2, 5, and 7) show little cross-reactivity either to house dust mites or to one another. In the majority of cases, allergies to storage mites develop parallel to house dust mite allergies and need to be treated separately.

Allergies that are caused exclusively by storage mites without reactions to house dust mites are being observed ever more frequently. For this reason, storage mites should be included in the standard allergy diagnostic repertoire alongside house dust mites.

Treatment options

Although avoidance measures appear to be beneficial also in storage mite allergy, there are virtually no data on outcome. As with all IgE-mediated allergies, allergen-specific immunotherapy (AIT) is the only causal treatment, besides avoidance [4].

Whereas house dust mite allergy is regularly diagnosed as the cause of persistent rhinitis and treated using AIT, there are only scant data as yet on AIT with storage mites [8]. However, on the basis of data from individual data collections and a handful of controlled studies [9], AIT appears to be a beneficial and effective treatment option for patients with storage mite allergy.

The problem with rare allergens

Storage mites as therapeutic allergens belong to the group of “rare allergens.” They also continue to be available as individual formulations (i. e., not as finished medical products produced in batches) within the framework of TAV provisions and are subject only to the manufacturer’s in-house quality control in line with the Good Manufacturing Practice (GMP) guideline and without monitoring by the Paul Ehrlich Institute (exception: distribution in mixtures with TAV

allergens). At present, rare allergens account for less than 3% of the AIT market, and storage mites, in turn, represent only a fraction of this. Thus, it seems understandable that the production and marketing costs for AIT products with storage mites sharply exceed sales revenues in some cases. In particular, the labor-intensive production of individual products of this kind contributes significantly to their high cost. However, from a global perspective, one must bear in mind that, particularly in tropical and subtropical regions, the incidence of storage mite allergy exceeds that of house dust mite allergy in some areas [5].

At present, many manufacturers are ceasing the production and marketing of storage mite allergens for AIT due to current economic conditions. The group of experts on “Rare Allergies” of the Medical Association of German Allergists (Ärzteverband Deutscher Allergologen, AeDA) are of the opinion that, despite these problems, this patient group also has the right to diagnostic investigations and AIT.

How to solve this dilemma

One way out of the dilemma of an ongoing loss of yet more rare allergens for AIT lies in open talks with the allergen manufacturers, some of which, fortunately, consider it important to maintain comprehensive patient care by offering a wide spectrum of allergens for AIT. The storage mite preparations currently available from various manufacturers for AIT in Germany are listed in Table 2. The reader is advised to address queries concerning individual products directly to the relevant allergen manufacturer.

From the perspective of affected patients, their treating physicians, as well as allergology as a whole, storage mites should continue to be available for AIT. This patient group has just as much right to causal treatment as do patients with allergies to house dust mites, birch and grass pollen, or insect venom.

Conflict of interest L. Klimek has received research support, fees for consulting and/or expert testimony, fees for lectures and/or educational presentations and/or fees for board membership from ALK-Abelló, Allergopharma, Bencard, Bionorica, Biomay, Boehringer Ingelheim, Cytos, Circassia, HAL, GSK, Leti, Lofarma, MEDA, Novartis, Stallergenes und Roxall. K.-C. Bergmann declare that they have no competing interests. R. Brehler declares the following competing interests: Lectures: ALK, Allergopharma, Almirall, Astra Zeneca, Bencard, GSK, Dr. Pflieger, HAL, Leti, Merck, Novartis, Pierre Fabre, Pohl Boskamp, Stallergenes, ThermoFischer. Consultancy: Allergopharma, Bencard, HAL, Leti, Novartis. Clinical trials: Allergopharma, Bencard, Biotech Tools, Genentech, Leti, Novartis, Circassia.

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