

CME Article

Atopic dermatitis and allergic rhinitis – do co-effects in therapy exist?

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Summary

Atopic dermatitis and allergic rhinitis frequently appear together in the same patients. The pathogenesis of both disorders is complex and still incompletely understood. Nevertheless, pathophysiological overlaps suggest the existence of potential therapeutic co-effects. While data pointing towards a positive effect of allergen elimination for both diseases is still limited, there is now increasing evidence showing beneficial effects of specific immunotherapy in patients suffering from atopic dermatitis and additional type I allergies. H₁-antihistamines were also found to exert moderate positive effects on the symptoms of atopic dermatitis in single studies. In summary, a limited therapeutic co-effect of the above mentioned treatment options can be expected in case of the parallel existence of atopic dermatitis and allergic rhinitis in the same patient. More studies on this issue during the next years are desirable. In addition, a better understanding of the pathophysiology should have a positive impact on the treatment of atopic manifestations such as atopic dermatitis and allergic rhinitis.

Introduction

Atopic dermatitis (AD) is defined as a chronic or chronically recurrent skin disease with classical morphology and location in an age-dependent varying clinical manifestation that is usually characterized by severe pruritus [1]. A large proportion of those affected have IgE-mediated type I sensitizations to various allergens. Among adults up to 80 % are affected by this [1] and aeroallergens clearly stand in the forefront. In early childhood this rate is still lower and in contrast to adults food allergens more frequently play a role [2].

Not rarely, type I sensitizations are clinically relevant for AD and exposure to type I allergens can lead to an exacerbation of cutaneous symptoms in AD patients. Inversely, it is known that the prevalence of type I sensitizations increases with the severity of AD [3].

Both AD as well as allergic rhinitis (AR) can cause a reduction in quality of life, a reduction of concentration and productivity as well as disturbances of sleep. Often people associated with the patient are affected also and the socioeconomic impact of both diseases can be significant [4, 5]. The impact on the economy is estimated to be in the range of 1.5–3.5 billion Euros annually in Germany [4].

While the association between AD and AR has been known for a long time, pathogenetic interrelationships are only incompletely understood and are the subject of controversial debates. For patients and the treating physicians it is first of all important, if co-effects in the therapy of both diseases exist and how these can be utilized optimally for safe, simple, effective and economical therapy.

A large proportion of patients with atopic dermatitis have IgE-mediated type I sensitizations to various allergens such as aeroallergens and/or food allergens.

Exposure to relevant type I allergens can lead to triggering and/or exacerbation of cutaneous signs and symptoms in patients with atopic dermatitis.

While no doubt exists with respect to the association of atopic dermatitis and allergic rhinitis, the degree of the causal relationship of the atopic diseases still remains unclear and is a subject of current discussion.

The disturbed skin barrier in patients with atopic dermatitis might facilitate the penetration of allergens with the resulting development of type I allergies.

The genesis of atopic dermatitis is multifactorial. Beyond the barrier disturbance genetic polymorphisms also appear to be responsible for alterations of the acquired immune system including increased IgE production and the priming of T cells in the direction of Th2 typical for atopy.

The aim of this paper is to offer current insight into the discussion of pathogenetic interrelationships of both diseases and particularly to illustrate possible co-effects of therapeutic options.

Atopic dermatitis and allergic rhinitis – association or causality?

Epidemiological studies of recent decades show that associations exist between the atopic diseases AD, AR and asthma. Thus, about 30–50 % of patients with AD also suffer from AR and about 10–20 % of patients with AR also have AD [6–8]. The supporters of the hypothesis of the “atopic march” assume that there is a causal connection between the atopic diseases. According to this, they typically manifest in a fixed order, with AD standing at the beginning, followed by asthma and AR. Actually, the peak incidence of AD is in the first two years of life [8], while that of asthma is only found around the fifth year of life. The incidence of AR especially increases considerably between the 5th and 10th year of life [12]. While these numbers suggest a fixed sequence of development, this is often not seen in clinical reality. Thus, AD not infrequently develops only after the manifestation of asthma [11]. Altogether, about every second child with severe AD seems to develop asthma during the course and three of four of these children AR [12]. With respect to the coexistence of AD and AR it must be kept in mind that in about one-half of all affected children AD disappears again in the course of time [8, 13] and that the severity of AR can fluctuate considerably over time.

The disturbance of the epidermal skin barrier plays a key role in the pathogenesis of AD. It was shown that the widespread loss-of-function mutation in the filaggrin gene, which results in a disturbed skin barrier, increases the risk of AD as well as the combination of AD and asthma by more than threefold [14, 15]. In contrast to this, the risk of asthma does not appear to rise, when no parallel AD exists [14, 15]. Subsequent studies were further able to demonstrate, that these mutations are also associated with type I sensitizations and AR [16–18]. Concretely, the risk for developing AR rises by more than double in the presence of the mutation [18]. Overall, about 20 % of AD patients possess a mutation in the filaggrin gene. These carriers of the mutation also have significantly elevated total IgE serum levels and the disease often begins earlier [19].

The epidermal skin barrier protects from excessive water loss through the skin and offers protection from irritants, allergens and other pathogens. When it is disturbed, the probability of developing a type I sensitization possibly also increases, as allergens can penetrate and come into contact with allergen-presenting cells more readily. Clinically these type I sensitizations may become relevant in the form of AR or other allergic diseases. In fact, it was shown in mice with a filaggrin mutation resembling the human one that this predisposes to the development of percutaneous sensitization. After allergen contact an inflammatory skin infiltration developed and the animals displayed an allergen-specific immune response [19, 20]. Nonetheless, the genesis of AD is complex and multifactorial. Correspondingly, beyond mutation-induced barrier disturbance further mechanisms may play a pathogenetic role. To these belong altered responses of the acquired immune system including the production of IgE [21]. Interleukin (IL)-4 and IL-13 are important cytokines of Th2 cells that are relevant in the pathophysiology of both diseases, AD and AR. Under their influence B cells are stimulated to produce IgE [19]. Interestingly, candidate gene studies indicate that polymorphisms in the genes of the IL-4 and IL-13 receptor are associated with the common extrinsic AD, that variant that goes along with type I sensitizations and allergies [22, 23]. There are also indications of an association of a variant in the region coding for IL-13 with AD and elevated serum IgE levels [24].

A further common factor for the development of atopic diseases could be thymic stromal lymphopoietin (TSLP). TSLP plays a role in priming naive T cells in the direction of Th2 by human dendritic cells. Recently, indications surfaced that polymorphisms in the TSLP gene may be associated with AD [19]. Further, it was shown that TSLP in the nasal mucosa is up-regulated in AR patients and correlates with the severity of AR [25]. If further interest exists for the genetic background, we can recommend the paper by Bussmann and coworkers [19].

Altogether, despite these important observations, it has to date not been decisively determined if and in which manner a causal relationship actually exists between the

atopic diseases or if they only co-manifest due to a common pathogenetic background. At least for AD and asthma data exist that place this relationship in question [26]. It was shown that in children AD in the first two years of life was associated with asthma in school age, but only in those who before or parallel to the development of AD already displayed expiratory wheezing. Oppositely, those with AD without additional wheezing had no increased risk of developing asthma during the course.

Co-effects in therapy?

Independent of a causal relationship between AD and AR, there are doubtlessly common features in the pathophysiology. Correspondingly, co-effects in therapy can be expected when both diseases are present. In the following, data available on this point and the resulting therapeutic recommendations are presented. The main focus will be on allergen elimination, specific immunotherapy and the use of antihistamines.

Allergen elimination

Complete as possible elimination of relevant allergens is an important column in AR treatment. Studies show, for example, that the use of bed covers impermeable to mites (encasing) leads to a reduction in the mite concentration in mattresses [27]. Nevertheless, this alone is not sufficient to achieve a significant reduction in clinical symptoms in AR patients [27].

While contact with the allergen is a prerequisite for the occurrence of symptoms in AR patients, this also may play an important role for the course of symptoms in patients with AD. Thus, provocation of eczematous cutaneous lesions in patients with AD is possible e. g. by aeroallergens such as house dust mites [3]. Data on the benefit of allergen elimination in AD are available particularly for mite-sensitized patients. A placebo-controlled study by Tan et al. [28] demonstrated improvement of AD by use of encasing, use of acaricides and a special vacuum cleaner with a micro-filter [28]. A study on 41 children [29], in which in addition to encasings also further preventive measures were undertaken (among others, regular vacuuming, prohibition of pets), demonstrated beyond a significant reduction of major allergens of *Dermatophagoides pteronyssinus* and *farinae* also an improvement of cutaneous symptoms (SCORAD) of the affected children.

AD is a disease with a multifactorial cause with individual trigger factors, where a house dust mite allergy only represents an individual factor. Therefore, it is not surprising that also studies exist on the effectiveness of encasing in reducing the house dust mite concentration that did not demonstrate a significant improvement of AD [30]. One possible explanation of the lack of demonstration of a benefit might lie in the fact that the studies themselves led to regular laundering of bed linen and careful and more frequent vacuuming even in the placebo group.

The goal of elimination measures in house dust mite allergy is to reduce exposure to mite antigens. Important measures here are reduction in the number of mites (e. g. through regular vacuum cleaning, washing bed linen at >60 °C), creating unfavorable environmental conditions for surviving mites as well as encasing. Unfavorable environmental conditions for mites may be achieved by lowering room humidity to <50 % as well as room temperature to <20 °C. The selection of an encasing should in addition to effectiveness with respect to allergen exposure (impermeability for very small particles) also take characteristics important for the quality of sleep, such as e. g. water vapor permeability into consideration [4].

Among animal allergens cat or guinea pig allergies are, for example, of significance. For patients with perennial AR with a relevant sensitization allergen elimination, i. e. elimination of exposure, is recommended. According to the Guideline on Allergy Prevention [31] the results of holding pets on the development of allergy in children at risk (children with a genetic predisposition to atopic diseases) cannot be assessed precisely at this time. Keeping cats should probably be avoided, while keeping dogs is probably not associated with an increased allergy risk [31, 32]. A publication by Bisgaard and coworkers [32] on the barrier defect of the skin in filaggrin mutations shows, that the risk of developing AD is increased in carriers of the mutation (hazard ratio 2.3), and that this risk is again dramatically increased when a cat is kept in the home (hazard ratio 11.1).

Independent of an actual causal relationship between atopic dermatitis and allergic rhinitis, overlaps exist in the pathophysiology. Correspondingly, co-effects in the therapy of both diseases can be expected.

Provocation of eczematous cutaneous lesions by aeroallergens in patients with AD is possible.

The goal of elimination measures in mite allergy is to reduce exposure to mite allergens.

The selection of an encasing should in addition to effectiveness with respect to allergen exposure (impermeability for very small particles) also take characteristics important to the quality of sleep into consideration, such as e. g. good water vapor permeability.

For patients with allergic rhinitis with a relevant sensitization to pet allergens, elimination of the responsible animal is recommended.

To clarify, if type I allergens play a role in the course of AD, the atopy patch test (APT) can be employed. Here, the suspected type I allergens are applied under patches to the back and as in the standard patch test the results are read after 48 and 72 hours.

The result of the atopy patch test (APT) should due to the limited specificity be evaluated carefully together with clinical findings and history.

Should the presence of AD causally promote the development of AR, consistent topical therapy of AD with the goal of remission should lower the probability that type I allergies of the respiratory tract develop in the course. To date, no controlled, prospective studies exist on this issue.

Specific immunotherapy (SIT) is – next to allergen elimination – the only potentially curative therapy option in allergic rhinitis and asthma. Its benefits have been proven in a multitude of randomized, placebo-controlled clinical studies.

In comparison to house dust mites and animal allergens the situation is more complex for pollen allergens. Due to their ubiquitous presence complete allergen elimination is hardly possible. Behavioral recommendations and technical devices (e. g. pollen filters) are supposed to help prevent massive allergen exposures. Pollen filters are available and may be useful for selected AR patients. It is imaginable that pollen filters can have positive effects on a concomitant AD. Controlled studies on this issue have not yet been published, however.

If a sensitization to aeroallergens is clinically relevant in AD, can be determined on the basis of history and clinical findings. Affected house dust mite allergic patients report, for example, of improvement of cutaneous symptoms during stays at high altitudes, affected patients allergic to pollen report of exacerbation during the pollen season. Here, clinical symptoms are of importance; in AD patients particularly skin regions exposed to air display eczematous skin lesions (airborne type), while covered skin areas are less affected. To clarify if aeroallergens play a role in the course of AD, the atopy patch test (APT) can be employed. Here, the suspected type I allergens are applied under patches to the back and results are read after 48 and 72 hours. Both measuring of specific IgE and prick testing reveal multiple sensitizations in patients with AD without actual clinical relevance for the course and severity of the eczema [33]. In contrast, several publications demonstrate the benefit of APT for detecting the clinical relevance of type I allergens in AD [34, 35]. Nonetheless, positive reactions can also occur in patients without AD. For example, a study with mite allergens showed a positive ATP result in 49 % of all patients with AD, but 23 % of participants without AD were also positive [36]. A possible cause for positive APT reactions in patients without AD might be serine and cystine proteinases contained in house dust mite allergens. These activate PARs (proteinase-activated receptors) that are, among others, expressed in the skin and lead to the release of proinflammatory mediators such as IL-6 and IL-8. This results in an unspecific inflammation [37] not dependent on IgE.

Altogether, the APT can help to recognize type I allergens as trigger factors of AD. Its results should be evaluated carefully together with clinical findings and history due to the limited specificity.

Topical therapy

Should it be true that the presence of AD is causally involved in the development of AR in some patients, consistent topical therapy of AD with the goal of total healing of the skin should reduce the probability of AR and/or asthma becoming manifest during the course. To date, no controlled, prospective studies exist. Interestingly, in a recent small, open and uncontrolled study by Virtanen and coworkers [38] for the first time indications were found, that intermittent topical treatment of moderate to severe AD with tacrolimus can have favorable effects on respiratory symptoms and bronchial hyperreactivity. These results must, nonetheless, be confirmed in larger and especially controlled clinical studies. In order to study a protective effect of topical AD therapy on development of AR and asthma, it would further be necessary to follow a patient population that at the start of the study had AD but not yet any respiratory complaints, in a prospective manner.

Irrespective of this, good topical treatment of AD patients is to be recommended in principle. The quality of life of those affected is often reduced and sleeping disturbances can lead to exhaustion, difficulties in concentration and reduced productivity in school and at the workplace [39].

Specific immunotherapy

Besides allergen elimination, specific immunotherapy (SIT) is the only potentially curative therapy option in AR and asthma. Its benefits were proven in a multitude of randomized, placebo-controlled clinical studies [40]. In the meantime even studies exist on the benefits in patients with AD and accompanying type I sensitizations.

The goal of SIT is to generate tolerance to relevant inhalative allergens and thus remission of the misdirected allergic immune response. Even though SIT has already been employed for decades, its immunological mechanism of action is even today not completely understood. To a large degree consensus exists that there is a shift of immune response from a Th2 to a Th1 pattern, an induction of regulatory T cells, a

reduction of allergen-specific IgE production with a simultaneous induction of blocking, allergen-specific IgG antibodies and a reduction of mediator release by mast cells [41]. Probably increased release of inhibitory mediators such as, e. g. interleukin-10, is of significance in this scenario.

In the pathogenesis of AD, too, the dominance of Th2 cells in the acute inflammatory infiltrate and the recognition of allergens via specific IgE bound to Langerhans cells play a role [42]. Exposure to inhalative allergens can trigger symptoms or exacerbate cutaneous findings. Of particular significance are the house dust mites *Dermatophagoides pteronyssinus* and *farinae* as the most important perennial, ubiquitous indoor allergens. Seasonal allergens, such as birch or grass pollen, also can aggravate signs and symptoms of AD [42]. Overall, 70–80 % of all patients with AD possess type I sensitizations [43] and elevated total IgE levels or elevated specific IgE levels to inhalative or food allergens. It therefore seemed likely that SIT could also be effective in patients with AD and accompanying type I sensitizations. In fact, studies published to date are promising, Table 1 provides an overview [37, 44–57].

In a key paper Werfel and coworkers [56] were able to show that patients with AD and proven type I sensitization to house dust mite antigen benefit from SIT applied subcutaneously (SCIT) over one year. In this multicenter, randomized and placebo-controlled trial not only did clinical complaints decline, but also reduced use of topical corticosteroids and oral antihistamines was observed. One peculiarity of the study was, nonetheless, that unlike other studies on SCIT administration was once weekly and thus comparatively time-consuming. In addition, the dose administered was 1/5 of the usual SCIT maintenance dose. A follow-up study with the maximum allergen dose is currently under way; the results are not yet available. At the EAACI Congress 2011 in Istanbul the results of a new multicenter double-blind, placebo-controlled study with a depigmented, chemically modified house dust mite extract were presented [58]. Efficacy and safety of an 18-month treatment were examined on 164 adult patients with AD and proven type I sensitization to house dust mite allergens. The dose increase scheme, the maximum dose and the administration interval corresponded to those already established in AR therapy. While in patients with mild to moderate AD no superiority of verum treatment as opposed to placebo in terms of improvement of clinical findings were seen, in the post-hoc analysis a significant effect in the subgroup of severely affected AD patients was demonstrable. Further, the good tolerability of SIT in AD patients was confirmed.

For sublingual immunotherapy (SLIT) to house dust mites a placebo-controlled clinical study has also been published in the meantime [57]. Here, too, improvement of AD symptoms as well as reduced need for concomitant medication, i. e. corticosteroids and antihistamines, through therapy was seen. Studies with the opposite results do, however, also exist (Table 1) and further research is needed.

A series of further publications usually with open design and without a control group exist with matching results (Table 1). These suggest the efficacy of SIT not only in house dust mite allergy, but also in patients with AD and birch or grass pollen sensitization. For the interpretation, it is nonetheless necessary to remember that the placebo effect of SIT can be unusually large. Thus, Glover et al. in their study of the effects of SCIT with house dust mite extract on the symptoms of AD did find a distinct improvement of all clinical symptoms with an almost complete disappearance of pruritus, but this was not superior to the placebo group [59]. Also in the study by Werfel and coworkers [56] patients treated with placebo demonstrated an improvement of complaints.

In the past possible exacerbation of AD during SIT was pointed to again and again. Altogether, the studies published to date do not confirm this. In individual papers there are reports on a few cases of an increase in AD symptoms during SIT [57, 60]. This often occurs, however, for only a few days [61] and does not appear to be a regularly occurring reaction pattern. In the opposite, a generally good tolerability of the therapy was shown even in this patient group.

In summary, existing studies speak for a favorable effect of SIT on disease symptoms of AD when accompanying relevant type I sensitizations are present. For SCIT the data are somewhat better in comparison to sublingual therapy (SLIT). Particularly patients with house dust mite allergy have been studied relatively well. For this group it could also be shown in a small pilot study, that patients with a positive atopy patch

For the aggravation of atopic dermatitis the house dust mites *Dermatophagoides pteronyssinus* and *farinae* as the most important perennial, ubiquitous indoor allergens are of particular importance. Exposure to seasonal allergens, such as birch or grass pollen, also can impact cutaneous symptoms.

In a key paper it was shown that patients with atopic dermatitis and proven type I sensitization to house dust mite antigen benefit from subcutaneously administered specific immunotherapy. In addition to a decline of clinical symptoms, the use of topical corticosteroids and oral antihistamines also declined during a one-year immunotherapy.

Exacerbation of existing atopic dermatitis during specific immunotherapy was feared repeatedly. Up to now, there is no indication that this is a regularly occurring reaction pattern. In the opposite, existing studies show good tolerability of specific immunotherapy even in this patient group.

Specific immunotherapy appears to be particularly promising in patients with atopic dermatitis and a positive atopy patch test.

Table 1: Studies examining the benefit of specific immunotherapy in patients with atopic dermatitis.

Author	Year	SIT type	Allergen	Study type	Number of patients	Age of patients	Duration of SIT	Main results	Exacerbation of AD	Evaluation of SIT
Di Prisco De Fuenmayor et al.	1979	SCIT	House dust mite, grass pollen, horse hair, algae	Open, no control group	15	6–14 years	No statement	Improvement of clinical findings, reduction of medication	Transiently for 2–3 days in almost all patients	Positive
Glover et al.	1992	SCIT	House dust mite	R, DB, PC	26	5–16 years	8 (14) months	Improvement of clinical findings with verum and placebo. No superiority of verum group	Not reported	No effect
Leroy et al.	1993	i.c.	House dust mite, autologous specific antibodies	R, DB, PC	24	15–64 years	12 (16) months	Improvement of clinical findings, no alteration of total IgE, decline of specific IgE only in subgroup of responders to therapy	Not reported	Positive
Galli et al.	1994	SLIT	House dust mite	R, open, with control group	60	Up to 12 years	On average > 15 months	Improvement of clinical findings in the verum group and in the control group. No superiority of the verum group	In 2 patients	No effect
Pacor et al.	1994	SCIT	House dust mite	Open, no control group	32	15–45 years	36 months	Improvement of clinical findings, decline of specific IgE, no alteration of total IgE	Not reported	Positive
Mastrandera et al.	2000	SCIT	House dust mite, grass pollen, Parietaria, olive	Open, no control group	35	3–30 years	36 months	Improvement of clinical findings	In 2 patients	Positive
Petrova et al.	2001	SLIT	House dust mite	PC, unclear if open or DB	99	16–52 years	6 months	Improvement of clinical findings, no alteration of specific IgE	In 19 patients	Positive
Silny et al.	2006	SCIT	House dust mite, grass pollen	R, DB, PC	20	5–40 years	12 months	Improvement of clinical findings, trend towards decline of specific IgE	Transiently in both treatment arms	Positive

Continued

Table 1: Continued.

Author	Year	SIT type	Allergen	Study type	Number of patients	Age of patients	Duration of SIT	Main results	Exacerbation of AD	Evaluation of SIT
Werfel et al.	2006	SCIT	House dust mite	R, DB, PC	89	18–55 years	12 months	Improvement of clinical findings, reduction of medication, no alteration of total IgE and specific IgE (weekly injection intervals)	No	Positive
Bussmann et al.	2007	SCIT	House dust mite	Open, no control group	25	5–65 years	6 months	Improvement of clinical findings, decline of specific IgE, increase of allergen-specific IgG4 antibodies, no alteration of total IgE	In 1 patient	Positive
Cadario et al.	2007	SLIT	House dust mite	Open, no control group	86	3–54 years	12 months	Improvement of clinical findings, decline of total IgE and specific IgE, trend towards reduction of medication	Not reported	Positive
Pajno et al.	2007	SLIT	House dust mite	R, DB, PC	56	5–16 years	18 months	Improvement of clinical findings, reduction of medication	In 2 patients	Positive
Nahm et al.	2008	SCIT	House dust mite plus histamine-gamma globulin complex	Open, no control group	20	7–58 years	12 months	Improvement of clinical findings	Not reported	Positive
Novak et al.	2010	SCIT	Birch pollen	Open, no control group	55	18–65 years	12 weeks	Improvement of clinical findings, improvement of quality of life	Not reported	Positive
Kwon et al.	2010	SCIT	House dust mite	Open, no control group	20	6–33 years	12–60 months	Improvement of clinical findings, no alteration of total IgE and specific IgE	No	Positive

R = randomized, DB = double-blind, PC = placebo-controlled, SCIT (subcutaneous immunotherapy), SLIT (sublingual immunotherapy), i.c. = intracutaneous

In the future the already known positive results of SIT in patients with AD should be confirmed on larger patient collectives and important remaining questions be clarified, for example what are the ideal target groups and optimal administration schemes.

Mast cell mediators – among them histamine, leukotrienes and prostaglandins – are substantially responsible for the early phase of inflammation in allergic rhinitis. During the course the inflammatory reaction increases further through immigration of lymphocytes, granulocytes and the production of additional proinflammatory mediators.

In contrast to allergic rhinitis, much less is known about the pathogenetic role of histamine in atopic dermatitis.

In atopic dermatitis histamine is assigned an proinflammatory effect and a role in the development of pruritus.

In clinical reality the suspected antipruritic effect of H₁-antihistamines is a major reason for their widespread use in atopic dermatitis.

First indications exist that in selected patients with pruritus an increase of the H₁-antihistamine dose up to the fourfold approved dosage can be useful.

test appear to respond particularly well to SCIT [60]. The basis for the positive effects of SIT on the symptoms of AD remains an important question.

In the future the already known positive results of SIT in patients with AD should be confirmed on larger patient collectives and important remaining questions be clarified. These include among others:

- Do differences in the efficacy of SIT exist between mono- and polysensitized AD patients?
- Do differences exist in the efficacy of SIT depending on the allergen?
- Does the allergen formulation (depot, aqueous solution, allergoids) impact the efficacy of SIT on AD?
- Does the route administration form (subcutaneous vs. sublingual) impact the efficacy of SIT on AD?
- Can alterations of the administration intervals in comparison to classical SIT in AR and/or asthma improve the efficacy of SIT on AD?

Antihistamines

Histamine plays an important role in the pathogenesis of allergic rhinitis (AR). Triggered by allergen binding via specific IgE mast cells degranulate with release of proinflammatory mediators in the nasal mucous membranes. These mediators – among them histamine – but also other factors such as leukotrienes and prostaglandins are substantially responsible for this early phase of allergic inflammation. During the course the inflammatory reaction further increases through immigration of lymphocytes, granulocytes and the production of additional proinflammatory mediators. Histamine was identified as a central mediator of nasal symptoms such as obstruction, pruritus, sneezing and rhinorrhea in AR. The effects of histamine are transmitted through histamine receptors that are found, among others, on nerve and blood vessel wall cells. To date four different receptors (H₁R, H₂R, H₃R and H₄R) have been identified. Studies with selective receptor agonists were able to show that stimulation of H₁R, but not H₂R results in sneezing, pruritus and rhinorrhea [62]. In nasal obstruction, in contrast, the H₂R might also play a role [62]. On the other hand, it was demonstrated that sneezing, pruritus, rhinorrhea and nasal obstruction after nasal provocation with the allergen can be reduced in patients with AR by application of an H₁-antihistamine (AH) beforehand [63, 64]. Data for H₂-antihistamines are less convincing in this respect. For H₃R and H₄R, too, studies exist making a role in the pathogenesis of AR probable [65, 66]. As to date no medications are available with an effect on these receptors in clinical routine, these insights remain without impact on therapy at the moment.

In contrast to AR, much less is known about the pathogenetic role of histamine in AD. An indirect indication for possible relevance is the fact that both mast cell density [67] as well as histamine levels [68] is elevated in lesional skin in AD patients. Further, a reduction of AD symptoms was observed during a histamine-poor diet [69, 70]. In recent scientific discussion histamine was assigned a role particularly in the development of pruritus [71]. An inflammation-promoting effect was also suspected [71]. Pruritus is not only one of the key symptoms, but it is primarily responsible for the reduction in the quality of life of those affected. In clinical reality the antipruritic effect of H₁-antihistamines (AH) is a major reason for their widespread use in AD, usually as an additive medication together with topical basic therapy and with topical treatment with corticosteroids and calcineurin inhibitors. It is undisputed, that histamine can trigger pruritus. Concretely, this functions via stimulation of pruritus-specific, slowly transmitting afferent C-nerve fibers [72]. This triggers as a motor response involuntary scratching, which again contributes to irritation of the skin and ends in an itch-scratch cycle. Scratching leads to (further) damage of the epidermal skin barrier with resulting increased water loss as well as increased impact of environmental factors and allergens [73]. Correspondingly, AH are recommended for use in chronic pruritus [74]. A recently published case series on use of AH in patients with chronic pruritus of differing genesis suggests that, just as in chronic urticaria, an increase of the dosage up to fourfold of the approved dose can be useful to effectively treat pruritus [75]. As diverse further mediators that can cause pruritus exist in addition to the release of histamine, on the basis of these data it is in no way certain that histamine is exclusively responsible for the development

of pruritus in AD patients. Experimental data actually do exist that cast doubt on the prominent role of histamine in the pruritogenesis of AD [76, 77], and it appears likely that other mediators are responsible for the development of pruritus in AD besides histamine.

All in all, pruritogenesis is a highly complex process, which is still insufficiently understood in most diseases; fortunately, it is increasingly coming into the focus of science. In recent years several new pathways of pruritus transmission and new pruritus modulators have been identified. Among others, it has been shown that pharmacological blockade of H₄R in the mouse model reduces pruritus [78]. H₄R antagonists are already in clinical development and appear, at least in experimentally induced pruritus, to be superior to traditional AH [79]. The newly discovered pruritus modulators include IL-31. Interestingly, IL-31 levels correlate both with pruritus (scratching behavior) in the mouse model as well as with disease severity in AD patients [80]. In animal models anti-IL-31 has already been successfully employed in the treatment of pruritus [80]. Thus, both H₄R and IL-31 represent new targets in therapy of pruritus and especially also of AD in humans. If interest in these new developments exists, we would like to recommend reading Metz et al. [78] as well as Raap et al. [80].

For the treatment of those affected in clinical routine it is decisive, if the AH available today have a demonstrable clinical benefit for AD patients. Only high-quality, i. e. randomized, double-blind and placebo-controlled studies can clarify this. These exist for AR [81, 82]. Correspondingly AH are recommended as therapy of first choice for AR in current guidelines [40]. It became clear in the clinical studies, however, that AH as monotherapy do not always lead to complete improvement of symptoms. It is therefore useful in many patients with AR to combine AH with other agents, such as e. g. a topical nasal corticosteroid, which also acts locally to inhibit the allergic inflammation. For optimal therapy it is also of importance, that long-term administration is superior to use as needed in the event of symptoms [83, 84].

For AD the status of studies is limited in comparison to AR. Table 2 gives an overview of published randomized, double-blind, placebo-controlled studies [73, 85–96]. Studies which examine the use of AH in patients with AD and concomitant AR in a targeted manner are not available to the best of our knowledge.

In principle, AH of the first and of the second generation must be differentiated. In contrast to drugs of the first generation, that are still associated with marked sedating effects, drugs of the second generation possess no or hardly any sedating characteristics. This is especially due to the fact that the latter bind distinctly more specifically to H₁R and in addition hardly penetrate into the central nervous system. The additional differentiation of a third generation is at present not viewed as being justified [97, 98].

For sedating H₁-antihistamines (sAH) only one randomized, double-blind, placebo-controlled study with more than 100 patients is available [95]. This demonstrated no improvement of AD symptoms (pruritus and severity of cutaneous findings) under therapy with chlorphenamine over 4 weeks in children up to age 12. In the other smaller studies with sAH in AD the majority also showed no effects [85, 86, 89, 90]. For non-sedating H₁-antihistamines (nsAH) three larger randomized, double-blind, placebo-controlled studies are available. These differ from each other significantly in design and will be discussed briefly in the following.

In the most recent study Kawashima and coworkers [96] demonstrated that treatment with 120 mg fexofenadine daily (as medication additive to topical corticosteroid therapy) is capable of reducing daytime and night-time pruritus in comparison to placebo. The effect is supposed to have a rapid onset, but to be only slight as opposed to placebo.

In the ETAC study (Early Treatment of the Atopic Child study) the primary goal was to determine if an 18-month treatment of AD children with cetirizine prevents the development of asthma. The results showed no preventive effects. Further, the impact of cetirizine on the symptoms of AD was examined [73]. On the whole, AD complaints were reduced, but the treatment with cetirizine was not superior to placebo. However, in the subgroup of severely affected children (SCORAD ≥ 25) a significant steroid-sparing effect and in the subgroup of children with AD and additional sensitization to grass pollen or house dust mite an almost significant effect was seen.

H₁-antihistamines are recommended as therapy of first choice for the treatment of allergic rhinitis on the basis of good evidence. As monotherapy they are not always sufficient.

Among H₁-antihistamines drugs of the first generation must be differentiated from drugs of the second generation. In contrast to the first generation the latter possess no or hardly any sedating characteristics.

Studies on the efficacy of sedating H₁-antihistamines in atopic dermatitis showed no benefit in the majority.

Table 2: Studies examining the benefit of H1-antihistamines in patients with atopic dermatitis.

Author	Year	Agent	Dosage	Study type	Number of patients	Age of patients	Duration of therapy	Main results	Evaluation of efficacy in AD
Savin et al.	1979	Trimiprazine, trimipramine	20 mg, 50 mg	R, DB, PC	12	23–38 years	Single dose	Slight reduction of nocturnal scratching under trimiprazine and trimipramine	Positive
Frosch et al.	1984	Chlorphenamine, chlorphenamine plus cimetidine	16 mg, 16 mg plus 1600 mg	R, DB, PC	18	14–43 years	4 weeks	No improvement of pruritus and cutaneous findings under chlorphenamine and chlorphenamine plus cimetidine	Negative
Berth-Jones et al.	1989	Terfenadine	240 mg	R, DB, PC	28	11–67 years	1 week	No improvement of pruritus under terfenadine	Negative
Doherty et al.	1989	Acrivastine, terfenadine	24 mg, 180 mg	R, DB, PC	49	16–58 years	10 days	Improvement of pruritus under acrivastine and terfenadine	Positive
Wählgren et al.	1990	Terfenadine, clemastine	120 mg, 4 mg	R, DB, PC	25	17–42 years	3 days	No improvement of pruritus in comparison to placebo, sedation under clemastine	Negative
Monroe	1992	Loratadine, hydroxyzine	10 mg, 75 mg	R, DB, PC	41	18–65 years	1 week	Improvement of pruritus under loratadine, frequent sedation under hydroxyzine	Positive
Hannuksela et al.	1993	Cetirizine	10, 20, 40 mg	R, DB, PC	178	> 18 years	4 weeks	Improvement of pruritus under 20 mg cetirizine, improvement of cutaneous findings only under 40 mg cetirizine, increasing sedation with increasing dose	Positive
Langland et al.	1994	Loratadine	10 mg	R, DB, PC	16	19–37 years	3 x 2 weeks	Improvement of daytime and night-time pruritus and cutaneous findings under loratadine	Positive
La Rosa et al.	1994	Cetirizine	5–10 mg (adapted to body weight)	R, DB, PC	23	6–12 years	8 weeks	Improvement of pruritus and cutaneous findings under cetirizine, no occurrence of side effects	Positive
Henz et al.	1998	Cetirizine, azelastine	10 mg, 4 mg	R, DB, PC	74	17–67 years	2 weeks	No improvement of pruritus in patients with atopic dermatitis under cetirizine and azelastine	Negative
Diepgen	2002	Cetirizine	0,25 mg/kg twice daily	R, DB, PC	817	1–2 years	18 months	In children with SCORAD ≥ 25 steroid-sparing effect under cetirizine. In children with additional sensitization to grass pollen or house dust mites almost significant steroid-sparing effect under cetirizine	Positive
Munday et al.	2002	Chlorphenamine	1–4 mg	R, DB, PC	155	1–12 years	4 weeks	No improvement of pruritus and cutaneous findings under chlorphenamine	Negative
Kawashima et al.	2006	Fexofenadine	120 mg	R, DB, PC	411	18–55 years	1 week	Improvement of daytime and night-time pruritus under fexofenadine, rapid onset of action	Positive

R = randomized, DB = double-blind, PC = placebo-controlled

In the third large study by Hannuksela et al. [91] cetirizine was administered in up to fourfold of the approved dosage (10 mg, 20 mg and 40 mg daily) in adults with AD. Significant improvement as opposed to placebo was observed for a dose of at least 20 mg for pruritus and for 40 mg also for other parameters of the cutaneous findings. At the latter dose sedating effects did occur. This result is in agreement with the data already reported by Ständer and coworkers [75], who likewise found benefits of a higher dosage of AH for pruritus. In the smaller studies published in addition to these three papers, nsAH in AD also display in part positive effects on pruritus and cutaneous findings [88, 92, 93].

It has been speculated again and again that the effect of AH on pruritus is primarily due to central sedation and less on peripheral inverse agonism at H₁R [99]. This would imply better efficacy of sAH in comparison to the non-sedating preparations, but this is not supported by the current status of studies. Even those studies that compared H₁-antihistamines of both generations directly with one another found no superiority of the sedating preparations in AD [89, 90]. On the other hand, Savin et al. also demonstrated that AD patients scratched less while sleeping under the influence of the sedating substances trimipramine and trimeprazine due to an altered sleeping cycle [85].

According to the current German guideline the AH side effect sedation may be utilized therapeutically in AD (expert opinion) [1]. In the current position paper of the ETFAD/EADV eczema task force, also, sAH are still found in level 3 of AD therapy [100]. This must surely be viewed critically on the basis of current knowledge of side effects of sAH. Church and coworkers have examined the risks in their current position paper once again [101]. Sedating AH alter not only the sleeping patterns, but also reduce the ability to learn and productivity at work. In addition, their use appears to increase the risk of traffic accidents and an overdose can be life-threatening [101].

Overall, the existing studies demonstrate a moderate efficacy of non-sedating AH on the symptoms of AD. Therefore, from the viewpoint of the current S2 guideline atopic dermatitis, treatment of AD with AH as a supporting concomitant medication in addition to basic therapy and antiinflammatory topical treatment can be undertaken [1]. Possibly the employment of higher dosages (up to fourfold of the approved dose) can bring additional benefits for the patient. When AR is present in addition to AD, the use of AH is particularly justified. For the efficacy of sedating AH in AD no convincing evidence exists. Their use is associated with substantial disadvantages and risks [101]. Therefore, modern non-sedating preparations should be favored perhaps “updosing” should be considered.

Summary

The association of AD and AR as well as common features in their pathogenesis makes co-effects in the therapy of both diseases likely. It is particularly interesting, if elimination of type I allergens, the use of H₁-antihistamines and specific immunotherapy have positive effects on the symptoms of AD, when parallel, clinically relevant type I allergies are present.

Although study data on the benefits of allergen elimination on the symptoms of AD are still limited, measures to reduce exposure to relevant allergens, such as e. g. the use of encasing, pollen filters or pollen screens may be useful. For the benefits of specific immunotherapy for patients with AD and type I allergies a certain degree of evidence exists in the meantime, particularly for patients with house dust mite allergy. Nonetheless, further prospective, controlled studies must follow in order to prove efficacy. This is particularly true with respect to suitable target groups and optimal administration schemes. For the H₁-antihistamines particularly for non-sedating preparations a moderate positive effect on the symptoms of AD was shown. Their use in AD is justifiable as a supporting concomitant medication in addition to basic skin care and antiinflammatory topical treatment, particularly when AR is present simultaneously. The use of sedating preparations must be viewed critically on the basis of current knowledge with respect to the side effects.

In summary, both diseases (AD and AR) possess pathophysiological overlaps that should be considered within the therapy concept and make co-therapeutic effects seem likely.

The efficacy of non-sedating H₁-antihistamines in atopic dermatitis has been examined in a few randomized, double-blind, placebo-controlled studies. The results suggest a moderate benefit of the treatment.

The efficacy of non-sedating H₁-antihistamines in atopic dermatitis has been examined in a few randomized, double-blind, placebo-controlled studies. The results suggest a moderate benefit of the treatment.

Overall, a moderate effect of H₁-antihistamines on the symptoms of atopic dermatitis appears to exist. Thus, treatment as concomitant medication in addition to basic therapy and antiinflammatory topical therapy can be considered.

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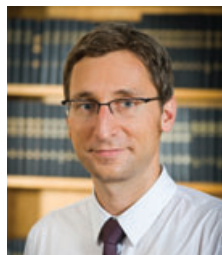
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Conflicts of interest

None.

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