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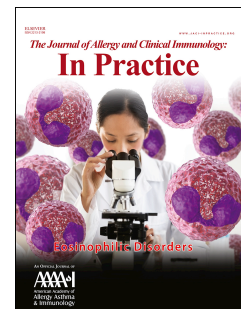
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Preventive Effect of Allergen Immunotherapy on Asthma and New Sensitizations

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24 **Abstract**

25 Allergen immunotherapy (AIT) is a disease-modifying treatment for some IgE-mediated allergic
26 diseases with the potential to have important preventive effects. Children with allergic rhinitis
27 have a high risk of developing asthma, and treating allergic rhinitis with AIT may interfere with
28 disease progression and prevent onset of asthma. Although the evidence is limited due to relatively
29 few and heterogeneous studies, data nevertheless suggests that AIT has a preventive effect on
30 development of asthma especially in children with rhinitis due to grass pollen allergy. AIT may also affect
31 the development of new sensitizations. Both the degree of sensitization and the specific
32 sensitization pattern may influence future disease severity and development of comorbidities.
33 Hitherto, the indication for AIT for prevention of development of asthma in grass/birch pollen
34 allergic children has been the same as for treatment of allergic rhinitis. Probably, AIT should be
35 applied in the early stage of the allergic disease to have the greatest preventive effect on disease
36 progression. Consequently, in the future the potential preventive effects should influence the
37 timing of initiating AIT. The window of opportunity to prevent asthma may primarily exist in young
38 children with mild symptoms and a low degree of sensitization.

39

40 **Key words:** allergen immunotherapy, prevention, asthma, sensitization, children

41

42 Highlights box

43 Key points

44 AIT may prevent development of asthma in children with allergic rhinitis.

45 The evidence is strongest for grass pollen.

46 The effect may be best in younger children, which may influence the indication and timing of AIT in the future

47

48 Abbreviations

49 AIT: Allergen immunotherapy

50 AR: Allergic rhinitis

51 CI: confidence interval

52 CRD: component resolved diagnostics

53 HDM: House dust mites

54 RCT: Randomized controlled trial

55 SCIT: Subcutaneous immunotherapy

56 SLIT: Sublingual immunotherapy

57

58

59

60 Introduction

61 Allergic diseases are very common and comprise atopic eczema, allergic rhinitis (AR) / rhinoconjunctivitis
62 and asthma. Especially in infants and young children, allergy symptoms are often caused by food allergy,
63 whereas later on allergy to inhalant allergens are dominating. (1-3) In addition, it appears that AR most
64 often is associated with allergy to outdoor allergens (i.e. pollen) and allergic asthma with indoor allergens
65 such as house dust mites (HDM) and furry pets. There is a high degree of comorbidity and AR often
66 precedes and represents a high-risk factor for development of asthma, which often persists into
67 adulthood.(1-5)

68 For more than 100 years, allergen immunotherapy (AIT) has been used and accepted as a treatment option
69 for allergic diseases, especially AR, asthma, and venom allergy with the best documented effect for pollen,
70 HDM- and venom allergens and less documented for cat, dog and horse allergens, and with the effect
71 lasting beyond end of treatment. (6-8) During the last decades, focus has also been on the possible
72 preventive potential of AIT. Most of these studies have addressed the possible prevention of development
73 of asthma in children with AR and some have investigated the possible preventive effect on the
74 development of new allergic sensitizations.

75 This has been thoroughly reviewed in a recent EAACI systematic review published in 2017 (9), resulting in
76 the EAACI Guidelines on AIT for prevention of allergic diseases. (10) This review demonstrated a potential
77 preventive effect on development of asthma in children with AR, especially pollen allergy and possibly HDM
78 allergy, whereas there was no documentation for other populations or allergies.

79 The aim of this review is to summarize the present knowledge on the preventive capacity of AIT according
80 to the different allergens used with focus on prevention of development of asthma in different clinical
81 situations and discuss its clinical implications and future perspectives.

82

83 Preventive effect of AIT on development of asthma

84 Allergic rhinitis is a significant risk factor of asthma in children and adults.(11-13) The correlation may be
85 stronger in cases of severe rhinitis symptoms (14), in cases of early onset of allergic rhinitis(15, 16), and also
86 polysensitization seems to increase this risk. (16) Moreover, serum IgE to specific molecules may predict
87 the persistence and severity of AR, and the development of an IgE response to other molecules (molecular
88 spreading) may predict onset and persistence of asthma.(16)

89 It is obvious that a higher risk of developing asthma is associated with a higher potential of a preventive
90 effect of AIT. Consequently, one may expect young age and severe symptoms to be associated with the
91 greatest preventive effect of AIT on onset of asthma in AR patients. A systematic review from 2017
92 concluded that a three-year course of AIT significantly reduced the risk of onset of asthma in patients with
93 allergic rhinitis with the greatest effect in children, those receiving subcutaneous immunotherapy (SCIT) or
94 sublingual immunotherapy (SLIT) and for pollen AIT.(9) This effect was found up to two years after end of
95 treatment, but data was inconclusive regarding a maintained effect over a longer period.. The evidence is,
96 however, limited due to relatively few, often small and heterogeneous studies. None of the studies on
97 preventive effect of AIT on development of asthma included pre-school age children, and thus we have no
98 evidence for a possible preventive effect in this age group.

99

100 Grass-pollen

101 Grass pollen studies provide the most data on the preventive effect of AIT. Three large multicenter
102 randomized controlled trials (RCTs) have studied the preventive effect of grass pollen AIT on development
103 of asthma/asthma symptoms in children with allergic rhinitis. In an open randomized study including 205
104 children (mean age 10.7 years) with birch and/or grass pollen allergy (n=165), 3 years of SCIT had a

105 preventive effect on developing asthma at end of treatment and at five and 10 years follow up, odds ratio
106 2.5 and 2.7 (95% confidence interval (CI): 1.1-5.9), respectively. (17-19)

107 In an open Italian study with 113 grass pollen allergic children (mean age 7.7 years), 3 years of coseasonal
108 SLIT drops reduced onset of asthma symptoms. (20) At the end of treatment, the relative risk of
109 development of asthma symptoms was 3.8 (95%CI: 1.5-10.0) in the control group compared with the SLIT
110 group. No further follow-up was published.

111 In a multinational double-blind placebo controlled RCT, 812 children (mean age 8.7 years) were randomized
112 to SLIT tablet grass pollen or placebo for 3 years, and a subsequent blinded post-AIT follow-up period of
113 two years. (21) At the end of the five-year trial period, 8.5% had asthma diagnosed by means of strict
114 predefined criteria, including lung function and reversibility test, compared with 9.4% in the in the control
115 group ($p=0.67$). Meanwhile, at the end of trial the number of subjects with asthma symptoms and/or
116 asthma medication usage was significantly less in the SLIT group compared with the placebo group, odds
117 ratio: 0.66 ($p=0.036$). In addition, data from this study indicated that younger children had a higher
118 probability of developing asthma symptoms than older children, and thus the preventive effect was
119 greatest among the younger children. (21)

120

121 Overall, data supports that SCIT has a preventive effect on asthma in children with grass and/or birch pollen
122 allergy and in parallel, SLIT has demonstrated a preventive effect on onset of asthma symptoms and use of
123 asthma medication up to two years post-AIT.

124

125 **Birch pollen**

126 In a double blind Swedish study from 1986, none of 14 children treated with birch pollen capsules for 10
127 months developed asthma during treatment compared with five of 16 children in the placebo group. (22)
128 The previous mentioned open randomized study demonstrated an asthma preventive effect of three years
129 SCIT in children with birch and/or grass pollen allergy, but it is not possible to distinguish the effect of grass
130 and birch pollen SCIT. (17-19). Thus, there are insufficient data for birch pollen AIT in itself for prevention of
131 development of asthma.

132

133 **Parietaria judaica**

134 In an Italian double-blind study, 30 adults with allergic rhinitis were randomized to SCIT with *Parietaria*
135 *judaica* or placebo for three years. (23) Two patients (9%) developed asthma at the end of treatment
136 compared with nine patients (47%) in the placebo group, with no significant difference between the groups
137 ($p=0.056$).

138

139 **House Dust Mites**

140 Based on data from three RCTs, HDM AIT may have a preventive effect on asthma onset in children with
141 allergic rhinitis. In an open study including 216 children with allergy to pollen or HDM and AR +/-
142 intermittent asthma, 144 were randomized to SLIT drops for 3 years, of which 98 were allergic to HDM. At
143 the end of treatment, the risk of onset of intermittent or mild persistent asthma was lower in the AIT group
144 compared with the control group, odds ratio 0.04 (95%CI 0.01-0.17). (24)

145 In an open small Chinese study, none of 51 children with AR and HDM allergy treated for 3 years with SCIT
146 had developed asthma two years post treatment compared with 9/41 (22%) in the control group ($p<0.01$).
147 (25)

148 In a small double-blind RCT of 44 children and adults with house dust mite allergy and AR, none developed
149 asthma during 2 years of treatment with SCIT compared with 2 (9%) in the placebo group ($p=0.49$). (26)

150

151 **Prevention of development of asthma in children with no sensitization to inhalant allergens**

152 Only few RCTs have investigated the preventive effect of AIT on asthma in infants with no sensitization to
153 inhalant allergens. In children aged 12-30 months with atopic dermatitis, 12 months of SLIT drops with
154 HDM, grass and cat allergen extracts, had no effect on asthma onset. (27) Also, in a recent double-blind RCT
155 12 months of oral AIT with HDM allergen extract had no preventive effect on onset of wheeze, eczema or
156 food allergy in high risk infants <1 year. (28)

157

158 **Prevention of development of allergic symptoms in sensitized asymptomatic subjects**

159 A Japanese study randomized asymptomatic cedar sensitized adults to receive SLIT or placebo 5 months a
160 year for two years. (29) Four out of 13 patients in the active group developed allergic rhinoconjunctivitis
161 compared with 8 out of 14 patients in the placebo group.

162

163 **Prevention of new allergen sensitizations**

164 A systematic review from 2017 found that 10 of 18 studies reported a reduction in the onset of new
165 sensitizations in allergic mono- or polysensitized patients treated with AIT, but this was not confirmed in a
166 sensitivity analysis. The authors concluded that a low-grade level of evidence supports that AIT can prevent
167 onset of new allergen sensitizations.(30) The two RCTs including non-sensitized infants report conflicting
168 results. In infants with atopic dermatitis, AIT with HDM, grass and cat had no effect on new sensitizations

(27), whereas oral AIT with HDM in non-sensitized infants born to atopic parents reduced the risk of developing any sensitization to food or aeroallergens compared with placebo (9% vs. 26%, $p=0.03$). (28)

Sensitizations to allergen components and AIT

The development of molecular allergology and component resolved diagnostics (CRD) has potentially provided new possibilities for improving the effect of AIT and may predict the progression of AR to asthma. (31). It has been suggested that stratification of patients according to molecular sensitization profiles may enhance success of AIT. (32). In addition, it has been hypothesized that starting AIT at an early stage of sensitization to prevent progression of sensitization to more molecules would prevent development of comorbidities such as asthma. (31)

A few studies have found that AIT per se may pose a risk for development of new sensitizations to molecular components included in the vaccine that the patients were not sensitized to beforehand. A recent retrospective study suggested that patients undergoing SCIT might carry an enhanced risk of sensitization towards formerly unrecognized allergen components. (33) Out of 51 SCIT patients, 12 (24%), had new specific IgE against allergen components of the SCIT allergen source (grass pollen, birch pollen, HDM). Also in an adult population, SCIT with HDM induced a *de novo* development of allergen-specific IgE against HDM molecules that were not recognized before AIT in seven out of 24 HDM-allergic patients. (32) In contrast, however, 33 adults receiving SCIT with grass pollen and 30 children treated with SLIT with grass pollen had no new sensitizations against individual *Phleum pratense* molecules. (34, 35)

In conclusion, one may speculate that CRD can be a valuable tool for future precision medicine in AIT. It is possible that AIT can be matched to the sensitization pattern of the individual patient making the therapy more effective, and may also have a positive effect on sensitization pattern and development of asthma. However, although the use of molecular profiling is promising, we lack good studies to document its benefits for the preventive effects of AIT.

192

193 Safety

194 Safety issues for using AIT for prevention is regarded the same as for treatment of allergic rhinitis, which
195 has been thoroughly described previously (6, 10, 36) , and the RCTs on AIT for prevention do not add
196 further to this. AIT is regarded as a safe treatment, although adverse effect are described - mainly mild local
197 reactions but also systemic reactions including rare cases of anaphylaxis. In general, SLIT has a better safety
198 profile than SCIT with less systemic reactions and no fatalities as described in a metaanalysis (20), in a
199 recently published pooled analysis of data from grass tablet studies (37), and in two real life clinical studies.
200 (38, 39)

201

202 Clinical implications: who should receive AIT for prevention?

203 The decision to provide AIT should be individualized and based on a reflection of possible benefits and
204 harms. Evidence is insufficient to recommend AIT for prevention of allergic disease alone. Subsequently,
205 the indication for AIT should be as for the existing allergic disease. Thus, in a recently published guideline
206 from EAACI (10) it is recommended that a 3-year course of SCIT or SLIT can be recommended for children
207 and adolescents with moderate-to-severe AR triggered by grass/birch allergy to prevent asthma for up to
208 two years post-AIT in addition to its sustained effect on AR symptoms and medication. The effect is possibly
209 strongest for younger children (21), which may influence the decision when to treat grass pollen allergic
210 children with AIT. The timing is important, and it may be optimal to initiate AIT treatment relatively soon
211 after onset of clinical symptoms. (Figure 1)

212 The available data on the preventive effect of AIT are almost exclusively based on immunotherapy with a
213 single or very few allergens. The preventive effect on asthma of polyallergen AIT is unknown. Besides, it is

214 unknown if continuous high daily exposure to an allergen affects the preventive effect of AIT with the
215 specific allergen.

216

217 **Future perspectives**

218 There is a high degree of heterogeneity of AIT prevention studies, which makes it difficult to make strong
219 conclusions about the effects - it is difficult to distinguish if an observed effect in a study is a specific
220 product-and-protocol effect or is a class effect of AIT. The studies use different populations and diagnostic
221 criteria, if any, and therefore it is difficult to compare and evaluate the effects found. In addition, no studies
222 compare the preventive effect of different AIT products or doses. High quality RCTs are necessary to
223 confirm if AIT with all inhalant allergens have the potential to prevent asthma and to investigate the impact
224 of the route of administration, dose and duration of AIT. In addition, there is a need to investigate how to
225 design the most optimal study, how to select patients (e.g. optimal age, sensitization pattern, and disease
226 severity/duration) and not least how to define the best outcome measure for preventive AIT.(10, 40)

227 The potential of AIT to affect the sensitization pattern and the clinical relevance needs further research.
228 Based on birth cohort studies a theory of molecular spreading has evolved. (31) Data from longitudinal
229 studies suggests that sensitization to inhalant allergens often follows a certain pattern in children. (15, 41,
230 42) The initial IgE response is directed against one or few specific molecules (e.g. Phl p 1, Bet v 1 and Der p
231 1/ Der p 2/ Der p 23) at a time when the child has no symptoms and then broadens to polymolecular
232 sensitization. A broad sensitization pattern is found to be associated with an increased risk of rhinitis and
233 asthma. Thus, it would be interesting to see in future research if AIT in healthy children with
234 monomolecular sensitization can prevent subsequent polymolecular sensitization and the development of
235 allergic symptoms.

236

237 Conclusion

238 AIT has a potential to modify the natural course of allergic diseases. AIT can prevent the development of
239 asthma symptoms in children allergic to grass pollen especially. There are indications that AIT must be
240 applied early in the phase of increasing sensitizations and allergic symptoms to achieve the greatest
241 potential of a disease-modifying effect. Consequently, in the future the indication for AIT probably should
242 be different for children and adults. Young children with mild symptoms during a single/few allergen
243 season(s), probably have the greatest potential of achieving an asthma preventive effect in addition to
244 alleviation of current symptoms. In adults on the other hand, the indication to apply AIT should be based on
245 severity of symptoms.

246

247

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369

370 Legends

371

372 Figure 1

373

374 The window of opportunity of AIT to prevent asthma.

375 A left shift of the AIT indication to younger age / milder disease may increase the preventive effect on
376 asthma.

