Research Article

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Immunotherapy

Patient needs and benefits of sublingual immunotherapy for grass pollen-induced allergic rhinitis: an observational study

Toni Maria Klein*[,1], Meike Hadler[2], Matthias Augustin[1] & Christine Blome[1]

[1]Institute for Health Services Research in Dermatology and Nursing (IVDP), University Medical Center Hamburg-Eppendorf (UKE), Martinistraße 52, Hamburg, 20246, Germany

[2]Stallergenes GmbH, Carl-Friedrich-Gauß-Straße 50, Kamp-Lintfort, 47475, Germany

*Author for correspondence: Tel.: +49 040 7410 55428; t.klein@uke.de

Aim: Clinical efficacy of sublingual immunotherapy for grass pollen-induced allergic rhinitis (AR) needs to translate into patient benefit. **Patients & methods:** Patients received Oralair (Stallergenes, Antony, France) in real-life medical practice. Patient-relevant treatment benefits were measured with the AR-specific Patient Benefit Index. Subgroups were analyzed regarding distinct patient characteristics. **Results:** Data of 883 patients (children, adolescents, and adults) were analyzed. The highest-ranked patient needs referred to having less AR-symptoms, being able to go outdoors, and being free in the choice of leisure activities. Most patients (89.2–94.6%) attained at least minimally relevant benefit. All subgroups reported relevant benefits, with significantly higher scores in some subgroups. **Conclusion:** Treatment with Oralair was associated with considerable patient-relevant benefit in all age groups.

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Keywords: adolescents • adults • allergic rhinitis • children • grass pollen • patient-relevant benefit • patient-reported outcomes • rhinoconjunctivitis • sublingual immunotherapy • treatment goals

Allergy is a widespread pathology across the world. Its major manifestation is allergic rhinitis (AR), which is characterized by sneezing, congestion, clear rhinorrhea, and nasal or palatal pruritus [1]. AR is an immunoglobulin E (IgE)-mediated allergic reaction caused by inflammation of the nasal mucosa triggered by an allergen [2]. Across Europe, the prevalence of AR is estimated to be around 23% and it often remains undiagnosed [3]. Prevalence increases from infancy to childhood, has its peak in teenage years, and decreases in the elderly [4,5]. Allergic rhinoconjunctivitis (i.e., simultaneous presence of both AR and allergic conjunctivitis [AC]) is prevalent in 8.5% of children aged 6–7 and in 14.6% of children aged 13–14, worldwide [4]. Grass pollen are the major cause of AR in Europe with some regional variations [6].

According to the Allergic Rhinitis and its Impact on Asthma (ARIA) classification, four types of AR can be distinguished, which are characterized by two dichotomous categories. The first category is severity, where AR can be characterized as mild (i.e., causing no interferences in daily life) or moderate-to-severe. The latter means that patients experience impairments in at least one area of daily living [1], such as performance at work or school, daily activities, sleep, or patients' mood [7]. The second category is the pattern of occurrence, being either intermittent or persistent [1]. Especially persistent forms of AR can have major impact on patients' health-related quality of life (HRQoL), but also a large share of patients with intermittent courses of AR report impairments in at least one domain of HRQoL [7]. Overall, HRQoL is worse in patients with AR than in people without nasal allergies [8]. Moreover, up to 38% of AR patients have asthma, and uncontrolled AR can impair asthma control [9].

The management of AR includes avoidance of allergens and reduction of symptoms through pharmacotherapeutic interventions. The only currently available treatment that alters the course of the allergic disease by targeting its immunological mechanisms is allergen immunotherapy (AIT), which can be administered subcutaneously or sublingually (SLIT). Several randomized controlled clinical trials using standardized AIT products have shown that

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AIT provides short-term effects for seasonal and perennial AR. Also, evidence for long-term effects, lasting after AIT discontinuation, is found, especially for SLIT tablet treatment of grass pollen–induced seasonal AR [10].

While in the past the benefits of a treatment, such as AIT, were mainly assessed based on measurable clinical efficacy (measured in terms of reduced symptoms and/or a reduced need for AR medication), the evaluation of treatment benefit from the patients' perspective has become increasingly important in recent years. Age-specific evaluations (i.e., in children, adolescents, and adults) of patient-reported outcomes are of particular importance as they may differ between age groups [11].

In addition to being relieved from symptoms, patients generally expect the morbidity and the treatment burden to be reduced, and HRQoL to be improved [12]. Patients' needs and expectations result not only from their individual clinical profile and how their HRQoL is affected but also from their lifestyle and preferences. Therefore, patient-relevant benefits may differ between patients even when clinical efficacy and/or HRQoL are equal. Thus, successful treatment of AR requires not only clinical efficacy but should also consider patients' individual needs. To evaluate how clinical benefit translates into patient benefit is pivotal in two ways: First, by assessing patient-perceived benefits, it can be determined whether clinical benefits actually improve the individual's well-being. Second, patient-perceived benefits may increase treatment satisfaction, which in turn enhances patient adherence [13,14], a major factor for clinical efficacy [15].

Patient-relevant benefits can be determined with standardized and validated tools, such as the Patient Benefit Index (PBI) [16]. For the assessment of patient needs and benefits in the treatment of AR, a disease-specific version of the PBI has been developed: the Patient Benefit Index Allergic Rhinitis (PBI-AR) [17]. For AIT, data on what benefits patients derive from treatment are yet scarce. Recently, a study using the PBI-AR has shown the patient-relevant benefit of a birch pollen SLIT [18].

This real-life medical practice study assessed the patient-relevant benefits of Oralair (Stallergenes, Antony, France), a 5-grass pollen tablet SLIT. This treatment has previously shown clinical efficacy in adults [19–21], adolescents, and children [22]. Based on the PBI-AR and its newly developed version for children and adolescents (PBI-AR-K), the benefit of this treatment was evaluated from the perspective of adults, adolescents, and children with grass pollen allergy. The primary aim of this study was to determine the PBI-AR global benefit score. Secondary outcomes were the subscale scores and the ratings (treatment needs/goals and goal achievement) for each item as well as the associations of the PBI-AR global scale and subscales with specific patient characteristics (i.e., gender, concomitant allergies, asthma, symptom severity, ARIA classification of AR).

Patients & methods

Study design

This was an open, prospective, multicenter, longitudinal, noninterventional study in patients receiving an AIT with Oralair for the treatment of grass pollen-induced AR. Ethical approval was received from the Freiburg Ethics Commission International (012/1889). Patients gave written informed consent.

Procedure

Patients were recruited in two periods by 145 allergologically experienced physicians (ear, nose, and throat specialists; pulmonologists; dermatologists; pediatricians; internists) across Germany. Physicians were asked to recruit consecutive patients for whom the initiation of Oralair had already been decided independent of this study. Both nationwide recruitment of physicians and consecutive enrollment of patients were measures to ensure the selection of a representative sample.

Patients were eligible when being at least 5 years of age and having AR and/or AC induced by grass pollen or, due to its cross-reactivity, by rye pollen or other cereal pollen. Exclusion criteria were having contraindications according to the summary of product characteristics.

Patients were observed from the first exposure to Oralair until the end of the first treatment year (i.e., one pre-/co-seasonal treatment cycle). The study initiation visit (visit 1) took place in fall/winter 2012/2013 or fall/winter 2013/2014. The study end visit (visit 2) took place after the respective grass pollen season (2013 or 2014). At each visit, patients answered a paper-based questionnaire and physicians completed an electronic case report form. At visit 1, physicians documented patient's sociodemographic data, allergological medical history (clinical manifestations, i.e., rhinitis, conjunctivitis, asthma, neurodermatitis and concomitant allergies), symptoms and medication use in the grass pollen season before treatment start (including ARIA classification [1] of AR symptoms, severity of symptoms), comorbidities, and start date of the treatment with Oralair. Patients rated their treatment

goals (i.e., their patient-relevant needs and expectations) using the first part of the PBI-AR; additionally, they documented their ability to work and their impairments due to their allergy during the previous grass pollen season. At visit 2, both patients and physicians judged the patient's improvements compared with the previous grass pollen season, assessed the patient's tolerance of Oralair, and the patient's improvement in well-being. Additionally, patients assessed the achievement of their therapy goals (patient-relevant benefit) using the second part of the PBI-AR and rated their working ability and impairments.

In this article, we report the main outcomes of the study, in other words, patient needs and benefits as measured with the PBI-AR.

Study treatment

Patients were treated with Oralair, a sublingual tablet containing grass pollen allergen extract from cock's-foot (*Dactylis glomerata* L.), sweet vernal grass (*Anthoxanthum odoratum* L.), ray grass (*Lolium perenne* L.), meadow grass (*Poa pratensis* L.), and timothy (*Phleum pratense* L.). The biological activity of the tablet is expressed in the manufacturer-specific unit index of reactivity (IR). Treatment is recommended to be initiated approximately four months prior to the expected start of the pollen season and is composed of two phases: the three-day dose escalation phase (day 1: 1 × 100 IR tablet; day 2: 2 × 100 IR tablets; day 3: 1 × 300 IR tablet) is followed by a maintenance phase until the end of the pollen season with 1 × 300 IR tablet per day. For tablet intake, the tablets are kept under the tongue until complete dissolution and are subsequently swallowed.

Patient benefit index

The PBI is a standardized and validated instrument assessing the patients' treatment needs and benefits. Both a general version for dermatological diseases [16] and several indication-specific versions exist. The PBI for patients with AR (PBI-AR) contains 25 items and has been previously developed and validated [17]. It has been shown that patients' needs are more comprehensive than the mere reduction of symptoms [17]. Accordingly, the items of the PBI-AR are assigned to the subscales 'psychological burden' (e.g., 'have no fear that the diseases will become worse'), 'treatment burden' (e.g., 'need less time for daily treatment'), 'physical burden' (e.g., 'be healed of all symptoms'), and 'activity/physical capability' (e.g., 'be more productive in everyday life'), which reveals the wide range of patient-relevant benefits [18]. For this study, an additional version for children and adolescents has been developed (PBI-AR-K), which contains 19 items (nine of which have the same wording as the adult version and six of which only slightly differ from the wording of the adult version). Development and validation of the PBI-AR-K will be published separately.

Each PBI version consists of two distinct questionnaires: the Patient Needs Questionnaire (PNQ) and the Patient Benefit Questionnaire (PBQ). The PNQ is completed prior to the treatment by rating the importance of each item (i.e., each treatment goal). The same items are answered in the PBQ during or after the treatment by rating the achievement of the goals. Both importance and achievement are rated on a Likert scale ranging from 0 ('not at all') to 4 ('very'). Alternatively, patients can tick 'does not apply to me' in the PNQ and 'did not apply to me' in the PBQ; the respective items are not considered for score computation. From PNQ and PBQ items, a weighted index value is calculated: first, the achieved benefit (PBQ) of each item is multiplied by its importance (PNQ) and divided by the sum of all important items; these quotients are then summed up. The PBI global score can range from 0 ('no benefit') to 4 ('maximal benefit'), with a score ≥ 1 being considered a relevant benefit, based on unpublished analyses. For the PBI-AR and the PBI-AR-K, a global score and subscale scores can be calculated accordingly. Though the PBI-AR-K is suitable for both children and adolescents, subscales differ between both age groups. The four subscales for children's samples are 'treatment burden', 'fatigue/social life', 'physical symptoms', and 'being outdoors'; the three subscales for adolescents' samples are 'treatment burden', 'physical symptoms', and 'psychosocial burden'.

Statistical analysis

Patient characteristics and response behavior were described descriptively (frequencies, percentages, means, standard deviations and 95% CI range). For the PBI-AR scores, median and interquartile range were calculated additionally. For subgroup analyses, independent samples t-tests were computed analyzing differences in PBI-AR global and subscale score with regard to patients' gender (male vs female), concomitant allergies (mono- vs polyallergic; here, polyallergy is defined as 'a documented, causal relationship between exposure to two or more specific, sensitizing allergens and the subsequent occurrence of relevant clinical symptoms of allergy' [23]), concomitant asthma (no

Table 1. Patient characteristics at visit 1.

	Total (n = 883)	Children (n = 223)	Adolescents (n = 122)	Adults (n = 538)
Age				
Mean (SD) (years)	26.5 (15.8)	9.2 (2.1)	14.6 (1.5)	36.4 (12.5)
Range (years)	5–78	5–12	13–17	18–78
Gender				
Male (n [%])	443 (50.2)	144 (64.6)	66 (54.1)	233 (43.3)
Female (n [%])	439 (49.8)	79 (35.4)	56 (45.9)	304 (56.5)
Not answered (n [%])	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)
Symptoms				
Allergic rhinitis (n [%])	876 (99.2)	220 (98.7)	122 (100)	543 (99.3)
Allergic conjunctivitis (n [%])	676 (76.6)	184 (82.5)	94 (77.0)	398 (74.0)
Asthma (n [%])	244 (27.6)	87 (39.0)	34 (27.9)	123 (22.9)
Severity of rhinoconjunctivitis†				
Mild (n [%])	218 (24.7)	60 (26.9)	34 (27.9)	124 (23.0)
Severe (n [%])	665 (75.3)	136 (73.1)	88 (72.1)	414 (77.0)
ARIA classification of AR‡				
Intermittent	294 (33.3)	77 (34.5)	47 (38.5)	170 (31.6)
Persistent	584 (66.1)	144 (64.6)	75 (61.5)	365 (67.8)
Not answered (n [%])	5 (0.6)	2 (0.9)	0 (0.0)	3 (0.6)
Type of allergy				
Grass (n [%])	871 (98.6)	218 (97.8)	121 (99.2)	532 (98.9)
Rye or other cereals (n [%])	546 (61.8)	133 (59.6)	77 (63.1)	336 (62.5)
Concomitant allergies (other than grasses or other cereals)				
No (= monoallergic) (n [%])	346 (39.2)	80 (35.9)	43 (35.2)	223 (41.4)
Yes (= polyallergic) (n [%])	537 (60.8)	143 (64.1)	79 (64.8)	315 (58.6)

†Severe rhinoconjunctivitis was assumed if the sum of the severity assessments for rhinitis and conjunctivitis symptoms was ≥4 according to physicians' global rating with the following response options for each of the two variables: 0 = none, 1 = mild, 2 = moderate, 3 = severe.
‡According to AR and its impact on asthma classification [1]: symptoms occurring <4 days a week or <4 consecutive weeks = intermittent AR; symptoms occurring ≥4 days a week AND ≥4 consecutive weeks = persistent AR.
AR: Allergic rhinitis; n: Number; SD: Standard deviation.

vs yes), severity of rhinoconjunctivitis symptoms (mild vs severe; see definition provided in Table 1), and ARIA classification of AR (intermittent vs persistent). Significance level was set at p = 0.05; no adjustment for multiple testing was made due to the exploratory nature of the study.

This was a per-protocol analysis without imputation of missing data. Data were analyzed using SPSS 22 (IBM, NY, USA).

Results

General data

The study included 1126 patients. Of these, 36 were excluded from the overall analysis due to retrospective documentation (n = 34) and failure to take Oralair (n = 2). Further, 207 patients were excluded from the PBI analysis because the PNQ was completed more than 21 days after treatment onset (at this time, first effects of the treatment may occur, which may impact patients' needs ratings; n = 82), the PBQ was completed already at the day of or before treatment start (n = 8), the PBQ was completed before the start of the grass pollen season (n = 9), patients under the age of 18 completed the PBI-AR instead of the PBI-AR-K (n = 9), patients were under the age of five (n = 1), or patients completed neither the PNQ nor the PBQ (n = 98).

Of the remaining 883 patients with partial or complete PBI data, 25 had not completed the PNQ, 179 had not completed the PBQ, and 11 had too many missing values or 'does not apply to me' responses for calculating the PBI-AR global score, resulting in 668 patients for whom a PBI-AR global score could be computed. The number of completions of the PBI-AR questionnaires is presented in Supplementary Table 1, split by age group.

Mean age of the total sample (n = 883) at visit 1 was 26.5 years (standard deviation [SD] 15.8 years) with 25.3% children (5–12 years), 13.8% adolescents (13–17 years) and 60.9% adults (18 years and older). The sample

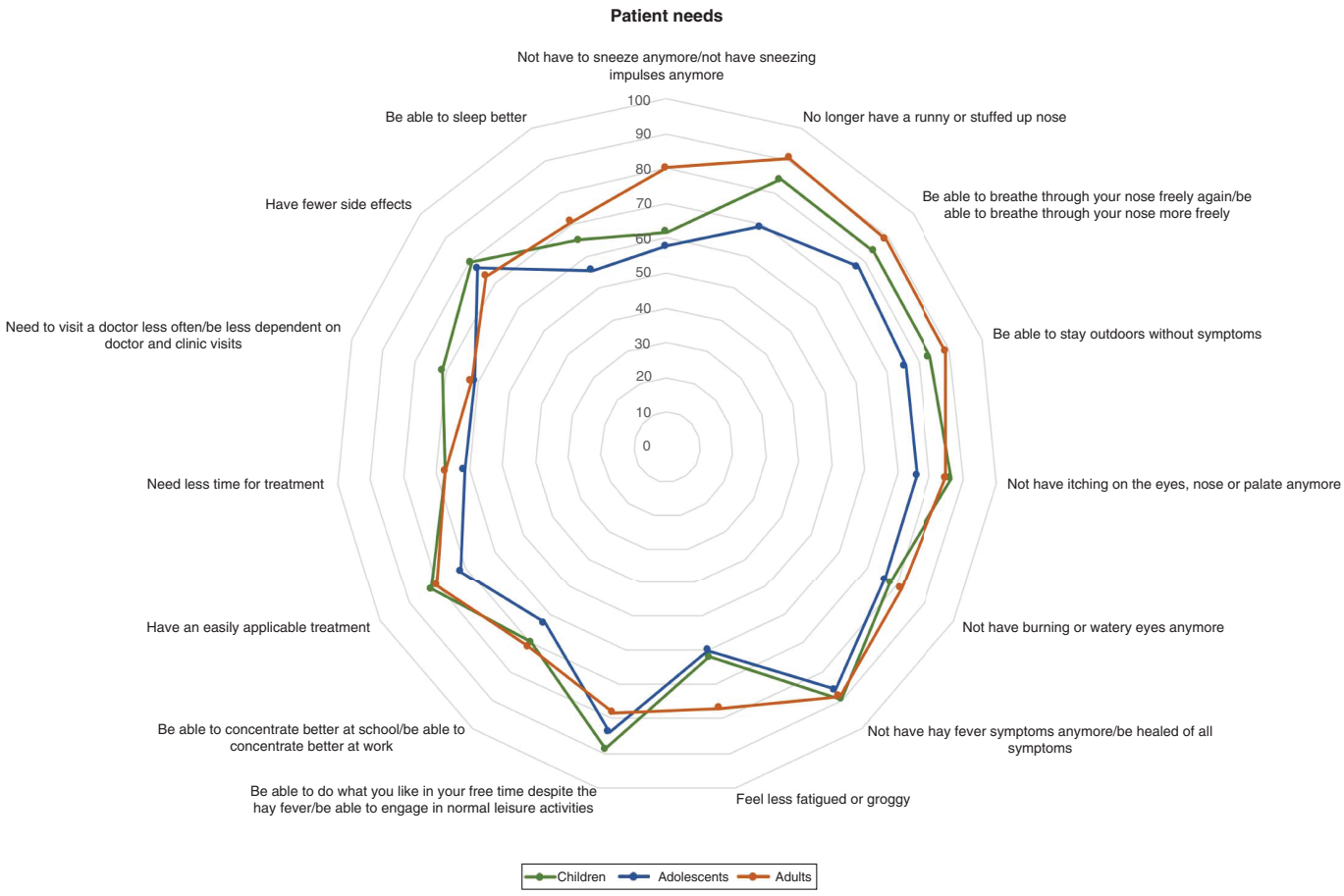

Figure 1. Percentage of patients rating need items as important (ticking quite or very important). Only items assessed in all age groups are displayed.

included 50.2% male patients. AR was present in 99.2% of the patients, AC in 76.6%. Most patients had grass allergies (98.6%) and 60.8% were polyallergic. Asthma was prevalent in 27.6%. Patient characteristics by age group are summarized in Table 1.

Patient-relevant needs

In both children (Supplementary Table 2) and adolescents (Supplementary Table 3) the three most important treatment goals were 'feel well even with having hay fever' (90.1% of children ticking quite or very important, 77.6% of adolescents), 'no longer have hay fever symptoms' (children: 89.7%; adolescents: 86.3%), and 'be able to do anything you want in your free time even while having hay fever' (children: 88.8%; adolescents: 83.8%). In adults (Supplementary Table 4), the three most important treatment goals were 'no longer have a runny or stuffed up nose' (90.8%), 'be able to breathe through your nose more freely' (89.0%) and 'be able to stay outdoors without symptoms' (88.9%). All goals were important for at least 30.0% of the patients, with the least important treatment goal being 'not be excluded by others' in children and adolescents (46.3 and 32.2%, respectively) and 'be able to have a normal sex life' in adults (42.8%). Need ratings of items assessed in all age groups are displayed in Figure 1.

Patient-relevant benefits

In each age group, the items 'need less time for treatment' (children: 79.3%; adolescents: 75.0%; adults: 58.5%) and 'have an easily applicable treatment' (children: 78.9%; adolescents: 69.5%; adults: 71.6%) were among the three highest ranked benefits (with regard to those patients to whom the respective goal applied). The remaining item among the three highest ranked benefits was 'have a comfortable treatment' in children (74.5%), 'feel well even when having hay fever' in adolescents (70.4%), and 'have confidence in the therapy' in adults (67.1%). The items with the lowest benefit ratings were 'be able to breathe through your nose freely' (41.0%) in children

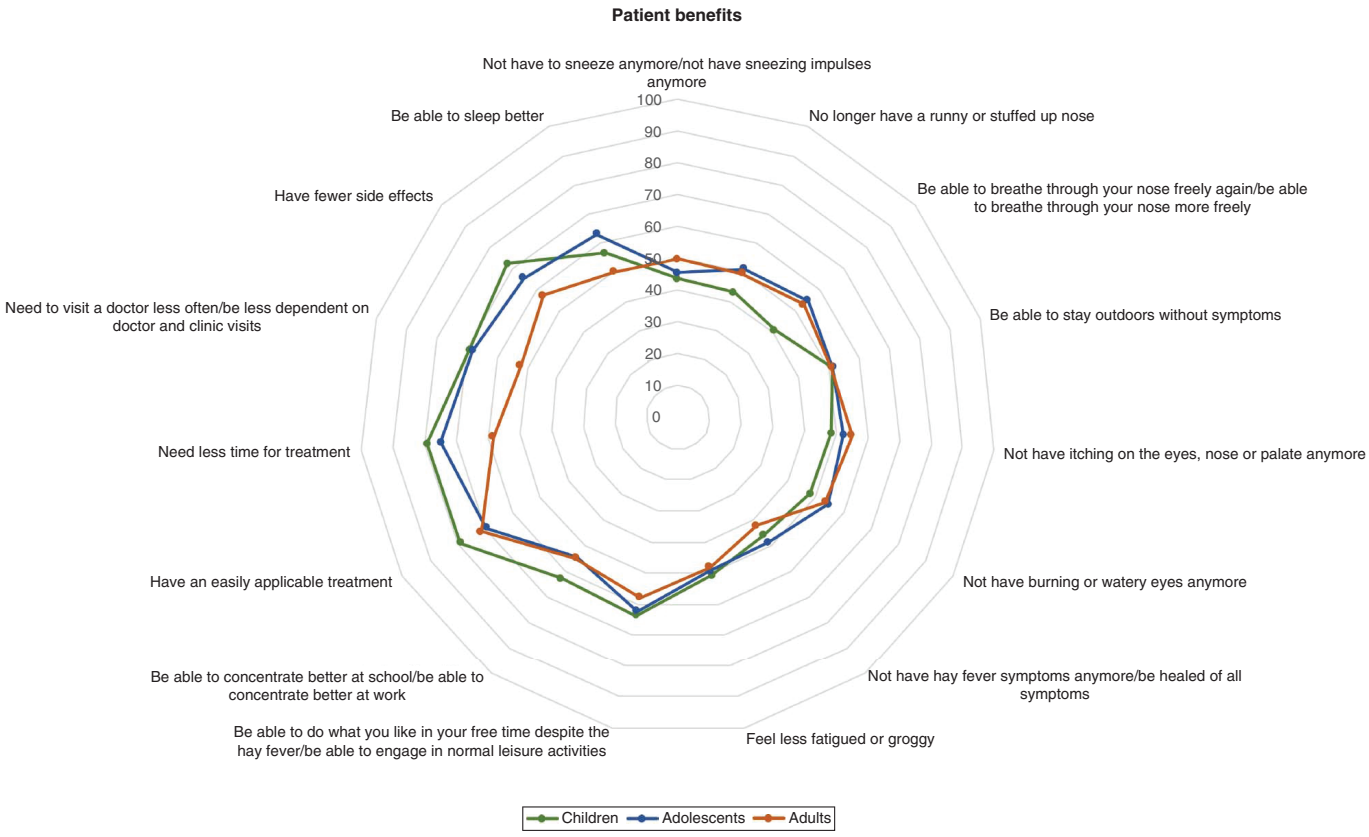

Figure 2. Percentage of patients reporting benefits per item (ticking quite or very). Only items assessed in all age groups are displayed.

(Supplementary Table 2), 'no longer have to sneeze' (45.6%) in adolescents (Supplementary Table 3), and 'be healed of all symptoms' (42.1%) in adults (Supplementary Table 4). The three most important treatment goals were reported to be achieved by 45.8–60.3% of the children, 48.4–70.4% of the adolescents, and 49.5–53.0% of the adults. Benefit ratings of items assessed in all age groups are displayed in Figure 2.

PBI global & subscale scores

The average weighted PBI-AR-K global score in children was 2.61 (SD: 0.99; 95% CI: 2.46–2.76) with 94.6% (n = 140) of the patients attaining an at least minimally relevant benefit of 1.0 and above. In adolescents, the average weighted PBI-AR-K global score was 2.55 (SD: 1.04; 95% CI: 2.33–2.77) with 90.7% (n = 68) attaining an at least minimally relevant benefit. The average weighted PBI-AR global score in adults was 2.43 (SD: 1.05; 95% CI: 2.33–2.53) with 89.2% (n = 372) attaining an at least minimally relevant benefit (Figure 3).

The average weighted subscale scores ranged from 2.08 to 2.82 in children, from 2.30 to 2.68 in adolescents, and from 2.05 to 2.52 in adults with the subscale 'treatment burden' being the subscale with the highest benefit score for each age group (Table 2).

Subgroup analyses

The PBI-AR global score revealed no significant differences regarding gender, severity of rhinoconjunctivitis, or ARIA classification of AR for neither age group (Table 3). However, polyallergic patients reached significantly higher PBI-AR global scores than monoallergic patients in both adolescents (2.76 vs 2.17; p = 0.010) and adults (2.53 vs 2.29; p = 0.028). Nonasthmatic adults showed higher PBI global scores than asthmatic adults (2.50 vs 2.20; p = 0.041). Further group differences could be detected in the PBI-AR subscales: In the children subsample, males showed higher benefit in the subscales 'treatment burden' (2.99 vs 2.52; p = 0.020) and 'physical symptoms' (2.42 vs 1.92; p = 0.007). Polyallergic patients reached higher scores regarding the subscale 'treatment burden' in adolescents (2.85 vs 2.33; p = 0.048) and in adults (2.68 vs 2.30; p = 0.001). Finally, nonasthmatic adults stated higher benefit regarding 'physical symptoms' (2.37 vs 2.05; p = 0.036) and 'activity/physical capability' (2.41 vs

Table 2. Distribution of patient benefit index allergic rhinitis for children and adolescents and patient benefit index allergic rhinitis global and subscale scores.

	n	Mean (SD)	95% CI	Median (IQR)	Min–max
PBI-AR-K: children (5–12 years)					
Global score	163	2.61 (0.99)	2.46–2.76	2.78 (2.00–3.33)	0–4
Subscale 1: treatment burden (five items)	159	2.82 (1.14)	2.74–3.10	3.00 (2.11–3.80)	0–4
Subscale 2: fatigue/social life (six items)	153	2.08 (1.17)	1.92–2.29	2.08 (1.00–3.00)	0–4
Subscale 3: physical symptoms (four items)	162	2.24 (1.13)	2.10–2.46	2.25 (1.28–3.00)	0–4
Subscale 4: being outdoors (four items)	160	2.24 (1.16)	2.10–2.47	2.38 (1.50–3.00)	0–4
PBI-AR-K: adolescents (13–17 years)					
Global score	88	2.55 (1.04)	2.33–2.77	2.68 (1.87–3.40)	0–4
Subscale 1: treatment burden (five items)	84	2.68 (1.15)	2.52–3.10	2.85 (1.80–3.77)	0–4
Subscale 2: physical symptoms (seven items)	88	2.30 (1.06)	2.16–2.61	2.36 (1.65–3.10)	0–4
Subscale 3: psychosocial burden (seven items)	78	2.35 (1.22)	2.10–2.65	2.55 (1.29–3.38)	0–4
PBI-AR: adults (≥18 years)					
Global score	417	2.43 (1.05)	2.33–2.53	2.57 (1.75–3.22)	0–4
Subscale 1: psychological burden (eight items)	398	2.05 (1.17)	1.95–2.18	2.09 (1.08–3.00)	0–4
Subscale 2: treatment burden (six items)	413	2.52 (1.12)	2.42–2.65	2.70 (1.85–3.38)	0–4
Subscale 3: physical symptoms (seven items)	416	2.30 (1.11)	2.20–2.42	2.46 (1.50–3.15)	0–4
Subscale 4: activity/physical capability (four items)	413	2.32 (1.17)	2.23–2.47	2.50 (1.50–3.25)	0–4

IQR: Interquartile range; Min: Minimum; Max: Maximum; n: Number of patients; PBI-AR: Patient benefit index allergic rhinitis; PBI-AR-K: Patient benefit index allergic rhinitis for children and adolescents; SD: Standard deviation.

Table 3. Treatment benefit according to patient benefit index allergic rhinitis for children and adolescents and patient benefit index allergic rhinitis global and subscales scores depending on patient characteristics.

	Gender	Concomitant allergies	Asthma	Severity of RC	ARIA classification of AR
	Male versus female	Poly- versus monoallergic	No versus yes	Mild versus severe	Intermittent versus persistent
PBI-AR-K children					
Global score	2.71 vs 2.42	2.64 vs 2.55	2.60 vs 2.62	2.63 vs 2.60	2.76 vs 2.54
Treatment burden	**2.99 vs 2.52**†	2.87 vs 2.73	2.81 vs 2.84	2.86 vs 2.81	2.88 vs 2.77
Fatigue/social life	2.12 vs 2.01	2.08 vs 2.09	2.12 vs 2.02	1.89 vs 2.14	2.26 vs 2.00
Physical symptoms	**2.42 vs 1.92**‡	2.24 vs 2.26	2.29 vs 2.17	2.07 vs 2.30	2.34 vs 2.19
Being outdoors	2.35 vs 2.05	2.27 vs 2.20	2.26 vs 2.21	2.15 vs 2.27	2.42 vs 2.16
PBI-AR-K adolescents					
Global score	2.69 vs 2.42	**2.76 vs 2.17**†	2.57 vs 2.51	2.43 vs 2.58	2.48 vs 2.58
Treatment burden	2.89 vs 2.49	**2.85 vs 2.33**†	2.73 vs 2.54	2.50 vs 2.72	2.44 vs 2.78
Physical symptoms	2.44 vs 2.16	2.40 vs 2.11	2.37 vs 2.11	2.19 vs 2.32	2.25 vs 2.31
Psychosocial burden	2.40 vs 2.32	2.53 vs 2.00	2.35 vs 2.38	2.14 vs 2.42	2.29 vs 2.38
PBI-AR adults					
Global score	2.37 vs 2.47	**2.53 vs 2.29**†	**2.50 vs 2.20**†	2.49 vs 2.41	2.46 vs 2.42
Psychological burden	2.01 vs 2.07	2.06 vs 2.03	2.07 vs 1.97	2.16 vs 2.01	2.14 vs 2.01
Treatment burden	2.46 vs 2.58	**2.68 vs 2.30**‡	2.59 vs 2.31	2.60 vs 2.50	2.52 vs 2.52
Physical symptoms	2.25 vs 2.33	2.34 vs 2.23	**2.37 vs 2.05**†	2.34 vs 2.28	2.36 vs 2.27
Activity/physical capability	2.30 vs 2.33	2.41 vs 2.20	**2.41 vs 2.06**†	2.35 vs 2.31	2.28 vs 2.33

Bold: significant results.
†Significance level: $p < 0.05$.
‡Significance level: $p < 0.01$.
AR: Allergic rhinitis; ARIA: Allergic Rhinitis and its impact on asthma; PBI-AR: Patient benefit index allergic rhinitis; PBI-AR-K: Patient benefit index allergic rhinitis for children and adolescents; RC: Rhinoconjunctivitis.

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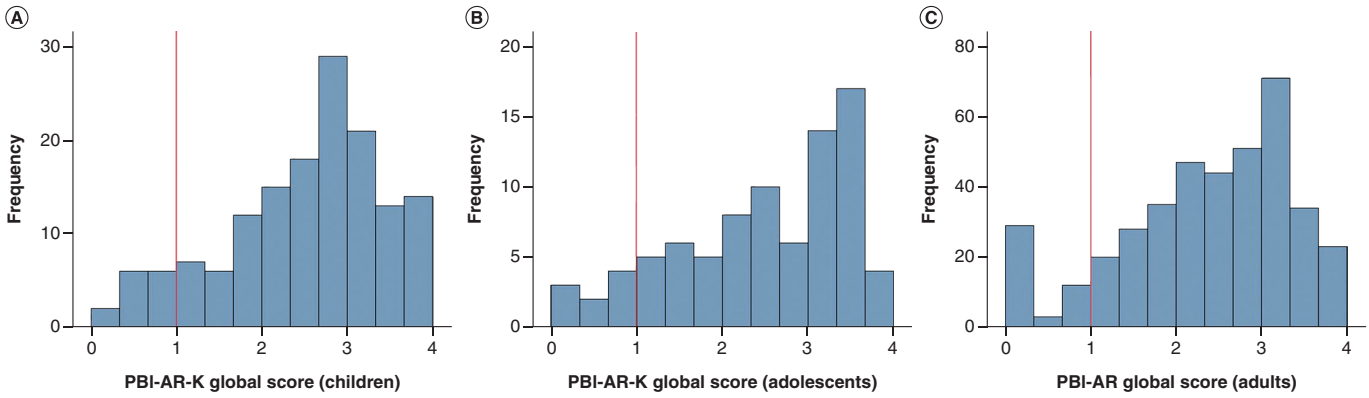

Figure 3. Distribution of patient benefit index for allergic rhinitis global scores in children, adolescents, and adults (patient benefit index allergic rhinitis). Red line marks patient benefit index ≥1 indicating relevant benefit.
PBI-AR: Patient benefit index allergic rhinitis; PBI-AR-K: Patient benefit index allergic rhinitis for children and adolescents.

2.06; p = 0.029). However, for all subgroups the PBI global score was well above the minimal relevant benefit value (i.e., ≥1).

Discussion

The aim of this study was to assess the patient-reported benefit of treatment with Oralair in children, adolescents, and adults with grass pollen-induced AR. To identify various patient-relevant needs and benefits, the AR-specific PBI was applied. The adult version of the PBI-AR has previously demonstrated validity and feasibility [17]. Additionally, a new version for children and adolescents, the PBI-AR-K, was introduced in this study.

Prior to treatment with Oralair, the patients' most important treatment goals were to have less AR-specific symptoms, to be free in the choice of leisure activities, and to be able to go outdoors. This is in line with the needs of patients with birch pollen-induced AR [18]. Especially, the high need for reduced symptoms confirms findings from previous studies [24], revealing patients' great burden due to their symptomatology and their unmet need for an effective treatment.

The weighted PBI-AR revealed a great share of patients (89–95%) achieving an at least minimally relevant benefit of PBI ≥1.0. This indicates that the vast majority of patients (9 out of 10 in each age group), for whom treatment with Oralair was documented during the observation phase of this study, assessed the treatment as at least partially successful in achieving the treatment goals they individually defined. Especially children benefited from treatment: the PBI-AR global score was slightly higher in children (2.61) than in the other two age groups (adolescents: 2.55; adults: 2.43).

Also, all subscales revealed considerable treatment benefits with average values above 2.0. For all age groups, highest scores were achieved for the subscale 'treatment burden' (children: 2.82; adolescents: 2.68; adults: 2.52), confirming that independent of age, treatment with Oralair was considered as an easy treatment. In general, SLIT is reported to be a safe and well-tolerated treatment option [10]. After the first dose, this noninvasive medication can be taken by the patients at home, leading to low treatment burden, which is of great importance for patients with chronic conditions [25]. Furthermore, all age groups benefited from an improvement of their physical symptoms (children: 2.24; adolescents: 2.30; adults: 2.30).

As the burden of the disease is likely to differ in patients with different clinical profiles (e.g., mono- vs polyallergic patients; patients with vs without asthma), treatment needs and goals, and subsequently treatment benefit, may vary depending on the patients' characteristics. To this end, we compared the patient-relevant benefit between different subgroups (gender, concomitant allergies, asthma, symptom severity, ARIA classification of AR). While the global benefit score was not associated with any of the characteristics in children, being polyallergic was correlated with higher global benefit scores in adolescents and adults. This might be promising, as patients with concomitant allergies often have increased disease burden [1,23,24]. In contrast, comorbid asthma was associated with reduced global benefit scores in adults. Adult patients with asthma reported a patient-relevant benefit (2.20); however, this benefit was lower than in adults without asthma (2.50). This lower response in adults with asthma might be explained by a higher burden of disease on the one hand, possibly linked with higher expectations on treatment

on the other hand. Due to higher expectations, patients might be more hesitant to give a good benefit assessment. Interestingly, the impact of asthma on treatment benefit seems to be lower in children and adolescents than in adults: in children and adolescents, benefit scores were similar for asthmatic and non-asthmatic patients.

In summary, patients with grass pollen-induced AR perceived treatment with Oralair in a real-life medical practice setting as beneficial. In combination with the positive results of previous randomized, double-blind, placebo-controlled (DBPC) clinical trials conducted with this treatment [19–22], this study shows that Oralair combines both clinical and patient-relevant benefits. As perceived benefit can be expected to impact positively on treatment satisfaction and adherence [18], this is a crucial finding.

Nevertheless, this study has some limitations that need to be mentioned. Data from 243 patients were excluded, which is 21.6% of the initial sample. Additionally, of the 883 patients considered for the PBI-AR analysis, the PBI global score could be calculated only for 75.7%. The latter was mainly due to patients not completing one of the two questionnaires, which seems unlikely to be associated with treatment benefit and therefore is not assumed to introduce a bias.

The primary end point of this study was the PBI global score in each of the three age groups. For the additional subgroup and subscale analyses, significance levels were not adjusted for multiple testing. Therefore, these results should be interpreted with caution; in particular because only few differences were found and most significance levels were close to the 0.05 level, which means that they would not be considered significant after adjustment for multiple testing.

The study used two different versions of the PBI-AR depending on the patients' age. This limits comparability between adults and younger patients. However, the structure of both PBI-AR versions is similar and there is a high overlap in treatment goals; using the exact same treatment goals for all age groups would not have been adequate as, for example, some goals do not apply to children. Similarly, the comparability of subscale results between children and adolescents might be restricted due to differences in assigning items to subscales.

According to its real-world design, no control group was included in this study. Thus, no direct comparison to other treatments or nontreatment is possible. Accordingly, this study was not designed to assess clinical treatment efficacy but aimed to investigate patients' subjective evaluation of this treatment. Clinical efficacy of treatment with Oralair has been confirmed previously in several randomized DBPC clinical trials [19–22] revealing the benefit of this treatment compared with placebo.

While the DBPC clinical trials assessed the efficacy of the treatment in patients with moderate-to-severe RC symptoms, the patients in this real-life medical practice study had varying degrees of symptom severity at inclusion, including patients with mild RC symptoms. Our subgroup analyses did not reveal any significant differences in patient benefit depending on the severity of RC in either age group. Therefore, we assume that including patients with mild RC in the study did not affect overall results of the PBI.

In this study design, it could not be controlled for effects of changes in the pollen load. But as grass pollen load increased from 2012 to 2014 (i.e., it was higher in each of the treatment seasons compared with the seasons before treatment [26]), benefits and improvements of symptoms cannot have been caused by reduced pollen load.

It is recommended that AIT is conducted over a period of at least three years [10]. While the present study showed patient-reported benefits of the treatment with Oralair during one pollen season, a longitudinal study should investigate whether the treatment also shows long-term patient benefits comparable to the sustained and long-term effects previously shown [27,28]. An increasing patient benefit during this period can potentially be expected.

Conclusion

Children, adolescents, and adults treated with Oralair for grass pollen-induced AR in a real-life medical practice setting during the observation period of this study reported a considerable patient-relevant benefit, with the greatest benefits related to a reduction of treatment burden and of achieving better physical and psychosocial conditions. Benefits were observed regardless of the patients' clinical profiles. Successfully achieving self-defined treatment goals is an important factor which may favorably impact treatment adherence.

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Summary points

- Sublingual immunotherapy for grass pollen-induced allergic rhinitis is a clinically efficacious treatment; however, it is pivotal that clinical efficacy also translates into patient benefit.
- In this prospective, open, multicenter, longitudinal, noninterventional study, 883 patients (223 children, 122 adolescents, 538 adults) receiving Oralair in real-life medical practice completed the Patient Benefit Index Allergic Rhinitis (PBI-AR).
- Across all age groups, the items 'need less time for treatment' (58.5–79.3%) and 'have an easily applicable treatment' (69.5–78.9%) were among the top three highest-ranked benefits.
- Nine out of ten patients in all age groups (89.2–94.6%) attained at least minimally relevant benefit (i.e., PBI-AR $\geq$1.0).
- The average PBI-AR global score ranged from 2.43 to 2.61 on the scale from 0 to 4 (with 4 indicating maximum benefit); the average subscale scores ranged from 2.05 to 2.82.
- All subgroups reported relevant benefits (PBI-AR $\geq$1.0), albeit scores were significantly higher in some subgroups (adults: patients without asthma; adults/adolescents: polyallergic patients).
- In patients of all age groups, treatment with Oralair was associated with considerable patient-relevant benefit, especially regarding reduced treatment burden.
- Successfully achieving self-defined treatment goals is an important factor which may favorably impact treatment adherence.

Author contributions

M Augustin and M Hadler contributed to the study design and conduct. TM Klein and C Blome conducted statistical analyses. All authors contributed to data interpretation. TM Klein drafted the manuscript. All authors critically reviewed the report and approved the final version.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The study protocol was approved by the Freiburg Ethics Commission International (012/1889). Patients gave written informed consent and the study conformed with the Helsinki Declaration of 1964, as revised in 2013, concerning human rights.

Availability of data & materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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