The RHINASTHMA GAV scores without SLIT, at the beginning and at the end of seasonal SLIT

Jochen Sieber,[1] Anna Gross,[2] Kija Shah-Hosseini[2] and Ralph Mösges[2]

Summary

Background: **The impact of treatments for allergic rhinitis on health-related quality of life (HRQL) becomes more and more important in the view of patients, physicians and payers, but not much is known about the effect of sublingual immunotherapy (SLIT) on this outcome parameter.**

Methods: **In a prospective observational study, health-related quality of life was assessed with the German adapted version of a new specific questionnaire (RHINASTHMA GAV) in patients with allergic rhinitis with or without mild to moderate asthma due to grass, cereal, and/or rye pollen who were treated with seasonal high-dose SLIT with standardized allergen extracts.**

Results: **358 patients aged 5 - 68 years, mean ± SD disease duration of 8.8 ± 9.2 years were evaluated. During SLIT, the mean total score and all 5 mean sub-scale scores were substantially reduced by 36% to 55%. Sub-group analyses did not reveal any clinically relevant deviations from the results in the total study population. At the end of SLIT, mean total score and sub-scale scores were virtually identical to those scores assessed during the validation procedure of RHINASTHMA GAV in healthy subjects without rhinitis, conjunctivitis, or asthma. These improvements in HRQL during SLIT were paralleled by substantially reduced disease-related burden, in terms of symptom scores and health-related impairment in daily life and at work.**

Conclusion: **The improvement in HRQL during seasonal SLIT was clinically relevant and reached scores close to normal already in the first pollen season.** ***(Asian Pac J Allergy Immunol 2010;28:232-6)***

Key words: *Sublingual immunotherapy, Allergic rhinitis, Grass pollens, Quality of life. RHINASTHMA.*

From the [1]Stallergènes, Kamp-Lintfort, Germany
[2]University of Cologne, Institute of Medical Statistics, Informatics and Epidemiology, Cologne, Germany
Corresponding author: Jochen Sieber
E-mail: HSieber@stallergenes.de
Submitted date: 12/4/2010
Accepted date: 22/9/2010

Introduction

Allergic rhinitis is a symptomatic disorder of the nose induced after allergen exposure by an immunoglobulin E (IgE)-mediated inflammation of the membranes lining the nose.[1,2] It is now recognized that allergic rhinitis comprises more than the classical symptoms of sneezing, rhinorrhea, and nasal obstruction due to its association with impairments in how patients function in day-to-day life. The severity of allergic rhinitis was therefore classified as "mild" or "moderate/severe" not only depending on symptoms but also on quality of life.[1] Quality of life was found to be impaired in patients with allergic rhinitis when studied using the generic SF-36 questionnaire in the European Community Respiratory Health Survey, a population-based study of young adults.[3]

The recommendation to use sublingual immunotherapy (SLIT) in children and adults with allergic rhinitis evolved over several years, based on the following key publications: the World Health Organization (WHO) position paper on allergen immunotherapy,[4] the Allergic Rhinitis and its Impact on Asthma (ARIA) Workshop Group paper in collaboration with the WHO (2001)[1] and its 2008 update,[2] the Cochrane review of SLIT for allergic rhinitis,[5] a meta-analysis evaluating the efficacy of SLIT in the treatment of allergic rhinitis in children and adolescents aged 3 - 18 years[6] and the position paper of the World Allergy Organisation. Quality of life was improved in patients receiving specific

immunotherapy in clinical studies[7-9] using the Rhino-conjunctivitis Quality of Life Questionnaire (RQLQ).[10]

In 2003, development and validation procedures of a new specific quality of life questionnaire for patients with allergic rhinitis with coexisting asthma (RHINASTHMA) was published.[11] In 2007, the validation procedure of the German adapted version of RHINASTHMA (RHINASTHMA GAV) was published.[12] The RHINASTHMA GAV is a self-assessment 4-point rating scale of 42 items in 5 sub-scales. The sub-scales are limitations in daily life, respiratory problems, rhino-conjunctivitis score, treatment and medication problems, and impairment in sensory perceptions (smell and vision).

We conducted a prospective observational study to assess health-related quality of life (HRQL) using the RHINASTHMA GAV in patients with grass pollen-allergic rhinitis with or without mild to moderate asthma treated with seasonal SLIT.

Methods

Patients and study design

Patients with a medical history of allergic rhinitis with or without mild to moderate asthma due to grass (cocksfoot, meadow grass, rye grass, sweet vernal grass, timothy) and/or cereal (oat, barley, wheat, maize) and/or rye pollens were included. Positive skin prick tests to at least one of the aforementioned allergens and presence of specific IgE ≥ 0.7 kU/L were required.

This prospective observational study with 3 mandatory visits (patient enrolment (January – March), start of SLIT (January - May), and end of SLIT (July - September)) and 2 optional visits during the 6- to 9-month SLIT from January to September 2007 was performed in Germany. The grass pollen season in Germany covers mainly the period from May to August with slight deviations depending on the local micro-climate in this country.

Ultra-rush titration high-dose SLIT regimen reaching the maintenance dose of 240 IR within 90 min (30–60–120–240 IR) or classical titration over 11 days were used before or at the start of the pollen season. The subsequent maintenance phase at 240 IR once daily, 240 IR 3 times a week, or 120 IR once daily lasted 6 to 9 months.

Study drug

Standardized allergen extract in aqueous solution was used for SLIT (STALORAL 300®, Stallergènes, Antony, France). Biological activity of the extract was assessed in comparison with an internal standard *in vitro* and *in vivo*, and expressed as index of reactivity (IR).[13] The allergen extracts used contained allergens of the following allergen groups: grasses (sweet vernal grass, cocksfoot, rye grass, timothy, meadow grass), cereals (oat, barley, wheat, maize) and rye in accordance with the prescriptions of individualized allergen extracts by the investigators.

Measurements

Self-assessments of HRQL were performed at patient enrolment, start of SLIT and end of SLIT using RHINASTHMA GAV.[12] Impairment of HRQL was assessed using a 4-point scale for 42 individual items: 0 = not important, 1 = low importance, 2 = rather important, and 3 = very important. In addition, 5 questions were asked about health-related impairments in daily life and at work.

Table 1. Demographic data of the patients (total *n* = 358)

	Patients		Duration*			
	Number	%	Mean	SD	Minimum	Maximum
Age (male patients)	158	44.1	31.6	13.1	5.0	67.0
Age (female patients)	190	53.1	33.9	12.1	8.0	68.0
Rhinoconjunctivitis	319	89.1	8.8	9.2	0	51.1
Asthma	112	31.3	7.4	8.1	0	46.8
Poly-allergy	247	69.1	N.A.**	N.A.**	N.A.**	N.A.**

*Duration given in years, SD = standard deviation

** Not applicable

Table 2. Mean RHINASTHMA GAV sub-scale score and total scores at the three evaluation time points, n = 358 [mean ± SD (range)]

	Season w/o SLIT	Start of SLIT	End of SLIT	% Improvement*
Sub-scale "limitations in daily life"	1.35 ± 0.59 (0.00 - 2.93)	1.18 ± 0.67 (0.00 - 4.40)	0.60 ± 0.57 (0.00 - 2.73)	49.1
Sub-scale "respiratory problems"	0.97 ±0.60 (0.00 - 3.00)	0.90 ±0.81 (0.00 - 10.55)	0.46 ± 0.52 (0.00 - 4.09)	48.9
Sub-scale "rhinoconjunctivitis score"	1.34 ± 0.87 (0.00 - 3.00)	1.26 ± 0.85 (0.00 - 3.00)	0.57 ± 0.61 (0.00 - 3.00)	54.7
Sub-scale "treatment and medication problems"	1.52 ± 0.70 (0.00 - 3.00)	1.44 ± 0.74 (0.00 - 3.00)	0.92 ± 0.73 (0.00 - 3.00)	36.1
Sub-scale "impairment in sensory perceptions"	1.54 ± 0.66 (0.00 - 4.00)	1.35 ± 0.80 (0.00 - 8.75)	0.72 ± 0.62 (0.00 - 2.50)	46.7
Total score of HRQL	1.33 ± 0.48 (0.05 - 2.67)	1.21 ± 0.56 (0.00 - 2.88)	0.63 ± 0.48 (0.00 - 2.01)	48.0

*Calculated as (score at start - score at end)/score at start*100

Effectiveness was assessed using rhinitis and conjunctivitis symptom scores as well as the combined rhino-conjunctivitis symptom score, which consisted of 6 symptoms: sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes. No symptoms and mild, moderate, and severe intensity of the individual symptoms were scored as 0, 1, 2, and 3, respectively. The frequency of symptoms was described as rare, sometimes, frequent, and very frequent and scored as 1, 2, 3, and 4, respectively.

Patient compliance and patient assessments of tolerability were assessed by 4-point scoring scales. Demographics and disease-related baseline data were documented as well. Adverse events (AE) were documented on separate AE-forms.

Statistical analysis

Descriptive statistics were applied. The RHINASTHMA GAV total score and the scores of the 5 sub-scales [limitations in daily life, respiratory problems, rhino-conjunctivitis score, treatment and medication problems, and impairment in sensory perceptions (smell and vision)] were used to assess changes in HRQL during seasonal SLIT. The total score was calculated as the sum of the 5 sub-scale scores divided by 5. The scores were compared by analysis of variance (ANOVA).

Results

In total, 358 patients (158 men, 190 women, 10 without gender information, mean ± SD age

Table 3. Evaluation of the RHINASTMA GAV health related quality of life scores with parametric ANOVA tests for univariates. For underlying values, ref. Table 2.

Variables	Type III Sum of Squares	df*	Mean Square	F**	p-level
Limitations in daily life	64,252	1,651	38,925	178,738	<0.001
Respiratory problems	39,624	1,919	20,653	119,725	<0.001
Rhinoconjunctivitis score	85,329	1,938	44,03	108,724	<0.001
Treatment and medication problems	51,968	1,603	32,422	91,729	<0.001
Impairment in sensory perceptions	80,256	1,841	43,593	164,465	<0.001
Total score of HRQL	62,853	1,723	36,485	199,348	<0.001

* degrees of freedom size

** variance ratio size

2.9 ± 12.6 years, range 5 - 68 years and mean ± SD disease duration 8.8 ± 9.2 years) were included. From those, 69.1% were poly-sensitized mostly to grass and birch pollens and 31.3% had concomitant asthma. More details are given in Table 1. Nearly all patients (98.1% to 99.2%) were assessed by the investigators as "always" (drug intake every day as prescribed) or "nearly always" (drug intake > 75%) compliant during SLIT.

HRQL results are summarized in Table 2. During SLIT, all 5 RHINASTHMA GAV mean sub-scale scores were substantially reduced by 36% to 55%. The mean total score was reduced by 48%. All differences were significant with $p < 0.001$ (Table 3). Sub-group analyses of HRQL results considering age (5 - 12 years, 13 - 18 years, < 18 years), gender, presence of concomitant asthma, ultra-rush titration versus classical titration, sensitization to grass, cereal, and/or rye pollens, and mono-sensitization versus poly-sensitization did not reveal any clinically relevant deviations from the results in the total study population.

Patient assessment of effectiveness was very similar to the RHINASTHMA GAV sub-scale rhino-conjunctivitis score. This symptom score was reduced by 53% from 9.72 to 4.53 on average.

Figure 1 displays the results of the rhinitis, conjunctivitis, and rhino-conjunctivitis scores assessed by the patients at enrolment, start of SLIT, and end of SLIT. All 3 scores decreased substantially during SLIT.

At enrolment, patients reported health-related impairments in daily life (73.2%) and at work (46.1%), whereas only 30.9% and 18.1% of the patients reported such impairments at the end of SLIT.

The vast majority of patients assessed tolerability as "very good" (67.0%) or "good" (31.0%). 2% of the patients assessed the tolerability as moderate (4 patients) or poor (1 patient). In total, 11 adverse events were reported, mostly mild to moderate application site reactions in the oral cavity. Only 2 patients discontinued SLIT prematurely due to adverse events. One patient reported burning and swelling in the mouth, the other one feeling of pressure in the chest. None of the reported adverse events was assessed as serious by the investigators.

Discussion

This prospective observational study on high-dose seasonal SLIT using standardized allergen extract (STALORAL 300®) demonstrated that SLIT clearly improved HRQL in patients aged 5 - 68 years suffering from allergic rhinitis, with or without asthma. The German adapted version of a new specific HRQL questionnaire for patients with allergic rhinitis with coexisting asthma (RHINASTHMA GAV) proved to be applicable in the daily medical practice setting. At the end of SLIT, mean RHINASTHMA GAV total score and

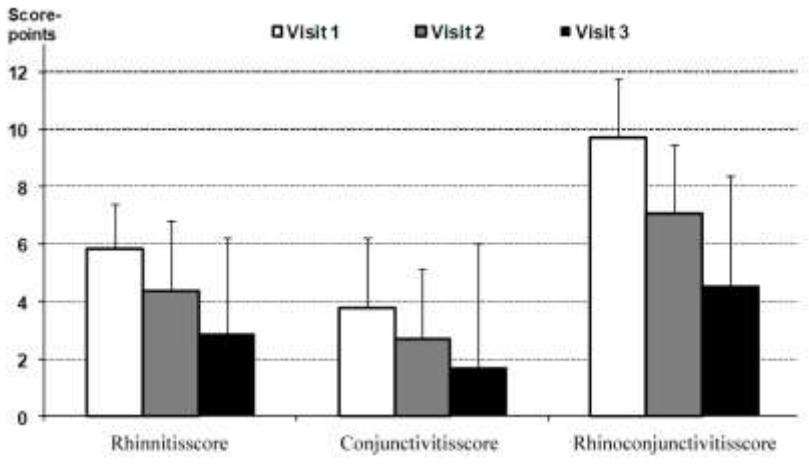

Figure 1. Rhinitis, conjunctivitis, and combined rhinoconjunctivitis scores (means and standard deviations). Visit 1: at enrolment (assessment of symptoms in the preceding pollen period without SLIT), visit 2: at start of SLIT, visit 3: at end of SLIT. N=358 patients. The differences of all scores between visit 1 and visit 3 were significant with $p < 0.001$

sub-scale scores were virtually identical to those scores assessed during the validation procedure in healthy subjects without rhinitis, conjunctivitis, or asthma.[12]

These improvements in HRQL during SLIT were paralleled by substantially reduced disease-related burden, in terms of symptom scores and health-related impairment in daily life and at work.

Our study was observational which accounts for generalizability to actual users by the evaluation of SLIT in real-world conditions, but has limitations like lower internal validity or lack of tightly-controlled research conditions compared to randomized controlled trials which may bias the results. On the other hand, similar observations could be shown in a randomized, double-blind, placebo-controlled study in 157 adult patients with a history of moderate to severe grass pollen-allergic rhino-conjunctivitis inadequately controlled by symptomatic medications who received a 3-year high-dose SLIT and 126 placebo.[14] HRQL assessments were based on RQLQ.[10] During the follow-up grass pollen season without SLIT treatment, 139 and 112 patients of the SLIT and placebo groups, respectively, provided RQLQ data. The mean total RQLQ score was about 23% lower in the SLIT group than in the placebo group. This difference was statistically significant and thus demonstrated a sustained effect of SLIT on HRQL. This study used a tablet form of SLIT whereas in our study, drops were used. It cannot be excluded that there may be differences in effect sizes between both application forms. However, clinical experience and comparison of randomized controlled trials with the one or the other application form do not indicate that there are clinically relevant differences.

In conclusion, the improvement in HRQL during seasonal SLIT in the daily medical practice setting was clinically relevant and reached scores close to normal already in the first pollen season.

Acknowledgements

Previous Publication:

The results of this observational study were submitted in part for poster presentation at the XXVIII Congress of the European Academy of Allergology and Clinical Immunology in Warsaw, Poland, 6 - 10 June 2009.

Funding Sources:

This study was sponsored by Stallergènes GmbH, Kamp-Lintfort, Germany.

Jochen Sieber is an employee of Stallergènes. Anna Gross and Kija Shah-Hosseini declared no conflict of interests.

Ralph Mösges received consulting fees from and/or conducted contract research for several companies including Stallergènes.

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