

Change in visual analog scale score in a pragmatic randomized cluster trial of allergic rhinitis

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Background: Most patients with allergic rhinitis consult in primary care. A simple test is needed to evaluate globally the severity of allergic rhinitis to assess the efficacy of treatment. **Objective:** This study compared the responsiveness of visual analog scale (VAS) scores between baseline and treatment with the 2 gold-standard outcomes (symptom score and quality of life). Five hundred eighty-six subjects were included, all with allergic rhinitis caused by grass pollens and all seen in primary care.

Methods: A randomized, multicenter, open-label parallel study was designed to compare 2 therapeutic strategies in patients with allergic rhinitis. The disease-specific Rhinoconjunctivitis Quality of Life Questionnaire total score, the symptom score, and the VAS score (0-10 cm) were all self-assessed by the patient before and after 2 weeks of treatment. Receiver operating characteristic curves and cost function were used to assess VAS cutoff scores and to distinguish between patients with no clinical improvement and patients with improvement in symptoms, quality of life, or both.

Results: The optimal cutoff in VAS score change separating the patients without improvement from those with improvement is 0.30 cm. By using the cost of false-positive and false-negative results, a difference of more than 1 cm is significant. However, when patients show an improvement in both symptoms and Rhinoconjunctivitis Quality of Life Questionnaire scores, the median improvement on the VAS is 7 cm.

Conclusions: A VAS, when used for a global evaluation of rhinitis, is highly responsive to change during the treatment of a large number of patients in a cluster randomized pragmatic trial. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Allergic rhinitis, Allergic Rhinitis and Its Impact on Asthma, visual analog scale, pragmatic cluster randomized clinical trial

Abbreviations used

ARIA: Allergic Rhinitis and Its Impact on Asthma
AUC: Area under the curve
QOL: Quality of life
ROC: Receiver operating characteristic
RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire
RTSS: Rhinitis total symptom score
VAS: Visual analog scale

Most patients with allergic rhinitis seeking medical help consult with primary care physicians.^{1,2} A simple test is needed to enable physicians to evaluate the severity of allergic rhinitis to assess the efficacy of a treatment for this disease.

Visual analog scales (VASs) are quantitative measures that have been extensively used to assess the severity of rhinitis.³⁻⁶ The VAS was proposed by the Joint Task Force on Practice Parameters for the symptom severity assessment of allergic rhinitis.⁷ This Task Force proposed to use several VASs to account for the different symptoms of allergic rhinitis given that some, such as nasal congestion, might be more relevant to rhinitis severity.⁸ However, several VAS scores can be difficult to combine, and a single VAS scale should be favored to assess the global perception of rhinitis severity. This simplified instrument has been found to correlate well with the severity of rhinitis, as assessed by the Allergic Rhinitis and Its Impact on Asthma (ARIA) trial.^{9,10}

VASs have been used in clinical trials to assess the efficacy of therapeutic interventions in rhinitis.^{4,7,11-13} However, there has been no clear evaluation of the value of these scales.

It is now recognized that allergic rhinitis comprises more than just the classical symptoms of sneezing, rhinorrhea, and nasal obstruction and that it is also associated with impairments in how patients function in day-to-day life.¹⁴⁻¹⁶ However, the impairment in quality of life (QOL) is only poorly related to symptoms because symptoms assess different parameters of the patient's impairment.¹⁵ In some clinical trials, QOL has been used as a primary end point.^{4,17}

Randomized, placebo-controlled clinical trials are key in the assessment of the efficacy and safety of treatments, but they are based on selected patients. Therefore they often fall short of representing the entire population and should be complemented by pragmatic trials.⁴ A pragmatic cluster randomized trial was carried out on 796 subjects to compare 2 strategies for the treatment of pollen-induced rhinitis (the ARIA method and free-treatment choice). As part of this study, several outcomes were assessed before and after 2 weeks of treatment (symptom score, Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ] score, and VAS score).

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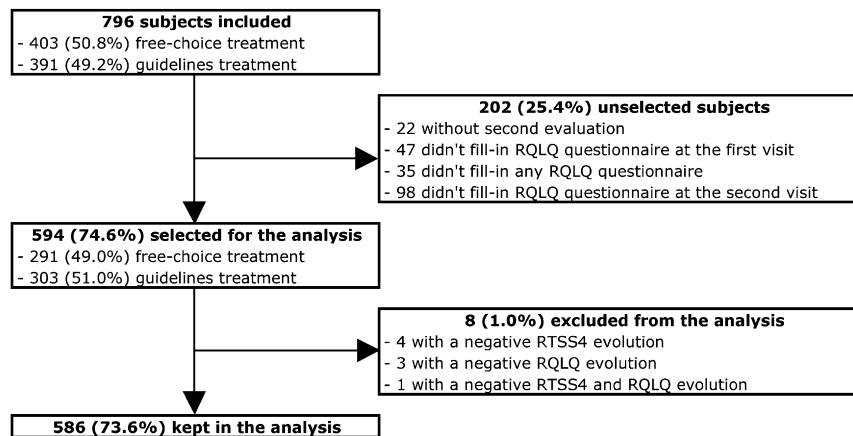


FIG 1. Flow chart.

The aim of the present study was to compare the responsiveness of VAS scores between baseline and treatment with the 2 gold-standard outcomes (symptom score and RQLQ score¹⁵). The study was carried out by means of a cluster randomized pragmatic trial and included subjects presenting with allergic rhinitis caused by grass pollens and seen in primary care.

METHODS

Patients

Patients were included in the study after written informed consent was obtained and after approval of the protocol by the Ethics Committee of Montpellier, France. All patients had to fulfill the following inclusion criteria: (1) a history of allergic rhinitis¹⁸ during the grass pollen season; (2) a diagnosis of grass pollen allergy based on skin prick test responses, serum grass pollen-specific IgE levels, or both (CAP System; Pharmacia, Uppsala, Sweden); and (3) no concomitant treatment. Patients were categorized as having intermittent, persistent, mild, or moderate-to-severe rhinitis according to the ARIA classification.⁹ None of the patients were excluded for comorbidity.

Design of the study

A randomized, multicenter, multinational, open-label parallel study was designed to compare 2 therapeutic strategies in patients with allergic rhinitis during a 2-week treatment period. Allergy, chest, and ear, nose, and throat specialists were randomized into one of 2 groups and had to enroll the first 2 patients seen between March 8 and July 15, 2002, for allergic rhinitis caused by pollen allergy. Physicians in the first group (the guidelines group) enrolled patients and followed a simple strategy based on the ARIA guidelines.¹⁹ Physicians from the second group (the free-choice treatment group) enrolled patients and treated them as they usually would in normal practice. Depot corticosteroids were not allowed.

The only patients considered for the analysis were those who completed the evaluation at baseline and after treatment of RQLQ scores, symptom scores, and VAS.

Outcomes

The disease-specific RQLQ total score,²⁰ the symptom score (rhinitis total symptom score [RTSS] 4), and the VAS score were self-assessed by the patient before and after 2 weeks of treatment. Variations were then computed.

The total symptom score rated 4 symptoms (RTSS4: nasal obstruction, pruritus, sneezing, and rhinorrhea) from absent (0) to very severe (3). Ocular symptoms were not considered. The total score ranged from 0 (absence of symptoms) to 12 (very severe). The VAS score ranged from 0 (absence of symptoms) to 10 cm (very severe symptoms) for all combined nasal symptoms.¹⁰

The proposed clinically important difference in the global RQLQ change in score on a scale of 0 to 6 was 0.5.²¹ This was based on the mathematic model on a scale of 0 to 6. However, in most trials patients receiving placebo have an improvement of RQLQ score of close to or greater than 1.^{11,17,22,23} We therefore considered a change in score of 1 or greater as a clinically relevant improvement in RQLQ score. The total symptom score was considered to be improved if patients had a 40% improvement of symptoms. The baseline RTSS4 was around 7, and we considered a change in score of 3 or more as a clinically relevant improvement of symptoms because in randomized, placebo-controlled clinical trials a RTSS4 reduction of 20% to 35% is observed in the placebo group, whereas a 40% to 50% reduction in RTSS is observed in the active group.²²⁻²⁹ These cutoff levels were an *a priori* choice. Finally, because QOL and symptoms do not assess the same dimension, RQLQ score and RTSS4 variations were combined. Patients were then divided into one of 5 groups:

- *clinically relevant improvement*: improvement of RQLQ score of 1 or greater and RTSS4 of 3 or greater;
- *clinically relevant improvement of QOL*: improvement of RQLQ score of 1 or greater and RTSS4 of less than 3;
- *clinically relevant improvement of symptoms*: improvement of RQLQ score of less than 1 and RTSS4 of 3 or greater;
- *no improvement*: improvement of RQLQ score of less than 1 and RTSS4 of less than 3; and
- *worsening of RQLQ score or RTSS4*.

Statistical analysis

Qualitative data were expressed as percentages and frequencies. Because distributions were not normal (Shapiro-Wilks, kurtosis, and skewness tests), median and 25th to 75th percentiles defined quantitative distributions. The present analysis being part of a larger study, comparisons for the principal patient characteristics at inclusion were carried out between included and nonincluded patients by using χ^2 and Kruskal-Wallis tests, respectively. After assessing the baseline demographic characteristics of the patients for each RQLQ/RTSS4 group, changes in RQLQ score, RTSS4, and VAS score were observed. Absolute values were computed for the VAS score evolution to take positive and negative evolutions into account. Correlations (Spearman rank test) were also assessed among the 3 scales (RQLQ, RTSS4, and VAS).

Finally, by using receiver operating characteristic (ROC) curves³⁰ and cost function,³¹ cutoffs were established to distinguish between patients with no clinical improvement and patients with clinical improvement in symptoms or QOL, as well as those with clinical improvement in both symptoms and QOL. For the cost function [$Cost_{false-negative} \times Prevalence \times (1 - Sensitivity) + Cost_{false-positive} \times (1 - prevalence) \times (1 - Specificity)$], the cost of a false-negative result was assumed to be similar to that of a false-positive result, and the prevalence was the one observed in the present study.

The analysis was performed with SAS version 8.1 software (SAS Institute, Inc, Cary, NC), with the significance level set at 5% (.05).

TABLE I. Demographic characteristics of the patient population

	RQLQ score <1 RTSS4 <3	RQLQ score <1 RTSS4 ≥3	RQLQ score ≥1 RTSS4 <3	RQLQ score ≥1 RTSS4 ≥3	P value
No.	66	105	36	379	
Age (y)	32.9 (25.2-42.5)	36.4 (27.2-43.1)	29.3 (24.2-42.3)	35.1 (25.7-42.6)	.38
Sex (male)	29 (43.9%)	49 (46.7%)	14 (38.9%)	163 (43.4%)	.87
Smokers or ex-smokers	24 (36.4%)	35 (33.3%)	17 (47.2%)	128 (34.0%)	.71
Asthma	17 (25.8%)	18 (17.1%)	7 (19.4%)	88 (23.4%)	.48
Conjunctivitis	31 (47.0%)	48 (45.7%)	18 (50.0%)	219 (58.2%)	.07
Rhinitis (ARIA classification)					
Mild intermittent	8 (12.1%)	12 (11.4%)	2 (5.7%)	24 (6.4%)	
Moderate-to-severe intermittent	11 (16.7%)	17 (16.2%)	7 (20.0%)	71 (18.9%)	
Mild persistent	13 (19.7%)	19 (18.1%)	6 (17.1%)	33 (8.8%)	
Moderate-to-severe persistent	34 (51.5%)	57 (54.3%)	20 (57.1%)	247 (65.9%)	.03
Patients with ARIA-based (guideline) treatment	31 (47.0%)	47 (44.8%)	20 (55.6%)	201 (53.5%)	.35

Results are expressed as medians and 25th-75th percentiles.

TABLE II. Correlation between RQLQ score, RTSS4, and VAS score

	Baseline	Treatment	Evolution of outcome between baseline and treatment
RQLQ vs VAS	0.36 ($P < .001$)	0.66 ($P < .001$)	0.54 ($P < .001$)
RQLQ vs RTSS4	0.40 ($P < .001$)	0.61 ($P < .001$)	0.51 ($P < .001$)
RTSS4 vs VAS	0.45 ($P < .001$)	0.73 ($P < .001$)	0.66 ($P < .001$)

Analysis was performed with Spearman rank correlation.

RESULTS

Baseline characteristics of patients

Among the 796 subjects included in the initial study, 594 (74.6%) were selected for the present analysis (Fig 1).

There were no differences between the selected and nonselected subjects at inclusion with regard to treatment group ($P = .09$), sex ($P = .49$), age ($P = .13$), socioeconomic class ($P = .83$), smoking habit ($P = .99$), asthma ($P = .12$), allergic conjunctivitis ($P = .68$), rhinitis (ARIA classification, $P = .74$), and symptoms (ocular symptoms, $P = .60$; sneezing, $P = .33$; nasal obstruction, $P = .65$; rhinorrhea, $P = .17$; and nasal pruritus, $P = .15$).

Among the 594 patients, 8 (1.3%) were not analyzed because of the very low number of patients with a negative evolution of their QOL (RQLQ score worsening between visits 1 and 2) or symptom score (RTSS4 worsening between visits 1 and 2).

The baseline characteristics of the patients included in the present analysis were similar and nonsignificantly different in the 4 RQLQ/RTSS4 groups for age, sex, smoking habit, asthma, and conjunctivitis and for the type of treatment (guideline group versus free-choice treatment, Table I).

Correlation between QOL, symptom, and VAS scores

Correlations between RQLQ score, RTSS4, and VAS score were poor at baseline (Table II). They were more significant after treatment at the second visit ($\rho = 0.61$ - 0.73). Similar findings were observed for the evolution in outcome scores ($\rho = 0.51$ - 0.66).

Evolution of VAS score depending on RQLQ/RTSS4 groups

Patients who were *a priori* not improving (difference in RTSS4 of <3 and RQLQ score of <1) had the lowest reduction in VAS scores (0.5 cm; Table III and Fig 2). Patients with a clinically meaningful improvement in RQLQ score only or RTSS4 only had an intermediate reduction in VAS scores (2.2 and 2.9 cm, respectively; $P = .09$). Finally, those with a clinically significant improvement in RQLQ score and RTSS4 had a median reduction of 5.0 cm in VAS score ($P < .001$). The VAS score reduction was statistically significant between the patients *a priori* not improved and those with a clinically meaningful improvement in RQLQ score only or RTSS4 only ($P < .0001$ in both cases). The VAS score reduction in these groups was less than in the patients with a clinically significant improvement in RQLQ score and RTSS4 ($P < .0001$ in all cases). However, there were no differences between the patients with a clinically meaningful improvement in RQLQ score only and RTSS4 only ($P = .11$).

By using ROC curves and cost function, it appeared that the optimal cutoff point in VAS score difference separating patients without improvement from those with improvement (difference in RTSS4 of ≥ 3 , RQLQ score of ≥ 1 , or both) was 0.30 cm (Fig 3). However, the cost of false-positive and false-negative results remained similar up to 1 cm of difference in VAS score (always <69, for a minimum at 61 and a maximum at 514). The optimal cutoff point in VAS score difference separating patients with no improvement or an intermediary improvement (difference in RTSS4 of ≥ 3 or RQLQ score of ≥ 1) from those with a clinical improvement in RQLQ score (difference in RQLQ score of ≥ 1) and RTSS4 (difference in RTSS4 of ≥ 3) was 2.6 cm. At this point, the cost function was equal to 127, for a maximum at 373. The areas under the curve (AUCs) of the 2 ROC curves were 0.89 (0.86-0.92) and 0.77 (0.73-0.81), respectively.

DISCUSSION

In the present study we found that for a global evaluation of rhinitis, a VAS is highly responsive to change during the treatment of a large number of patients in a cluster randomized pragmatic trial.

We used a cluster randomized trial in the study, aiming to mimic real life. There was no exclusion of patients, as is often the case in clinical trials,³² because we needed to study the whole

TABLE III. Evolution of outcomes during treatment

	RQLQ score <1 RTSS4 <3	RQLQ score <1 RTSS4 ≥3	RQLQ score ≥1 RTSS4 <3	RQLQ score ≥1 RTSS4 ≥3	P value
RTSS4					
Baseline	6 (5 to 8)	8 (6 to 9)	6 (4 to 7)	8 (7 to 10)	
Treatment	5 (4 to 7)	2 (1 to 4)	5 (3 to 7)	1 (0 to 3)	
Evolution	1 (0 to 2)	5 (4 to 7)	1 (1 to 2)	7 (5 to 8)	<.001
RQLQ					
Baseline	2.2 (1.7 to 2.9)	1.8 (1.0 to 2.8)	2.8 (2.5 to 3.4)	3.0 (2.4 to 3.6)	
Treatment	2.0 (1.2 to 2.9)	1.2 (0.6 to 2.5)	1.0 (0.7 to 1.6)	0.5 (0.2 to 1.0)	
Evolution	0.3 (0.0 to 0.6)	0.5 (0.2 to 0.8)	1.7 (1.4 to 2.1)	2.2 (1.7 to 3.0)	<.001
VAS					
Baseline	6.0 (4.3 to 7.5)	6.1 (4.8 to 7.7)	6.0 (4.6 to 7.5)	7.0 (5.5 to 8.0)	
Treatment	5.1 (3.5 to 7.0)	2.4 (1.0 to 4.0)	2.9 (2.3 to 5.0)	1.5 (0.6 to 2.3)	
Evolution	0.5 (-0.1 to 2.0)	2.9 (1.0 to 5.3)	2.2 (1.0 to 3.2)	5.0 (3.5 to 6.5)	<.001

Results are expressed as medians and 25th-75th percentiles.

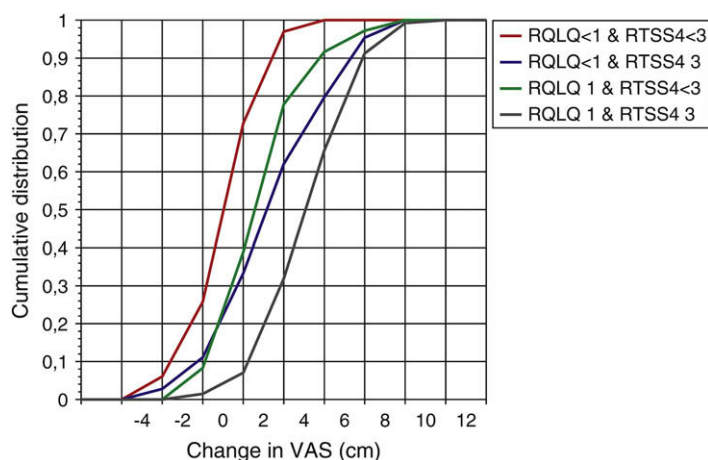


FIG 2. Cumulative distribution of VAS score changes depending on RQLQ score and RTSS4 changes.

range of patients regularly seen by physicians. We wanted to study patients in primary care (because the vast majority of patients with allergic rhinitis are seen in this setting) and also to use a simple instrument that could prove to be important to the physician. The benefits of the trial were not assessed in this part of the study. Furthermore, the study has not been carried out in the general population, and the percentage of patients with moderate-to-severe disease is higher. Finally, we used the ARIA classification,⁹ being the most widely accepted.

There are many methods assessing the efficacy of a treatment for allergic rhinitis, but in primary care there is no validated objective test.³³ Symptom scores and QOL measurements have been used. These 2 methods assess different characteristics of the patients,¹⁵ and this was confirmed by the present study because there was a significant but rather poor correlation between changes in RQLQ score and RTSS4, confirming that these factors are not completely related. Thus it appeared appropriate to combine the 2 outcomes as the gold standard for the study. We also used a cutoff value for RQLQ score and RTSS4 that appeared to be clinically relevant. In clinical trials the RTSS4 of the placebo group is usually improved by 30% to 40%.^{11,23,34-37} In the present study all patients were treated, and we wanted to have a safe margin to assess the clinical relevance of the study. On the other hand, the RQLQ score is proposed to be

significantly improved when the within-group difference is greater than 0.5.²¹ However, in most trials the difference in the placebo group is greater.^{11,17,22,23} This is why we selected a cut-off value of 1.

An ROC curve is a graphic plot of the number of true positive results (True-positive results/[True-positive results + False-negative result]) versus the number of false-positive results (False-positive results/[True-negative results + False-positive results]) for a binary classifier system because its discrimination threshold is varied. In addition, calculations of the area under the ROC curve provide a summary measure of the accuracy of the test. For a perfect test, the ROC AUC would have to be 1.0, whereas for a test that is no better than chance, the AUC would be 0.5. ROC analyses have been used in allergy.^{10,38-42} The cost curves introduced by Drummond and Holte³¹ assessed the effect of patients wrongly classified (ie, false-positive and false-negative results). It therefore appears that the use of both ROCs and cost curves will make it possible to optimally compare tests. The study shows that the optimal cutoff point is 1.00 cm.

The VAS is a technique used to measure subjective phenomena.⁴³ It is a self-reporting device consisting of a line of predetermined length that separates extreme boundaries of the phenomenon being measured. The VAS provides a continuous scale for subjective magnitude estimation and consists of a

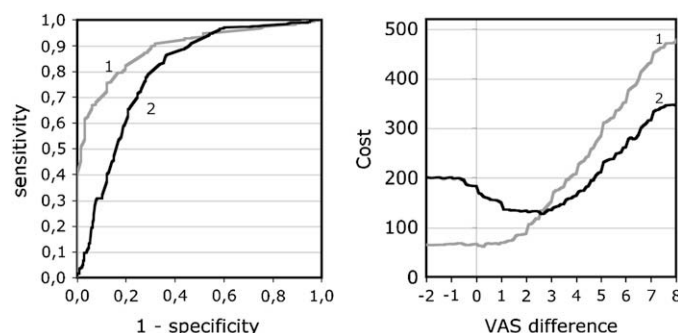


FIG 3. ROC curves (*left*) and cost function (*right*) evaluating VAS score evolution depending on clinical improvement. 1, No clinical improvement versus a clinical improvement in RQLQ score, RTSS4, or both. 2, No clinical improvement or clinical improvement in RQLQ score or RTSS4 versus clinical improvement in both RQLQ score and RTSS4.

straight line, the limits of which carry a verbal description of each extreme of the symptom to be evaluated. In addition, it takes relatively little time to complete and allows cross-cultural comparisons because of minimal language translation difficulties. The VAS has been widely used for the assessment of subjective symptoms, such as pain,⁴⁴ and it is considered to be a robust, sensitive, and reproducible method of expressing pain severity. However, the interaction between the behavioral tendencies of patients and the physical characteristics of the scale causes it to be nonlinear and prone to response bias.^{44,45} As such, an assessment is clearly highly subjective, and these scales are of most value when looking at changes within individuals and are of less value for comparing across a group of individuals at 1 time point.⁴³ The VAS was found to correlate with the severity of rhinitis,¹⁰ but changes in VAS score might accurately reflect changes during treatment that are not completely clear.^{4,7,11-13} The present study is the first to investigate changes in VAS scores during treatment in a large number of patients. Large variations in VAS scores were observed in the present study. However, it is interesting to note that patients without improvement can easily be differentiated from those with a dissociated improvement and those with an improvement in symptoms and QOL. By using ROC curves and cost function, it appeared that the optimal cutoff point in VAS score difference separating patients without any improvement from patients with an improvement (difference in RTSS4 of ≥ 3 , RQLQ score of ≥ 1 , or both) was 0.30 cm. Moreover, the cost of false-positive and false-negative results remains similar up to 1 cm of difference in VAS score, showing the precision of the instrument. Thus it appears that a difference of greater than 1 cm is significant. However, when patients show improvement in both symptoms and RQLQ scores, the median improvement in VAS score is 7 cm, and there is no overlap with patients without *a priori* improvement. It appears that VAS score changes are very precise, even though very large effects can be shown. These results have been reproduced in 2 double-blind, placebo-controlled clinical trials with desloratadine in patients with intermittent (547 patients⁴⁶) and persistent (648 patients⁴⁷) allergic rhinitis. By using the same scale, a mean change in VAS score of 1.1 to 1.4 cm was found in the placebo groups. The present study therefore represents a step forward in the standardization and comparison of clinical trials for the treatment of allergic rhinitis. The VAS score might become a very simple and precise measurement that could be a primary outcome in clinical trials, as well as an important measurement in clinical practice.

Clinical implications: A global VAS score for rhinitis symptoms can provide a simple tool to assess the efficacy of the treatment in patients with allergic rhinitis.

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