Triamcinolone Acetone in the Treatment of Perennial Allergic Rhinitis: A post hoc Analysis of Quality of Life during a Phase III Study

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Keywords
Allergic rhinitis · Triamcinolone acetone · Quality of life · Allergic conjunctivitis · Perennial allergic rhinitis

Abstract

Introduction: Allergic rhinitis (AR) is a disease that affects ≤24% of people in Russia, significantly impairing quality of life (QoL). Intranasal corticosteroids, such as triamcinolone acetone (TAA), are considered effective drugs for treatment. A post hoc analysis of data (phase III NASANIF trial) examined weekly QoL changes in patients receiving TAA for the treatment of perennial AR (PAR). Methods: NASANIF (NCT03317015) was a double-blind, parallel group, multicenter, prospective, noninferiority, phase III clinical trial. Patients with PAR were randomized (1:1) to receive TAA or fluticasone propionate (FP) for 4 weeks. Here, a post hoc analysis measures QoL using a shortened Rhinoconjunctivitis Quality of Life Questionnaire (miniRQLQ). Differences in miniRQLQ score were evaluated using a mixed linear model and descriptive statistics. A subgroup analysis was performed in patients with a previous diagnosis of allergic conjunctivitis. Results: Of 260 patients eligible for randomization, 128 each completed treatment with TAA or FP. Overall and individual domain scores progressively improved and were significantly different versus baseline at week 4 in both treatment groups: LS mean difference TAA: −30.92 (95% CI [−33.01 to −28.83]), \(p<0.001\), and FP: −31.13 (−33.23 to −29.04), \(p<0.001\). In both arms of the subgroup, there was a significant reduction in eye symptoms. There was no significant difference between the TAA and FP treatment groups in any analyses. Conclusions: TAA is effective in improving overall and individual domains of QoL in patients with PAR, over 4 weeks. Patients with a previous diagnosis of allergic conjunctivitis experienced significant improvements in QoL related to the resolution of these symptoms.

Introduction

Allergic rhinitis (AR) is a multifactorial disease that can be classified as either seasonal or perennial (PAR). In accordance with the Allergic Rhinitis in the Impact of Asthma (ARIA) guidelines, AR can also be classified based on the duration of the disease, intermittent or perennial.
sistent, or based on severity, that is, mild, moderate, or severe [1]. AR is a widespread health problem that affects up to 24% of the population in Russia [2]. 

Nasal symptoms of AR include rhinorrhea, sneezing, itching, and obstruction, which can impair quality of life (QoL). While nasal symptoms are those that are often described as the most troublesome by patients, eye symptoms are also an important and overlooked effect of AR as they can greatly impact QoL [3]. Furthermore, studies have shown that AR significantly influences many other areas of life, such as work productivity [4, 5], highlighting the importance of effective intervention in countries (such as Russia) where it is prevalent. Intranasal corticosteroids are considered to be the most effective drugs for treating AR symptoms, as they provide precise treatment by reducing inflammation in the nasal mucosa [6]. Delivering high drug concentrations directly to the area of allergic inflammation inhibits reactivity to allergens and effectively improves symptoms [7].

Triamcinolone acetonide (TAA) is a synthetic fluorinated corticosteroid approved for the treatment of AR in adults and pediatric patients [8]. In the phase III NASANIF trial, which was conducted in Russia, TAA was shown to have a good safety profile and noninferior efficacy to FP in adults with persistent PAR [9]. We undertook a post hoc analysis of the NASANIF trial to examine and quantify weekly changes in QoL during the course of treatment with TAA or FP.

**Methods**

**Study Design**

The NASANIF trial was a randomized (1:1), double-blind, parallel group, multicenter, prospective, noninferiority, phase III clinical trial (NCT03317015) conducted between November 30, 2016, and July 10, 2017, in 12 study centers in Russia. The study design has been published previously [9]. In brief, 260 patients with previously diagnosed persistent PAR were randomized (1:1) to receive either intranasal TAA (220 μg/day, administered as 2 × 55 μg sprays per nostril) or intranasal FP (200 μg/day, administered as 2 × 50 μg sprays per nostril) for 4 weeks. In the original study, QoL was assessed at baseline and week 4 using a patient-administered short version of the Rhinoconjunctivitis Quality of Life Questionnaire (miniRQLQ), which contains 14 items in 5 domains: activity limitations, practical problems, nasal symptoms, eye symptoms, and other symptoms. All items on the miniRQLQ are scored using a 7-point response scale (online suppl. Table S1; see www.karger.com/doi/10.1159/000518753 for all online suppl. material) [10]. In this post hoc analysis, QoL scores were calculated, both overall and for individual domains, at baseline (analysis day 1), week 1 (analysis days 8–10), week 2 (analysis days 15–17), week 3 (analysis days 22–24), and week 4 (analysis days 29–31) [10].

**Results**

Two hundred and sixty patients were randomized (TAA, n = 129; FP, n = 131), and 256 completed the 4-week trial (n = 128 per arm). Patient population, baseline demographics, and clinical characteristics were previously reported [9].

**Overall miniRQLQ Score**

The mean (standard deviation) overall miniRQLQ scores at baseline were 38.14 (13.45) for TAA and 38.56 (13.63) for FP. Mean overall scores were significantly reduced (p < 0.001), versus baseline, in each week of treatment in both treatment groups (Table 1; Fig. 1). At week 4, the LS mean (95% CI) change from baseline was −30.92 (−33.01 to −28.83) in the TAA arm (p < 0.001) and −31.13 (−33.01 to −29.37) in the FP arm (p < 0.001). Comparisons between baseline, each week of treatment, and final visit were calculated, both overall and for individual domains, at baseline (analysis day 1), week 1 (analysis days 8–10), week 2 (analysis days 15–17), week 3 (analysis days 22–24), and week 4 (analysis days 29–31) [10].

**Statistical Methods**

Mean overall and individual domain scores were calculated weekly for each treatment, both for the overall study population and the subgroup of patients with comorbid allergic conjunctivitis. Scores for individual components of the “eye symptoms” domain were also analyzed.

Changes from baseline in miniRQLQ scores were calculated and analyzed using a linear mixed model. To calculate and compare least-squares (LS) means, a mixed model with categorical time (weeks of treatment), random intercept, treatment, and time/treatment interaction terms was estimated. No simplification or building strategy was applied to these models. For comparisons between visits, LS mean differences were reported together with 95% confidence intervals (CIs). Comparisons between treatments were calculated, and significance was reported using 2-sided p values from the mixed model.

The main analyses were performed on the per-protocol population, and sensitivity analyses were performed on the ITT population. All statistical analyses were performed using SAS® Version 9.4 (Cary, NC, USA). In general, substitution of missing data was not done; missing data were not imputed but instead were handled as “missing” in the statistical evaluation.

**Subgroup Analysis**

A subgroup analysis was performed of patients in the per-protocol population who had eye symptoms at baseline. This subgroup of eye symptoms was defined by a previous diagnosis of concomitant allergic conjunctivitis, as informed by the patients. These patients were identified from data gathered during screening.

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**Table 1.** Change from baseline in least-squares mean overall score and scores for individual domains of the miniRQLQ

| Domain               | TAA (n = 128)          | FP (n = 128)          | p value |
|----------------------|------------------------|-----------------------|---------|
| Overall miniRQLQ score |                        |                       |         |
| Week 1               | −10.68 (−12.77 to −8.59) | −11.28 (−13.37 to −9.19) | p < 0.001 | 0.9999 |
| Week 2               | −20.09 (−22.19 to −18.00) | −19.33 (−21.42 to −17.24) | p < 0.001 | 0.9996 |
| Week 3               | −26.66 (−28.75 to −24.56) | −26.44 (−28.53 to −24.34) | p < 0.001 | 1.000  |
| Week 4               | −30.92 (−33.01 to −28.83) | −31.13 (−33.23 to −29.04) | p < 0.001 | 1.000  |
| Activity limitations |                        |                       |         |
| Week 1               | −2.41 (−2.94 to −1.87) | −2.64 (−3.18 to −2.10) | p < 0.001 | 0.9988 |
| Week 2               | −4.91 (−5.45 to −4.37) | −4.82 (−5.36 to −4.28) | p < 0.001 | 1.000  |
| Week 3               | −6.44 (−6.98 to −5.90) | −6.53 (−7.07 to −6.00) | p < 0.001 | 1.000  |
| Week 4               | −7.55 (−8.10 to −7.02) | −7.92 (−8.46 to −7.38) | p < 0.001 | 0.9815 |
| Practical problems   |                        |                       |         |
| Week 1               | −1.90 (−2.28 to −1.51) | −1.74 (−2.13 to −1.36) | p < 0.001 | 0.9993 |
| Week 2               | −3.38 (−3.77 to −3.00) | −3.03 (−3.4 to −2.65)  | p < 0.001 | 0.9112 |
| Week 3               | −4.42 (−4.81 to −4.04) | −4.12 (−4.50 to −3.73) | p < 0.001 | 0.9574 |
| Week 4               | −5.17 (−5.56 to −4.79) | −5.06 (−5.45 to −4.68) | p < 0.001 | 0.9999 |
| Nasal symptoms       |                        |                       |         |
| Week 1               | −2.73 (−3.28 to −2.17) | −2.98 (−3.53 to −2.42) | p < 0.001 | 0.9985 |
| Week 2               | −5.12 (−5.67 to −4.56) | −4.95 (−5.50 to −4.39) | p < 0.001 | 0.9999 |
| Week 3               | −6.89 (−7.44 to −6.34) | −6.85 (−7.41 to −6.30) | p < 0.001 | 1.000  |
| Week 4               | −8.07 (−8.62 to −7.52) | −8.15 (−8.70 to −7.60) | p < 0.001 | 1.000  |
| Eye symptoms         |                        |                       |         |
| Week 1               | −1.41 (−2.00 to −0.81) | −1.57 (−2.16 to −0.98) | p < 0.001 | 0.9999 |
| Week 2               | −2.41 (−3.01 to −1.82) | −2.33 (−2.92 to −1.74) | p < 0.001 | 1.000  |
| Week 3               | −3.30 (−3.89 to −2.70) | −3.20 (−3.80 to −2.61) | p < 0.001 | 1.000  |
| Week 4               | −3.84 (−4.44 to −3.25) | −3.67 (−4.27 to −3.08) | p < 0.001 | 0.9999 |
| Other symptoms       |                        |                       |         |
| Week 1               | −2.24 (−2.87 to −1.61) | −2.35 (−2.98 to −1.72) | p < 0.001 | 1.000  |
| Week 2               | −4.27 (−4.90 to −3.63) | −4.20 (−4.84 to −3.57) | p < 0.001 | 1.000  |
| Week 3               | −5.61 (−6.24 to −4.98) | −5.73 (−6.37 to −5.10) | p < 0.001 | 1.000  |
| Week 4               | −6.28 (−6.91 to −5.65) | −6.33 (−6.96 to −5.70) | p < 0.001 | 1.000  |

Data in brackets show 95% confidence intervals. FP, fluticasone propionate; miniRQLQ, mini-Rhinoconjunctivitis Quality of Life Questionnaire; TAA, triamcinolone acetonide.

There were no significant differences between treatment groups.

**Individual miniRQLQ Domains**

Scores in each of the 5 domains (activity limitations, practical problems, nasal symptoms, eye symptoms, and other symptoms) significantly reduced (p < 0.001) from baseline in each week of treatment with TAA or FP (Table 1; Fig. 2). The greatest change from baseline in the TAA group was seen in nasal symptoms, with an LS mean (95% CI) reduction of −8.07 (−8.62 to −7.52) at week 4 (p < 0.001) (Table 1). Similar reductions were observed in the FP treatment group in each analysis, with no significant differences between groups.

Within the eye symptoms domain, scores for individual items (symptoms) also significantly decreased (p <
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The greatest change from baseline in the TAA group was in itchy eyes, with an LS mean (95% CI) reduction of $-1.45 (-1.68$ to $-1.23$) at week 4. Similar reductions were observed in the FP treatment group in each analysis, with no significant differences between groups.

**Subgroup Analysis**

The subgroup analysis included 37 patients from the TAA arm and 43 patients from the FP arm. After 4 weeks of treatment, overall miniRQLQ scores had greatly decreased versus baseline (Fig. 3), with LS mean (95% CI) reductions of $-34.84 (-38.85$ to $-30.83$) and $-33.02 (-36.74$ to $-29.30$) for TAA and FP, respectively (online suppl. Table 2); no significant difference was observed between the TAA and FP treatment groups. In the subgroup, successive weekly reductions in scores were also seen in individual domains (online suppl. Table 2) and for individual components of the eye symptom domain (Fig. 4). Similar reduc-
tions were observed in the FP treatment group in each analysis, with no significant differences between groups.

Discussion

The intranasal administration of TAA or FP significantly improved miniRQLQ scores, both overall and in the 5 individual domains, over 4 weeks in patients with PAR in Russia. Other studies have demonstrated improvements in QoL in patients with seasonal or persistent AR who received TAA [7, 11, 12]. Our analysis has been broadened to study the effects of TAA in patients with PAR. The change in miniRQLQ score from baseline was statistically significant at each week of treatment, and there was no statistically significant difference between treatments. Considering the low proportion of patients who had a previous diagnosis of eye symptoms at baseline, we performed a subgroup analysis of these patients and found that the improvement of eye symptoms by TAA in these patients was far greater than that shown in the overall study population.

Intranasal corticosteroids are most commonly associated with improvements in nasal symptoms due to their localized effects in the nasal tissue [13]. These treatments act in the early and late phases of allergic reactions [14] and have been shown to be superior to oral corticosteroids and antihistamines, particularly in the treatment of nasal symptoms [15, 16]. Previous trials have shown that TAA is effective in reducing these symptoms in patients with AR [9, 17], and the results of our post hoc analysis are consistent with these findings. Furthermore, we have shown that TAA provides effective and prolonged improvement of PAR symptoms in another post hoc analysis of the same trial (Karaulov et al. [18], submitted).

Nasal symptoms of AR can impair QoL including interfering with sleep, most likely due to nasal congestion, and AR-related sleep disturbance is a defining feature of severe AR that has direct effects on fatigue, mood, and daytime somnolence [19]. In an open-label primary care
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study, TAA was found to improve both sleep quality and nocturnal rhinitis-related QoL [19].

Additionally, intranasal corticosteroids also have a significant impact on nonnasal symptoms of AR. Eye symptoms, such as itching, lacrimation, and eyelid edema, are troublesome to patients and can significantly impair QoL [3]. In previous studies, TAA has been shown to improve eye symptoms, particularly lacrimation [14, 15]. In addition, a 2020 meta-analysis by Bielory et al. [17] found a significant reduction in the occurrence of eye symptoms, especially watery eyes, in patients treated with TAA. In our analysis, among the 128 patients who completed 4-week treatment with TAA, only 37 had a previous diagnosis of eye symptoms. A subgroup analysis of these patients was therefore performed to minimize potential bias introduced by the inclusion of patients with no eye symptoms at baseline and to better characterize the effects of TAA on these symptoms. This analysis showed that changes from baseline in overall miniRQLQ scores were greater, at each week of the study, in the subgroup compared with the whole study population. The main post hoc analysis showed change from baseline data for the eye symptom domain that is suggestive of a dramatic reduction in eye symptoms at week 4, and the subgroup analysis reinforces this. In patients with AR, intense eye symptoms are mostly associated with seasonal AR [17], but our findings suggest that eye symptoms can impact QoL of at least some patients with PAR. The improvements in eye symptom scores during our study suggest that TAA has the potential to improve QoL in patients for whom eye symptoms are troublesome.

TAA has similar efficacy and safety to other intranasal corticosteroids in the treatment of AR [11, 20]; however, the bioavailability of some intranasal corticosteroids including TAA is much higher (23–46%) than others such as FP and mometasone (<1%) [21, 22]. The primary concern of high bioavailability is related to potential adverse events; however, bioavailability of an intranasal corticosteroid does not predict the incidence of adverse events nor the efficacy. Many different properties of each intranasal corticosteroid have a direct or indirect correlation that will determine their safety and efficacy, such as volume of distribution, tissue deposition, receptor binding targeting, tissue retention, lipophilicity, glucocorticoid potency, systemic potency, and elimination half-life [14, 23, 24]. Comparative studies that have evaluated TAA and FP demonstrated a similar safety profile of these intranasal corticosteroids despite the difference in bioavailability [9, 11, 12]; therefore, TAA can be considered a well-tolerated choice.

TAA is often a preferred choice by patients because of its perceived sensory attributes (e.g., feel of spray in nose and throat) [20]. In addition, compared with other intranasal steroids, TAA is associated with less odor, less aftertaste, and greater overall patient liking [25]. Patient satisfaction with efficacy and sensorial attributes of treatment

Table 2. Change from baseline in least-squares mean scores for individual items in the “eye symptoms” domain of the miniRQLQ

|                  | TAA (n = 128) | FP (n = 128) | p value |
|------------------|--------------|--------------|---------|
| **Watery eyes**  |              |              |         |
| Week 1           | −0.52 (−0.74 to −0.29) | p < 0.001 | −0.60 (−0.83 to −0.37) | p < 0.001 | 0.9995 |
| Week 2           | −0.83 (−1.06 to −0.60) | p < 0.001 | −0.87 (−1.10 to −0.64) | p < 0.001 | 1.0000 |
| Week 3           | −1.14 (−1.37 to −0.91) | p < 0.001 | −1.20 (−1.43 to −0.97) | p < 0.001 | 0.9999 |
| Week 4           | −1.36 (−1.59 to −1.13) | p < 0.001 | −1.34 (−1.57 to −1.12) | p < 0.001 | 1.0000 |
| **Itchy eyes**   |              |              |         |
| Week 1           | −0.49 (−0.72 to −0.27) | p < 0.001 | −0.54 (−0.77 to −0.31) | p < 0.001 | 1.0000 |
| Week 2           | −0.92 (−1.15 to −0.70) | p < 0.001 | −0.85 (−1.08 to −0.62) | p < 0.001 | 0.9999 |
| Week 3           | −1.25 (−1.48 to 1.02) | p < 0.001 | −1.19 (−1.41 to −0.96) | p < 0.001 | 0.9999 |
| Week 4           | −1.45 (−1.68 to −1.23) | p < 0.001 | −1.34 (−1.57 to −1.12) | p < 0.001 | 0.9977 |
| **Sore eyes**    |              |              |         |
| Week 1           | −0.40 (−0.60 to −0.19) | p < 0.001 | −0.43 (−0.64 to −0.22) | p < 0.001 | 1.0000 |
| Week 2           | −0.66 (−0.90 to −0.46) | p < 0.001 | −0.61 (−0.82 to −0.40) | p < 0.001 | 1.0000 |
| Week 3           | −0.91 (−1.11 to −0.70) | p < 0.001 | −0.81 (−1.02 to 0.61) | p < 0.001 | 0.9984 |
| Week 4           | −1.03 (−1.24 to −0.83) | p < 0.001 | −0.98 (−1.19 to −0.78) | p < 0.001 | 1.0000 |

Data in brackets show 95% confidence intervals. FP, fluticasone propionate; miniRQLQ, mini-Rhinoconjunctivitis Quality of Life Questionnaire; TAA, triamcinolone acetonide.
is likely to influence adherence and, consequently, the real-world effectiveness of treatment [25]. During the initial phase III NASANIF trial, patient and physician satisfaction was included as a secondary endpoint and measured on a 5-point scale. Most patients and physicians were satisfied with TAA treatment after 4 weeks, a finding that was consistent with the improvements of QoL seen across domains; a majority of patients showed substantial improvement after 4 weeks in both treatment groups; 85.5% of patients (83.6% for TAA and 87.5% for FP). Regarding physicians, 87.9% of reported substantial improvement in both treatment groups: 84.4% with TAA and 91.4% for FP (online suppl. Table 3) [9].

We acknowledge the limitations of our study. We did not compare improvements in QoL scores for subgroups of interest defined by age, sex, or ethnicity. Our study may also be limited by its short duration in the context of a year-round disease, and more data are needed to see whether the effects of TAA on QoL are sustained over a longer period.

In conclusion, improvement in QoL should be given due consideration in the treatment of AR, due to its high prevalence. This post hoc analysis demonstrates that treatment with intranasal TAA is associated with significant improvements in PAR-related QoL over 4 weeks, as measured using the miniRQLQ.

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Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and Russian regulations. Informed consent was obtained from all participants prior to their enrollment. The study protocol was approved by the research ethics committees at each study site.

Conflict of Interest Statement

A.V.K. acted as a clinical trial investigator during the study. N.N. has received consulting fees, honoraria for lectures, and/or research funding from AstraZeneca, ALK-Abello, Boehringer Ingelheim, Glenmark, MSD, Novartis, Sanofi, and Stallergenes Greer. Y.S. declares no conflicts of interest. A.M. and I.L. are Sanofi employees.

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Author Contributions

A.V.K. supervised the design of the study and acted as a clinical investigator during the study. All authors made substantial contributions to the study conception and design and to data acquisition, analysis, and/or interpretation. All authors contributed to drafting the article or revising it critically for important intellectual content, and all have given their final approval of the version submitted for publication.

Data Availability Statement

The data that support the findings of this study are not publicly available due to Sanofi policies, but are available from Sanofi company upon reasonable request.
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