Real-life effectiveness of dupilumab in chronic rhinosinusitis with nasal polyps. Results from eight Hungarian centres with 12-month follow-up

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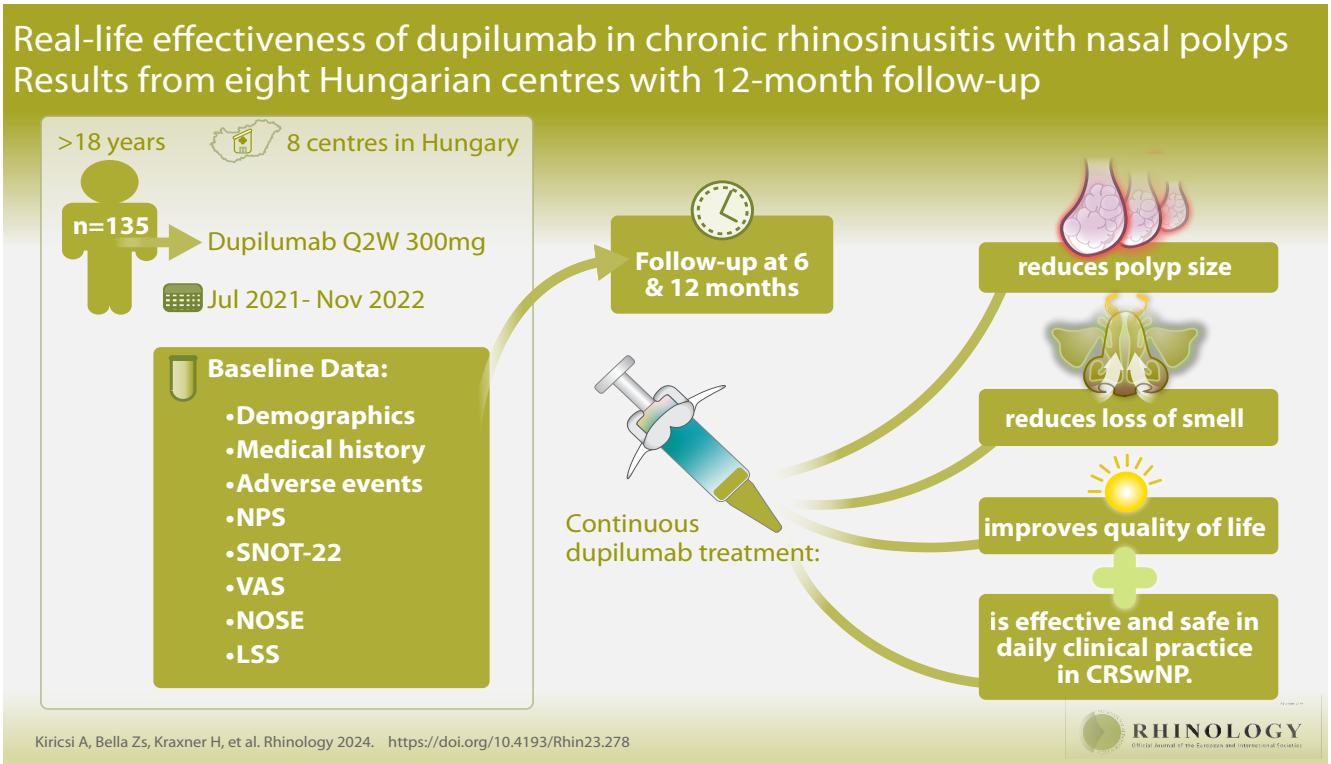

Abstract

Background: Research on the immune mechanism behind chronic rhinosinusitis (CRS) has revealed various new endotypes, leading to targeted therapies, especially for severe uncontrolled CRS. Biologics are novel therapeutic strategies providing targeted treatment for the difficult-to-treat recalcitrant CRSwNP patients. Dupilumab is a fully human-derived monoclonal antibody that binds to IL4Rα, inhibiting the signalling of both IL-4 and IL-13. In Hungary, it is approved for the treatment of uncontrolled CRSwNP according to criteria based on the EPOS2020 and the Hungarian guidelines. **Methodology**: This study aimed to collect and evaluate real-world therapeutic data of CRSwNP patients treated with dupilumab. One hundred thirty-five patients from eight different referral centres have been enrolled in this study, who received dupilumab since 2020. All subjects were adult patients (>18 years) with uncontrolled CRSwNP. Baseline data collection included demographics, medical history, previous surgeries, related comorbidities, total endoscopic nasal polyp score (NPS), SNOT22, nasal congestion parameters measured with visual analogue scale (VAS) and nasal obstruction evaluation scale (NOSE), loss of smell score (LSS) and eosinophil count. 300 mg dupilumab was administered subcutaneously every second week. Follow up visits were performed after 6 and 12 months. **Results**: After 6 and 12 months of treatment significant improvement was detected in all clinical parameters. Safety was proved, no severe side effects occurred, and no rescue treatment was necessary. **Conclusions**: Our real-life findings show that continuous dupilumab treatment is effective and safe in daily clinical practice in CRSwNP and other type 2 comorbidities such as bronchial asthma and NERD.

Key words: biologicals, chronic rhinosinusitis, nasal polyps, quality of life

Introduction

The sinonasal epithelium is considered the first-line defence mechanism in the nose, representing a physical barrier against various substances entering the body from the environment. Impairment of this sinonasal barrier not only results in increased permeability but also triggers different inflammatory responses. The persistent mucosal alterations lead to abnormal epithelial proliferation, goblet cell hyperplasia, basal membrane thickening, fibrosis, and oedema [1-3].

Chronic rhinosinusitis (CRS) is estimated to affect nearly 10 % of the adult population and is associated with significantly decreased quality of life, productivity, and significant financial impacts on disease management [4]. It is defined in adults as symptoms of sinonasal inflammation (nasal obstruction, nasal drainage, facial pain and decreased or loss of smell ability) for more than 12 weeks, with objective pathological evidence obtained with nasal endoscopy and/or radiological imaging [1]. CRS is a heterogeneous inflammatory disease, based on pathophysiological and histological findings [5]. One phenotype is chronic rhinosinusitis with nasal polyps (CRSwNP), where the immunological profile of approximately 85 % of the patients is associated with Th2 response, production of interleukin (IL) -4, IL-5, IL-13 and tissue eosinophilia [1,5,6]. This type 2 inflammatory endotype predominates in western nasal polyps and correlates with a higher recurrence rate and more severe symptoms [1,5].

IL-4 and IL-13 are critical to the induction and perpetuation of type 2 response. IL-4 is the differentiation factor polarizing naive $CD4^+$ T cells to Th2 phenotype, a growth factor for B cells, an initiator of isotype switch to IgE, and an activator and driver of chemotaxis of eosinophils. IL-13 influences isotype switch and chemotaxis of eosinophils, and is responsible for goblet cell hyperplasia, mucus secretion, airway hyperresponsiveness and smooth muscle contractility. IL-4 and IL-13 signals act through two potential heterodimer receptors with a shared receptor moiety called the IL-4α-chain [6, 7]. Intense eosinophilia and elevation in IgE are two hallmarks that implicate type 2 activation in the disease pathogenesis of CRSwNP.

The current standard of care for CRSwNP is intranasal corticosteroid spray, nasal saline irrigation, short courses of oral corticosteroids, antibiotics, and functional endoscopic sinus surgery (FESS), or if necessary, extended endoscopic sinus surgery (EESS) [1,7,8].

„Biologicals" have transformed the treatment methods for many immune-mediated disorders like cancer, autoimmune diseases, and allergic diseases. Biologicals are high molecular-weight products that may be produced by living organisms and are used to diagnose, treat or prevent diseases. Monoclonal antibodies (mABs) are one type of biologicals against specific targets and are suitable for precision medicine. They bind to specific epitopes with high affinity, ensuring safety and efficacy [9]. When conventional approaches fail, biologicals provide therapeutic options [1]. Several biologicals are approved for treating atopic diseases with type 2 immune-mediated mechanisms, such as atopic dermatitis, asthma, eosinophilic oesophagitis, food allergy and CRSwNP [1,9-11]. The efficacy of some biologicals targeting the type 2 cytokines have already been investigated in atopic diseases such as dupilumab (anti-IL4 receptor), reslizumab and mepolizumab (anti-IL5), benralizumab (anti-IL5 receptor) and omalizumab (anti-IgE) [10]. Dupilumab is a human-derived monoclonal antibody that binds to IL4Rα, inhibiting both IL-4 and IL-13 signalling. Moreover, placebo-controlled clinical studies have demonstrated the efficacy of dupilumab in atopic dermatitis, asthma and CRSwNP [11-14]. It was the first approved biological for CRSwNP in Hungary.

Bachert et al. published the results of two randomised double-blind, multicentre, placebo-controlled, parallel group phase 3 trials in which they evaluated dupilumab performance added to the standard-of-care in adults with severe CRSwNP. In the LIBERTY NP SINUS-24 study (LNPS-24), patients were treated with subcutaneous dupilumab 300mg or placebo for 24 weeks, in LIBERTY NP SINUS-52 for 52 weeks (LNPS-52) [11]. In both studies, treatment with dupilumab significantly improved sinonasal outcome test 22 (SNOT22), rhinosinusitis disease severity (VAS), nasal blockage, UPSIT smell score, nasal polyp score (NPS), Lund-Mackay Score (LMS), and asthma outcomes (FEV1) compared to control [1,11]. Hungarian centres participated in LNPS-24 studies and gained experience regarding the efficacy and safety of dupilumab. The real-life therapy with this biological was launched in 2020 with the reimbursement and approval of the Hungarian National Health Insurance.

The objective of the present analysis was to evaluate the clinical efficacy and safety of dupilumab therapy in CRSwNP patients in daily clinical practice.

Materials and methods

Study design

Patient materials from eight Hungarian centres assigned for biological treatment were selected for evaluation. The centres included Departments of Otorhinolaryngology from 4 medical universities and four teaching hospitals. The criteria for patient selection in uncontrolled CRSwNP were determined by the Hungarian Professional College [15] based on the EPOS2020 [1] and the EUFOREA [7] documents.

The indications for biological therapy of CRSwNP patients in Hungary are as follows (all the criteria are required):

1. Diagnosis of bilateral diffuse CRSwNP and the establishment of type 2 inflammation: blood eosinophil count (BEC) ≥ 250/μl or eosinophil tissue count ≥10/ hpf or total serum IgE ≥100 IU/ml or the presence of NERD+bronchial asthma;
2. At least one year of treatment with nasal isotonic saline irrigation and 200 μg intranasal mometasone furoate;
3. At least one short course of systemic corticosteroid (32-64

mg methylprednisolone for 14-21 days);
4. FESS within the last five years;
5. Nasal Polyp Score ≥ 4;
6. SNOT22 ≥ 40;
7. Severe nasal obstruction (VAS ≥ 7 and/or NOSE score ≥ 8);
8. Loss of smell score ≥ 2;
9. Lund-Mackay score ≥ 2 on sinus CT scan.

Our patients were selected according to these conditions, and 300 mg subcutaneous dupilumab was self-administered by them every 2 weeks. Data collection and analysis were performed until the 30th of November 2022. 135 subjects were treated for at least 6 months, and 41 of them administered dupilumab continuously for 12 months. At the baseline visit (V0), when patients started dupilumab treatment, we collected the following demographical data: sex, age, comorbidities, regularly taken medication, number of previous endoscopic sinus surgeries, blood eosinophil count and/or IgE concentration and Lund-Mackay CT score. A nasal endoscopy was performed, and nasal polyp score (NPS), SNOT22, NOSE, nasal obstruction VAS and Loss of Smell Score (LSS) were recorded. Patients were followed using electronic health-related quality-of-life questionnaires and nasal endoscopy at 6 (V1) and 12 months (V2) [11,16-23].
The national ethical committee approved the study (15202-5/2023 EÜIG).

Subjects

Adult patients (age >18 years) with uncontrolled CRSwNP and with an indication for biological treatment in accordance with the Hungarian guidelines initiated dupilumab treatment as primary biological. All patients underwent adequate conservative treatment for at least 1 year, including nasal isotonic saline irrigation and 200 µg daily mometasone furoate nasal spray and a minimum of one short course of systemic corticosteroid (32-64 mg methylprednisolone for 14-21 days) and at least one endonasal endoscopic surgery. Type 2 inflammation was established through eosinophil blood count (> 250 cells/µl) and/or elevated IgE concentration (> 100 IU/ml). Concomitant bronchial asthma and NERD were also accepted as markers of type 2 inflammation.
Patient Reported Outcome Measures (PROMs) are measures of health-related quality of life that are self-rated and reported directly by patients [18-20]. We used the following disease-specific questionnaires designed for use in patients with rhinosinusitis.

SNOT22

A validated Hungarian version of the rhinosinusitis-specific sinonasal outcome test 22 (SNOT22) was used to measure the patients' quality of life. It consists of 22 CRS-related questions scored between 0 and 5 points, ranging from 0 to 110. The questions are about nasal symptoms, sleeping behaviour, everyday activity, ear symptoms, dizziness and anxiety related to CRS. 40 points out of 110 was chosen as cut-off value for biologic therapy [16-18].

NOSE questionnaire

The nasal obstruction symptom evaluation scale (NOSE) was applied to measure the severity of nasal congestion. It is a brief and easy-to-complete questionnaire designed to assess nasal obstruction. 8 points out of 20 was considered as cut-off value [18].

Visual analogue scale (VAS)

The VAS technique was also utilized to assess nasal congestion/obstruction. In this self-administered test, patients mark on a 10-centimeter line (between 0 and 10) where symptom severity falls for nasal blockage or congestion (10 indicates the worst imaginable obstruction). The cut-off value for applying biologicals was 7 [16, 19, 20].

Loss of smell score (LSS)

Smell tests are not covered by the National Health Insurance in Hungary; moreover, established clinical tests for measuring olfactory function are available only in a few centres and from different companies. A simple 3-point self-assessment scale was used for the standardization of clinical data. 0 indicating normal sense of smell. 1 point for mild, 2 for moderate smell loss and 3 for severe or complete smell loss [11].

Nasal Polyp Score (NPS)

Nasal polyp score was evaluated bilaterally by an experienced specialist with standardized nasal endoscopy using a 4-point scoring system (0 = no visible polyps in the middle meatus; 1 = polyps confined to the middle meatus; 2 = larger polyps exceeding the lower border of the middle turbinate; 3 = polyps exceeding the lower border of the inferior turbinate, or causing complete obstruction of the nasal cavity or polyps between the middle turbinate and the nasal septum. Different 4-point scoring systems have been applied in the past decades, one of these was the Lund-Kennedy polyp grading system, which was adapted during an international workshop on nasal polyposis in Davos, it is still sometimes referred to as the Davos score [21,22]. Standardization was performed according to the European Academy of Allergy and Clinical Immunology recommendations [22].

Lund-Mackay Score

Lund-Mackay score ≥2 is one of the criteria for the indication of biologicals in the Hungarian guidelines and in the governmental regulations. Patients had to undergo a CT scan within a year before starting treatment. The staging of disease extent on the CT scan was evaluated according to Lund-Mackay scoring system. Each sinus group is graded between 0 and 2 (0: no abnormality;

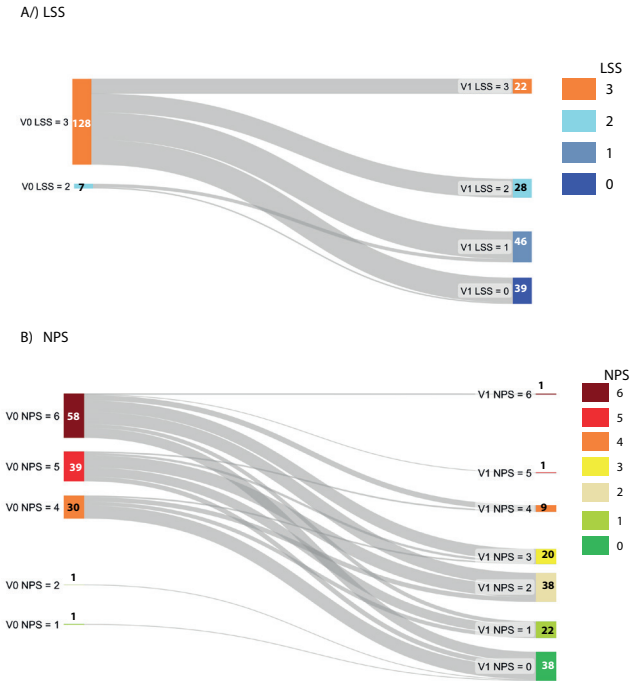

Figure 1. Sankey diagram of a; Loss of smell score (LSS) and b; NPS at baseline (Visit 0) and at six months follow-up (Visit 1).

1: partial opacification; 2: total opacification). The ostiomeatal complex is scored as "0" (not obstructed) or "2" (obstructed). A total score of 0-24 is possible, and each side can be considered separately (0-12) [23].

Statistical analysis

Statistical tests were performed using R statistical software version 4.2.3 (R Foundation, Vienna, Austria) and IBM SPSS software (IBM SPSS Statistics for Windows, Version 29.0, IBM Corp., Armonk, NY, USA). The R packages "ggpubr", "ggplot2" and "ComplexUpset" were used for visualization, while SankeyMATIC was used for Sankey plotting. Descriptive statistics were presented as the mean ± standard deviation of the mean (SD) and maximum and minimum values for continuous variables and as the count and percentage for categorical variables. Normality was tested by visual interpretations (histogram and density plot). Continuous variables were tested via the t-test, paired t-test (baseline and 6 months) or paired samples Wilcoxon test (after assumptions were checked in cases of each test). Repeated measures ANOVA was subsequently performed to compare baseline, 6- and 12-months follow-up visit data (SNOT22, VAS, NOSE, polyp score) and multiple comparisons were made between each level using the Bonferroni method. Where ANOVA was not applicable (Smell loss), the Wilcoxon test and Bonferroni multiple testing correction were used. All reported p-values were based on two-sided tests and were considered significant when the p-values were below 0.05.

Table 1. Demographics, baseline data (Visit 0).

		n=135	100%
		n	%
Gender	Male	76	56.3
	Female	57	42.2
	No data	2	1.5
Age	mean ± SD	49.9 ± 13.2	
	min-max	19 - 80	
	No data	1	0.7
Smoking habit	Yes	9	6.7
	No	123	91.1
	No data	3	2.2
Type 2 comorbidities	Bronchial asthma	109	80.7
	Allergic Rhinitis	95	70.4
	NERD	63	46.7
Endoscopic sinonasal surgeries	mean ± SD	5.1 ± 3.8	
	min-max	1 – 20	
	No data	4	2.9
Time since last endoscopic surgery at baseline (months)	mean ± SD	42.6 ± 32.3	
	min-max	2 – 168	
	No data	2	1.5
Blood eosinophils (cells/mm^3)	mean ± SD	588.2 ± 495.8	
	<500	67	49.9
	500-1500	60	44.4
	>1500	7	5.2
	No data	1	0.7
Previous biological therapy	No	128	94.8
	Benralizumab	5	3.5
	Mepolizumab	1	0.7
	Omalizumab	1	0.7
Lund-Mackay CT-score	mean ± SD	19.1 ± 4.0	
	min-max	6 – 24	
	No data	23	17.0

Results

Demographics

Data from 135 patients were evaluated. The number of previous endoscopic sinonasal surgeries was 5.1 ± 3.8. The mean time between the last endoscopic surgery and the initiation of dupilumab treatment was 42,6 ± 32,3 months. Lund-Mackay CT score at baseline was 19.1 ± 4.0. The mean pre-treatment values (V0) were the following: NPS 5.1 ± 0.9; SNOT22 68.4 ± 16; VAS 8.1 ± 1.7; NOSE 16.2 ± 3.3; LSS 2.9 ± 0.2, which indicates severe CRSwNP. The blood eosinophil count at baseline was 588.2 ± 495.8 mm^3. The distribution of the accompanying type 2 inflammatory comorbidities was the following: bronchial asthma was

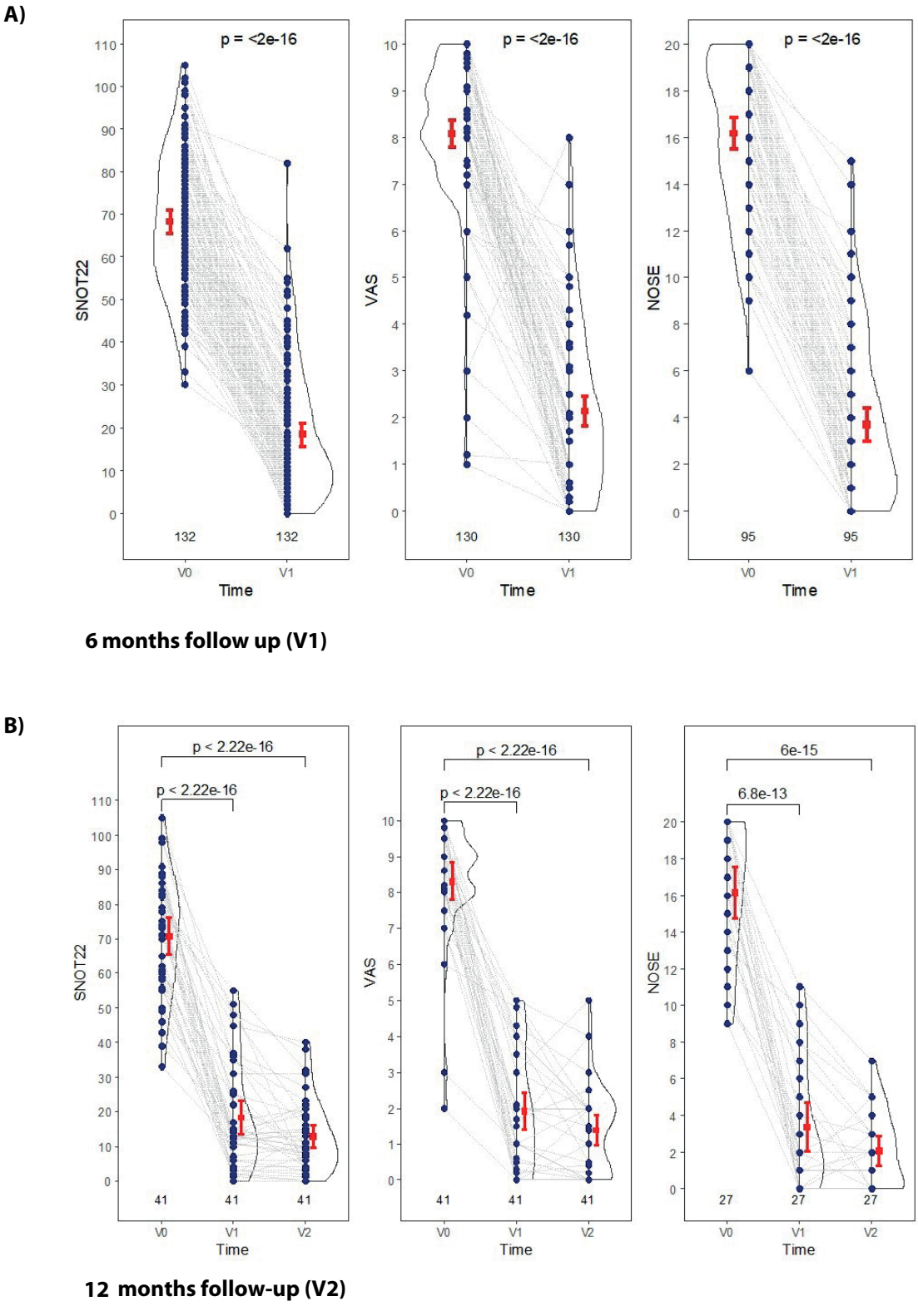

Figure 2. A) 6 months follow-up: Violin plot of SNOT22, VAS and NOSE at six months follow-up SNOT22, VAS and NOSE violin plot. The dark blue circles show the individual patient data, the grey dotted lines show the pairs (V0-V1), the red squares represent the mean, and the red whiskers are the 95% confidence intervals. V0: Baseline visit; V1: 6 months follow-up visit; (statistical significance was considered achieved at a p-value less than 0.05) B) 12 months follow-up: Violin plot of SNOT22, VAS and NOSE at twelve months follow-up: SNOT22, VAS and NOSE violin plot. The dark blue circles show the individual patient data, the grey dotted lines show the pairs (V0-V1, V1-V2), the red squares represent the mean, and the red whiskers are the 95% confidence intervals. V0: Baseline visit; V1: 6 months follow-up visit; V2: 12 months follow-up visit (statistical significance was considered achieved at a p-value less than 0.05).

Table 2. Results at the 6-months follow-up visit (V1).

	Visit	N	ND	Mean	SD	min – max	p	test; paired t-test
SNOT 22	V0	132	3	68.4	16.0	30 – 105	<0.001	paired t-test
	V1	132	3	18.4	15.6	0 – 82		
VAS	V0	130	5	8.1	1.7	1 – 10	<0.001	paired t-test
	V1	130	5	2.1	1.8	0 – 8		
NOSE	V0	95	40	16.2	3.3	6 – 20	<0.001	paired t-test
	V1	95	40	3.7	3.5	0 – 15		
LSS	V0	135	0	2.9	0.2	2 -3	<0.001	paired samples Wilcoxon test
	V1	135	0	1.2	1.0	0 – 3		
NPS	V0	127	8	5.1	0.9	1 – 6	<0.001	paired t-test
	V1	127	8	1.6	1.3	0 – 6		

N=135 patients (ND =Missing data)

Table 3. Results at twelve months follow up (V2), N=41 patients.

	Visit	N	ND	Mean	SD	min	max	p	test; paired t-test
SNOT 22	V0	41	0	70.78	16.87	33	105	V0 vs. V1 p<0.0001 V0 vs V2 p<0.0001	ANOVA with Repeated Measures Bonferroni multiple testing correction
	V1	41	0	18.32	15.57	0	55		
	V2	41	0	12.78	10.31	0	40		
VAS	V0	41	0	8.3	1.63	2	10	V0 vs. V1 p<0.0001 V0 vs V2 p<0.0001	ANOVA with Repeated Measures Bonferroni multiple testing correction
	V1	41	0	1.91	1.65	0	5		
	V2	41	0	1.39	1.26	0	5		
NOSE	V0	27	14	16.15	3.55	9	20	V0 vs. V1 p<0.0001 V0 vs V2 p<0.0001	ANOVA with Repeated Measures Bonferroni multiple testing correction
	V1	35	6	3.54	3.38	0	11		
	V2	37	4	1.95	1.96	0	7		
LSS	V0	41	0	2.98	0.16	2	3	V0 vs. V1 p<0.001 V0 vs V2 p<0.001	Non parametric Wilcoxon Signed Ranks Test Bonferroni multiple testing correction
	V1	41	0	1.34	1.13	0	3		
	V2	41	0	1.1	1.16	0	3		
NPS	V0	38	3	5.29	0.77	4	6	V0 vs. V1 p<0.0001 V0 vs V2 p<0.0001	ANOVA with Repeated Measures Bonferroni multiple testing correction
	V1	41	0	1.78	1.49	0	6		
	V2	39	2	1.31	1.51	0	6		

present in 80,7 % (n=109), allergic rhinitis in 70.4 % (n=95) and NERD in 46.7 % (n=63) of patients. All of the asthmatic patients were controlled with continuous inhalers. 6,7% of the subjects were smokers. Seven subjects were treated with other biologicals previously, 5 with benralizumab, 1 with omalizumab and 1 with mepolizumab. Baseline data are presented in Table 1.

Six months follow up (V1)

At six months follow-up visit significant improvement was found in all of the clinical parameters from baseline: NPS 1,6±1,3 (p<0,001), SNOT22 18,4±15,6 (p<0,001), VAS 2,1±1,8 (p<0,001), NOSE 3,7±3,5 (p<0,001) and LSS 1,2±1,0 (p<0,001) detailed in Table 2, Figure 1 and Figure 2/A.

12-months follow up (V2)

Of the 135 patients, 41 [24 male, 17 female, aged 50,3±14,0 (19-80)] were on dupilumab treatment for more than a year, 36 (87,8 %) with concomitant asthma, 25 (60,9 %) with allergic rhinitis and 23 (56 %) with NERD. All the parameters improved significantly at Visit 2: NPS from 5,29 ±0,77 to 1,31±1,51 (p<0,0001), SNOT22 from 70,78±16,87 to 12,78±10,31 (p<0,0001), VAS from 8,3±1,63 to 1,39±1,26 (p<0,0001), NOSE from 16,15±3,55 to 1,95±1,96 (p<0,0001) and LSS from 2,98±0,16 to 1,1±1,16 (p<0,001) reported in Table 3, Figures 2/B and Figure 3.

NERD and non-NERD patients

There was no statistical difference between the NERD (n=61) and non-NERD groups of patients at baseline. At six months

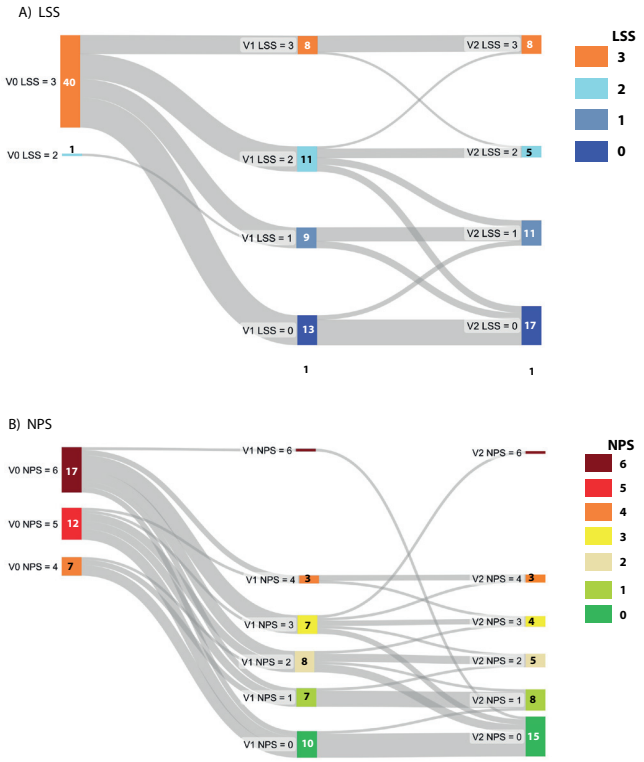

Figure 3. Sankey diagram of A) LSS and B) NPS at 12 months follow-up visit (V0 baseline visit, V1 6 months and V2 12 months follow-up visit).

follow-up regarding NPS, SNOT22, VAS and NOSE, no significant difference was observed.

Injection administration

132 patients (97,78 %) administered the dupilumab injection every second week during the 12-month follow-up period. In three cases we observed blood eosinophil count >1500 cell/µl at the control blood test between 16-18 weeks. The interdose intervals between the dupilumab injections were prolonged to three weeks, and BEC values returned to baseline in all cases, without oral corticosteroid treatment.

Safety

Safety was proved, no treatment-emergent adverse event, no eosinophilia-related clinical symptom, no eosinophilic granulomatosis with polyangiitis, and no treatment discontinuation by the closure of these data collection on the 30th of November 2022 were observed. In some of our patients, minor side effects were observed: injection site reaction, headache or increased watery nasal discharge, which did not require therapeutic intervention or delaying of drug administration.

In 3 cases, blood hypereosinophilia (>1500 cell/µl) was found without any clinical symptoms. With regular control and tapered injection administration every three weeks, the blood eosinophil count decreased to baseline.

Discussion

Among biological treatment options, dupilumab was the first approved therapy in Hungary. Based on the EPOS2020, The Hungarian Professional College of Oto-Rhino-Laryngology, Head & Neck Surgery assigned centres and formulated the national recommendation (guideline) regarding the indications and algorithm of biological therapy, finalized in 2022 [15, 24]. The first cases treated with dupilumab were launched in 2020. The National Health Insurance Company provides individual and complete treatment financing in selected cases if the necessary conditions and requirements are met. Specialists in these centres are trained for patient selection, treatment and follow-up examinations based on the same principles. We have prepared an educational booklet for patients and their families presenting the etiology, symptoms, and treatment options of CRSwNP. The first shot of the biologicals is administered in the ENT centres, under medical supervision. The patients are thoroughly educated how to manage the administration. Follow-up visits with nasal endoscopy were scheduled every 6 months, SNOT22, VAS and NOSE questionnaires every 3 months. Nasal congestion and runny nose are reduced by orders of magnitude, in many cases dramatically, with daytime activity and nighttime rest. The onset of therapeutic effect usually can be observed already within 1 month. Total nasal symptom scores improved very early and remained stable later. The results of the nasal symptoms, the endoscopic score, and the quality of life show significant and lasting reductions. We used the NOSE questionnaire to monitor nasal congestion, which is the most stubborn symptom of CRSwNP besides smell disorder. Data of the olfactory dysfunction exhibited a unique pattern. It proved to be a troublesome complaint in everyday life. The dynamics of the alterations displayed marked differences among patients and showed distinct patterns compared to the other symptoms. Two-thirds of our patients experienced an improvement in their smelling ability within a few weeks. In some cases, improvement was found after more than a year, but there were also patients with stable anosmia. If the therapy had to be interrupted, the symptoms worsened with similar dynamics. These changes coincide with those experienced in multicentre phase 3 randomized placebo-controlled clinical trials SINUS-24 and SINUS-52 [11].

Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NERD) is a chronic eosinophilic, inflammatory disorder of the respiratory tract occurring in patients with asthma and/or CRSwNP, where symptoms are exacerbated by NSAIDs, including aspirin [1,8]. They present a severe and recurrent clinical form with a pronounced disease burden [25,26]. In patients with CRSwNP, up to 65 % and 26 % have comorbid asthma and NERD, respectively [27-29]. Among patients with CRSwNP, asthma and NERD higher recurrence rate of nasal polyps, revision surgeries, and dependence of systemic corticosteroid and poor asthma control are everyday observations [27,28,30]. Approximately

15% of CRSwNP cases are challenging to treat [25, 31]. Patients who have persistently uncontrolled symptoms of CRS despite appropriate treatment (adequate surgery, intranasal corticosteroid treatment and up to two short courses of antibiotics or systemic corticosteroids) are defined as difficult-to-treat cases, for whom more effective therapeutic option was needed [1,8,32]. Nasal symptoms gradually return and increase severity between 6 and 24 months after surgery [30]. Patients with CRSwNP often require multiple revision surgeries [32,33].

In the last years, a few studies were published showing real-world data with different subject sizes ranging from 40 to 70 patients. Haxel et al. treated 70 CRSwNP patients with dupilumab or omalizumab [34]. They found that NPS decreased significantly after 3 months, quality of life and olfaction increased. More than 90% of subjects showed moderate to excellent response, and no difference between the two biologicals was observed. One-third of patients remained anosmic after 6 months of treatment. These data are in accordance with our findings. Furthermore, although Haxel et al. identified that comorbid asthma significantly affects the response, our real-world data suggest that neither asthma nor NERD significantly impacts treatment outcome.

The analysis of SINUS-24 and SINUS-52 trials demonstrated that patients with CRSwNP and NERD had more severe disease states at baseline compared to patients without NERD. A higher percentage of patients with NERD were anosmic, had comorbid asthma and had reduced lung function [35]. This correlates with other studies, reporting more severe disease in the difficult-to-treat subgroup [35,36]. The baseline data of our 63 NERD patients weren't significantly worse than those without NERD. We haven't observed any difference in treatment outcome either in this group.

Jansen et al. investigated 40 patients treated with dupilumab retrospectively, collecting data of SNOT22, NPS, Sniffin' Sticks 12 identification test, FEV1, as well as total serum IgE, eosinophil cationic protein and blood eosinophils at 1, 4, 7, 10 and 13 months [37]. They saw a clear improvement in all symptoms. The objectives of reduced nasal polyps, subjective improvement in nasal congestion, and health-related quality of life were proven. They observed a linear dependence over time and recommended the regular usage of this test during dupilumab treatment. They have seen FEV1 improvement during the study, pointing to the simultaneous improvement of sinonasal symptoms and lung function. Our real-world data showed improvement in lung functions, and 69 % of the patients reduced or stopped taking their regular asthma medication after 6 months of dupilumab therapy. Jansen et al. collected blood eosinophils, IgE and ECP data, and they saw a remarkable increase in absolute eosinophils in whole blood, with no linear trend. The increase of blood eosinophils was already proved by Bachert et al. in LIBERTY NP SINUS-24 and LNPS-52, assuming this value to be transient and being due to a decrease in eotaxin-3, preventing the migration of eosinophils from the serum to the tissues [11]. Owing to the lack of response of ECP in blood during dupilumab treatment, Jansen et al. didn't recommend establishing this measurement as an outcome marker [37]. Mullol et al. observed an increase of 40 % from baseline in the level of eosinophils in patients with NERD at week 24, but it was statistically not different from the placebo group and resolved to baseline at week 52 [35]. Böscke et al. reported a retrospective analysis obtained from 41 patients treated with dupilumab with a follow-up of 12 months. They found rapid and sustained improvements in endoscopy scores, patient-reported outcome measures and olfaction. A higher proportion of patients had elevated blood eosinophil count at month 12 compared to baseline, thus recommended the careful monitoring of this marker [38].

Bachert et al. observed eosinophilia during dupilumab treatment and suggested that is probably the result of the suppression of eotaxin-3 and vascular cell adhesion molecule 1 (VCAM-1), and the inhibition of trafficking of eosinophils from blood to the tissues, but not of the production in the bone marrow, thus it is most probably transient [11, 35]. We observed hypereosinophilia (>1500 cell/ µl) in our patients too, between weeks 16-18, without the need for rescue treatment, resolving spontaneously by the 6-month follow-up. This finding is consistent with the data published by Bachert, Mullol and Lee et al. [11,35,39].

In the pivotal studies LNPS-24 and LNPS-52, as well as in other studies primarily mild adverse events were found [11,37,38]. In some of our patients, minor side effects were observed: injection site reaction, headache or increased watery nasal discharge, which did not require therapeutic intervention or delaying of drug administration. No salvage surgery or discontinuation of dupilumab therapy was necessary.

In 3 cases out of 135, blood hypereosinophilia (>1500 cell/ µl) was found without any clinical symptoms. Dupilumab was administered by prolonging the interdose interval to three weeks, and blood eosinophil count was controlled regularly. In one case, BEC returned to baseline within 6 weeks, in two cases, it decreased below 1000 cell/µl within 8 weeks and returned to baseline value in three months. However, the percentage of hypereosinophilia is low, and the evaluation of these data needs precaution, because a regular blood test was not mandatory during the first six months of the treatment period according to the Hungarian guidelines. This might explain the low number of hypereosinophilia in our patient material, but none of the 135 patients presented clinical symptoms suspecting an unidentified severe hypereosinophilic adverse event. Van der Lans et al. evaluated long term results of therapeutic efficacy while tapering dupilumab, and suggested that dosing adjustments can be applied in case of treatment-emergent adverse events as well. They recommend standardised clinical follow-up with eosino-phil level determination, and responsive interim dosing adjustments and/or short oral corticosteroid courses to overco-

me (transient) hypereosinophilia [39]. In our cases administering dupilumab every third week without corticosteroid treatment abated blood hypereosinophilia.

Data from the literature show that, however, eosinophilia is a common adverse event in patients treated with dupilumab; most often, it is transient without any clinical impact and recovers after about six months [40]. Wechsler et al. found in their post hoc analysis of 11 clinical trials with dupilumab that the rates of eosinophilia treatment-emergent adverse event were 0% to 13,6 %. Clinical symptoms associated with increased eosinophils were rare (7 out of 4666 patients). However, it is essential for physicians to base judgement on individual patient history and baseline blood eosinophil count and to be alert to hypereosinophilic symptoms [41]. De Corso et al. presented their real-life data of 648 patients. They observed severe adverse events in the first 12 months of treatment: 4 cases of severe arthralgia (in one case after 12 months) and 2 cases of persistent severe hypereosinophilia (one with asthma exacerbation and eosinophilic pneumonia) [42]. They analysed in another study the temporal trends of blood eosinophilia in patients with severe uncontrolled CRSwNP treated with dupilumab in real-life settings. They found that a significant increase in the mean absolute eosino -phil count peaked at 3 months, still significant at 6 and 9 months, but decreased at 12 months to a value comparable to those at baseline. They evaluated safety in relation to blood eosinophilia values and didn't find any increased risk of developing related adverse events. They recommend close monitoring monthly in those presenting over 1500 cells/mm3 and tapered administration rather than premature discontinuation of the drug [43]. Kemp et al. published their data regarding hypereosinophilia during dupilumab treatment. Their results showed a peak in blood eosinophil count at week 12; transient hypereosinophilia occurred in 28,9 % of patients. Hypereosinophilic syndrome or manifesting organ damage did not happen. Switching to a different biological on the count of persisting hypereosinophilia was rarely needed, mainly based on authors' prudence, not based on symptoms of eosinophil-induced organ damage [44]. All these authors recommend close monitoring and being aware of symptoms possibly linked to increased eosinophil level.

The strength of this paper is in its real-life context from a diverse cohort of patients with standardised indication criteria, treatment regimens and follow-up schedules in 8 centres in Hungary. Our results are consistent with the experiences of other studies with dupilumab in CRSwNP patients. Due to high treatment costs, biologics are not available or reimbursed in many countries. In Hungary, there is growing evidence and real-life experience with many more than 300 patients.

The weakness of the paper is that only one type of biologics was available for the study until data collection. However, it would be of outstanding importance to compare different options in a standardised patient pool to favour therapeutic choices in the future. Hungarian guidelines differ in some points from EPOS2020 and EUFOREA: nasal polyp scoring system and loss of smell score, which makes direct comparison of our data with those from other countries difficult. However, standardisation was performed according to the recommendations of the international guidelines.

Conclusion

12 months of treatment with 300 mg dupilumab given every second week demonstrated significant improvement in all the clinical parameters of our difficult-to-treat CRSwNP patients in a real-life eight-centre study. All the significant results could already be detected at 6 months. Olfactory functions also improved significantly, though with different dynamics and special time courses compared to other measured parameters. No outcome differences were found between NERD and non-NERD groups. Safety was proved, no severe side effects occurred, and no rescue treatment was necessary. Our real-life findings show that continuous therapy with dupilumab tends to be effective and safe in daily clinical practice in CRSwNP and other type 2 comorbidities such as bronchial asthma and NERD.

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Authors' contributions

Substantial contribution to the conception of the work and data collection: all authors; Drafting the work AK, ZSB, AH; statistical analysis MM; Critical revision for content and interpretation of data AH, LL. All authors approved the final version of the manuscript and agreed to be accountable for the work.

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