ORIGINAL ARTICLE

Evaluation of clinical characteristics, ocular surface disease index and quality of life in glaucoma patients with ocular allergy to brinzolamide/brimonidine fixed combination

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ABSTRACT

Purpose: To describe clinical characteristics and quality of life (QoL) of glaucoma patients with ocular allergy to Brinzolamide 1% Brimonidine 0.2% fixed combination (BBFC).

Materials and Methods: 23 eyes of 16 patients with ocular allergy to BBFC were enrolled to this prospective study. Demographic and clinical characteristics were evaluated. Schirmer I test,Oxford corneal stain scale, tear break-up time, and Ocular Surface Disease Index (OSDI) score were performed to evaluate ocular surface disease. QoL was assessed with the Turkish version of the National Eye Institute Visual-Function Questionnaire (NEIVFQ-25 TR).

Results: Duration of BBFC treatment was 6.1±3.3 months and duration of allergy symptoms was 3.6±2.4 months. Mean OSDI score was 34.48±26 indicating severe dry eye disease. There was a positive correlation between OSDI scores and duration of glaucoma (p=0.0001, R:0.89, CI:0.3-0.6) and duration of BBFC treatment. (p=0.02, R:0.58, CI:-8.2- -0.7) There was no correlation between mean duration of allergy symptoms and OSDI scores. (P=0.14 R:0.38, CI:-9.1- -1.5) The development of BBFC ocular allergy caused a decrease in the results of all NEI VFQ-25/TR subscales except driving and color vision. Negative correlation was found between OSDI and subscales of general vision (p=0.04 R=-0.509, CI=-0.9 - -0.35) and vision specific social functioning (p=0.007 R=-0.64, CI=-1.5- -0.3), driving (p=0.01 R=-0.82, CI=-2.7- -0.49) and color vision. (p=0.02 R=-0.55, CI=-1.9- -0.08) There was a positive correlation between OSDI and subscales of ocular pain. (p=0.01 R=0.61, CI=-0.9- -0.19).

Conclusion: Development of ocular allergy to BBFC has a quantitatively negative effect on the ocular surface and QoL.

Keywords: Brinzolamide brimonidine fixed combination, Glaucoma, ocular allergy, Ocular surface disease index, Quality of life.

INTRODUCTION

Glaucoma remains a leading cause of irreversible vision loss globally and is associated with a reduced quality of life (QoL).[1,2] The condition causes irreversible damage to the optic disc and visual field (VF), ultimately leading to blindness.[3,4] It is widely recognized that the sole modifiable risk factor is intraocular pressure (IOP).[5] Numerous IOP-lowering topical agents with diverse mechanisms, such as prostaglandin analogues (PGAs), β-blockers, carbonic anhydrase inhibitors (CAIs), α2-adrenergic agonists, and parasympathomimetic agents, are available.[6] However, these IOP-lowering topical agents can induce adverse effects, stemming either from the primary agent or the preservatives utilized.[7] The strategy of simplifying medical treatment for glaucoma patients to a single agent devoid of preservatives helps mitigate adverse effects and enhance patient adherence. Nonetheless, for some patients, controlling elevated IOP necessitates fixed combination therapies.

In 2012, the Brinzolamide 1% and Brimonidine 0.2% fixed combination (BBFC) was developed and subsequently gained widespread utilization in the medical management of glaucoma. A prospective study has indicated that transitioning to BBFC results in a notable reduction in

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IOP. Additionally, this combination can be employed either independently or in conjunction with β-blockers, PGAs, CAIs, or other combination drugs.[8] Although fixed combination therapies curtail exposure to ocular surface issues related to preservatives, it is regrettable that drug-induced allergies may still manifest with these therapies.[9]

Topical antiglaucoma drugs have the potential to cause varying degrees of ocular surface disease (OSD).[9] The Ocular Surface Disease Index (OSDI) is a commonly used questionnaire designed to rapidly assess the severity of OSD symptoms consistent with chronic dry eye and its impact on vision-related functioning. The presence of concomitant OSD, frequency of drug use, and surgical concerns all contribute to a negative impact on the QoL for glaucoma patients. Another frequently utilized questionnaire is the American National Eye Institute 25-Item Visual Functions Questionnaire (NEI VFQ-25), which measures the QoL across a wide range of eye diseases, including glaucoma.[10] The Turkish version of the NEI VFQ-25 (NEI VFQ-25/TR) has been published and proven useful in evaluating the impact of visual impairment on individuals' QoL.[11]

It is of utmost importance for clinicians to be aware of the effects of antiglaucoma drugs and drug-related ocular surface diseases and allergies on the QoL. This understanding is crucial for effectively managing this chronic and progressive disease. The current study aims to evaluate the clinical characteristics, OSD, and QoL in patients with BBFC-induced ocular allergy.

MATERIALS AND METHODS

This prospective study was conducted in the glaucoma department of a tertiary care eye center from May 2020 to May 2022. Ethical clearance was obtained from the institutional review board prior to commencing the study, and the principles of the Declaration of Helsinki were adhered to.

Primary inclusion criteria were as follows: individuals aged over 18 years, diagnosed with any types of mild (VF Mean Deviation (MD) >-6 dB) and moderate (-6dB>MD>-12dB) glaucoma according to Hodapp-Parrish-Anderson criteria,[12] and experiencing BBFC-induced ocular allergy. BBFC-induced ocular allergy was defined by the presence of conjunctival follicular reactions, hyperemia, blepharoconjunctivitis, and eyelid changes (ectropion, entropion) that initiated after drug initiation and resolved upon discontinuation of the drug. The topical medication containing brimonidine 0.2% and brinzolamide 1% (Simbrinza; Alcon Inc, Geneva, Switzerland) was included. Primary exclusion criteria encompassed allergy to another glaucoma drug, seasonal allergic conjunctivitis, and persistent symptoms despite discontinuation of the drug. We also excluded individuals with a history of previous ocular surgery, refractive laser procedures or contact lens use, severe glaucoma patients (MD<-12dB), and those with systemic allergic problems and diseases such as asthma or rheumatologic diseases such as Sjogren's syndrome. Eligible patients with complete records who met all inclusion and exclusion criteria were enrolled in the study.

Demographic and clinical characteristics, including age, gender, type of glaucoma, mean duration of glaucoma, mean duration of BBFC treatment, duration of allergy symptoms, glaucoma medication history, and glaucoma stage were documented. Glaucoma staging was carried out using the Hodapp-Parrish-Anderson criteria.[12] Comprehensive ophthalmologic examinations, including anterior-posterior segment examination, IOP measurement, VF testing, Schirmer I test, Oxford corneal stain scale assessment, tear break-up time (TBUT) measurement, and OSDI scoring (OSDIs) were conducted. OSDI is a 12-item questionnaire, and the total OSDIs is calculated according to the questionnaire's algorithm. OSDIs range from 0 to 100, with higher scores indicating greater disability.[13] OSDIs indicate mild dry eye (13-22), moderate dry eye (23-32), and severe dry eye (33-100). Additionally, after obtaining written informed consent from all patients, they were evaluated using the NEI VFQ-25/TR. NEI VFQ-25/TR comprises 25 questions and 13 subscales (general health, general vision, ocular pain, vision expectations, near activities, distance activities, vision-specific social functioning, vision-specific mental health, vision-specific role difficulties, vision-specific dependency, driving, peripheral vision, and color vision). Subscale scores range from 0 to 100, with higher scores indicating better visual function.

In all patients, BBFC was discontinued, and oral carbonic anhydrase inhibitor (CAI) therapy, a short course of topical corticosteroid drops, and frequent lubricant eye drops were initiated. Ophthalmologic evaluations were conducted on a weekly basis. Once inflammation was controlled, another glaucoma drop was initiated for glaucoma/IOP management. Figure 1 displays photos of a patient with BBFC-induced ocular allergy.

Statistical Analysis

All statistical analyses were performed using SPSS version 20. Data were presented as mean ± standard deviation.

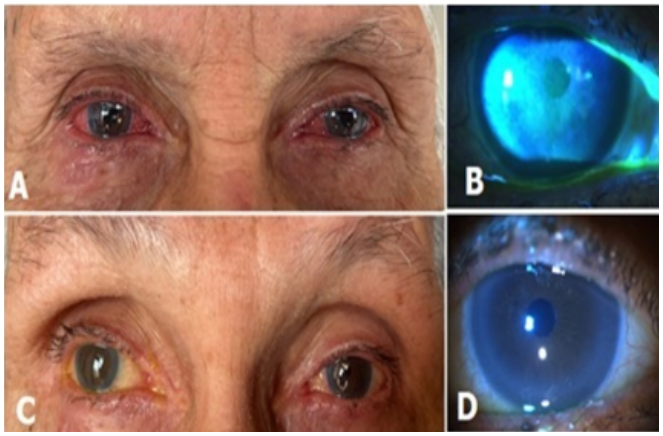

Figure 1: *Patient with Brinzolamide Brimonidine Fixed Combination-Induced Allergy: A: The patient exhibited conjunctival hyperemia, chemosis, swelling of the eyelid margin, eyelid erythema, and a deepened upper eyelid sulcus due to periorbital fat atrophy. B: Corneal punctate epitheliopathy was observed. C: One week following treatment, there was a noticeable reduction in conjunctival hyperemia, eyelid margin swelling, and eyelid erythema. D: The corneal epitheliopathy had resolved.*

Linear regression analysis was conducted to assess associations among NEI VFQ-25/TR, OSDI, and other parameters. The correlation coefficient was categorized as weak (0.2-0.4), moderate (0.4-0.6), high (0.6-0.8), and very high (0.8-1.0). A p-value <0.05 was considered statistically significant.

RESULTS

This prospective study encompassed 23 eyes of 16 patients (9 males, 7 females) with a mean age of 61.7 ± 6.8 years. Among these patients, 5 (6 eyes) had primary open-angle glaucoma, 9 (13 eyes) had pseudoexfoliation glaucoma, and 2 (4 eyes) had primary angle-closure glaucoma. Demographic-clinical features and ocular surface characteristics of the patients are outlined in Table 1. The outcomes of NEI VFQ-25 TR are presented in Table 2. The mean IOP was 15.2 ± 3.5 mmHg before ocular allergy treatment and 16.2 ± 5.1 mmHg after ocular allergy treatment.

Multiple regression analysis revealed a negative correlation between age and the subscales of general health (p=0.028, R=-0.566, CI=0.16-0.237), general vision (p=0.04, R=-0.528, CI=0.012-0.663), and driving (p=0.014, R=-0.81, CI=-0.8- -0.14). Negative correlations were also observed between OSDI and the subscales of general vision (p=0.04, R=-0.509, CI=-0.9- -0.35), vision-specific social functioning (p=0.007, R=-0.64, CI=-1.5- -0.3), driving

Table 1: *Demographic-clinical characteristics and ocular surface parameters of the patients.*

Variables	
Age (year, mean ± SD)	61.7 ± 6.8
Gender (F/M)	7/9
Type of glaucoma (n) POAG PXF PACG	 6 eyes 13 eyes 4 eyes
Duration of glaucoma (m) (mean ± SD)	33.3 ± 31
Duration of BBFC treatment (m) (mean ± SD)	6.1 ± 3.3
Duration of allergy symptoms (m) (mean ± SD)	3.6 ± 2.4
Glaucoma medication history	8 eyes (β-B) 6 eyes (CAI) 4 eyes (PGA)
Stage of glaucoma (n,mean Md) Mild Moderate Severe	 8 eyes (-4.41) 15 eyes (-8.47) -
Schirmer I test (mm) (mean ± SD)	9.5 ± 5.1
Oxford corneal stain scale(mean ± SD)	2 ± 1.2
Tear break-up time(mean ± SD)	6.5 ± 2.7
OSDI (mean ± SD)	34.48 ± 26

F: female, M:male, m:month, POAG: primary open-angle glaucoma, PXF: pseudoexfoliation glaucoma, PACG: primary angle closure glaucoma, OSDI: Ocular surface disease ındex, SD: standard deviation, Md: mean deviation, n: number, β-B: β- Blocker, CAI: carbonic anhydrase inhibitors (CAIs), PGA: prostaglandin analogue

Table 2: *The results of NEI VFQ-25/TR*

Scales	
General Health (mean ± SD)	50 ± 30
General Vision (mean ± SD)	61.2 ± 11
Ocular Pain (mean ± SD)	62.5 ± 22
Near Activities (mean ± SD)	72.3 ± 22
Distance Activities (mean ± SD)	81 ± 25
Vision specific (mean ± SD)	
Social Functioning	88.2 ± 18
Mental Health	60.9 ± 22.8
Role difficulties	69.5 ± 28.1
Dependency	72.8 ± 30.5
Driving (mean ± SD)	90.6 ± 12.9 (n:8)
Color Vision (mean ± SD)	93.7 ± 25
Peripheral Vision (mean ± SD)	71.8 ± 25.6

(p=0.01, R=-0.82, CI=-2.7- -0.49), and color vision (p=0.02, R=-0.55, CI=-1.9- -0.08). Additionally, a positive correlation was found between OSDI and the subscale of ocular pain (p=0.01, R=0.61, CI=-0.9- -0.19). However, no correlation was identified between the duration of BBFC treatment and any subscales of NEI VFQ-25 TR (Table 3). The duration of glaucoma and BBFC treatment exhibited correlations with higher OSDIs (p=0.0001, R=0.89, CI=0.3-0.6; p=0.02, R=0.58, CI=-8.2- -0.7, respectively). Notably, no significant correlation was observed between OSDI and the duration of allergy symptoms (p=0.14) (Table 4).

Table 4: *Regression analysis for associations between demographic characteristics and OSDI.*

Variables	OSDI
Duration of glaucoma	**P=0.0001** R:.89, CI:0.3-0.6
Duration of BBFC treatment	**p=0.02** R: .58, CI: -8.2- -0.7
Duration of allergy symptoms	P=0.14 R: .38, CI: -9.1- -1.5

OSDI: Ocular surface disease ındex, CI: confidence interval, BBFC: Brinzolamide/Brimonidine Fixed Combination
Bold values denote statistical significance at the p < 0.05 level

DISCUSSION

Topical IOP-lowering medications are commonly employed as the primary treatment for glaucoma patients. These medications not only contain the active ingredients for IOP reduction but also incorporate preservatives, drug vehicles, and viscosity agents, all of which can potentially have negative effects on the ocular surface and trigger allergic reactions.[7] Allergic reactions and OSD in glaucoma patients can lead to reduced medication compliance and diminished QoL.[14,15] To our knowledge, there has been a lack of detailed data on OSD and QoL in patients experiencing topical fixed combination antiglaucomatous drop induced ocular allergy. Our findings indicate that the development of allergy increases the OSDIs and reduces QoL in these patients.

The utilization of combination drugs in glaucoma treatment can mitigate the cumulative irritating effects caused by

Table 3: *Regression analysis for associations between NEI VFQ-25/TR and other parameters.*

Scales	**Age**	**Duration of BBFC treatment**	**OSDI**
General Health	**p=0.028** R=-.566, CI=0.16-0.237	p=0.64 R=.11, CI=-0.04-0.06	p=0.86 R=-.04, CI=-0.54-0.46
General Vision	**p=0.04** R=-.528, CI=0.012-0.663	p=0.14 R=.36, CI=-0.04-0.25	**p=0.04** R=-.509,CI=-0.9. - -0.35
Ocular Pain	p=0.67 R=.119, CI=-0.20-0.13	p=0.24 R=.29, CI=-0.03- 0.1	**p=0.01** R=.61, CI=-0.9- -0.19
Near Activities	p=0.38 R=.243, CI=-0.24-0.1	p=0.27 R=.28, CI=-0.03- 0.11	p=0.06 R=-.47, CI=-1.1- 0.03
Distance Activities	p=0.66 R=.117, CI=-0.12-0.18	p=0.3 R=.26, CI=-0.03-0.1	p=0.18 R=-.34, CI=-0.92-0.19
Vision specific			
Social Functioning	p=0.39 R=.23, CI=-0.13-0.3	p=0.1 R=.4, CI=-0.01-0.17	**p=0.007** R=-.64, CI=-1.5- -0.3
Mental Health	p=0.18 R=.35, CI=-0.05-0.26	p=0.8 R=.06, CI=-0.07- 0.08	p=0.14 R=-.37, CI=-1.05-0.17
Role difficulties	p=0.42 R=.22, CI=-0.08-0.19	p=0.75 R=.08, CI= -0.05- 0.07	p=0.13 R=-.38, CI=-0.8-0.13
Dependency	p=0.79 R=.07, CI=-0.11-0.14	p=0.88 R=.037, CI=-0.05-0.06	p=0.21 R=-.32, CI=-0.75-0.18
Driving	**p=0.014** R=-.81, CI=-0.8- -0.14	p=0.35 R=0.35, CI=-0.1-0.2	**p=0.01** R=-.82, CI=-2.7- -0.49
Color Vision	p=0.25 R=.31, CI=-0.06-0.23	p=0.08 R=.43, CI=-0.008-0.12	**p=0.02** R=-.55, CI=-1.9- -0.08
Peripheral Vision	p=0.55 R=.16, CI=-0.14-0.2	p=0.65 R=.11, CI=-0.05-0.08	p=0.11 R=-.409, CI=-0.9-0.1

OSDI: Ocular surface disease index, CI: confidence interval
Bold values denote statistical significance at the p < 0.05 level

preservatives from multiple agents.[16] The BBFC is a relatively new combination therapy that is often chosen for its effectiveness in lowering intraocular pressure.[17] Onoe et al.[18] reported that switching from individual brinzolamide and brimonidine to BBFC resulted in reduced superior punctate keratopathy and increased patient satisfaction. Although BBFC's tolerability was reported to be 87%, a portion of patients (13%) experienced intolerance due to allergies and adverse effects.[8] Hyperemia, visual disturbances, ocular discomfort, and the development of ocular allergic reactions were among the most common adverse effects reported in clinical studies involving BBFC use.[19,20]

The initial aim of this study was to investigate the impact of BBFC-induced allergy on the ocular surface. OSD's prevalence in glaucoma patients is estimated to range from 37% to 91%.[21] Employing the OSDI questionnaire enables rapid assessment of OSD symptoms in a clinical setting. In this study, the OSDIs averaged 34.48 ± 26, indicating severe dry eye disease among these patients. This result could be attributed to the side effects stemming from prolonged use of glaucoma medications. Support for this notion comes from the positive correlation observed between OSDIs and the duration of both glaucoma and BBFC treatment (p=0.0001, p=0.02, respectively) (Table 4). Conversely, the study did not identify a significant correlation between the mean duration of allergy symptoms and OSDIs. Another study noted a weak relationship between OSDIs and TBUT, Schirmer test, and Oxford corneal staining score.[22] In contrast to the OSDIs suggesting severe OSD, the Schirmer test scores indicated moderately dry eyes (9.5 ± 5.1), TBUT indicated an abnormal tear film (6.5 ± 2.7), and the mean Oxford corneal stain score was mild (2 ± 1.2) in our study. The lack of significant correlation among OSDIs, Schirmer test, TBUT, and Oxford corneal staining could suggest that the duration of allergy symptoms has less influence on OSD than the duration of glaucoma and long-term use of glaucoma medications in the current study. A noteworthy factor is that benzalkonium chloride (BAC) might trigger the development of allergy to BBFC, and it is well-established that BAC dosage correlates with OSD prevalence in glaucoma patients.[23,24] A study suggested that BAC-free formulations of brimonidine resulted in a lower risk of allergy development.[25] The BBFC used in our study contains 0.03 mg of BAK per mL of suspension. A comparative study involving a BAC-free BBFC formulation could provide further insights into this matter.

The second question addressed in this study aimed to determine the impact of ocular BBFC allergy on QoL. As discussed in the literature review, it is well-established that glaucoma itself leads to a reduction in QoL.[14,26] VF loss and central visual acuity impairment in glaucoma patients can significantly affect daily activities, such as reading or driving.[27] Moreover, the need for regular use of topical medications, long-term follow-up, and potential surgeries can directly influence QoL.[27] While BBFC is generally recognized as a well-tolerated combination drug, the development of allergy resulted in a decrease in the scores for all NEI VFQ-25/TR subscales, except for the driving and color vision subscales in our study (Table 2). This observation aligns with previous research that highlighted the relatively higher score of the color vision subscale compared to other subscales in glaucoma patients.[26] The lack of an effect in the driving subscale could potentially be attributed to the limited number of patients who were drivers in our study (only 8 drivers). The lowest scores were noted in the general health (50 ± 30), vision-specific mental health (60.9 ± 22.8), general vision (61.2 ± 11), and ocular pain (62.5 ± 22) subscales of NEI VFQ-25/TR. A study reported that glaucoma over a 12-month period decreased scores in the general health, general vision, ocular pain, near activities, mental health, and driving subscales of NEI-VFQ-25.[26] Comparing our study with the study by Riva et al.,[26] we observed that the scores in our study were lower. However, as a result of regression analysis (Table 3), it is observed that the decrease in QoL is not directly related to the duration of BBFC use, but rather associated with changes occurring on the ocular surface and consequently with a decrease in OSDI score. A comparative study would be beneficial to establish a more comprehensive relationship between these scores and BBFC intolerance. Additionally, decreased scores in the general health, general vision, and driving subscales correlated with increased age (R=-0.566, R=-0.528, and R=-0.81, respectively) (Table 3). This observation is consistent with earlier findings that suggest these subscales are influenced by aging.[28]

A negative correlation was observed between OSDI and the subscales of general vision (R=-0.509), vision-specific social functioning (R=-0.64), driving (R=-0.82), and color vision (R=-0.55) in glaucoma patients with ocular BBFC allergy. A recent study demonstrated a negative correlation between VFQ-25 score and overall OSDIs in dry eye patients, which aligns with our findings.[29] Nordmann et al.[14] reported that poor vision-related QoL was linked to side effects of topical antiglaucomatous drugs, and patients

generally had high QoL scores (>70) on most subscales except for general health. In our study, only the subscale scores for general vision, ocular pain, vision-specific mental health, and role difficulties were below 70.

Major limitations of this study primarily stem from its small sample size. Larger studies could potentially yield more robust results. Furthermore, a substantial portion of the patients had been under long-term glaucoma treatment involving various agents. The absence of data on ocular surface parameters, OSDIs, and QoL values prior to the onset of ocular allergy symptoms attributed to BBFC is another limitation. A comparative study design covering the period before BBFC treatment and after the development of allergy would undoubtedly be more beneficial to clarify the relationship between QoL and OSDI scores and BBFC allergy. However, considering that the incidence of BBFC intolerance is 13%,[8] it would be technically very challenging to organize such a study since predicting which patient will develop an allergy would not be possible. Additionally, a study design encompassing treatment-naive patients initiating BBFC therapy for the first time would likely provide more insightful outcomes. However, it's important to note that the recommended first-line approach in glaucoma treatment is monotherapy rather than fixed combinations.[30] Fixed combinations are typically favored for patients with notably high initial IOP and/or advanced glaucoma. Another notable limitation is the absence of a control group consisting of separate brinzolamide and brimonidine treatments. Designing such a study could indeed be challenging. Notwithstanding these limitations, this study stands as the first of its kind to investigate the effects of ocular BBFC allergy on the ocular surface and QoL. We believe that this study contributes significantly to comprehending the impact of BBFC in glaucoma treatment on the corneal surface and QoL.

In conclusion, this study aimed to present the clinical characteristics and assess QoL in glaucoma patients experiencing ocular allergy to BBFC. The findings demonstrated that OSDIs indicated severe dry eye disease among glaucoma patients with BBFC-induced ocular allergy. Higher OSDIs correlated with reduced scores in the general vision, color vision, vision-specific social functioning, and driving subscales of NEI VFQ-25/TR. The second significant finding indicated that ocular allergy to BBFC was linked to reduced scores in all NEI VFQ-25/TR subscales, except for driving and color vision. However, no correlation was established between the duration of BBFC treatment and NEI VFQ-25/TR scores. As a result of regression analysis, it is observed that the decrease in QoL is not directly related to the duration of BBFC use, but rather associated with changes occurring on the ocular surface and consequently with a decrease in OSDI score. Increased awareness and recognition of the presented clinical profile and the potential for lower QoL in patients with ocular allergy to BBFC by both general ophthalmologists and glaucoma specialists can lead to effective and timely management strategies, thereby minimizing discomfort and improving patient compliance.

Conflict of interest The authors have not declared affiliations with or involvement in any organization or entity with any financial or financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards..

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