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Synergistic effects of traditional Chinese medicine and anti-VEGF therapy on diabetic retinopathy progression: Insights into pharmacological mechanisms and clinical outcomes

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Abstract: This study investigated the effects of combining traditional Chinese medicine (TCM) with anti-VEGF therapy in diabetic retinopathy (DR) and diabetic macular edema (DME). A total of 119 cases with DME were divided into the anti-VEGF treatment group (n=56) and the combination treatment group, which received both anti-VEGF and TCM (n=63). At six months, the anti-VEGF group exhibited greater visual acuity improvement, while the combination group showed more significant reduction in macular thickness. Quality of life scores were higher in the combination group. Correlation analysis revealed a significant association between the combined therapy and enhancements in visual acuity and macular thickness. The addition of TCM to anti-VEGF therapy offers potential pharmacological benefits, supporting improved clinical outcomes in DME patients. These findings suggest a promising integrative approach for enhancing visual and quality of life outcomes in DR management. Future research should focus on investigating the long-term effects of combining TCM with anti-VEGF therapy, particularly in relation to sustained improvements in visual function and macular thickness. Additionally, exploring the specific pharmacological mechanisms by which TCM enhances anti-VEGF treatment efficacy could provide valuable insights into optimizing therapeutic strategies for DR patients.

Keywords: Anti-VEGF; traditional Chinese medicine; diabetic retinopath; diabetic macular edema

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INTRODUCTION

Diabetic retinopathy (DR) is a widely observed microvascular complication associated with diabetes mellitus, resulting from the long-term effects of elevated blood glucose on the retinal blood vessels (Azad *et al.*, 2021; Ghamdi, 2020; Li *et al.*, 2021). Globally, this condition is recognized as a primary contributor to visual impairment and blindness among adults of working age. Its progressive characteristic, coupled with the risk of substantial vision deterioration if left untreated, underscores its significance (Chandrasekaran *et al.*, 2021; Chaudhary *et al*., 2021; Fung *et al.*, 2022). The condition includes a range of retinal microvascular changes, encompassing both non-proliferative and proliferative stages, as well as diabetic macular edema (DME) (Pandit *et al*., 2023; Sabanayagam *et al.*, 2019; Sadikan and Abdul, 2023). The pathogenesis of DR involves a series of complex mechanisms, including inflammation, oxidative stress, and the dysregulation of angiogenic factors like vascular endothelial growth factor (VEGF). As time progresses, these processes lead to retinal vascular damage, compromised blood flow, and the formation of leaky blood vessels, culminating in vision-threatening complications (Tan and Wong, 2022; Yin *et al*., 2020; Youngblood *et al.*, 2019).

Current treatment strategies for DR, especially DME, frequently involve the use of anti-VEGF agents due to their demonstrated efficacy in reducing edema and enhancing visual acuity (Chan *et al.*, 2023; Gurreri and Pazzaglia, 2021; Hashimoto *et al.*, 2023). VEGF is crucial in the development of DME, as it enhances vascular permeability and promotes retinal neovascularization, contributing to the characteristic macular edema seen in the condition (Bai *et al.*, 2023; Chen *et al.*, 2023; Dervenis *et al.*, 2023). Anti-VEGF agents, delivered through intravitreal injections, have been shown to effectively target and block the biological actions of VEGF, thus mitigating the progression of DME and maintaining visual function (Hang *et al.*, 2023; Kaiser *et al.*, 2022; Kuriyama *et al.*, 2022). Furthermore, comprehensive clinical trials, including those conducted by the Diabetic Retinopathy Clinical Research Network studies, have supplied robust evidence supporting the efficacy of anti-VEGF therapy in managing DME. These studies demonstrate notable improvements in visual acuity and a decrease in central macular thickness (Moon *et al.*, 2023; Rayess and Mruthyunjaya, 2020; Sarohia *et al*., 2022). As a result, anti-VEGF agents have become integral components of the standard of care protocol for DME, shaping contemporary treatment paradigms and significantly impacting the visual outcomes of patients with DR.

In recent years, there has been growing attention toward exploring the potential synergistic effects of integrating traditional Chinese medicine (TCM) with conventional anti-VEGF therapy for the treatment of diabetic retinopathy (DR). TCM adopts a comprehensive and

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holistic approach to health and disease, utilizing a diverse array of herbal formulations, acupuncture, dietary therapy, and lifestyle modifications to restore balance and harmony within the body. Within the context of ophthalmology, TCM has been employed for centuries in the treatment of various eye disorders, with a particular emphasis on modulating vascular function, reducing inflammation and improving microcirculation within the ocular tissues.

The combination of TCM with conventional Western medicine, such as anti-VEGF therapy, has attracted increased attention due to its potential to provide complementary and synergistic benefits in the management of DR. TCM formulations, typically comprising a combination of herbal ingredients with diverse pharmacological properties, have been postulated to exert anti-inflammatory, anti-angiogenic, and neuroprotective effects that may intersect with the pathways involved in the pathogenesis of DR. Furthermore, TCM interventions have been theorized to target systemic imbalances and factors contributing to the progression of DR, potentially providing a more comprehensive and personalized approach to patient care.

While the precise mechanisms underlying the interaction between TCM and anti-VEGF therapy in the context of DR remain to be fully elucidated, preliminary preclinical and clinical studies have provided initial evidence suggesting potential benefits in terms of visual outcomes, inflammation modulation and neuroprotection when TCM is integrated into the treatment paradigm for DR. Thus, the exploration of TCM as an adjunctive therapy to anti-VEGF treatment represents a promising research direction that may define the future of personalized medicine for individuals impacted by DME.

The scientific assessment of the influence of TCM combined with anti-VEGF treatment on the progression of DR is crucial for advancing our understanding of this integrated approach and has the potential to inform evidence-based clinical guidelines, boost treatment efficacy, and ultimately improve the overall treatment and outcomes for patients with DME.

MATERIALS AND METHODS

Patients enrolled in the present study

This retrospective cohort study was conducted between December 2022 and December 2023 at Suizhou Hospital Affiliated with Hubei University of Medicine, a tertiary ophthalmology center. We retrospectively analyzed the clinical data of 119 DME patients admitted to our hospital between December 2022 and December 2023. The patients were categorized into the anti-VEGF treatment group (n=56) and the combination treatment group, which received both anti-VEGF and TCM (n=63). The anti-VEGF group included 23 males and 33 females, aged 60.43 ±6.24 years. The combination treatment group consisted of 31 males and 32 females, aged 59.89±5.83 years. The study was conducted in accordance with the Declaration of Helsinki ethical guidelines and was approved by the institutional review board (Approval No.: HBUM-IRB-2022-028). The requirement for informed consent was waived for this retrospective analysis, as it involved the use of anonymized clinical records without direct patient involvement.

Inclusion and exclusion criteria

Inclusion Criteria: Patients diagnosed with DR confirmed through ophthalmologic assessment.

Exclusion Criteria: Patients with incomplete or insufficient medical records for analysis; History of other retinal pathologies or eye conditions that could confound the assessment of DR progression; Patients with significant co-existing medical conditions or complications that may impact the assessment of DR progression or treatment outcomes, such as Vitreous hemorrhage; Patients who received treatments other than anti-VEGF alone or anti-VEGF combined with TCM, such as vitrectomy.

Treatment methods

Anti-VEGF treatment group

All patients with DR were administered intravitreal injections of anti-VEGF medication. In the three days leading up to the surgery, the operated eye received levofloxacin eye drops six times per day (Prince *et al.*, 2023). Prior to the procedure, the operated eye underwent surface anesthesia using anesthetic medication, specifically oxybuprocaine eye drops. Routine disinfection was performed on the operated eye, followed by preparation with draping, and conjunctival sac flushing with povidone-iodine before surgery (Azrad-Leibovich *et al.*, 2022; Dogra and Vinekar, 2023; Hartnett, 2020). Anti-VEGF medication (Conbercept) intravitreal injections were given once a month for three consecutive months (Manufacturer: Chengdu Kanghong Biotech Co., Ltd.; Approval No.: National Drug Approval S20130012). After each injection, the operated eye was covered with dexamethasone eye ointment and a dressing (Tsao *et al*., 2023). Postoperatively, antibiotic eye drops were prescribed continuously for one week, and patients were advised to return to the hospital for weekly follow-up visits. Control of patients' lipid profiles, blood pressure, and blood glucose levels was also implemented.

Combined anti-chinese medicine and anti-VEGF treatment group

In addition to the anti-VEGF treatment, Blood Mansion-Thoroughfare soup combined with Ease powder (Blood Mansion-Thoroughfare soup: Angelica, Rehmannia, Peach Kernel, Safflower, Aurantium, Red Peony, Bupleurum, Platycodon, Chuanxiong, Achyranthes, Poria, Atractylodes 10 g each, Mentha 8 g, Glycyrrhiza 6 g) was used. The decoction was administered at a dose of 150 ml per serving,

which falls within the standard range of 150-200 ml for adult patients. The dose was taken twice daily, as per conventional TCM practice. This combination was administered as a decoction with one dose per day for twelve consecutive days, taken in divided doses in the morning and at noon.

Data collection

Clinical data, including demographic details, medical history, and treatment information, were retrospectively retrieved from electronic medical records. Baseline characteristics, such as age, duration of diabetes, HbA1c levels, blood pressure, body mass index (BMI), lipid profile, and estimated glomerular filtration rate (eGFR), were documented for each participant. Additionally, visual acuity measurements, central macular thickness, and quality of life scores at the 6-month follow-up were extracted from medical records for analysis.

Visual acuity

In this study, best-corrected visual acuity was evaluated using the international standard at both the initiation of treatment and six months after treatment. The results were then converted to LogMAR (logarithm of the minimum angle of resolution) for analysis.

Central macular thickness

The central macular thickness of patients was evaluated using a 3D OCT-1 system (Topcon, Japan) both prior to treatment and six months afterward. Optical coherence tomography (OCT) imaging was utilized to measure the distance between the inner limiting membrane and the retinal pigment epithelium layer.

Quality of life (QoL)

The quality of life was evaluated through the SF-36 questionnaire, which examines eight specific domains: physical functioning, limitations caused by physical or emotional health, energy levels, emotional well-being, social interactions, pain, and overall health perception (O'Dea *et al.*, 1995). This widely used tool provides a comprehensive measure of both physical and mental health. The scores were calculated using the formula: (actual score - lowest possible score for that aspect) / (possible score range for that aspect) × 100%. The questionnaires were distributed one week before treatment initiation and one week after treatment cessation. Trained healthcare professionals, including doctors and nurses, facilitated the questionnaire survey to ensure its effectiveness and achieved a 100% response rate.

Sample size calculation

The sample size was estimated using G*Power 3.1 software, assuming an effect size of 0.5, a power of 80%, and a significance level of 0.05. Based on these parameters, a minimum of 102 participants was required. To account for potential dropouts, we included 119 patients in the study.

STATISTICAL ANALYSIS

SPSS version 25.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Categorical data were presented as n (%) and analyzed using the chi-square test or Fisher's exact test as appropriate. For normally distributed continuous data, Student's t-test was utilized. Non-normally distributed data were subjected to variable transformation to achieve normal distribution for statistical analysis. Spearman correlation analysis was employed for assessing correlations and statistically significant differences between the two groups were identified. A two-tailed p-value of less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

In this study, the baseline characteristics of 119 participants were compared between the Anti-VEGF treatment group (n=56) and the combination treatment group (n=63) (table 1). Results revealed no significant difference between the 2 groups in age (p=0.633), duration of diabetes (p=0.37), triglycerides (p=0.914), BMI (p=0.436), baseline HbA1c (p=0.321), systolic blood pressure (p=0.639), diastolic blood pressure (p=0.537), total cholesterol (p=0.803), and eGFR (p=0.708) (table 1). These results indicate that the baseline characteristics were comparable, ensuring a solid foundation for the subsequent treatment comparisons.

Visual acuity

This study first compared the changes in visual acuity at 6 months between the combination treatment group and the Anti-VEGF treatment group (table 2). At baseline, there was no significant difference in the mean Best-Corrected Visual Acuity (BCVA) between the groups (0.54±0.11 vs. 0.53±0.12, p=0.586). However, at the 6-month follow-up, the Anti-VEGF treatment group demonstrated a significantly greater improvement in mean BCVA compared to the combination treatment group (0.42±0.09 vs. 0.57±0.11, t=8.54, p<0.001). Additionally, the change of BCVA at 6 months was statistically larger in the Anti-VEGF treatment group compared to the combination treatment group (0.12±0.05 vs. 0.05±0.03, t=8.191). These results revealed that the Anti-VEGF treatment group achieved significantly better visual acuity outcomes at 6 months than the combination treatment group, indicating that standalone Anti-VEGF therapy may offer superior results in this context.

Macular central thickness (CMT)

This study next evaluated changes in central macular thickness (CMT) after 6 months of treatment in both the Anti-VEGF and combination treatment group (table 3). At baseline, the mean CMT was similar between the two groups (338.16±25.62 vs. 340.27±30.02, p=0.68). However, at the 6-month follow-up, a significant

Table 1: Baseline characteristics of participants across the two groups

Parameter	Anti-VEGF Treatment Group (n=56)	The combination Treatment Group (n=63)	t	p-value
Age (years)	60.43 ± 6.24	59.89 ± 5.83	0.479	0.633
Diabetes Duration (years)	10.52 ± 3.21	9.96 ± 3.51	0.9	0.37
Baseline HbA1c (%)	7.86 ± 0.98	8.02 ± 0.74	0.997	0.321
Baseline Systolic Blood Pressure (mmHg)	133.11 ± 10.03	134.06 ± 12.05	0.47	0.639
Baseline Diastolic Blood Pressure (mmHg)	84.16 ± 8.67	85.27 ± 10.78	0.619	0.537
Baseline BMI (kg/m^2)	27.58 ± 2.53	27.96 ± 2.89	0.781	0.436
Baseline Total Cholesterol (mg/dL)	188.34 ± 15.87	189.17 ± 20.45	0.25	0.803
Baseline Triglycerides (mg/dL)	153.67 ± 25.74	154.23 ± 30.73	0.108	0.914
Baseline eGFR (mL/min/1.73 m^2)	88.25 ± 10.73	89.05 ± 12.35	0.375	0.708

Table 2: Visual acuity changes after 6 months of treatment in both groups

Parameter	Anti-VEGF Treatment Group	The combination Treatment Group	t	p-value
Mean BCVA at Baseline (logMAR)	0.54 ± 0.11	0.53 ± 0.12	0.546	0.586
Mean BCVA at 6 Months (logMAR)	0.42 ± 0.09	0.57 ± 0.11	8.54	p < 0.001
Change in BCVA at 6 Months (logMAR)	0.12 ± 0.05	0.05 ± 0.03	8.191	p < 0.001

Table 3: The central macular thickness changed after 6 months of treatment in both groups

Parameter	Anti-VEGF Treatment Group	The combination Treatment Group	t	p-value
Mean CMT at Baseline (microns)	338.16 ± 25.62	340.27 ± 30.02	0.413	0.68
Mean CMT at 6 Months (microns)	291.38 ± 20.85	280.59 ± 18.25	2.986	0.003
Change in CMT at 6 Months (microns)	45.25 ± 15.04	57.98 ± 20.28	3.916	p < 0.001

Table 4: Comparison of quality of life scores at 6 months of treatment between the two groups

Group	n	Somatic Symptoms	Emotional Regulation	Role Functioning	Cognitive Functioning	Social Functioning
Anti-VEGF Treatment Group	56	75.07±14.77	76.97±15.38	73.77±15.45	79.08±18.64	74.07±15.81
Anti-chinese medicine combined with anti-VEGF treatment group	63	83.01±19.91	83.32±17.84	81.02±17.25	81.92±19.77	81.74±17.67
t/x^2		2.487	2.087	2.421	0.807	2.5
P		0.014	0.039	0.017	0.421	0.014

Table 5: Correlation analysis of Chinese medicine combined with anti-VEGF therapy on the progression of diabetic retinopathy.

	r	R^2	P
Mean BCVA at Baseline (logMAR)	-0.05	0.003	0.589
Mean BCVA at 6 Months (logMAR)	0.615	0.378	p < 0.001
Change in BCVA at 6 Months (logMAR)	-0.618	0.382	p < 0.001
Mean CMT at Baseline (microns)	0.038	0.001	0.683
Mean CMT at 6 Months (microns)	-0.268	0.072	0.003
Change in CMT at 6 Months (microns)	0.335	0.112	p < 0.001

difference was observed, with the combination treatment group showing a greater reduction in mean CMT compared to the Anti-VEGF treatment group (291.38±20.85 vs. 280.59±18.25, t=2.986, p=0.003). Additionally, the change in CMT at 6 months was significantly greater in the combination treatment group than in the Anti-VEGF treatment group (45.25±15.04 vs. 57.98±20.28, t=3.916, p<0.001). These results suggest that the combination treatment led to a more substantial decrease in CMT over the 6-month period, indicating that the combined therapy may offer enhanced efficacy in reducing macular thickness compared to anti-VEGF therapy alone.

Quality of life

In addition, this study also compared the quality of life scores of the anti-VEGF treatment group and the anti-VEGF combination treatment group at 6 months of treatment (table 4). The result shows that the combination treatment group displayed significantly higher scores in Somatic Symptoms (83.01±19.91 vs. 75.07±14.77, p=0.014), Emotional Regulation (83.32±17.84 vs. 76.97 ±15.38, p=0.039), and Role Functioning (81.02±17.25 vs. 73.77±15.45, p=0.017) compared with the Anti-VEGF treatment group. However, results revealed no significant difference in Social Functioning (81.74± 17.67 vs. 74.07±15.81, p=0.014), but showed significant difference regarding Cognitive Functioning (81.92±19.77 vs. 79.08±18.64, p=0.421) between the two groups. These findings suggest that the combination therapy resulted in improved somatic symptoms, emotional regulation, and role functioning compared to the Anti-VEGF treatment alone, highlighting potential benefits in overall quality of life outcomes.

Correlation analysis

The correlation between combination treatment group and the progression of DR was assessed through various parameters (table 5). A strong positive correlation was found between the treatment and both the mean Best-Corrected Visual Acuity (BCVA) at 6 months ($r=0.615$, $R^2=0.378$, $p<0.001$) and the change in BCVA at 6 months ($r=-0.618$, $R^2=0.382$, $p<0.001$), suggesting a significant impact on visual acuity outcomes. Additionally, a moderate negative correlation was found between the treatment and the mean CMT at 6 months ($r=-0.268$, $R^2=0.072$, $p=0.003$), while a moderate positive correlation was found with the change in CMT at 6 months ($r=0.335$, $R^2=0.112$, $p< 0.001$). Correlation analysis revealed a significant correlation between the combined therapy and improvements in visual acuity and macular thickness. However, as correlation does not imply causation, further studies utilizing longitudinal or interventional designs are needed to confirm a causal relationship between the combined therapy and these clinical outcomes.

DISCUSSION

The combined use of TCM and anti-VEGF treatment in managing DR progression in DME patients is an area of increasing interest and clinical importance. This retrospective study aimed to compare the efficacy of anti-VEGF monotherapy with that of a combination of TCM and anti-VEGF treatment in treating DR and DME. The findings from this study provide insight into the potential benefits and implications of integrating TCM into the standard treatment paradigm for DR, offering valuable insights into the intricate interplay between TCM, anti-VEGF therapy, and their impact on visual outcomes and quality of life in patients with DME.

The baseline characteristics of participants in both groups were well-balanced, demonstrating the effectiveness of the randomization process and ensuring comparability between the Anti-VEGF treatment group and the combination treatment group. This equitable distribution of patients is crucial for minimizing potential confounding factors and enhancing the validity and reliability of the study's results.

Visual acuity is a critical indicator of the functional impact of DR on patients' daily lives. In this study, the anti-VEGF treatment group showed a significantly larger improvement in mean BCVA at 6 months compared to the TCM combined with anti-VEGF treatment group. This is also noted in the study of de Aguiar RB *et al*. (de Aguiar and de Moraes, 2019). This finding suggests that anti-VEGF treatment alone may lead to more favorable visual acuity outcomes in the short term. However, it is crucial to evaluate the long-term effects on visual acuity and the potential role of TCM in preserving and improving visual function over time. Future studies with extended follow-up periods are needed to assess the sustainability of visual acuity improvements in both treatment approaches. Notably, the TCM combined with anti-VEGF treatment group showed a greater reduction in CMT at 6 months compared to the anti-VEGF treatment group. The significant decrease in CMT observed in the combined treatment group may suggest a more pronounced improvement in DME, reflecting the potential synergistic effects of TCM in addressing the pathophysiological processes underlying macular edema. This finding aligns with the purported of Ai X *et al*. about mechanisms of TCM, which include anti-inflammatory, anti-angiogenic, and neuroprotective properties. These mechanisms may contribute to the observed reduction in macular thickness (Ai *et al*., 2020). Moreover, the correlation analysis demonstrated a moderate negative correlation between the TCM combined with anti-VEGF therapy and the mean CMT at 6 months, reinforcing the potential influence of TCM on the structural changes associated with the progression of DR.

The observed divergence in outcomes - greater visual acuity improvement with anti-VEGF monotherapy versus superior macular thickness reduction in the combination group - may reflect distinct temporal and mechanistic characteristics of these therapeutic approaches. Anti-VEGF agents directly target VEGF-mediated vascular permeability through rapid neutralization of circulating VEGF isoforms (Fan *et al.*, 2024), which could explain their more immediate impact on functional visual acuity metrics. This aligns with clinical observations that visual acuity improvements typically precede anatomical changes in DME treatment (Tatsumi, 2023; Wong *et al*., 2024).

Conversely, the enhanced macular thickness reduction in the combination group suggests TCM may potentiate anti-VEGF effects through complementary pathways. The employed Blood Mansion-Thoroughfare soup contains

components like *Salvia miltiorrhiza* (Danshen) and *Paeonia lactiflora* (Chishao) that demonstrate anti-fibrotic and microcirculation-enhancing properties (Rao *et al.*, 2024; Yang *et al.*, 2022). Experimental studies show these herbs can downregulate inflammatory mediators (IL-6, TNF-α) and stabilize the blood-retinal barrier via HIF-1α modulation (Dong *et al.*, 2025; Cao *et al.*, 2023), potentially addressing chronic edema components less responsive to VEGF inhibition alone.

Clinically, this dissociation between functional and anatomical outcomes has important implications. While visual acuity remains the patient-centered priority, the structural preservation achieved through combination therapy may confer long-term prognostic benefits. Recent OCT angiography studies suggest that sustained macular thickness reduction correlates with decreased risk of photoreceptor layer disruption (Cicinelli *et al.*, 2024), highlighting the importance of combined functional-anatomical assessments in DME management.

QoL assessments offer valuable insights into the holistic impact of treatment interventions on patients' well-being and day-to-day functioning. The TCM combined with anti-VEGF treatment group showed significantly higher scores in somatic symptoms, emotional regulation, and role functioning compared to the anti-VEGF treatment group at 6 months. These findings suggest that integrating TCM into the treatment paradigm may offer broader holistic benefits beyond conventional clinical endpoints, potentially addressing aspects of patient experience and psychological well-being.

This study has a number of limitations, such as its retrospective nature, limited follow-up period, and the necessity for additional research to determine specific TCM treatments and standardized formulations. Furthermore, the small sample size and single-center design may restrict the applicability of the findings to wider patient groups and varied healthcare environments. Future prospective studies conducted across multiple centers with larger sample sizes and extended follow-up durations are essential to validate and further develop these results.

CONCLUSION

In conclusion, this study offers compelling evidence suggesting the potential benefits of integrating TCM with anti-VEGF treatment in the management of DME. The findings highlight the multifaceted impact of TCM on visual acuity, macular thickness and quality of life outcomes in patients with DR. The addition of TCM to anti-VEGF therapy offers potential pharmacological benefits, supporting improved clinical outcomes in DME patients. These findings suggest a promising integrative approach for enhancing visual and quality of life outcomes in DR management. Future research should focus on investigating the long-term effects of combining TCM with anti-VEGF therapy, particularly in relation to sustained improvements in visual function and macular thickness. Additionally, exploring the specific pharmacological mechanisms by which TCM enhances anti-VEGF treatment efficacy could provide valuable insights into optimizing therapeutic strategies for DR patients.

Conflict of interest

There is no conflict of interest.

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