·康弘征文论著·

Effect of Conbercept on serum lncRNA MALAT1 levels and central macular thickness in patients with diabetic macular edema

Wen-Jun Gou, Heng Li, Hui You, Yi-Fan Tao, Bo Li, Hui Zhang

引用:苟文军,李恒,游慧,等.康柏西普对糖尿病性黄斑水肿患者血清中 lncRNA MALAT1 水平及黄斑中央区厚度的影响.国际眼科杂志 2023;23(1):10-16

Foundation item: Scientific Research Project of Suining Central Hospital (No.2022ypj40)

Department of Ophthalmology, Suining Central Hospital, Suining 629000, Sichuan Province, China

Correspondence to: Heng Li. Department of Ophthalmology, Suining Central Hospital, Suining 629000, Sichuan Province, China. liheng1-1@163.com

Received: 2022-01-27 Accepted: 2022-07-19

康柏西普对糖尿病性黄斑水肿患者血清中 lncRNA MALAT1 水平及黄斑中央区厚度的影响

苟文军,李 恒,游 慧,陶依凡,李 博,张 慧

基金项目:遂宁市中心医院科研课题(No.2022ypj40)

作者单位:(629000)中国四川省遂宁市,遂宁市中心医院眼科中心

作者简介:苟文军,毕业于泸州医学院,硕士,副主任医师,研究方向:玻璃体视网膜疾病。

通讯作者:李恒,毕业于遵义医学院,硕士,主任医师,研究方向:玻璃体视网膜疾病. liheng1-1@163.com

摘要

目的:探讨康柏西普对糖尿病性黄斑水肿(DME)患者血清 lncRNA MALAT1 水平、黄斑中央区厚度(CMT)及最佳矫正视力(BCVA)的影响,观察其治疗的有效性与安全性。

方法:纳入 DME 患者 300 例 300 眼,均为单眼病变。按照随机数字表法进行分组:非注射组 100 例 100 眼,对照组 100 例 100 眼给予雷珠单抗治疗,研究组 100 例 100 眼给予康柏西普治疗。

结果:治疗前与治疗后 1、2、3mo 测定患者 BCVA、血清 lncRNA MALAT1 水平及 CMT,同时对比临床疗效,并对患者进行随访,记录不良反应发生情况。非注射组患者的 BCVA(LogMAR)、血清 lncRNA MALAT1 水平与 CMT 均无明显变化($P>0.05$)。对照组、研究组患者治疗后 1、2、3mo 的 BCVA(LogMAR)与治疗前相比明显提高(均 $P<0.05$),但研究组与对照组相比,差异无统计学意义。对照组患者治疗后 1、2、3mo 血清 lncRNA MALAT1 水平降低,研究组患者治疗后 1、2、3mo 血清 lncRNA MALAT1 水平降低更明显,研究组治疗后血清 lncRNA MALAT1 水平明显低于对照组(均 $P<0.05$)。对照组患者治疗后 1、2、3mo CMT 降低,研究组患者治疗后 1、2、3mo CMT 降低更明显,研究组治疗后 CMT 明显低于对照组(均 $P<0.05$)。研究组不良反应发生率(2.0%)明显低于对照组(11.0%)。

结论:康柏西普能够显著降低 DME 患者血清 lncRNA MALAT1 水平,降低 CMT、减轻黄斑水肿,改善视力,其治疗有效性与安全性明显优于雷珠单抗。

关键词:康柏西普;雷珠单抗;注射;注射治疗糖尿病性黄斑水肿;lncRNA;MALAT1;黄斑中央区厚度

Abstract

• AIM: To investigate the effect of Conbercept on serum lncRNA MALAT1 levels, central macular thickness (CMT) and best corrected visual acuity (BCVA) in patients with diabetic macular edema (DME), and to observe its efficacy and safety.

• METHODS: A total of 300 patients (300 eyes) with DME were included in this study, all of whom had monocular lesions. They were divided into non-injection group with 100 patients (100 eyes), control group with 100 patients (100 eyes) treated with Ranibizumab injections and study group with 100 patients (100 eyes) treated with Conbercept injections according to a random numbers table.

• RESULTS: The BCVA, serum lncRNA MALAT1 level and CMT were measured before and 1, 2 and 3mo after treatment. In addition, the clinical efficacy was assessed and the patients were followed up to record the adverse reactions. There were no significant changes in BCVA (LogMAR), serum lncRNA MALAT1 level and CMT in the non-injection group ($P>0.05$). The BCVA(LogMAR) in the control group and study group at 1, 2 and 3mo after treatment was significantly higher than that before treatment (all $P<0.05$). The BCVA(LogMAR) of patients in the study group at 1, 2 and 3mo after treatment was significantly higher than that before treatment (all $P<0.05$), but there was no significant difference between the study group and control group. The level of serum lncRNA MALAT1 in the control group decreased at 1, 2 and 3mo

after treatment, and it decreased more significantly in the study group at 1, 2 and 3mo after treatment. The level of serum lncRNA MALAT1 in the study group was significantly lower than that in the control group (all $P<0.05$). The CMT of patients in the control group decreased at 1, 2 and 3mo after treatment; however, the CMT of patients in the study group decreased more significantly at 1, 2 and 3mo after treatment. The CMT of the study group was significantly lower than that of the control group (all $P<0.05$). The incidence of adverse reactions in the study group (2.0%) was significantly lower than that in the control group (11.0%).

• CONCLUSION: Conbercept can significantly reduce the level of serum lncRNA MALAT1, CMT and macular edema and improve BCVA in patients with DME. Its therapeutic efficacy and safety are significantly better than Ranibizumab.

• KEYWORDS: Conbercept; Ranibizumab; injections; injection for diabetic macular edema; lncRNA; MALAT1; central macular thickness

DOI:10.3980/j.issn.1672-5123.2023.1.03

Citation: Gou WJ, Li H, You H, *et al*. Effect of Conbercept on serum lncRNA MALAT1 levels and central macular thickness in patients with diabetic macular edema. *Guoji Yanke Zazhi* (*Int Eye Sci*) 2023;23(1):10-16

INTRODUCTION

Diabetes mellitus (DM) is a common chronic metabolic disorder caused by abnormal blood glucose levels[1]. With the development of the social economy and changes in lifestyle, DM affects about 10% of the world's population[2-3]. The incidence rate of the disease is expected to continue to increase significantly in the near future. Besides the abnormal physiological conditions caused by DM itself, complications from the disease also seriously affect human health[4]. Diabetic retinopathy (DR) is one of the common microvascular complications of diabetes. Diabetic macular edema (DME) is the main cause of blindness in DR patients[5]. It is reported that 28.8% of DM patients develop DR, while 22.2% of DM patients do not develop DR regardless of blood glucose levels. These studies indicate that genetic factors play an important role in the pathogenesis of DR[6].

Long noncoding RNA (lncRNA) is a group of noncoding transcriptional RNA with more than 200 nucleotides. It regulates gene expression through epigenetic, transcriptional, and post transcriptional levels and plays an important role in regulating the physiological and pathological processes of the cardiovascular system. Metastasis associated lung adenocarcinoma transcript 1 (MALAT1) is an evolutionarily conserved lncRNA. It was initially shown to be associated with lung metastasis of cancer, but the latest research has shown that it can regulate the proliferation, migration and vascular growth of vascular endothelial cells in heart failure, myocardial infarction and congenital heart disease. DR plays an important role in vascular diseases[7].

Ranibizumab and Conbercept are two kinds of commonly used anti-VEGF drugs[8-13]. Conbercept injections can competitively bind VEGF receptors and inhibit VEGF activation from preventing the formation of pathological neovascularisation[14-17]. In this study, DME patients treated with Ranibizumab and Conbercept were assessed. The clinical effects of the two drugs were retrospectively analysed and compared.

METHODS

Subjects A total of 300 DME patients (300 eyes, all monocular lesions) treated in the Eye Center of Suining Central Hospital from January 2021 to October 2021 were included in the study. One hundred cases (100 eyes) were recruited in the non-injection group, including 55 males and 45 females, aged 46-61 years, with an average age of (53.56±7.03) years. The duration of diabetes was (10.61±4.52) years. According to a random numbers table, 100 cases (100 eyes) were assigned to a control group and were treated with Ranibizumab injections, including 53 males and 47 females, aged from 45 to 60 years, with an average age of (53.03±7.01) years. The duration of diabetes in this group was 10.63±4.54 years. In the study group, 100 patients (100 eyes) were treated with Conbercept, including 55 males and 45 females, aged 47~63 years, with an average age of 55.79±7.21 years. The duration of diabetes was 10.57±4.51 years. The general characteristics of the two groups were comparable. The design of this study was in line with the Helsinki Declaration and the informed consent of the patients was obtained.

The inclusion criteria were in accord with the 2014 Guidelines for Clinical Diagnosis and Treatment of Diabetic Retinopathy in China. Ophthalmoscopy, fundus photography, optical coherence tomography (OCT), and fundus fluorescein angiography were performed to diagnose nonproliferative DR combined with DME. The central macular thickness (CMT) was >250μm. The preoperative BCVA (LogMAR) was 0.9~0.4 and CMT was 321.04~451.73 μm. The average CMT was 320.33±130.81μm. The exclusion criteria were fundus diseases, such as retinal vein occlusion or age-related macular degeneration, glaucoma, optic neuritis and other eye diseases. Patients with a history of retinal laser photocoagulation, intravitreal drug injection and internal eye surgery were also excluded. Patients with turbid quality and poor coordination that affected imaging clarity, failure to follow the treatment plan, or were lost to follow-up were also excluded.

Methods Operation method: Vitreous cavity injection was performed according to the internal eye operation standard, which included routine disinfection and laying of towels, surface anaesthesia with promecaine hydrochloride eye drops, flushing of the conjunctival sac with iodophor and normal saline, special filtering of the drug with, removal of liquid with an 18G blunt needle, inserting the needle into the eye at 3.5 mm behind the corneal limbus above the temporal area, slowly injecting 0.05 mL of the drug into the vitreous cavity, and pressing the puncture point for 30s after pulling the needle out to prevent reflux. The intraocular pressure was stabilised as normal, tobramycin dexamethasone eye ointment was applied to the operated eyes, and the operated eyes were bandaged. Levofloxacin eye drops were given after the operation. Patients in both groups were injected once a month for 3mo. All operations were performed by the same operator. The control group was treated with Ranibizumab injections (Novartis Pharma Stein AG, Switzerland, Registration No. s20140003) and the study group was treated with Conbercept injections (Chengdu Kanghong Biotechnology Co., Ltd., National Drug Standard s20130012).

Index observation: The same examination equipment and methods as used previously were used for measurements during the 3mo after treatment. The changes in BCVA(LogMAR), serum lncRNA MALAT1 and CMT were observed during the 3mo after treatment. All measurements were completed by the same researcher.

BCVA: According to the low visual acuity grading standard formulated by the World Health Organization, patients were examined with the international standard visual acuity chart before treatment and during the 3mo after treatment. Tropicamide eye drops were used for mydriasis, and measurement values were converted to the minimum visual angle logarithm (LogMAR) for visual acuity analysis. The visual acuity evaluation criteria were divided into three levels: BCVA increase ≥2, behavioural visual acuity improvement, BCVA decrease ≥2, behavioural visual acuity decreased, fluctuated up and down and behavioural visual acuity was stable.

Serological indexes: A total of 5 mL of elbow vein blood of all subjects were taken on an empty stomach before and for 3mo after treatment. After centrifugation, serum samples were stored in a refrigerator at −70℃. The level of lncRNA MALAT1 in serum was measured with a double antibody sandwich enzyme-linked immunosorbent assay.

Anatomical indexes: The CMT was measured with OCT before treatment and in during the 3mo after treatment.

Observation of adverse reactions: We observed the general situation, adverse reactions and complications in the eyes.

Statistical Treatment The SPSS 190 analysis system was used for statistical analysis of the obtained data. Each index was expressed as the mean±standard deviation ($\bar{x}\pm s$). The LogMAR, BCVA, serological indexes and anatomical indexes between the two groups before treatment and during the 3mo after treatment were tested, with a statistical significance of $P<0.05$.

RESULTS

Baseline Characteristics Three hundred eyes of patients were randomly divided into the non-injection group ($n=100$), control group ($n=100$) and study group ($n=100$). There was no significant difference among the three groups ($P>0.05$; Table 1).

Comparison of LogMAR BCVA among the three groups after treatment The BCVA(LogMAR) of patients in the non-injection group before treatment and 1, 2 and 3 mo after treatment were 0.69±0.21, 0.71±0.18, 0.70±0.23 and 0.69±0.31 respectively, and there was no statistical significance ($P>0.05$). The BCVA(LogMAR) of patients in the control group before treatment and during the 3mo after treatment were 0.67±0.23, 0.46±0.12, 0.41±0.14, and 0.38±0.09, respectively,

BCVA was significantly higher after treatment compared to before treatment ($P<0.05$). The BCVA(LogMAR) of patients in the study group before treatment and for 3mo after treatment were 0.71±0.13, 0.41±0.22, 0.41±0.35, and 0.36±0.17, respectively. After treatment, compared with before treatment, the BCVA was significantly improved ($P<0.05$). However, there was no significant difference between the study group and the control group ($P>0.05$; Table 2).

Comparison of serum lncRNA MALAT1 among the three groups before and after treatment The serum levels of lncRNA MALAT1 in the non-injection group before treatment and 1, 2 and 3mo after treatment, were 156.31±13.96 ng/L, 156.40±14.01 ng/L, 156.41±13.99 ng/L, and 156.36±13.98 ng/L, respectively. There was no statistically significant change in the level of serum lncRNA MALAT1 ($P>0.05$). The levels of serum lncRNA MALAT1 in the control group were 158.21±14.36 ng/L, 103.26±11.21 ng/L, 103.31±12.53 ng/L and 100.48±9.53 ng/L before treatment and during the 3mo after treatment, respectively. The levels of lncRNA MALAT1 after treatment were significantly lower than those before treatment ($P<0.05$). The levels of serum lncRNA MALAT1 in the study group before treatment and for 3mo after treatment were 155.67±22.01ng/L, 81.14±13.01ng/L, 79.69±11.54ng/L and 77.26±10.32ng/L, respectively. The level of lncRNA MALAT1 after treatment was significantly lower than that before treatment ($P<0.05$). Compared with the control group, the level of lncRNA MALAT1 decreased significantly in the study group ($P<0.05$; Table 3).

Comparison of central macular thickness among the three groups before and after treatment The CMT of patients in the non-injection group before treatment and 1, 2 and 3mo

Table 1 Baseline data for the three groups before treatment

Parameters	Non-injection group(n=100)	Control group (n=100)	Study group (n=100)	t	P
Gender				0.411	0.762
Male	55	53	55		
Female	45	47	45		
Ages range (years)	46~61	45~60	47~63		
Average ages($\bar{x}\pm s$, years)	53.56±7.03	53.03±7.01	55.79±7.21	0.176	0.612
The duration of diabetes ($\bar{x}\pm s$, years)	10.61±4.52	10.63±4.54	10.57±4.51	0.067	0.943
BCVA Before treatment	0.69±0.21	0.67±0.23	0.71±0.13	0.511	0.728

BCVA: Best corrected visual acuity.

Table 2 Comparison of best corrected visual acuity among the three groups before and after treatment ($\bar{x}\pm s$, LogMAR)

Groups	n	Before treatment	1mo after treatment	2mo after treatment	3mo after treatment	t	P
Non-injection group	100	0.69±0.21	0.71±0.18	0.70±0.23	0.69±0.31	0.731	8.295
Control group	100	0.67±0.23	0.46±0.12	0.41±0.14	0.38±0.09	8.732	0.000
Study group	100	0.71±0.13	0.41±0.22	0.41±0.35	0.36±0.17	9.011	0.000

Table 3 Comparison of serum lncRNA MALAT1 levels among the three groups before and after treatment ($\bar{x}\pm s$, ng/L)

Groups	n	Before treatment	1mo after treatment	2mo after treatment	3mo after treatment	t	P
Non-injection group	100	156.31±13.96	156.40±14.01	156.41±13.99	156.36±13.98	0.824	8.932
Control group	100	158.21±14.36	103.26±11.21	103.31±12.53	100.48±9.53	25.041	0.000
Study group	100	155.67±22.01	81.14±13.01	79.69±11.54	77.26±10.32	36.011	0.000

after treatment were (324.81±130.90) μm, (324.86±131.06) μm, (324.75±130.87) μm and (324.83±130.66) μm respectively. There was no significant difference in CMT (P>0.05). The CMT of patients in the control group before treatment and 1, 2 and 3mo after treatment were (322.89±131.62) μm, (289.74±101.24) μm, (277.68±102.52) μm, and (264.49±100.71) μm, respectively. As such, CMT decreased significantly after treatment compared with that before treatment (P<0.05). The CMT of patients in the study group before treatment and at 1, 2 and 3mo after treatment were (320.71±129.87) μm, (221.47±90.01) μm, (220.69±92.58) μm and (209.26±87.52) μm respectively. Similarly, CMT decreased significantly after treatment compared with that before treatment (P<0.05). In addition, compared with the control group, CMT decreased more significantly in the study group (P<0.05). (Table 4; Figure 1 A-L).

Adverse Events There were no mental diseases, nervous system diseases, allergies and other adverse reactions in the two groups during treatment observation and follow-up. The adverse reaction rate of patients in the control group during follow-up was 11.0% (11/100). Eight cases and 8 eyes had different degrees of the subconjunctival haemorrhage, which was absorbed within 10d, and 3 cases (3 eyes) had mild inflammatory reactions in the anterior chamber on the second day after the operation, which recovered within 3d. The adverse reaction rate in the study group was 2.0% (2/100). Two subjects (2 eyes) had different degrees of the subconjunctival haemorrhage, which was absorbed within 7d without other adverse reactions. The incidence of adverse eye reactions in the study group was significantly lower than that in the control group.

DISCUSSION

Due to continuous hyperglycemia and insulin metabolism disorder, DM may be associated with increased blood viscosity and abnormal vascular endothelial function, resulting in blood retinal barrier damage, microvascular leakage and finally DR with microaneurysms, hard exudation, cotton wool spots and macular edema as the main manifestations. Thus, due to DME in DR, patients can have a serious visual impairment or even blindness[18-19]. DR is a complex process involving various internal and external factors. The lncRNA is a group of RNA transcripts composed of more than 200 nucleotides and it has no protein coding ability. MALAT1 is an evolutionarily conserved lncRNA. It has been reported that some lncRNAs are involved in the occurrence and development of DR[20]. In addition, many studies have shown that MALAT1 also plays an important role in the occurrence and development of DR[21-22]; for example, yes-associated protein-1 (YAP1) may promote the occurrence and development of DR by regulating the MALAT1/miR/200b-30p/VEGFA axis and regulating the miR-125b/VE-CaALAN1 axis can promote angiogenesis of DR[23]. Previous studies have shown that some lncRNAs are involved in the development of retinal injury caused by hyperglycemia. The expression of lncRNA MALAT1 is up-regulated in high glucose-induced retinal injury. The expression of lncRNA MALAT1 was positively correlated with

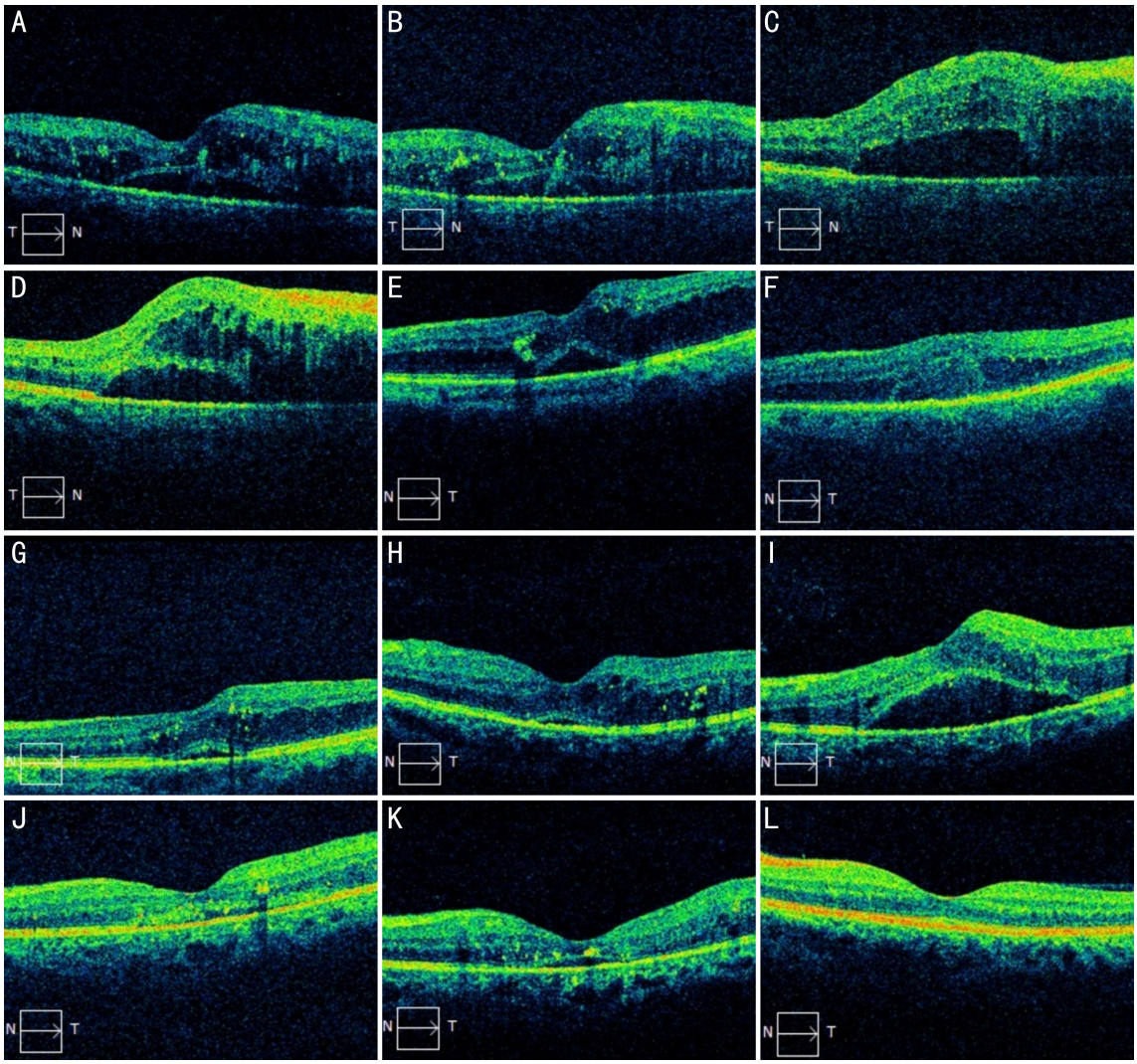

Figure 1 Changes of central macular thickness before and after treatment. A-D: Changes of central macular thickness in non-injection group before treatment and 1, 2 and 3mo after treatment; E-H: Changes of central macular thickness in control group before treatment and 1, 2 and 3mo after treatment; I-L: Changes of central macular thickness in study group before treatment and 1, 2 and 3mo after treatment.

Table 4 Comparison of central macular thickness among the three groups before and after treatment ($\bar{x}\pm s$, μm)

Groups	n	Before treatment	1mo after treatment	2mo after treatment	3mo after treatment	t	P
Non-injection group	100	324.81±130.90	324.86±131.06	324.75±130.87	324.83±130.66	0.802	8.733
Control group	100	322.89±131.62	289.74±101.24	277.68±102.52	264.49±100.71	29.167	0.000
Study group	100	320.71±129.87	221.47±90.01	220.69±92.58	209.26±87.52	54.481	0.000

the severity of DM[24]. In addition, studies have found that the expression of lncRNA MALAT1 is up-regulated in DR, resulting in an increase in the expression of serine enriched splicing factor (ASF/SF2), which leads to the development of the disease[25]. In addition, studies have shown that lncRNA MALAT1 is continuously up-regulated in DR renal tissue. The level of lncRNA MALAT1 in HK-2 cells is time-dependent, and the knockout of MALAT1 can inhibit renal tubular epithelial cell fibrosis[26]. In addition, an increase in lncRNA MALAT1 was observed in the retinal tissues of DR patients and Hg exposed human renal glomerular endothelial cells[27]. Therefore, the study of lncRNA MALAT1 will help provide new ideas for the prevention and treatment of DR.

At present, great progress has been made in research on the treatmentof DME, and this new progress is due to the emergence of anti-VEGF drugs, such as Conbercept and Ranibizumab, which can reduce the concentration of VEGF and prevent angiogenesis[28-34]. Therefore, selecting reasonable anti-VEGF drugs and employing standardised treatment is an important means to treat DME and delay the development of the disease. In this study, Ranibizumab were selected for the control group and Conbercept were chosen for the research group to treat DME patients. There were no significant changes in LogMAR BCVA, serum lncRNA

MALAT1 and CMT in the non-injection group ($P>0.05$). The serum lncRNA MATAL1 level, CMT and BCVA were measured before and during the 3mo after treatment. The results showed that the LogMAR BCVA of the control group was significantly higher than that before treatment ($P<0.05$). The LogMAR BCVA of patients in the study group for 3mo after treatment was significantly higher than that before treatment ($P<0.05$), but there was no significant difference between the study group and the control group ($P<0.05$). The level of serum lncRNA MALAT1 in the control group decreased during the 3mo after treatment, and the level of serum lncRNA MALAT1 in the study group decreased significantly in the 3mo after treatment. The level of serum lncRNA MALAT1 in the study group was significantly lower than that of the control group ($P<0.05$). The CMT of patients in the control group decreased during the 3mo after treatment, and the CMT of patients in the study group decreased significantly during the 3mo after treatment. The CMT of the study group was significantly lower than that of the control group ($P<0.05$). The incidence of adverse reactions in the study group (2.0%) was significantly lower than that in the control group (11.0%). Therefore, our study showed that Conbercept injections can more effectively reduce the level of lncRNA MATAL1 in serum, inhibit neovascularisation, reduce CMT, reduce DME, inhibit disease progression, improve vision and significantly reduce the risk of blindness in patients with DME.

In conclusion, Conbercept injections can significantly reduce the level of serum lncRNA MALAT1, reduce CMT, reduce DME and improve vision in patients with DME. The therapeutic effectiveness and safety of Conbercept are significantly better than Ranibizumab.

REFERENCES

1 American Diabetes Association. Diabetes. *American Diabetes Association*; 1966

2 Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;3(11):e442

3 Boyle JP, Thompson TJ, Gregg EW, *et al*. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. *Popul Health Metr* 2010;8:29

4 Huang ES, Laiteerapong N, Liu JY, *et al*. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. *JAMA Intern Med* 2014;174(2):251-258

5 Ting DSW, Cheung GCM, Wong TY. Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review. *Clin Exp Ophthalmol* 2016;44(4):260-277

6 Cai J, Boulton M. The pathogenesis of diabetic retinopathy: old concepts and new questions. *Eye (Lond)* 2002;16(3):242-260

7 Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. *Nat Rev Genet* 2016;17(1):47-62

8 Gross JG, Glassman AR, Liu DN, *et al*. Five-year outcomes of panretinal photocoagulation *vs* intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA Ophthalmol* 2018;136(10):1138-1148

9 Stahl A, Lepore D, Fielder A, *et al*. Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. *Lancet* 2019;394(10208):1551-1559

10 Glassman AR, Wells JA III, Josic K, *et al*. Five-year outcomes after initial aflibercept, bevacizumab, or ranibizumab treatment for diabetic macular edema (protocol T extension study). *Ophthalmology* 2020;127(9):1201-1210

11 Woo SJ, Veith M, Hamouz J, *et al*. Efficacy and safety of a proposed ranibizumab biosimilar product *vs* a reference ranibizumab product for patients with neovascular age-related macular degeneration: a randomized clinical trial. *JAMA Ophthalmol* 2021;139(1):68-76

12 Cui J, Sun D, Lu H, *et al*. Comparison of effectiveness and safety between conbercept and ranibizumab for treatment of neovascular age-related macular degeneration. A retrospective case-controlled non-inferiority multiple center study. *Eye (Lond)* 2018;32(2):391-399

13 Liu K, Song YP, Xu GZ, *et al*. Conbercept for treatment of neovascular age-related macular degeneration: results of the randomized phase 3 PHOENIX study. *Am J Ophthalmol* 2019;197:156-167

14 Zhang YD, Gao Z, Zhang XM, *et al*. Effect of intravitreal conbercept injection on VEGF-A and-B levels in the aqueous and vitreous humor of patients with proliferative diabetic retinopathy. *Exp Ther Med* 2021;21(4):332

15 Shi LK, Yang J, Lin JY. What is the impact of intravitreal injection of conbercept on neovascular glaucoma patients: a prospective, interventional case series study. *BMC Ophthalmol* 2019;19(1):128

16 Xu Q, Gong CJ, Qiao L, *et al*. Downregulation of angiogenic factors in aqueous humor associated with less intraoperative bleeding in PDR patients with NVG receiving conbercept: a randomized controlled trial. *BMC Ophthalmol* 2022;22(1):224

17 Hu ZZ, Cao X, Chen L, *et al*. Monitoring intraocular proangiogenic and profibrotic cytokines within 7 days after adjunctive anti-vascular endothelial growth factor therapy for proliferative diabetic retinopathy. *Acta Ophthalmol* 2022;100(3):e726-e736

18 Hung CC, Lin HYH, Hwang DY, *et al*. Diabetic retinopathy and clinical parameters favoring the presence of diabetic nephropathy could predict renal outcome in patients with diabetic kidney disease. *Sci Rep* 2017;7(1):1236

19 Zhang PC, Wu CR, Wang ZL, *et al*. Effect of lutein supplementation on visual function in nonproliferative diabetic retinopathy. *Asia Pac J Clin Nutr* 2017;26(3):406-411

20 Zhou L, Xu DY, Sha WG, et al. Long non-coding MIAT mediates high glucose-induced renal tubular epithelial injury. *Biochem Biophys Res Commun* 2015;468(4):726-732

21 Liu B, Qiang L, Wang GD, *et al*. LncRNA MALAT1 facilities high glucose induced endothelial to mesenchymal transition and fibrosis *via* targeting miR-145/ZEB2 axis. *Eur Rev Med Pharmacol Sci* 2019;23(8):3478-3486

22 Li YB, Ren DJ, Xu GS. Long noncoding RNA MALAT1 mediates high glucose-induced glomerular endothelial cell injury by epigenetically inhibiting klotho *via* methyltransferase G9a. *IUBMB Life* 2019;71(7):873-881

23 Fawzy MS, Abu AlSel BT, Al Ageeli E, *et al*. Long non-coding RNA MALAT1 and microRNA-499a expression profiles in diabetic ESRD

patients undergoing dialysis: a preliminary cross-sectional analysis. *Arch Physiol Biochem* 2020;126(2):172-182

24 Tan AJ, Li TR, Ruan LB, *et al*. Knockdown of Malat1 alleviates high-glucose-induced angiogenesis through regulating miR-205-5p/VEGF-Aaxis. *Exp Eye Res* 2021;207:108585

25 Hu MS, Wang R, Li XB, *et al*. LncRNA MALAT1 is dysregulated in diabetic nephropathy and involved in high glucose-induced podocyte injury *via* its interplay with β-catenin. *J Cell Mol Med* 2017;21(11):2732-2747

26 Zheng H, Li PX, Kwok JG, *et al*. Alcohol and hepatitis virus-dysregulated lncRNAs as potential biomarkers for hepatocellular carcinoma. *Oncotarget* 2017;9(1):224-235

27 Soares do Amaral N, Cruz E Melo N, de Melo Maia B, *et al*. Noncoding RNA profiles in tobacco- and alcohol-associated diseases. *Genes* 2016;8(1):6

28 Yu YY, Cheng Y, Chang LB, *et al*. Triamcinolone as an adjunct to the combination of anti-VEGF for the management of diabetic macular edema. *Int J Ophthalmol* 2021;14(6):869-874

29 Cheng Y, Yuan L, Zhao MW, *et al*. Real-world outcomes of two-year Conbercept therapy for diabetic macular edema. *Int J Ophthalmol* 2021;14(3):416-422

30 Zhang Y, Yao J, Quan Y, *et al*. Treatment response to Conbercept of different types of diabetic macular edema classified based on optical coherence tomography. *Nan Fang Yi Ke Da Xue Xue Bao* 2021;41(10):1501-1508

31 Liu K, Wang HY, He W, *et al*. Intravitreal conbercept for diabetic macular oedema: 2-year results from a randomised controlled trial and open-label extension study. *Br J Ophthalmol* 2022;106(10):1436-1443

32 Payne JF, Wykoff CC, Clark WL, *et al*. Randomized trial of treat and extend ranibizumab with and without navigated laser for diabetic macular edema. *Ophthalmology* 2017;124(1):74-81

33 Vader MJC, Schauwvlieghe AS ME, Verbraak FD, *et al*. Comparing the efficacy of bevacizumab and ranibizumab in patients with diabetic macular edema (BRDME). *Ophthalmol Retina* 2020;4(8):777-788

34 Holekamp N, Duff SB, Rajput Y, *et al*. Cost-effectiveness of ranibizumab and aflibercept to treat diabetic macular edema from a US perspective: analysis of 2-year Protocol T data. *J Med Econ* 2020;23(3):287-296