Comparative Study of the Intravenous Infusion of Umbilical Cord Mesenchymal Stem Cells and A Modified Sub-Tenon’s Capsule Injection of Triamcinolone Acetonide in Retinitis Pigmentosa Combined with Macular Edema

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Research

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Abstract

Background: Retinitis pigmentosa (RP) is a hereditary retinal degenerative disease leading to eventual blindness. Macular edema (ME) is a frequent complication in RP. When RP is combined with ME, the visual impairment further worsens. Well controlled ME is crucial to prevent RP from advancing. We compared the intravenous infusion of umbilical cord mesenchymal stem cells (UCMSCs) and a modified sub-Tenon's capsule injection of triamcinolone acetonide (TA) in the treatment of RP combined with ME to assess their safety and efficacy in eliminating macular edema.

Methods: A phase I/II clinical trial enrolled 20 patients was conducted. Patients in the UCMSCs infusion group received a single intravenous infusion of $3 \times 10^6$ UCMSCs, and patients in the TA injection group received a modified sub-Tenon's capsule injection of 20 mg of TA. All patients were followed up for 6 months. Systemic and ophthalmological investigations were performed to assess the safety and efficacy.

Results: There were no severe adverse effects in both groups. At 2\textsuperscript{nd} month follow up, the thickness of the central fovea in TA injection group was significantly lower than that in UCMSCs infusion group (P<0.05). The gradient of decrease of average macular thickness in TA injection group was significantly higher than that in UCMSCs group (P<0.05). At 6\textsuperscript{th} month follow up, the central fovea thickness was higher in the TA injection group than that in UCMSCs infusion group (P<0.05). The average amplitude/latency (A/L) of the P2 wave in the flash visual evoked potential (FVEP) in UCMSCs infusion group was significantly higher at 6\textsuperscript{th} month follow up than that in TA injection group (P<0.05).

Conclusions: This study suggests TA injection is more effective at reducing ME in a short term. UCMSC intravenous infusion exerts slow but persistent action in reducing ME, and can maintain the visual function for a longer time. These approaches can be applied separately or jointly depending on the disease condition for patients to benefit maximumly.

Trial registration: chictr.org.cn: ChiCTR-ONC-16008839. Registered on July 14, 2016.

Introduction

Retinitis pigmentosa (RP) is a group of hereditary retinal degenerative diseases characterized by progressive RPE dysfunction and photoreceptor loss. The clinical symptoms include poor night vision, visual field constriction and eventual blindness[1]. To date, there are no effective interventions to prevent this disease from advancing. When RP is combined with macular edema (ME), the condition is more difficult to treat, and the visual impairment becomes worse. The prevalence of ME in RP ranges from 11–49% depending on different approaches used for examination[2–4]. Thus, for patients who have RP combined with ME, effective control of the ME is crucial in order to rescue visual function.

Umbilical cord mesenchymal stem cells (UCMSCs) have a wide range of biological effects, such as anti-inflammation, immune modulation, paracrine and neurotrophy[5–7]. Some clinical trials have demonstrated beneficial effects of intravenous infusion of UCMSCs in the treatment of different systemic
diseases including neurological, cardiac and osteoarticular disorders[8–10]. Our previous study indicated intravenous infusion of UCMSCs can improve the visual function and life quality of RP patients[11]. However, it is still unknown if UCMSCs can help alleviate the ME secondary to RP. Triamcinolone acetonide (TA) is a widely used steroid that has long-acting anti-inflammation and immune modulation effects[12]. Systemic and local administration of TA have been applied in many retinal pathological conditions combining with ME [13]. Since UCMSCs and TA have different delivery routes and pharmacological mechanisms of action, their effectiveness may also vary in onset time, maintaining duration or magnitude of improvement. To know the differences between these two agents and make single or combined treatment regime accordingly will help patients get the maximum benefit. In this study, we compared the safety and efficacy of an intravenous infusion of UCMSCs and a modified sub-Tenon’s capsule administration of TA in patients who have RP combined with ME. Here, we report the results of our study.

**Materials And Methods**

**Study Design**

This is a prospective, open label, randomized, phase I/II clinical trial. This study was approved by the Medical Ethics Committee of Southwest Hospital, the Army Medical University, and conducted between July 2016 and March 2018. The subjects in the UCMSCs infusion group received a single intravenous infusion of $3 \times 10^6$ UCMSCs, and the subjects in the TA injection group received a single injection of 20 mg of TA. All of the subjects were followed for 6 months. Systemic and ophthalmological examinations were performed to assess the safety and efficacy (Fig. 1). The study adhered to the principles of the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Human Subjects and was registered in the Chinese Clinical Trial Registry (Primary Registry of the International Clinical Trials Registry Platform of the World Health Organization) (ChiCTR-ONC-16008839). Every patient that was recruited for the study signed a written informed consent form.

**UCMSCs Preparation**

The UCMSCs used for this study were derived from neonatal umbilical cord tissue according to the standard protocol and met the criteria approved by the International Society for Cellular Therapy[14–17]. The preparation of the cells was performed by the Biotherapy Centre of the Army Medical University. Briefly, the Wharton's Jelly tissue was aseptically cut into a homogenate of 2-3mm$^3$ tissue blocks, then the blocks were seeded into T75 flasks in Mesenchymal Stem Cell Basal Medium (DAKEWE, Beijing, China) supplemented with 5% UltraGROTM (HPCFDCRL50, Helios). The tissue blocks were cultured at 37 °C, 5% CO2 for about 10 days for UCMSCs to reach confluence. Then cells were digested with 0.125% Trypsin and passaged at 1:3 ratio. Each enzymatic digestion step was considered to be a passage. Cells at P3-P5 were used for infusion. All infused UCMSCs were prepared based on the criteria approved by the International Society for Cellular Therapy. The final products met all of the following criteria: cell viability
was no less than 95%; the cells were sterile; the cells did not have endotoxins, mycoplasma, hepatitis B, hepatitis C, or syphilis; and the cells exhibited expression of the appropriate surface markers (the positive rate of CD34 and CD45 was less than 0.5%, the positive rate of CD29 was more than 95%, the positive rate of CD90 was more than 95%, the positive rate of CD105 was more than 95%, and the positive rates of CD71 and CD73 were more than 95%). (Supplementary data: Figure S1-S3)

**Patient Screening**

The inclusion criteria were as follows:

(1) Patients aged 18–65 years (including 18 and 65 years) who had signed an informed consent form.

(2) Patients with at least one eye or both eyes suffering from impaired vision caused by retinitis pigmentosa combined with macula edema.

(3) Patients who voluntarily selected UCMSCs infusion or TA injection for the treatment of retinitis pigmentosa combined with macula edema.

(4) Using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity checklist at a distance of 4 meters, the best corrected visual acuity scores was ≥ 19 letters and ≤ 73 letters (or the equivalent of about Snellen eyesight from 20/400 to 20/40).

(5) Patients who had the ability to adhere to the study follow-up and protocol requirements.

The exclusion criteria were as follows:

(1) Patients with any active intraocular inflammation, infection, or concomitant diseases in their eyes that may affect the interpretation of the results of the study or may lead to visual impairment, including severe cataracts, glaucoma, retinal vascular obstruction, retinal detachments, macular holes, vitreous macular traction, and choroidal neovascularization.

(2) Patients with a history of intraocular surgery.

(3) Patients with a stroke, coronary heart disease, renal insufficiency requiring dialysis or kidney transplantation, or other systemic chronic diseases.

(4) Patients with hypertension (systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg) or diabetes that cannot be controlled by drugs.

(5) Females who planned to become pregnant within the next 6 months, were pregnant or were lactating.

**Intravenous Infusion of UCMSCs**

The vital signs of all of the patients involved in this study, including their temperature, respiration rate, pulse, blood pressure, oxygen saturation, electrocardiogram signals and pain severity, were continuously monitored before, during and up to 2 hours after the infusion. The patients underwent treatment only
when all of their vital signs were normal. First, every patient received 5 mg of dexamethasone sodium phosphate in an injection and then received a sequential intravenous infusion of UCMSCs \((3 \times 10^6 \text{ cells}, 250 \text{ ml per person})\) through the dorsal hand vein within 60 minutes. The infusion was stopped immediately and treated in a timely manner when immune rejection, anaphylaxis, and infusion reactions, such as headache, dizziness, nausea and vomiting, occurred.

**Modified Sub-Tenon’s Capsule Injection of TA**

A 2 mm incision was made 10 mm to the limbus at the superotemporal bulbar conjunctiva. The conjunctiva, bulbar fascia and Tenon’s capsule were bluntly dissected exposing the sclera. A specially developed curved needle with a blunt tip was inserted through the incision and posteriorly run along the surface of the sclera until it reached the posterior pole that corresponded to the macular area. Then, 20 mg of TA was injected into the sub-Tenon’s capsule space. The needle was slowly withdrawn to avoid any leaking of the drug, and pressure was applied to the conjunctiva incision for a few seconds. No sutures were needed. An antibiotic ointment was applied in the injected eye, and the eye was patched for 1 day. Antibiotic eye drops were used for a few days following the injection.

**Clinical Evaluation**

The safety and efficacy parameters were evaluated at baseline and at 1 d, 1 w, 1 m, 2 m, 3 m, 6 m after the intravenous UCMSCs infusion or the TA injection. Relevant blood biochemical indexes were measured before and after treatment. The best corrected visual acuity (BCVA) was used as the standard for visual acuity evaluation and was determined by the Early Treatment Diabetic Retinopathy Study (ETDRS) alphabet. Optical computed tomography (OCT) scans were performed to evaluate the central fovea and average thickness of the macula. To calculate the average macular thickness, three concentric circles were made with the fovea as the center with diameters of 1,000 µm, 3,000 µm, and 6,000 µm, and two perpendicular lines were used to divide the whole macula into nine regions, and the average thickness of the nine regions represented the average macular thickness. The visual fields were tested using a Humphrey Visual Field Analyzer. The flash visual evoked potential (FVEP) was tested according to the standardized procedures developed by the International Society for Clinical Electrophysiology of Vision (ISCEV), and the latent time and amplitude of the P2 wave were analyzed.

**Statistical Analysis**

The SPSS18.0 software was used to describe and analyze the data. The measured data that had a normal distribution were expressed as the mean ± standard deviation. The comparison of the average value was performed by a paired-samples T test. The comparison of rate of change between groups was performed by Repeated Measurement ANOVA. P < 0.05 and P < 0.01 indicated significant differences between groups, and P > 0.05 indicated that there was no significant difference.

**Results**

**1. Safety of the UCMSCs infusion and the TA injection**
There were 20 patients enrolled in the study, and they were randomized into UCMSCs infusion group and TA injection group (Table 1). All of the patients were clinically diagnosed with RP combined with ME. The vital signs of the patients in the UCMSCs group were stable during the infusion process. There were no adverse effects, such as fever, infection, headache, vertigo, nausea, vomiting, allergic reactions or immune rejection reactions that happened during or after the UCMSCs infusion. There was a substantial increase of interleukin-6 (IL-6) for a few patients in both groups at 1st month, and then the IL-6 decreased to normal level subsequently. There were no significant changes in white blood cell, liver and renal function, C-reactive protein (CRP), procalcitonin (PCT) throughout the follow-up period. In the TA injection group, there were no local or systemic adverse effects for all of the patients before or after the injection. (Supplementary data: Table S1, S2)

![Table 1](image)

|                          | MSC              | TA               | P value |
|--------------------------|------------------|------------------|---------|
| Subjects                 | 10               | 10               |         |
| Male                     | 6                | 8                |         |
| Female                   | 4                | 2                |         |
| Average age              | 38.3 ± 13.5      | 45.6 ± 12.2      | >0.05   |
| Average fovea thickness  | 294.13 ± 29.11   | 330 ± 42.63      | >0.05   |
| Average macular thickness| 259.54 ± 18.24   | 259.92 ± 20.56   | >0.05   |
| Average BCVA             | 57.4 ± 20.3      | 56.0 ± 13.8      | >0.05   |
| Average visual field sensitivity | 538.56 ± 176.62 | 494.80 ± 114.53 | >0.05   |
| Average A/L in FVEP      | 0.106 ± 0.024    | 0.084 ± 0.013    | >0.05   |

2. Macular retinal thickness analysis

2.1 Thickness of the central fovea

There was no significant difference between the baselines of the two groups (P > 0.05). In the UCMSCs infusion group, the thickness of the central fovea did not change substantially until the 6th month follow up when it decreased significantly. In the TA injection group, the thickness of the central fovea decreased the most at the 2nd month follow up, when was significantly lower than that in the UCMSCs infusion group (P < 0.05), and then it gradually increased until the 6th month, when it was significantly higher than that in the UCMSCs infusion group (P < 0.05). (Fig. 2A,2B)

2.2 Average thickness of the macular region
The baselines of the average thickness of the two groups were not significantly different (P > 0.05). In the UCMSCs infusion group, the average macular thickness increased at the 3rd month follow up, and then gradually decreased up to the 6th month, when the value was lower than that at baseline, but there were no significant differences observed. In the TA injection group, there was an obvious decreasing trend in the average macular thickness during the first 2 months of follow up, and the gradient of decrease was significantly higher than that in the UCMSCs group (P < 0.05) which indicates a stronger effect of relieving macular edema in the TA injection group than in the UCMSCs group. (Fig. 2C)

3. Assessments of Visual Functions

3.1 Change of BCVA

In the UCMSCs group, the BCVA showed no significant difference at any of the follow ups. In the TA group, there was a rise in the 2nd and 3rd months, but it was not significantly different when compared with the other follow ups or with that in the UCMSCs group. (Fig. 3A)

3.2 Change of visual fields

The total value of visual field sensitivity was calculated. In the UCMSCs infusion group, the overall value continued to increase during the whole follow up period with a mild fluctuation in the 2nd month. In the TA injection group, this value peaked at the 1st month, and then gradually decreased to lower than the baseline level at the 6th months. The average values of visual sensitivity in the UCMSCs group were higher than those in the TA group in all of the follow ups, and the differences became larger as time progressed. However, the differences were not statistically significant (P > 0.05). (Fig. 3B)

3.3. Comparison of FVEP

The ratio of amplitude to the latency of the P2 wave (A/L) in the FVEP was calculated as an index reflecting the improvement in the FVEP. The results showed the A/L in the UCMSCs infusion group increased gradually and reached the peak value at the 6th month follow up in spite of a slight decrease at the 2nd month, which was still higher than the baseline value. In the TA injection group, the highest A/L value was observed at the 2nd month, and then it decreased to below the baseline at the 6th month when it was significantly lower than that in the UCMSCs group (P < 0.05). (Fig. 3C)

Discussion

As a major worldwide retinal degenerative disease that causes blindness, the hereditary modes of RP can be autosomal dominant (30–40%), autosomal recessive (50–60%), or a X-linked trait (5–15%)[18]. The inherited nature of RP leads to progressive photoreceptor apoptosis and irreversible visual loss. However, when RP is combined with ME, the impairment of visual function becomes worse. The impairment of the
blood retinal barrier (BRB) is thought to be the main cause of ME in RP[19, 20]. With the progression of RP, both retinal vascular endothelium and RPE lose their normal intercellular junctions, which gives rise to increased retinal vascular permeability and a flow of interstitial fluid from the choroid to the retinal tissue [19, 21, 22]. Inflammation and auto-immune processes play an important role in the pathogenesis of vascular endothelium and RPE dysfunction and the subsequent breakdown of the BRB[23–25].

Different methods have been used to treat ME in RP patients, such as systemic administration of carbonic anhydrase inhibitors or steroids, intravitreal injection of steroids or anti-VEGF agents, laser photocoagulation and surgery[26, 27]. Triamcinolone acetonide (TA) is a kind of synthetic long-acting steroid and has been widely used in the treatment of ME because of its pharmacological actions of anti-inflammation, immune modulation, BRB stabilization and VEGF downregulation[13, 28]. As far as systemic side effects and local risks are concerned, delivering steroids by a sub-Tenon’s capsule injection is a relatively safe approach for treating ME and has been applied in different retinal diseases[29]. Unlike a retrobulbar injection, the sub-Tenon’s capsule injection is able to keep and restrict drugs in the sub-Tenon’s capsule space for a relatively long time without allowing diffusion into the orbit tissue, which makes more drugs permeate into the choroid and retina. To treat ME more precisely, we modified the sub-Tenon’s capsule injection technique by replacing the traditional short, sharp needle with a long, curved, blunt needle that is able to run along the surface of the sclera and reach the posterior pole of the eyeball, where the placement of the needle accurately corresponds to the ME lesion. Delivery of TA by a modified sub-Tenon’s capsule injection can facilitate the drug diffusion while avoiding risks and complications secondary to intraocular administration.

Given the wide range of biological effects, such as anti-inflammation, immune modulation, neurotroph and paracrine, UCMSCs have been applied in many systemic diseases and have been shown to have promising therapeutic effects[8–10]. In animal models of RP, intravenously administered UCMSCs were found to produce large amounts of neurotrophic factors, and therefore, the photoreceptors were partially protected from apoptosis[30–32]. Additionally, the infused UCMSCs can directionally migrate to retinal lesions and exert their biological effects to promote the growth of blood vessels, improve the function of BRB and help reconstruct normal retinal structure[33, 34]. Local injection of UCMSCs has been applied in RP patients and has shown beneficial outcomes[35]. In our previous study, we found intravenous administration of USMSCs demonstrated beneficial effects on the improvement of overall visual function of RP patients and their vision related life quality as well[11]. However, it has not been reported if intravenous infusion of UCMSCs can help improve ME, a major pathological condition secondary to RP.

We compared the effects of these two agents in alleviating ME. All patients tolerated these two approaches well. There were no severe systemic or local adverse effects that occurred during the entire follow up, although a minority of patients in both groups showed a rise of IL-6 level early after treatment. In TA injection group, patients showed a more rapid reduction of the macular thickness in the first 2 months and then the macular thickness rebounded to the baseline level, which implied the quick but relatively short-term effect of the TA injection in relieving ME. Whereas in UCMSCs infusion group, the macular thickness did not change significantly until the sixth month, when it was lower than the TA
injection group, which indicated a slow but more persistent action of the UCMSCs. The BCVA and visual field sensitivity of all of the patients in the two groups did not change significantly, and there was no significant difference between the two groups, implying a limited improvement of photoreceptor function following the relief of ME. The FVEP in the UCMSCs infusion group improved the most at six months, at which point it was significantly higher than that in the TA injection group. This result implied that the UCMSCs infusion may be more beneficial than the TA injection in terms of improving the overall visual function, which may be due to the UCMSCs having more biological effects besides anti-inflammation, such as neurotroph, paracrine, or even cell replacement.

Conclusions

The modified sub-Tenon's capsule injection of TA and intravenous infusion of UCMSCs were both safe for RP patients with ME. Our results suggested that TA injection can reduce macular edema more quickly and effectively than UCMSCs infusion in the short term, but the effect of the UCMSCs infusion may be more persistent. UCMSCs infusion is more beneficial for improving the overall visual function. This study demonstrated that both modified sub-Tenon's capsule injection of TA and intravenous infusion of UCMSCs are promising therapeutic approaches for patients who have RP combined with ME. Because of the different characteristics, these approaches can be applied separately or jointly depending on the disease condition for patients to achieve maximum benefits. Nevertheless, more controlled cohorts and a larger number of subjects are needed to confirm the results.

Abbreviations

UCMSCs
Umbilical Cord Mesenchymal Stem Cells; TA = Triamcinolone Acetonide; ME = Macular Edema; FVEP = Flash Visual Evoked Potential; BCVA = Best Corrected Visual Acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; OCT = Optical computed tomography; A/L = amplitude / latency; IL-6 = interleukin-6; CRP = C-reactive protein; PCT = Procalcitonin

Declarations

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Author’s Contributions

TTZ: patient recruitment, data acquisition, analysis, manuscript writing; HXL: patient recruitment, data acquisition, analysis; FW: patient recruitment, data acquisition; YL: conception and design, revision of
manuscript; XHM: data analysis and interpretation, revision of manuscript; ZQY: conception and design, revision of manuscript; SYL: data analysis and interpretation, revision of manuscript.

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**Availability of data and materials**

All the data of the current trial are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

This clinical trial was approved by the Medical Ethics Committee of Southwest Hospital, the Army Medical University, and was registered in the Chinese Clinical Trial Registry (Primary Registry of the International Clinical Trials Registry Platform of the World Health Organization) (ChiCTR-ONC-16008839). All patients recruited for the study have signed a written informed consent.

**Consent for publication**

All patients have signed informed consents. No personal details or contact data of patient was included.

**Competing interests**

The authors declare that they have no competing interests

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**References**

1. Anasagasti A, Irigoyen C, Barandika O, Lopez de Munain A, Ruiz-Ederra J. Current mutation discovery approaches in Retinitis Pigmentosa. Vision Res. 2012;75:117–29.

2. Huckfeldt RM, Comander J. Management of Cystoid Macular Edema in Retinitis Pigmentosa. Semin Ophthalmol. 2017;32(1):43–51.

3. Salvatore S, Fishman GA, Genead MA. Treatment of cystic macular lesions in hereditary retinal dystrophies. Surv Ophthalmol. 2013;58(6):560–84.

4. Hajali M, Fishman GA, Anderson RJ. The prevalence of cystoid macular oedema in retinitis pigmentosa patients determined by optical coherence tomography. Br J Ophthalmol.
5. Xiuying LI, Bai J, Xiaofeng JL, Ronggui LI, Xuan Y, Wang Y. Comprehensive characterization of four different populations of human mesenchymal stem cells as regards their immune properties, proliferation and differentiation. Int J Mol Med. 2014;34(3):695–704.

6. Nagamura-Inoue T, He H. Umbilical cord-derived mesenchymal stem cells: Their advantages and potential clinical utility. World J Stem Cells. 2014;6(2):195–202.

7. Zou JP, Huang S, Peng Y, Liu HW, Cheng B, Fu XB, Xiang XF. Mesenchymal stem cells/multipotent mesenchymal stromal cells (MSCs): potential role in healing cutaneous chronic wounds. Int J Low Extrem Wounds. 2012;11(4):244–53.

8. Riordan NH, Morales I, Fernandez G, Allen N, Fearnot NE, Leckrone ME, Markovich DJ, Mansfield D, Avila D, Patel AN, Kesari S, Paz Rodriguez J. Clinical feasibility of umbilical cord tissue-derived mesenchymal stem cells in the treatment of multiple sclerosis. J Transl Med. 2018;16(1):57.

9. Mukai T, Tojo A, Nagamura-Inoue T. Mesenchymal stromal cells as a potential therapeutic for neurological disorders. Regen Ther. 2018;9:32–7.

10. Bartolucci J, Verdugo FJ, Gonzalez PL, Larrea RE, Abarzua E, Goset C, Rojo P, Palma I, Lamich R, Pedreros PA, Valdivia G, Lopez VM, Nazzal C, Alcayaga-Miranda F, Cuenca J, Brobeck MJ, Patel AN, Figueroa FE, Khoury M. Safety and Efficacy of the Intravenous Infusion of Umbilical Cord Mesenchymal Stem Cells in Patients With Heart Failure: A Phase 1/2 Randomized Controlled Trial (RIMECARD Trial [Randomized Clinical Trial of Intravenous Infusion Umbilical Cord Mesenchymal Stem Cells on Cardiopathy]). Circ Res. 2017;121(10):1192–204.

11. Zhao T, Liang Q, Meng X, Duan P, Wang F, Li S, Liu Y, Yin ZQ. (2020). Intravenous Infusion of Umbilical Cord Mesenchymal Stem Cells Maintains and Partially Improves Visual Function in Patients with Advanced Retinitis Pigmentosa. Stem Cells Dev.

12. Saraiva VS, Sallum JM, Farah ME. Treatment of cystoid macular edema related to retinitis pigmentosa with intravitreal triamcinolone acetonide. Ophthalmic Surg Lasers Imaging. 2003;34(5):398–400.

13. Ip MS, Gottlieb JL, Kahana A, Scott IU, Altaweel MM, Blodi BA, Gangnon RE, Puliafito CA. Intravitreal triamcinolone for the treatment of macular edema associated with central retinal vein occlusion. Arch Ophthalmol. 2004;122(8):1131–6.

14. Mushahary D, Spittler A, Kasper C, Weber V, Charwat V. Isolation, cultivation, and characterization of human mesenchymal stem cells. Cytometry A. 2018;93(1):19–31.

15. Salehinejad P, Alitheen NB, Ali AM, Omar AR, Mohit M, Janzamin E, Samani FS, Torshizi Z, Nemtatollahi-Mahani SN. Comparison of different methods for the isolation of mesenchymal stem cells from human umbilical cord Wharton's jelly. In Vitro Cell Dev Biol Anim. 2012;48(2):75–83.

16. Majore I, Moretti P, Stahl F, Hass R, Kasper C. Growth and differentiation properties of mesenchymal stromal cell populations derived from whole human umbilical cord. Stem Cell Rev Rep. 2011;7(1):17–31.
17. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop D, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8(4):315–7.

18. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. Lancet. 2006;368(9549):1795–809.

19. Larsen M, Engler CB, Haim M, Lund-Andersen H. Blood-retina barrier permeability is independent of trace substance lipid solubility in retinitis pigmentosa and in the healthy eye. Int Ophthalmol. 1997;21(4):229–34.

20. Vinores SA, Kuchle M, Derevjanik NL, Henderer JD, Mahlow J, Green WR, Campochiaro PA. Blood-retinal barrier breakdown in retinitis pigmentosa: light and electron microscopic immunolocalization. Histol Histopathol. 1995;10(4):913–23.

21. Vinores SA, Derevjanik NL, Ozaki H, Okamoto N, Campochiaro PA. Cellular mechanisms of blood-retinal barrier dysfunction in macular edema. Doc Ophthalmol. 1999;97(3–4):217–28.

22. Marmor MF. Mechanisms of fluid accumulation in retinal edema. Doc Ophthalmol. 1999;97(3–4):239–49.

23. Yoshida N, Ikeda Y, Notomi S, Ishikawa K, Murakami Y, Hisatomi T, Enaida H, Ishibashi T. Clinical evidence of sustained chronic inflammatory reaction in retinitis pigmentosa. Ophthalmology. 2013;120(1):100–5.

24. Strong S, Liew G, Michaelides M. Retinitis pigmentosa-associated cystoid macular oedema: pathogenesis and avenues of intervention. Br J Ophthalmol. 2017;101(1):31–7.

25. Narayan DS, Wood JP, Chidlow G, Casson RJ. A review of the mechanisms of cone degeneration in retinitis pigmentosa. Acta Ophthalmol. 2016;94(8):748–54.

26. Bakthavatchalam M, Lai FHP, Rong SS, Ng DS, Brelen ME. Treatment of cystoid macular edema secondary to retinitis pigmentosa: a systematic review. Surv Ophthalmol. 2018;63(3):329–39.

27. Liew G, Moore AT, Webster AR, Michaelides M. Efficacy and prognostic factors of response to carbonic anhydrase inhibitors in management of cystoid macular edema in retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2015;56(3):1531–6.

28. Moldow B, Sander B, Larsen M, Engler C, Li B, Rosenberg T, Lund-Andersen H. The effect of acetazolamide on passive and active transport of fluorescein across the blood-retina barrier in retinitis pigmentosa complicated by macular oedema. Graefes Arch Clin Exp Ophthalmol. 1998;236(12):881–9.

29. Koga T, Mawatari Y, Inumaru J, Fukushima M, Tanihara H. Trans-Tenon's retrobulbar triamcinolone acetonide infusion for refractory diabetic macular edema after vitrectomy. Graefes Arch Clin Exp Ophthalmol. 2005;243(12):1247–52.

30. Ding SLS, Kumar S, Mok PL. (2017). Cellular Reparative Mechanisms of Mesenchymal Stem Cells for Retinal Diseases. Int J Mol Sci 18(8).

31. Ng TK, Fortino VR, Pelaez D, Cheung HS. Progress of mesenchymal stem cell therapy for neural and retinal diseases. World J Stem Cells. 2014;6(2):111–9.
32. Wang S, Lu B, Girman S, Duan J, McFarland T, Zhang QS, Grompe M, Adamus G, Appukuttan B, Lund R. Non-invasive stem cell therapy in a rat model for retinal degeneration and vascular pathology. PLoS One. 2010;5(2):e9200.

33. Hou HY, Liang HL, Wang YS, Zhang ZX, Wang BR, Shi YY, Dong X, Cai Y. A therapeutic strategy for choroidal neovascularization based on recruitment of mesenchymal stem cells to the sites of lesions. Mol Ther. 2010;18(10):1837–45.

34. Shibata T, Naruse K, Kamiya H, Kozakae M, Kondo M, Yasuda Y, Nakamura N, Ota K, Tosaki T, Matsuki T, Nakashima E, Hamada Y, Oiso Y, Nakamura J. Transplantation of bone marrow-derived mesenchymal stem cells improves diabetic polyneuropathy in rats. Diabetes. 2008;57(11):3099–107.

35. Ozmert E, Arslan U. Management of retinitis pigmentosa by Wharton's jelly derived mesenchymal stem cells: preliminary clinical results. Stem Cell Res Ther. 2020;11(1):25.

Figures
Patients meeting inclusion criteria were enrolled

Clinical evaluations
Systemic examinations: laboratory assays, ECG, chest X-rays
Ophthalmological examinations: BCVA, slit lamp, fundus photography, FFA, OCT, FVEP

MSC infusion group

Preparation of UMSCs

Intravenous infusion of MSCs (single infusion of $3 \times 10^6$ cells)

TA injection group

Modified sub-Tenon's capsule injection of TA (20MG)

Following up for 6 months
Systemic and ophthalmological assessments at every visit (1d, 1w, 1m, 2m, 3m, 6m)

Evaluation of Safety and Efficacy

**Figure 1**

Flow chart of the study
Figure 2
Analysis of retinal thickness. A: Morphological changes in the UCMSCs infusion and TA injection groups. B: In the UCMSCs infusion group, the thickness of the central fovea decreased significantly at 6th month. In the TA injection group, the thickness of the central fovea decreased the most at the 2nd month follow up and was significantly lower than that in the UCMSCs infusion group (P<0.05). At 6th month, it was significantly higher than that in the UCMSCs infusion group (P<0.05). C: In the UCMSCs infusion group, the average macular thickness increased at the 3rd month follow up, and then gradually decreased up to the 6th month, but there were no significant differences. In the TA injection group, there was an obvious decreasing trend in the average macular thickness during the first 2 months follow up, and the degree of decrease was significantly higher than that in the UCMSCs group (P<0.05).

Figure 3
Assessments of visual functions. A: There were no significant differences in BCVA among each group or between the two groups. B: The average values of visual sensitivity in the UCMSCs group were higher than those in the TA group at all of the follow ups, and the difference became larger as time progressed. However, these differences were not statistically significant (P>0.05). C: The A/L in the UCMSCs infusion group increased gradually and reached the peak value at the 6th month follow up. In the TA injection group, the highest A/L value was observed at the 2nd month. Then, this value decreased to below the baseline level at the 6th month and was significantly lower than that in the UCMSCs group (P<0.05).

**Supplementary Files**

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- SupplementaryData.docx