

Subtenon implantation of wharton's jelly-derived mesenchymal stromal cells in retinitis pigmentosa

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ABSTRACT

Introduction: Retinitis pigmentosa (RP) is a clinically and genetically heterogeneous group of hereditary disorders in which there is progressive loss of photoreceptors and pigment epithelial function culminating in complete vision loss. Unfortunately, given the disease's devastating effects, it is untreatable and there is often little that can be done to improve visual outcomes in these patients. The lack of curative intervention creates a challenge in the management of RP and its progression. As such, the main goal is to slow down the apoptosis and loss of photoreceptors in order to delay visual deterioration.

Materials and Methods: We present two case illustrations of RP treated with WJ-MSC implanted in the deep subtenon space. Each patient underwent 4 sessions ranging from 1 to 3 months apart.

Results: At 3, 6, 9 and 12 months follow-up, the following were observed:(i) Both patients had no change in visual acuity and no further deterioration in vision or visual field.(ii) Optical coherence tomography showed a layer of hyperreflective material noted at the IO/OS junction area suggestive of a layer of new photoreceptors. The changes were noted in the macula and extramacular region for both patients.(iii) Both patients reported better discernment of colors and better vision at certain times during the day. (iv) No systemic or ocular adverse events were observed in the 12 month follow-up following the subtenon implantation of WJ-MSC.

Conclusion: Subtenon implantation of WJ-MSC appears to be a feasible and safe option to consider in delaying the progression of retinal degeneration and improving the quality of life affected by visual deterioration in patients with RP.

KEYWORDS:

Mesenchymal Stem Cells, Retinitis Pigmentosa, Subtenon implantation

INTRODUCTION

Retinitis pigmentosa (RP) is a group of hereditary degenerative disorder associated with retinal dystrophy of photoreceptors and an important cause of severe vision impairment. The degeneration of photoreceptors in RP is

usually associated with gene mutations which maybe inherited as autosomal recessive (50–60%), autosomal dominant (30–40 %), or X-linked recessive. It has a very variable clinical course, and in the initial stages, the disease involves the destruction of the rod photoreceptors causing loss of night vision and progressive peripheral visual field loss, leading to tunnel vision. Further progression to later stages results in degeneration of cones leading to loss of central and colour vision followed by blindness at age 40–50 years.^{1,2}

Part of the difficulty in treating RP is its complex and diverse genetic aetiology. While there are several different supportive treatments available, including supplementation with vitamin A and omega-3 fatty acids, or usage of neurotrophic factors and antioxidants, these therapies have often been shown to be ineffective, failing to address the root cause of the disease.³

Gene therapy has begun to show promising results for improving visual outcomes, as evidenced by new clinical trials like the one used to secure Luxturna's approval. However, there are still several important challenges for gene therapies including its severely limited therapeutic target and extremely high cost.⁴

Consequently, scientific interest is particularly directed at restoratory therapy based on stem cells. The latter aims to recover cell density as well as to preserve the remaining retinal cells by improving intra/extracellular conditions.^{6,7}

Mesenchymal stem cells are multipotent stromal cells with self-renewal and multi-differentiation abilities into various mesenchymal tissues, most notably bone, cartilage and adipose. Studies have also described the ability of MSC to differentiate into retinal progenitor cells, photoreceptors and retina neural-like cells whilst exerting neuroprotective and pro-regenerative effects via multiple paracrine factors.⁵

Özmert and Arslan recently reported the results of an open label, phase III clinical trial (NCT04224207) with WJ-MSCs. In this study, WJ-MSCs were implanted in the sub-tenon space in 32 patients (64 eyes) diagnosed with RP. In the 6-month follow-up period, a significant improvement in mean best corrected visual acuity (BCVA), outer retinal thickness values, mf-ERG results, and a decrease in the visual field mean deviation value were observed.⁸

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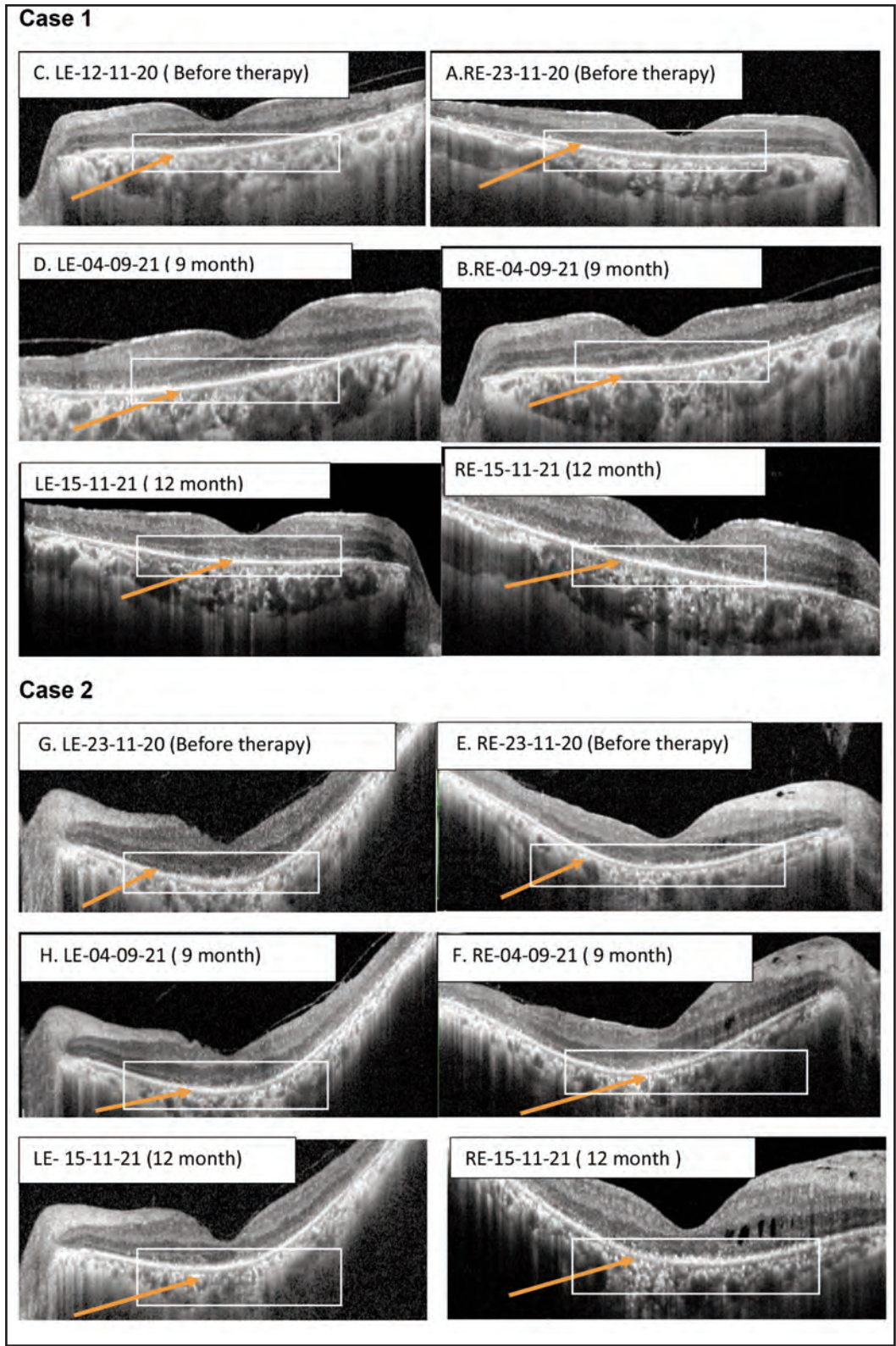


Fig. 1: OCT of Right Eye and Left Eye for both cases comparing the pre-treatment and 3rd and 4th post subtenon MSC implantations: (A,C &E,G): the OCT prior to MSC subtenon treatment- showing very minimal area of hyperreflectivity seen anterior to RPE layer. (B,D& F,H): OCT after the 4th dose of MSC and post follow up at 9 and 12 month respectively; showing increased area of hyperreflectivity (orange arrow) at the interdigitation zone anterior to the RPE layer signifying possible regeneration of the outer segment of PRC. The interdigitation zone is considered to be the contact cylinders formed by the apices of the RPE cells that encase part of the outer segment of the cones.

Findings were presented as numbers and percentages for categorical data and either median with interquartile range (IQR) or mean with standard deviation (SD) based on the parametric distribution of the data using Kolmogorov-Smirnov test. Missing values will be regarded as missing, and analysis will be performed on available data. All analyses were performed using SPSS version 26. This study received ethics approval from local Medical Research Ethics Committee (reference number: 2020525-8673).

RESULTS

Among the 200 patients, the majority were female and of Chinese ethnicity, and participants had a median (IQR) age of 83 (9) years (Table I).

During the terminal hospital admission, the median (IQR) number of hospital bed days was 6 (8) days. During the last 24 hours, patients were still on a median (IQR) of 8 (5) drugs. Many remained on vitamin and mineral supplementation (97/200 patients, 48.5%) and lipid-lowering therapy (70/200 patients, 35.0%). Table II summarises the key aspects of healthcare utilisation during the terminal admission.

In the preceding 6 months, the median (IQR) number of emergency department presentation and outpatient visits was 1 (1.0) episode, respectively. 72/200 patients (36%) had another hospital admission in the preceding 6 months, spending a median (IQR) of 9 (11) days. Five patients received specialist palliative input prior to their terminal admission.

DISCUSSION

This study has reported on the pattern of hospital healthcare utilisation by those aged over 70 who died in a Malaysian university hospital. More than half of the deceased spent at least 9 days in hospital and had either one emergency or outpatient visit in the preceding 6 months. Over one-third had also been admitted previously, spending almost 2 weeks in hospital. Most of them required radiological investigations, invasive procedures, antibiotics and had multiple medications that were continued up till the time of their death, some of which were non-beneficial.

This is the first study looking into healthcare utilisation among older adults in the last 6 months of life in the Malaysian hospital setting. The data reported represent those who passed away in the Department of Medicine, as participants were recruited across the different medical subspecialties. The stratified sampling method was followed by a randomised selection and minimised possible selection bias. The sample was also as representative as possible of all those aged 70 years and above that passed away in 2019. By extrapolating this study's sample to the total 472 patients that died in that year, it is possible to estimate that the overall healthcare utilisation by this older group of patients would be over 4200 inpatient bed days, 470 outpatient visits, 1800 radiological tests, and 210 nasogastric tube insertions.

However, there were limitations associated with this study. Important factors that could have influenced healthcare utilisation were not analysed, such as frailty, disability

morbidity, and illness severity. This would support targeting attention on factors associated with either high or low healthcare utilisation. Actual healthcare cost was not calculated and should feature in future studies. Additionally, this study's findings were from a single urban hospital which limits its generalisability to other setting. Malaysia's healthcare system consists of both public and privately funded healthcare providers delivered across urban and rural areas at the primary, secondary, and tertiary levels. Additionally, by its retrospective design, data accuracy, and reliability were entirely dependent on clinical notes and records obtained from the hospital electronic health record system. The accuracy of the ICD-10 coded cause of death provided by medical records may not necessarily reflect the true cause of death as these would often be entered by non-clinical coders. Death may also be a result of multiple factors yet only described as a single cause in death certificates and the coding system. Other aspects of healthcare usage such as blood investigations, oxygen tubing, and dressings, for example, were also not captured within this study. This study was also unable to conclude if the healthcare utilised was deemed appropriate or not. Foreseeable deaths due to underlying chronic illnesses and sudden, unexpected deaths will be treated very differently. Moreover, as data were limited to this hospital's electronic medical records, this study was unable to comment on the healthcare utilisation that could have been accessed in other healthcare facilities.

High healthcare utilisation among older people in hospital in the last year of life has previously been reported.¹³ In this study, several medical procedures and treatments contributed to the overall healthcare utilisation. Almost half of the patients had a nasogastric tube in-situ during the terminal admission. This echoes findings from a study done previously in this same hospital.²² Bypassing the swallowing mechanism and delivering food directly into the stomach tends to be the typical approach in people with swallowing difficulties, or with poor oral intake due to either an acute or chronic illness. However, this carries problems such as aspiration pneumonia, diarrhoea, and local trauma.^{23,24} Hence, whether nasogastric tube insertion and feeding should be done requires an individualised approach, an awareness of local cultural context and supported by clinical frameworks.²⁵⁻²⁷ Besides that, 28% of the patients required ventilatory support with either non-invasive or invasive mechanical ventilation during the last 6 months of life. Supported ventilation, similar to nasogastric tube feeding, also requires an individualised decision-making process to balance the goals of care and risk-benefit in the context of one's overall prognosis. Both procedures require trained personnel to initiate and monitor the care delivered.

This study also demonstrated that almost three-quarters of all patients received antibiotics up till the last 24 hours of life. Such high usage has also been described in other cohorts.²⁸ Infection is common and represents the terminal event in chronic conditions, such as dementia and frailty.^{29,30} Antibiotics have been reported to be frequently prescribed empirically in end-of-life care situations based on signs and symptoms without confirmatory imaging studies or laboratory tests.^{31,32} This study only reported whether patients were receiving antibiotics and did not explore the indication

or appropriateness for the treatment. There is a fine balance between active treatment which may still be beneficial for a reversible illness that entails a burden of treatment, against maximising comfort and minimising aggressive interventions for the dying.

Polypharmacy towards the end of life was a significant finding. Many older adults would have chronic illnesses necessitating the need for a number of medications.³³ However, as the chronic disease progresses towards its terminal stages, or when there is an irreversible acute illness, deprescribing needs to be part of the person's care. Guidance on prescribing and deprescribing in older people such as STOPP/START and Beers criteria, as well as those more specific to palliative care to support deprescribing in end of life can support more person-centred prescribing.³⁴⁻³⁷ Prescribing focus towards the end of life should be on anything that relieves distressing symptoms, provide comfort and optimise quality of life.

This study was not meant to determine if the healthcare utilisation was appropriate and beneficial or not. Clinicians work in a challenging environment to ensure that healthcare is delivered in the patient's best interest, i.e. to reverse what is reversible and to provide comfort when it is irreversible. Many of the patients included in this study did have a healthcare contact prior to their terminal hospital admission. Although each healthcare contact could be for very different reasons, it may also be possible that they were for a similar condition to their eventual hospital admission. The high overall healthcare use than could be a sign of chronic disease progression. Thus, each healthcare contact may represent an opportunity to consider how future care should be directed and individualised for the patient in the form of advance care planning (ACP).³⁸ ACP can set clear goals and care plans which could include decisions on artificial hydration and nutrition, preferred place of death, medication appropriateness, ceilings of treatment, and the extent of investigations.

This study has set the scene on what happens towards the end of life among older adults admitted to hospital. Further research to understand how healthcare decisions are made at this stage would provide insight into what clinicians deemed appropriate and how that decision was made. Besides that, risk stratification to determine characteristics and factors associated with high healthcare usage would allow clinician and stakeholders to focus efforts to better support care during this vulnerable period. A better understanding of this would allow better organisation of care and the delivery of high-quality end-of-life care services to address the healthcare needs of an expanding aging population. There is an emerging evidence that within our local context factors such as frailty and care need requirements were associated with higher healthcare utilisation.^{11,39} Further work needs to build on this to provide a clearer picture that is relevant to our local healthcare system.

CONCLUSION

This study has reported on the hospital healthcare utilisation among older adults admitted to hospital in the preceding 6

months before their passing. The majority had contact with a healthcare team prior to their terminal admission. During their terminal admission, many had healthcare procedures, investigations, antibiotics used, and issues of polypharmacy during this time. With an aging population, how care is organised and delivered is important in promoting good care in their later years.

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