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Background

Retinal degeneration is a leading cause of irreversible vision impairment, incurable low vision and blindness worldwide. Retinitis Pigmentosa (RP) is one of the leading hereditary degenerative retinal disorders affecting 1 in 4000 individuals worldwide, characterized by progressive outer retinal degeneration with rod and cone photoreceptors loss. It is a collective term describing the range of disorders with progressive photoreceptor and/or retinal pigment epithelial (RPE) cell degeneration and dysfunction. The clinical manifestation initially begins with night blindness, followed by progressive loss of peripheral vision (tunnel vision), loss of central vision and eventually total blindness. The natural course of RP involves an estimated loss of 4 to 12% of the visual field and 17% of electroretinography amplitude annually.

Common characteristic of this retinal diseases is the death or dying of specialized retinal cells, loss of integrity of the retina or degeneration of photoreceptors which lead to visual impairment and ultimately blindness. The photoreceptor plays indispensable role in sensing light signal and visual cues, whereas RPE transport ions, water and metabolic end products and provide ingested nutrients from blood to photoreceptors. Various growth factors are produced in RPE with many genes responsible for its production. Mutation of any of these gene causes retinal degeneration by ongoing loss of photoreceptors and RPE.

For a long time, RP was an incurable disease and only underwent conservative treatments, including careful refraction, cataract extraction, when indicated, management of macular edema, and referral for low-vision aids. Efforts to mitigate progressive visual loss in RP have previously been disappointing. Therapy with 15000 IU/day of vitamin A palmitate did not slow the RP progression in visual acquity or visual field. Docosahexanoic acid (DHA) therapy has no effect on the course of the disease. Up to now, there is no curative treatment for this retinal disease.

Recently, new treatment approaches have been introduced for RP, including stem cell implantation therapy, gene therapy and cytokine therapy. Advances arise in the use of stem cells as treatment modalities for retinal diseases including RP. Stem cells are undifferentiated cells which have the ability to self-renew and differentiate into mature cells. Various type of stem cells could contribute to support the survival of the residual retinal cells and to the inhibition of inflammation. A therapeutic possibility is offered by embryonic stem cells (ESC) which can be isolated from blastocysts with high differentiation potential, and by the induced pluripotent stem cells (iPSCs), prepared by the reprogramming of normal adult fibroblast or other cells. However, the use of ESC or iPSCs is limited by the possibility of immune rejection, teratogenicity and ethical restrictions in the case of ESCs.

Mesenchymal Stem Cells (MSC) are multipotent and self-renewing stem cell that can be induced to differentiate into bone marrow, cartilage, muscle, lipid, myocardial cells, glial cells and neurons. They possess potent immunomodulatory and anti-inflammatory properties, produce a number of cytokines and growth factors, and contribute to tissue healing and regeneration. These cells are multi-potent and its primary mechanism appears to be a paracrine trophic effect towards

RPE and photoreceptors. Its transplantation has been shown to delay retinal degeneration, support the regeneration of RPE, cone cells and axons, and improve the survival of retinal ganglion cells. Considering the low immunogenicity and ease of isolation and expansion, MSC become a promising candidate for retinal cell therapy. This MSC can be obtained from bone marrow or adipose tissue of a particular patient. The advantage of these cells is their relatively easy isolation from the source, good growth properties during their propagation in vitro and could be used as autologous (patient´s own) cells.

In Malaysia, currently there is no treatment available for patients with RP. Alternative gene therapy in these cases is more complex as the exact gene mutation need to be identified whereby there are more than 260 genes mutation from 90 genes have been notified to lead to RP. Retinal diseases contributed to 24% of blindness, nonetheless no treatment is currently available for RP. Hence, this necessitates the review of mesenchymal stem cells to ascertain its role as treatment modalities in RP. This review is conducted following the request from the Head of Ophthalmology Services, Ministry of Health to assess the evidence on MSC to be used in the treatment of patients with RP and other degenerative retinal disease.

Objective/ aim

The objective of this technology review is to assess the effectiveness, safety and cost-effectiveness of mesenchymal stem cells for the treatment of retinitis pigmentosa and other degenerative retina disease (Best disease, Beatti's macular dystrophy, cone-rod dystrophy and age-related macular degeneration).

Methods

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present. EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2022), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2022), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2022), EBM Reviews-Health Technology Assessment 1st Quarter 2022), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2022). Parallel searches were run in PubMed. Appendix 3 showed the detailed search strategies. No limits were applied to the search. The last search was run on 30 April 2022. Additional articles were identified from reviewing the references of retrieved articles. Among the tools used to assess the risk of bias and methodological quality of the articles retrieved is the Cochrane risk of bias tool and ROBINS-I. All full text articles were then graded based on guidelines from the US/Canadian Preventive Services Task Force.

Results and conclusion

The review included nine studies which were consisted of randomised controlled trials (five), non-randomised trial (three) and case report (1). The nine included articles in this review were in the effectiveness and safety section, with no evidence retrieved in the cost-effectiveness section. The included articles were published between 2011 and 2021. The studies were conducted in the Turkey (3), US (2), Brazil (2), Thailand (1) and Korea (1). This review included a total of 187 patients enrolled from all the studies, involving 231 eyes. Sample size for each of the included studies ranged from five to 82

patients (six to 124 eyes). Most of the studies were followed at six months and one year, with only one study followed their patients up to seven years. There was variation in the source of MSC (adipose tissue, Wharton jelly or bone marrow), with most MSCs in the included studies were derived from bone marrow. There was variation in the method of MSC delivery in the treated eyes including subtenon, intravitreal, subretinal, retrobulbar or intravenous implantation, as well variation in the amount of cells injected, ranging from single dose of 3.4 to five million cells. Most of the study participants were patients with advanced RP. No evidence retrieved on effectiveness of MSC in patients with other degenerative retinal diseases.

Effectiveness

Based on the above review, there was limited fair level of evidences on MSC to be used in the management of patients with degenerative retinal disease (retinitis pigmentosa). Administration of MSC showed short term beneficial effect on vision function namely best corrected visual acuity, visual field, electroretinography recordings (for parameters: ERG amplitudes, implicit time) and vision related quality of life, during six months and up to one year, compared to baseline, as well as improve retina structural changes in the treated eye of patients with RP.

Significant improvement in BCVA observed in the treated eyes;

- Improvement in logMAR (1.09 ± 0.60 vs 1.36 ± 0.64), at 6 months compared to baseline
- Mean improvement of three lines (ranged from 0 to 11 lines) during the six months follow-up and up to one year (mean BCVA 79.9 vs 70.5 letters)
- Improvement in visual acuity ranged from 23% to 90% with an average of 40.9% over baseline vision, up to 1 year (BMDSC)

Significant improvement in VF was observed in the treated eyes;

- 28.12 ± 3.18 vs 24.19 ± 3.23 dB at 6 months compared to baseline
- VF was stable in 58% participants at 12 months, indicating no remarkable disease progression

Significant improvement in the vision related QOL of patients observed at three months after BMDSC. Most participants experienced improvements in the QOL during the 12-month period after the BM-MSC injection however no significant difference from baseline by one year.

Improvement in the retina structure observed in the treated eyes;

- Mean outer retinal thickness (100.3µm, 119.1µm and 118.0µm, p = 0.01)
- Mean horizontal ellipsoid zone width (2.65 mm, 2.70 mm and 2.69 mm, p = 0.01). Ellipsoid zone width showed healthy photoreceptors.

Safety

The only USFDA-approved stem cell products was hematopoietic progenitor cells, derived from umbilical cord blood meant for use in patients with hematopoietic system disorders. MSC appeared safe with no ocular, systemic adverse events or hyperproliferation following MSCs injection among the study population at one year.

Transient vision loss, recovered slight VF deterioration and epiretinal membrane have been reported. MSCs has a lower risk of differentiating into undesired tissues, teratoma formation, immune rejection (even from allogeneic sources), and ethical concerns to its use, compared to Retinal Progenitor Cells (RPC), Embryonic Stem Cells (ESC), and induced Pluripotent Cells (iPSC).

Financial implication

In Malaysia, the complete breakdown of cost of activities entailed in the testing, harvesting, isolation and storage of MSC was not able to be retrieved fully. It was said that a treatment of MSC may cost MYR60,000 to MYR80,000 consisting of 100 million cells. It was reported two patients with retinitis pigmentosa have received retinal MSC injection in Malaysia and paid RM20,000 to RM30,000 per procedure. The average number of discharges of patients with retinal disease (degeneration of macula and posterior pole, peripheral retinal degeneration, hereditary retinal dystrophy) in the past five years (2017-2021) was 131 discharges per year. Hence, the cost implication will be approximately MYR 7,860,000 to MYR 10,480,000 per year.

Organizational

The International Society for Cellular Therapy highlighted minimal criteria before a cell can be considered as MSC; specific immunophenotype, tissue culture plastic-adherent and multilineage differentiation. MSCs production for clinical intervention needs to comply with good manufacturing practice (GMP). Processes involved need to be defined; the source for isolation, culture methods, procedures, materials and methods used for cell culture, and quality controls. Laboratories using clinical-grade MSCs should follow regulatory agency requirements on use of equipment, reagents and supplies, established procedures, and strict safety measures. In the US, the GMP hMSC production is regulated by FDA CFR Title 21 focusing on current good tissue practice requirements. In the European Union, the GMP production is regulated under the European Regulation No. 1394/2007. The MSC collection, processing, storage and infusion shall follow the requirements of the standards, in line with the Malaysia National Organ, Tissue and Cell Transplantation Policy.