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TECHNOLOGY REVIEW (MINI-HTA)

MESENCHYMAL STEM CELLS FOR RETINITIS PIGMENTOSA AND OTHER DEGENERATIVE RETINA DISEASE

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
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EXECUTIVE SUMMARY

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).

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.

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.

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ABBREVIATION

ADMSC	Adipose derived mesenchymal stem cells
AE	Adverse event
BMDSC	Bone marrow derived mesenchymal stem cells
CF	Counting finger
CI	Confidence Interval
CrI	Credible Interval
CST	Central subfield thickness
DHA	Docosahexanoic acid
ERG	Electroretinography
ESC	Embryonic stem cells
EZW	Ellipsoid Zone Width
FDPI	Fundus perimetry deviation index
FFA	Fundus fluorescein angiography
GMP	Good manufacturing practice
HM	Hand movement
HR	Hazard Ratio
HRQOL	Health related quality of life
HSC	Hematopoetic stem cells
iPSC	Induced pluripotent stem cells
IQR	Interquartile Range
ISCT	International Society for Cellular Therapy
logMAR	Logarithm of minimum angle of resolution
LP	Light perception
MHC-II	Major Histocompatibility Complex Class II
MOH	Ministry of Health
MSC	Mesenchymal stem cells
NGF	Neural growth factor
OCTA	Optical coherence tomography angiography
OD	Right eye
OS	Left eye
QOL	Quality of Life
RCT	Randomised controlled trial
RPC	Retinal progenitor cells
RPE	Retinal pigment epithelium
RR	Relative risk
SE	Standard error
SR	Systematic review
VF	Visual field
vs	Versus
WMD	Weighted mean difference

1.0 BACKGROUND

Retinal degeneration is a leading cause of irreversible vision impairment, incurable low vision and blindness worldwide.[1,2] Hereditary retinal dystrophies, such as retinitis pigmentosa (RP) or cone-rod dystrophy affect as many as one in 3,500 individuals.[3] As this disorder affects about 1 in 3,000 to 1 in 4,000 people in the world, it can be estimated approximately 1.7 to 2.3 million people worldwide have one of these disorders (PSE 24). In Malaysia, age adjusted prevalence of bilateral blindness and low vision was 0.29% (95%CI 0.19 to 0.39) and 2.44% (95%CI 2.18 to 2.69) respectively. Retinal diseases contributed to 24% of blindness cases.[4]

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.[5] It is a collective term describing the range of disorders with progressive photoreceptor and/or retinal pigment epithelial cell degeneration and dysfunction.[6] The clinical manifestation initially begins with night blindness (nyctalopia), followed by progressive loss of peripheral vision (tunnel vision), loss of central vision and eventually total blindness. Classical fundus appearance of typical RP includes optic disc pallor, attenuated retinal vessel, mottling of RPE and peripheral bone spicule pigmentation.[5,7] The natural course of RP involves an estimated loss of 4 to 12% of the visual field and 17% of ERG amplitude annually.[8] At least 50 to more than 100 separate genes have been reported to be associated with RP, with varied inheritance pattern. [9]

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. [10] The human retina is a delicate thin sheet composed on ten sublayers, including inner limiting membrane, nerve fiber layer, ganglion cell layer, inner plexiform layer, inner nuclear layer, outer plexiform layer, outer nuclear layer, outer limiting membrane, photoreceptor layer and retinal pigmented epithelium (RPE) monolayer. The photoreceptor plays indispensable role in sensing light signal and visual cues, whereas RPE transport ions, water and metabolic end products from subretinal space to blood and provide ingested nutrients from blood to photoreceptors. [11] 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 or photoreceptors and RPE.[12]

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.[13] Up to now, there is no curative treatment for this retinal disease. 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.[14] Docosahexanoic acid (DHA) therapy has no effect on the course of the disease.[15] Lutein supplementation increases macular pigment in 50% of patients with RP but without change in central visual acquity.[16]

Recently, new treatment approaches have been introduced for RP, including stem cell implantation therapy, gene therapy and cytokine therapy.[17] Since the advanced therapies availability, cell-based therapies offer a new all-encompassing approach.[18] Recently 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. Cell replacement therapy has been evaluated as a viable alternative in various pathologies.[19] 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. Another possibility is by the induced pluripotent stem cells (iPSCs), prepared by the reprogramming of normal adult fibroblast or other cells. Both ESCs and iPSCs have the potential for differentiation into various retinal cell types. However, the use of ESC or iPSCs is limited by the possibility of immune rejection, teratogenicity and ethical restrictions in the case of ESCs.[20]

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.[21] MSC possess potent immunomodulatory and anti-inflammatory properties, produce a number of cytokines and growth factors, and contribute to tissue healing and regeneration.[22] These cells are multi-potent and its primary mechanism appears to be a paracrine trophic effect towards RPE and photoreceptors.[23] These paracrine effects on the damaged retina represent a more viable approach to treating RD than direct cell replacement, since most retinal disorders are associated with damage to more than one retinal cell type and extensive remodeling often occurs in response to the damage.[24] 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. MSC spontaneously produce hepatocyte growth factor (HGF), nerve growth factor and vascular endothelial growth factor which act as tissue regeneration factors. MSC also produce immunomodulatory cytokine which inhibit the inflammatory cell reaction during disease progression. [25]

Considering the low immunogenicity and ease of isolation and expansion, MSC become a promising candidate for retinal cell therapy.[26] This MSC can be obtained from bone marrow or adipose tissue of a particular patient. After separation and culturing in vitro, it could be used as autologous cells without the danger of immune rejection as MSC do not express Major Histocompatibility Complex Class II (MHC-II) on their surface associated with transplant rejection. [27] 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. It has also been demonstrated that MSCs from different sources (bone marrow, adipose tissue, umbilical cord blood, etc.) have similar function properties.[22]

There is scarce evidence on magnitude of patients affected with degenerative retinal disorder or RP in Malaysia. The Health Informatic Centre (Ministry of Health) reported cumulative number of patients discharged with hereditary retinal dystrophies, peripheral retinal degeneration and degeneration of macula of 1052 cases (from 2012 to 2021). 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.

2.0 OBJECTIVE / AIM

The objective of this technology review is to assess the effectiveness, safety and cost-effectiveness of MSC in the treatment of patients with retinitis pigmentosa and other degenerative retina disease (Best disease, Beatti's macula dystrophy, cone-rod dystrophy & age-related macular degeneration early stages).

3.0 TECHNICAL FEATURES

Bone marrow contains the highest concentration of adult stem cells. These adult stem cells appear to play an important role in regenerating damaged tissue and organs. Two classes of bone marrow stem cells (BMSCs) that have been studied were mesenchymal stem cells (MSC) and hematopoietic stem cells.[24]

MSC was first described in 1968 where adherent, fibroblast-like clonogenic cells with a strong capacity to replicate and differentiate into osteoblasts, adipocytes and bone marrow stromal cells was isolated. MSC constitute less than 0.1% of the cells in bone marrow. In recent years, similar cells also have been harvested from adipose tissue, heart, skeletal muscle, synovial membrane, dental pulp, peritoneal ligaments, liver, cervical tissue, Wharton's jelly, amniotic fluid, and umbilical cord blood.[24]

MSC are easily harvested and expanded in tissue culture. These cells are isolated from bone marrow aspirate or mononuclear cell fraction of bone marrow aspirate by their ability to adhere to the plastic tissue culture plates and grow in culture. MSC are identified by the presence of specific cell surface markers (for instance CD105, CD73, stromal antigen 1, CD44, CD90, CD166, CD146 CD54, and CD49) and absence of cell surface markers for hematopoietic stem cells (CD14, CD45, CD11a, CD34), erythrocytes (Glycophorin A) and platelets (CD31).[28] In characterizing the immunophenotype of MSC, no unique single marker has been found for MSCs so far. Therefore, the combination of markers necessary to identify a homogeneous cell population should include CD105, CD73, CD90, CD44, CD29 (all expressed by MSCs), and CD34, CD45, CD11c, CD14, CD31=PECAM-1, and other endothelial markers, as illustrated in Figure 1.[50]

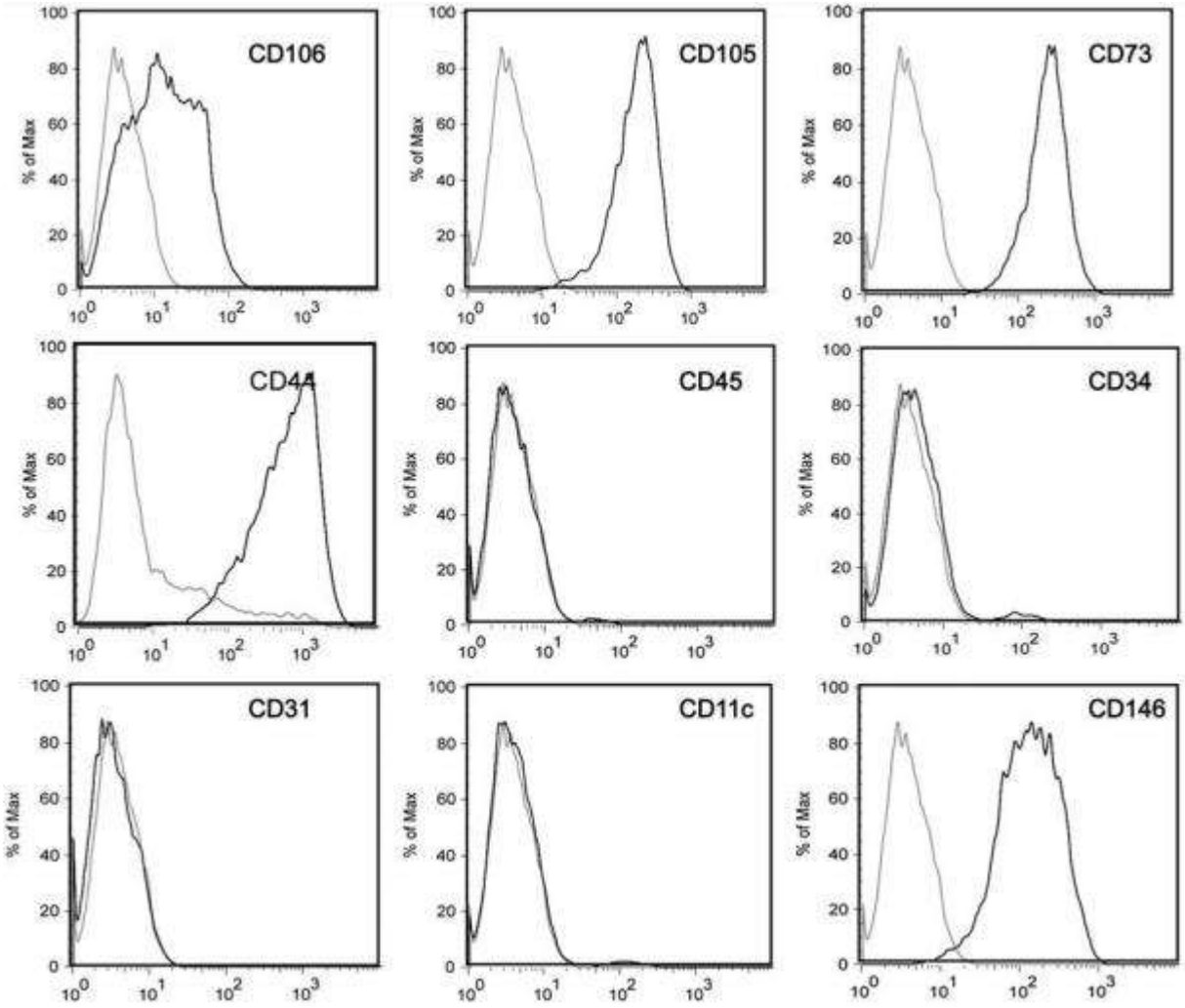


Figure 1: Examples of Immunophenotype of human BM-MSCs expanded in vitro. Expression of specific markers (black)

MSCs are multipotent stem cells which can be obtained relatively easily in a sufficient amount from various types of tissues and expanded in vitro for autologous application. MSCs currently represent the most frequently studied type of adult stem cells. Originally, these cells were described as a population of bone marrow-derived cells that adhere to plastic and form fibrocyte-like colonies. MSCs retain their differentiation potential during their in vitro expansion, and they can be differentiated into different cell types including cells expressing RPE or photoreceptor cell markers. Similarly, the anti-inflammatory properties of MSCs and their ability to support ocular surface healing have been well documented. [29]

For therapeutic purposes, MSCs are mainly isolated from the bone marrow or adipose tissue. However, no specific marker that could characterize these cells has been identified. According to the International Society of Cellular Therapy, human MSCs are characterized by the ability to adhere to plastic surfaces in standard culture conditions, by being positive for the surface markers CD105, CD73 and CD90, and negative for hematopoietic markers CD45, CD34, CD14, CD19 and CD11b, and by their ability to differentiate into adipocytes, chondroblasts and osteoblasts.[30] The cells are aspirated from bone marrow, adipose tissue, or umbilical cord and isolated by density gradient centrifugation. Then they are washed and

expanded. The key step in the cell culture is that MSCs adhere to a plastic substrate and hematopoietic cells do not. Finally, they are stored by cryopreservation until required.[31] Figure 2 showed the appearance of MSC culture.

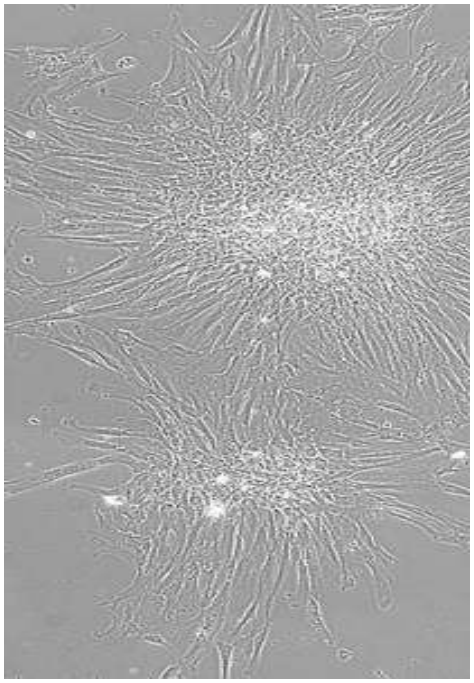


Figure 2: MSC culture in vitro showing clusters of BM-MSCs

Although bone marrow is the best source of obtaining MSC, its use is restricted by the limited growth rate, differentiation capability depending on the donor age, and risk inherited to sample collection. Umbilical cord as source of MSC required an optimal protocol such as time of recollection and process should less than 16hours and volume of collection should be higher than 30ml for successful culture. MSC obtained from by adipose tissue have similar morphology and phenotype to the bone marrow source, and these cells have high capability of proliferation and they are easier to be collected from liposuction.[32-34] Studies have demonstrated that BM-MSCs and ADSCs share similar immunomodulatory capacities. [2]

The immunomodulatory properties of MSCs are mediated by multiple mechanisms including regulation by direct cell-to-cell contact, the production of various immunomodulatory molecules, the negative effects on antigen-presenting cells or the activation of regulatory T cells. MSC possess potent immunomodulatory property, antiapoptotic property, and potent producers of various growth and trophic factors. Some of these factors are produced by MSCs constitutively, while others are only secreted after activation with proinflammatory cytokines, mitogens or other signals. Production of growth factors and their paracrine action have been suggested as the main mechanisms in the therapeutic action of MSCs. Among the growth factors produced by MSCs that could contribute to retinal regeneration are hepatocyte growth factor (HGF), nerve growth factor (NGF), glial cell-derived neurotrophic factor (GDNF), insulin-like growth factor-1 (IGF-1), pigment epithelium growth factor (PEGF), fibrocyte growth factor (FGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), angiopoietin1, erythropoietin, VEGF and TGF-β. In addition to the ability of MSCs to produce several growth, immunoregulatory or neurotrophic factors, MSCs release various

types of extracellular vesicles (EVs). These Cells particles encapsulate different functional molecules which could support the survival of cells.[10]

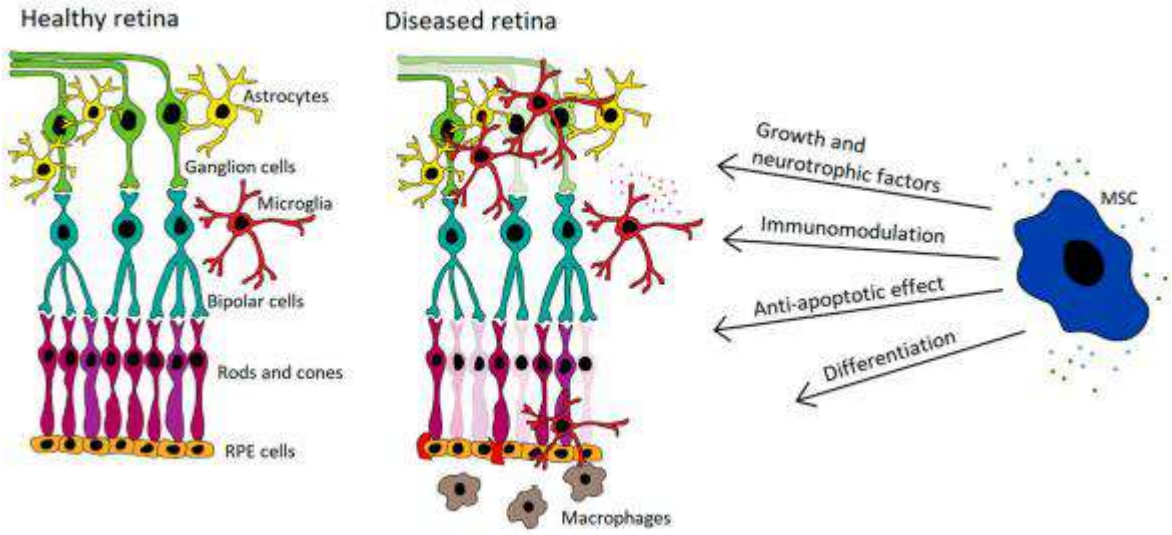


Figure 3: Main mechanism of therapeutic effect of MSC for retinal disease
(Source: Holan V et al. 2021)

Cryopreservation has been used primarily for preserving the hematopoetic stem cell population for transplantation. Currently, its use has been extended to allow the preservation of the biological potential and to retain the biological age at time of cryopreservation. In autologous patients, MSC is collected and cryopreserved for later clinical use. In allogenic patients, cryopreservation permits banking of cells for human leucocyte antigen typing and matching, facilitating the logical transport of cellular products to transplant centers, and allowing enough time for the screening of transmissible disease in the donated cells before transplantation. [36]

Investigators have employed several methods of intraocular delivery of cell therapies. (Figure 3), including intravitreal, internal subretinal and external subretinal. The internal subretinal approach accesses the subretinal space intraocularly (usually after vitrectomy), while the external subretinal approach accesses the subretinal space via choroid and sclera.[37]

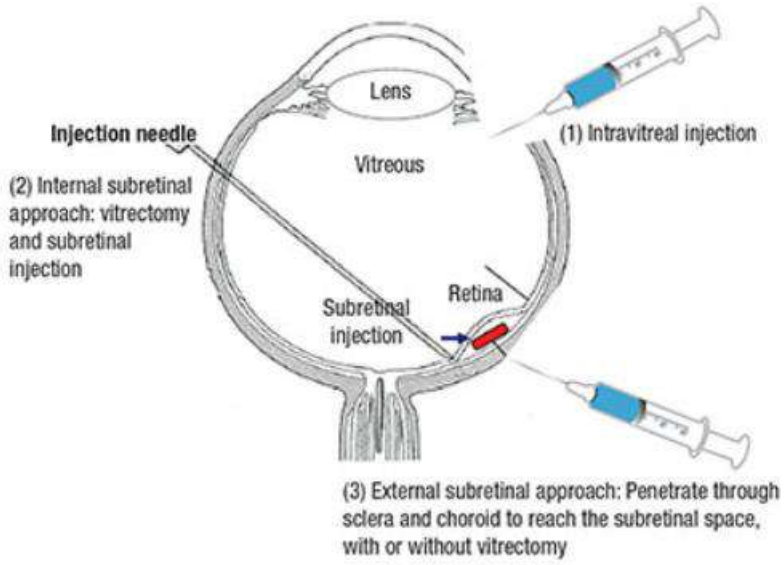


Figure 4: Method of delivery of intraocular cell therapies

Cells of retina consisted of several cells type, including the rod and cone photoreceptors that are supported by the retinal pigment epithelium. The other cell types above the photoreceptor (collectively called inner retinal cells) relay electrical signals to the brain. (Figure 5) Retina is organized into layers of cells comprising six unique neurons, namely rod and cone photoreceptors, ganglion cell, bipolar cell, amacrine cell and horizontal cell.[38] Any pathology in the eye may lead to death of retinal neurons, mainly photoreceptor and retinal pigmented epithelial (RPE) cells. Loss of these cell is non-replaceable and could contribute to blindness.[38] The RPE forms the outer blood-retinal barrier between photoreceptor cells and choroidal blood vessels. Photoreceptor cells are vitally and functionally dependent on the RPE.[39]

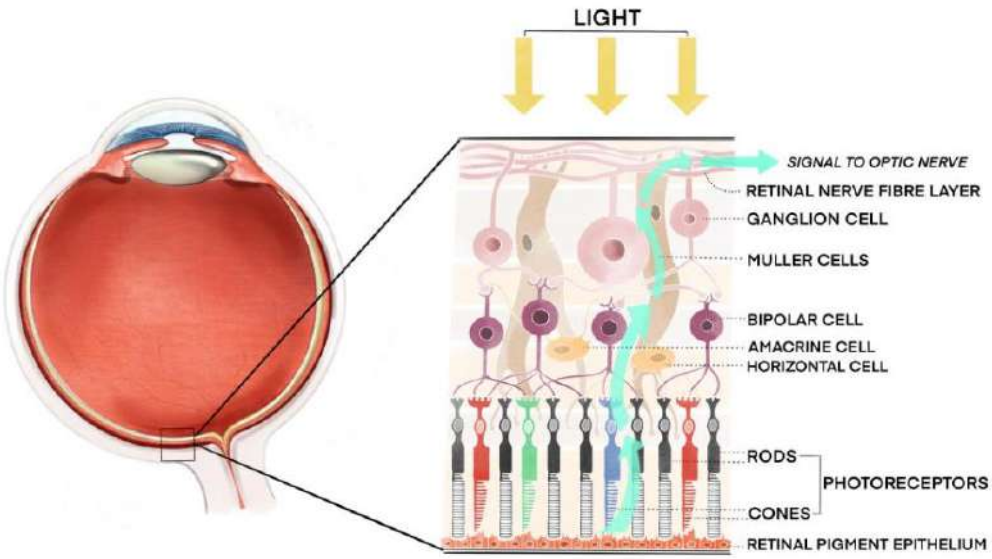


Figure 5: Microscopic view of cells in the retina

4.0 METHODS

4.1 SEARCHING

Electronic databases searched through the Ovid interface:

- MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to present
- EBM Reviews – Cochrane Central Registered of Controlled Trials – March 2022
- EBM Reviews – Database of Abstracts of Review of Effects – 1st Quarter 2022
- EBM Reviews – Cochrane Database of Systematic Reviews – 2005 to March 2022
- EBM Reviews – Health Technology Assessment – 1st Quarter 2022
- EBM Reviews - NHS Economic Evaluation Database – 1st Quarter 2022

Other databases:

- PubMed
- Horizon Scanning database (National Instutute of Health research (NIHR) Innovation Observatory, Euroscan International Network)
- Other websites: US FDA, INAHTA, MHRA

General databases such as Google and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles or contacting the authors. The search was limited to articles on human. No limitation in the study design. There was no language limitation in the search. Appendix 1 showed the detailed search strategies. The last search was conducted on the 30 April 2022.

4.2 SELECTION

Two reviewers screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection. The inclusion and exclusion criteria were:

Inclusion criteria

Population	Patients (adults and children) with retinitis pigmentosa or other degenerative retina disease (Best disease, Beatti's macular dystrophy, cone-rod dystrophy and age related macular degeneration)
Interventions	MSC, mesenchymal stromal cells
Comparators	Sham or no comparator
Outcomes	Best corrected visual acuity (or logarithmic visual acuity chart), visual field, electroretinography (full field, flicker), fundus fluorescein angiography (neovascularization), perimetry (Goldmann), optical coherence tomography, vision related quality of life, central subfield thickness, outer retinal layer diameter, complications, adverse events, intraocular pressure, cells and flare in anterior chamber using anterior

	segment biomicroscopy
Study design	Systematic reviews (SR), randomised control trials (RCTs), cohort study, case control study, case report
Type of publication	English, full text articles

Exclusion criteria

Study design	Survey, anecdotal, animal studies
Type of publication	Non-English
Setting	Studies evaluating MSC in clinical setting

4.3 RISK OF BIAS ASSESSMENT

Relevant articles were critically appraised according to the study design. Randomised controlled trial was appraised using ROB-2, and non-randomized trials were appraised using ROBINS-I and evidences were graded according to the US/Canadian Preventive Services Task Force (See Appendix 2). Data were extracted from included studies using a pre-designed data extraction form (evidence table as shown in Appendix 6) and presented qualitatively in narrative summaries. No meta-analysis was conducted for this review.

5.0 RESULTS

A total of 336 titles were identified 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) and PubMed.

Twenty-six articles were identified from references of retrieved articles. After removal of 38 duplicates, 362 titles were screened. A total of 362 titles were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, 341 abstracts were found to be irrelevant. Twenty-one potentially relevant abstracts were retrieved in full text. After applying the inclusion and exclusion criteria and critical appraisal to the 21 full text articles, nine full text articles were included and 12 full text articles were excluded. (Figure 6).

The review included nine studies which were consisted of randomised controlled trials (five), non-randomised trial (three), and case report (1).

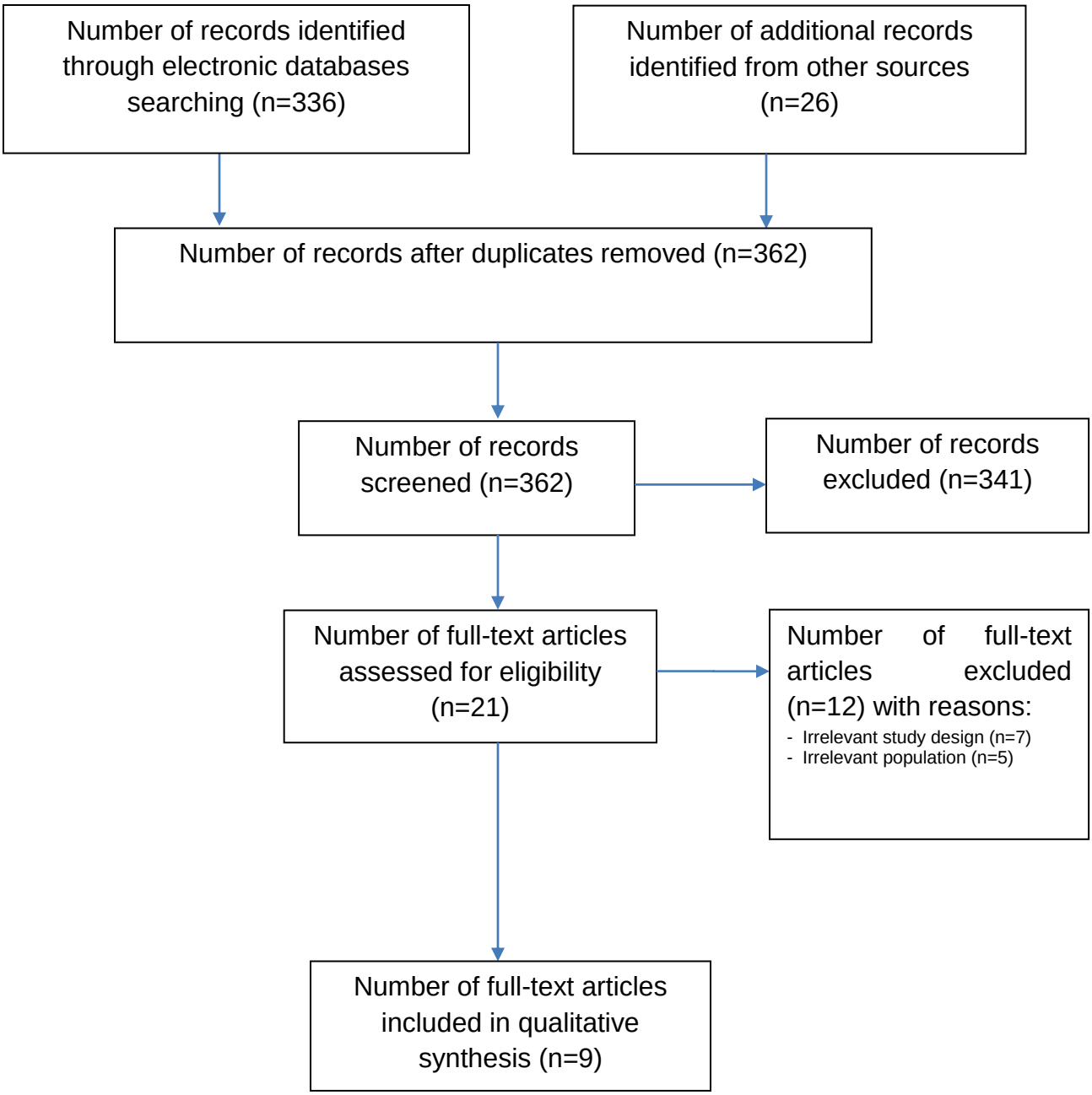


Figure 6: Flow chart of study selection in the review according to the PRISMA guidelines

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. The SR was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist guideline.

5.1 RISK OF BIAS ASSESSMENT OF INCLUDED STUDIES

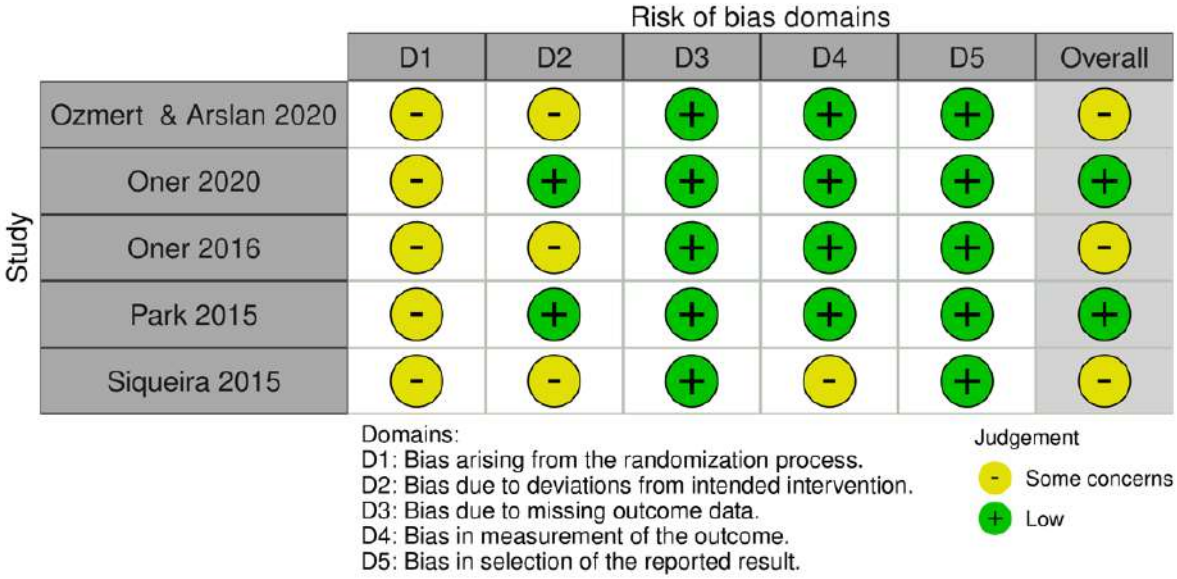
Risk of bias was assessed using Cochrane Risk of Bias (ROB) 2 for RCT, and Cochrane Risk of Bias In Non-randomised Studies of Interventions (ROBINS-I) for non-randomized trial. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias. The risk of bias of the included studies was assessed independently by two reviewers. Any disagreements were resolved through discussion until consensus was reached.

For RCT, assessment was done following the domain-based evaluation (RoB-2), addressing these domains: bias arising from randomization, deviation from intended intervention, missing outcome data, measurement of outcome and selection of reporting result. Trials having three or more high risk of bias were considered as having poor methodological quality. For non-randomized trial, assessment was independently done by the reviewers on specified domain using ROBINS-I. The plot of the domain-level judgements for each individual result was generated using robvis, a web app designed for visualizing risk-of-bias assessments. The results were illustrated in the figure as below.

Risk of bias assessment for included RCT

Park et al. (2015) and Oner et al (2020) were rated to have an overall low risk of bias. Overall, Ozmert and Arslan (2020), Oner et al (2016) and Siqueira et al. (2015) were rated as having some concerns. In assessing randomisation process, random sequence generation and allocation concealment were not mentioned. There was some concern with the blinding process as it was not possible to blind the ophthalmologist who perform the treatment procedure or the sham procedure. This could introduce performance bias. There was no report on participants being blinded on the procedure. Blinding was considered not relevant for objective measurements [major adverse events, best corrected visual acuity (BCVA), electroretinography (ERG), fundus fluorescein angiography (FFA)]. There was no information on whether these outcomes were analysed using intention to treat analysis. Selective reporting was considered to have a low risk of bias as all prespecified outcomes were reported and analysed. (Table 1).

Table 1: Summary of risk of bias assessment for RCT using ROB 2.0



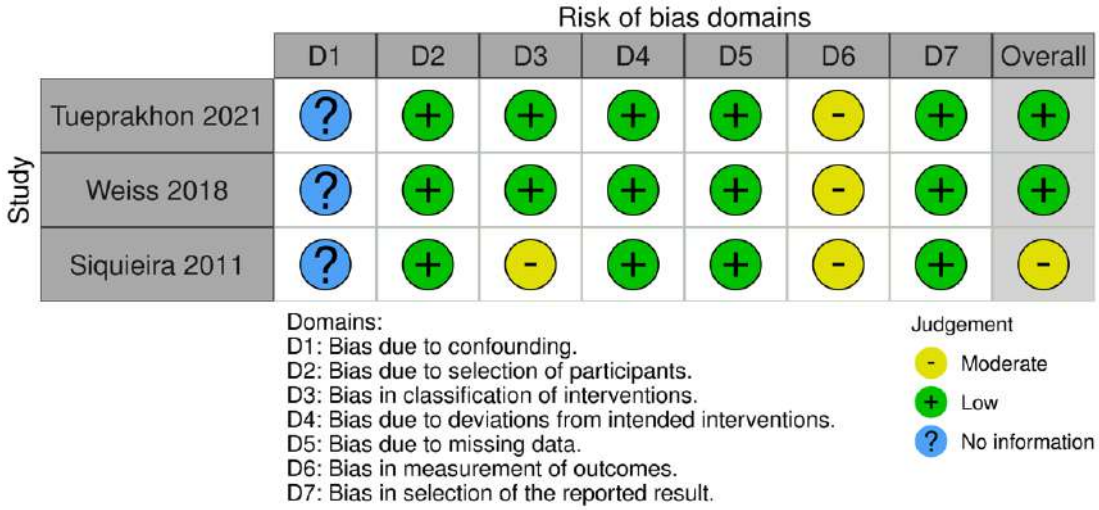
Risk of bias assessment for included non-randomized trial

In assessing bias due to confounding, factors such as patient's age, sex, hormone status, diseases such as diabetes or obesity, or the abuse of substances like nicotine and alcohol are potential confounding that had not been considered in these studies. Other factors, namely patient specific variabilities concerning cell proliferation rates, cell differentiation and cell vitality that were shown to limit inter-study comparability were also not considered. None of the studies reported these confounding or any statistical adjustment made to control for the confounding. Bias due to selection of participants among the included studies was rated as low risk of bias. All studies were rated as low risk of bias in classification of intervention for the mesenchymal stem cell therapy and bias due to deviations from intended interventions as the intervention was clearly defined, whereby misclassification of intervention status would be unlikely and all participants received the intended intervention. However, amount of injected cell slightly varied among the studies.

In assessing bias due to missing data, all the studies were rated low risk of bias whereby the data were reasonably complete for analysis. Given that in these non-randomized trials, blinding of the participants was not done, these studies were rated to be at moderate risk of bias due to measurement of outcomes. Lack of blinding might have influenced some participant-reported or subjectively assessed outcomes such as perception of quality of life, contributing to moderate risk of bias due to selective recall and delays in the recall period. However, many of the outcomes (BCVA, ERG, visual field, optical coherence tomography, fundus fluorescent angiography) were objectively measured, hence remain unaffected. The risk of bias in selection of the reported result was considered low in all studies, as all prespecified outcomes were reported and analysed. The overall judgement on risk of bias for each non-randomized trial

rated three studies. One study had moderate risk of bias (Siquiera 2011) and two studies had low risk of bias (Tueprakhon 2021, Weiss 2018).(Table 2)

Table 2: Summary of risk of bias assessment for non-randomized trial using ROBINS-I



5.2 EFFECTIVENESS

There were eight studies retrieved on the effectiveness of MSC in the treatment of retinitis pigmentosa and other degenerative retinal disease, consisted of five RCTs and three non-randomized trials.

5.2.1 Functional

a) Best corrected visual acuity (BCVA) (using Snellen chart or converted to logMAR)

Ozmert E and Arslan U (2020) investigated annual structural and functional results in a trial conducted in Turkey, and their correlation with inheritance pattern of patients with retinitis pigmentosa (RP) who were treated with Wharton's jelly-derived mesenchymal stem cells (WJ-MSC). This prospective, sequential, open-label phase-3 clinical study was conducted at Ankara University Faculty of Medicine, Department of Ophthalmology, between April 2019 and May 2020. The study included 34 eyes from 32 RP patients of various genotypes who were enrolled in the stem cells clinical trial. Of the 32 patients, 18 were male, and 14 were female. Median age was 39.7 years (range 19 to 59 years). The patients were followed for 12 months after the WJ-MSCs transplantation into subtenon space and evaluated with consecutive examinations. The primary diagnosis was confirmed by a genetic mutation RP panel test in addition to clinical findings. Genetic mutations and inheritance pattern were investigated using a DNA RP panel sequencing method consisting of 90 genes. All patients underwent a complete routine ophthalmic examination with BCVA, optical coherence tomography angiography (OCTA), visual field,

and full-field electroretinography (ERG). The patients underwent OCTA to confirm diagnosis and to analyze changes in the retinal layer. Structural examination of photoreceptors was followed by outer retinal thickness (ORT) and ellipsoid zone width (EZW) by the OCTA. Functional evaluation of photoreceptors was followed by visual field test and full-field flicker electroretinography. Visual field sensitivity was measured by fundus perimetry deviation index (FDPI) and mean deviation (MD). The FDPI value is more sensitive than the MD value for retinal disease. Flicker electroretinography is a non-invasive objective test that measures the electrical activity of the retina in response to a light stimulus. Intraocular or intraorbital mass lesion, inflammation, fibrosis, proptosis, diplopia, afferent pupillary defect, corneal/lenticular haze, ocular allergic reactions, intravitreal and/or subretinal hemorrhages, retinal artery/ vein occlusions, optic nerve changes, macular edema, vitreoretinal interface alterations, retinal tear(s) or retinal detachment (exudative, rhegmatogenous), and intraocular pressure change from baseline (≤ 5mmHg) were considered to be serious adverse ocular events. The MSC used was isolated from Wharton's jelly of the umbilical cord collected allogenicly from a single donor with the mother's consent. All cell preparation and cultivation procedure were conducted in a current good manufacturing practice accredited laboratory. The cells were characterized during cryopreservation using flow cytometric analysis to determine expression of positive cluster differentiation (CD) surface markers, CD90, CD105, CD73, CD44 and CD29. The MSC suspension was delivered to operating room by cold chain and used within 24hours.The MJMSC was administered via subtenon route to the affected eye. The patients were evaluated at baseline (T0), followed-up at six months (T1) and 12 months (T2).

They found according to time points, at T0, T1 (six months) and T2 (12 months), the mean BCVA were 70.5 letters, 80.6 letters and 79.9 letters (p= 0.01; T0 < T1, T2). Table 3 summarized findings of study outcome measured according to time point. Overall, subtenon WJMSC transplantation was safe and effective in the sixth month and first year, with no adverse events observed during the one-year follow-up.[42]

Table 3: Comparison of measurements according to study timepoints

Measurements	T0	T1	T2	*p*	Comparison**
	X ± s.s.	X ± s.s.	X ± s.s.		
ORT (μm)	101.29 ± 16.20	118.51 ± 17.36	118 ± 17.59	0.01*	T0 < T1, T2
HEZW (mm)	2.65 ± 1.12	2.70 ± 1.15	2.69 ± 1.16	0.01*	T0 < T1, T2
VEZW (mm)	2.51 ± 1.12	2.54 ± 1.14	2.53 ± 1.15	0.08	T0 = T1 = T2
BCVA (ETDRS)	70.5 ± 15.71	80.62 ± 16.26	79.97 ± 17.05	0.01*	T0 < T1, T2
FPDI (%)	8.00 ± 3.57	11.38 ± 4.84	11.59 ± 5.02	0.01*	T0 < T1, T2
ERG amplitude (mV)	2.37 ± 1.85	5.03 ± 4.21	4.53 ± 3.95	0.01*	T0 < T1, T2
ERG implicit time (ms)	43.28 ± 5.50	37.90 ± 7.88	38.58 ± 7.73	0.01*	T0 > T1, T2

**Repeated-measures analysis of variance test (rANOVA); *$p < 0.05$, statistically significant

HEZW horizontal ellipsoid zone width (mm); *VEZW* vertical ellipsoid zone width (mm); *ORT* outer retinal thickness (μm); *BCVA* best corrected visual acuity (ETDRS letters); *FPDI* fundus perimetry deviation index; *ERG amplitude* full-field flicker electroretinography; amplitude (mV); *ERG implicit time* full-field flicker electroretinography, implicit time (ms); *T0 (baseline)* just before the Wharton jelly-derived mesenchymal stem cell injection; *T1* 6th month after injection; *T2* 12th month after injection

Kahraman & Oner (2020) in another RCT assessed the efficacy and the safety of suprachoroidal umbilical cord derived mesenchymal stem cell (UC-MSC) implantation in patients with retinitis pigmentosa (RP). This prospective, open label, single-center, phase 3 trial enrolled 124 eyes of 82 RP patients. Inclusion criteria were patients older than 18 years, clinical diagnosis of RP confirmed by ophthalmological test, BCVA of 20/50, and various degree of visual field (VF) loss. The BCVA, VF and multifocal electroretinography (mfERG) were the main outcomes. VF examination was performed using Humphrey VF analyzer device, program 30-2 was used for testing of each eye. BCVA was evaluated using Snellen chart at a distance of three meter and presented as the logarithm of the minimum angle of resolution (logMAR). The mfERG was recorded on mfERG vision monitor and performed according to International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines. Another primary outcome was adverse events, defined as the presence of ocular (intraocular/intraorbital inflammation, infection, tumour formation, proptosis, diplopia or strabismus, corneal pathology, allergic reaction, any retinal pathology, vitreoretinal problem, intraocular pressure alteration, optic nerve pathology) or systemic complications. The stem cell was prepared from disinfected umbilical cord which was cultured in Dulbecco's modified Eagle's medium low glucose containing a concentration of 10% human serum and 1% penicillin/streptomycin. The culture medium changed every three days until reached minimum 70% confluency. The cells were analyzed for confirmation of phenotypic characteristics, and were positive for CD-73, CD-90 and CD-150. This procedure was performed under good manufacturing practice and assessed for cell appearance, viability, identification, purity, content and potency.

The patients received 5 million UC-MSCs to the suprachoroidal area with a surgical procedure done with local anaesthesia. Patients were evaluated on the 1st day, 1st, and 6th months postoperatively. Best corrected visual acuity (BCVA), anterior segment and fundus examinations, color photography, optical coherence tomography (OCT), and visual field (VF) tests were carried out at each visit. Fundus fluorescein angiography (FFA) and multifocal electroretinography (mfERG) recordings were performed at the end of the sixth month. Ocular and systemic adverse events of the surgical procedure were also evaluated. They found all of the 82 patients (124 eyes) completed the 6-month follow-up period. Median age was 38.5 years, and 42 patients (51.2%) received treatment for both eyes.

There were statistically significant improvements in BCVA and VF at first and sixth moth evaluations compared to baseline (all $p<0.05$). (Table 4) [41]

Table 4: Comparison of BCVA and VF findings post-intervention

Outcomes	**Preop**	**1-month post-op**	**6-months post-op**	**p**
BCVA (logMAR)	1.36 ±0.64	1.16 ±0.63	1.09 ±0.60	<0.05
VF(dB)	28.12 ±3.18	26.7 ±4.21	24.19 ±3.23	<0.05

BCVA: Best corrected visual aquity
VF: Visual field

Weiss & Levy (2018) in a non-randomized trial in the US evaluated bone marrow derived stem cells (BMDSC) in the treatment of Retinitis Pigmentosa (RP). This study involved 17 patients with bilateral visual loss due to RP. They underwent autologous bone marrow derived stem cell treatment within the Stem Cell Ophthalmology Treatment Study (SCOTS and SCOTS 2). SCOTS is an open label, non-randomized efficacy study. Bone marrow separated from posterior iliac crest is separated to provide bone marrow stem cell (BMSC) within the stem cell concentrate. The concentrate has averaged 1.2 billion Total Nucleated Cells including MSC in approximately 14 to 15cm of concentrate. Similar treatment protocols were continued in SCOTS2. Inclusion criteria for SCOTS were: i) Have objective, documented damage to the retina or optic nerve unlikely to improve OR have objective, documented damage to the retina or optic nerve that is progressive AND have less than or equal to 20/40 best corrected central visual acuity in one or both eyes AND/OR an abnormal visual field in one or both eyes; ii) Be at least three months post-surgical treatment intended to treat any ophthalmologic disease and be stable; iii) If under current medical therapy (pharmacologic treatment) for a retinal or optic nerve disease, be considered stable on that treatment and unlikely to have visual function improvement (for example, glaucoma with intraocular pressure stable on topical medications but visual field damage); iv) Have the potential for improvement with BMSC treatment and be at minimal risk of any potential harm from the procedure; v) 18 years or older; vi) Medically stable and medically cleared (the patient can reasonably be expected to undergo the procedure without significant medical risk to health). The pre-operative visual acuity ranged from light perception (LP) to 20/30. In this study, the average age of the patients treated was 48.8 years. The average duration of disease prior to treatment was 27.6 years and ranged from four to approximately 60 years. Affected eyes were treated with either retrobulbar, subtenon and intravenous BMSC or retrobulbar, subtenon, intravitreal and intravenous. With the exception of one patient with NLP vision in one eye, both eyes were treated (33 eyes in 17 patients). All surgeries were performed at out-patient ambulatory surgery center in Florida, US. Follow up was required at one, three, six and 12 months post treatment.The primary outcome was visual acuity as measured by Snellen or converted to logMAR. In calculating the percentage of change in treated eyes, the delta or difference between the logMAR pre-procedure acuity and post-procedure acuity was divided by the pre-procedure acuity. Binocular visual acuity using Snellen line equivalents of logMAR vision was used to assess overall patient results. Eyes with hand motion (HM) or counting fingers (CF) vision were converted to Snellen lines of vision equivalents. Per this formula, HM is considered 20/2000, decimal 0.001 and logMAR 3.0; while CF at 2 feet is considered 20/2000, decimal 0.01 and logMAR 2.0

They found following therapy in SCOTS or SCOTS 2, 11 patients (64.7%) showed improved binocular vision averaging 10.23 lines of Snellen acuity per eye over pre-treatment acuity; 8 patients (35.3%) remaining stable over the follow up period; no patients experiencing loss of overall acuity. In 33 treated eyes, 15 eyes (45.5%) improved an average of 7.9 lines of Snellen acuity, 15 eyes (45.5%) remained stable, and 3 eyes (9%) worsened by an average of 1.7

lines of Snellen acuity. Improvements ranged from 1 to 27 lines of vision. Using the LogMAR Scale and calculating delta as a ratio to pre-treatment vision in improved eyes, acuity improvement ranged from 23% to 90% with an average of 40.9% visual acuity improvement over baseline vision. Evaluation of all patients and eyes capable of LogMAR vision showed an average of 31% improvement in vision over baseline. Findings were of statistical significance (p=0.016). One patient, who reported the acute worsening of visual acuity several weeks before procedure obtained the most improvement in visual acuity following surgery. There were no surgical complications intraoperative or postoperatively. [46]

Park S et al. (2015) in earlier RCT in the US also evaluated autologous bone marrow (BM) CD34+ cell therapy for ischemic and degenerative retinal disorders. This pilot clinical trial explored the safety and feasibility of intravitreal autologous CD34+ BM cells as potential therapy for ischemic or degenerative retinal conditions. This single centre, prospective, open-labeled study enrolled six subjects (six eyes) with irreversible vision loss from retinal vascular occlusion, hereditary or non-exudative age-related macular degeneration (AMD), or retinitis pigmentosa, seen in the Retinal Centre at the University of California-Davis Eye Center between November 2012 and August 2014. Study population was adults above 18 years with irreversible loss of vision for over six months in the study eye from hereditary or non-exudative AMD, RP or retinal vascular occlusion. Enrollment BCVA was 20/100 to counting fingers in the study eye, with equal or better BCVA in contralateral eye. Bone marrow aspiration was performed from iliac crest, with approximately 40 to 50ml BM obtained from a single aspiration. CD34+ cells were isolated under Good Manufacturing Practice conditions from the mononuclear cellular fraction of the BM aspirate using a CliniMACs magnetic cell sorter. After intravitreal CD34+ cell injection, serial ophthalmic examinations, microperimetry/perimetry, fluorescein angiography, electroretinography (ERG), optical coherence tomography (OCT), and adaptive optics OCT were performed during the 6-month follow-up. A mean of 3.4 million (range, 1–7 million) CD34+ cells were isolated and injected per eye.

They found BCVA and full-field ERG showed no worsening after 6 months. Improvement in BCVA ranged from 0 to 11 lines during the six months follow-up (mean improvement of three lines). Improvement of two or more lines of BCVA (i.e. ten letters or more) was noted in four of six subjects. Time course of improvement varied among the subjects.[40]

Tueprakhon A et al. (2021) conducted a non-randomized trial to investigate the safety, feasibility, and short-term efficacy of intravitreal injection of bone marrow-derived mesenchymal stem cells (BM-MSCs) in participants with advanced RP. This trial was conducted in Siriraj Hospital Mahidol University from February 2012 to March 2020. This non-randomized phase I clinical trial enrolled 14 participants, which categorized the study population into three groups based on intervention; a single dose intravitreal BM-MSC injection of $1x10^6$, $5x10^6$, or $1x\ 10^7$ cells. The inclusion criteria were: (1) age between 18 and 65 years old, (2) BCVA of more than or equal to logarithm of minimum

angle of resolution (logMAR) of 0.48, (3) central visual field (VF) less than or equal to 20°, and (4) a nonrecordable electroretinogram (ERG) or an amplitude of less than 25% of the normal value. 20 ml of autologous bone marrow was aspirated from the posterior iliac crest in a sterile heparin-containing syringe and produced BM-MSCs under controlled condition in the cleanroom ISO 5 (class 100, Grade A). The third passage of BM-MSCs was used for intravitreal injection. The positive expression of cluster of differentiation (CD) 73, CD90, and CD105 and the lack of expression for the surface markers CD34, CD45, and human leukocyte antigen (HLA)-DR were ensured by flow cytometry. The product sterility, including aerobic and anaerobic bacteria, fungi, mycoplasma and endotoxin was tested prior to sending them to Siriraj Hospital Mahidol University, under a controlled temperature of 15-20°C. Under sterile condition, an intravitreal injection at the superotemporal quadrant, 3.5 mm posterior to the limbus, was performed by an experienced ophthalmologist under topical anesthesia. Indirect ophthalmoscopy was performed immediately after the procedure to ensure no central retinal artery occlusion. All participants received moxifloxacin eye drops for seven days post-intervention. They evaluated signs of inflammation and other adverse events (AEs), as well other outcomes; best corrected visual acuity (BCVA), visual field (VF), central subfield thickness (CST) and subjective experiences. Final study population consisted of 16 participants, nine males and five females, with ages ranging from 31 to 61 (mean ± SD, 46.2 ± 9.3) years. The average baseline BCVA was 2.00 ± 0.14 logMAR in the study eye. At baseline, an average intraocular pressure (IOP) of 13.11 ± 1.71 mmHg in the study eye. The ERG was non-recordable in all participants.

They found statistically significant improvements in the BCVA compared to baseline, although they returned to the baseline at 12 months. When compared to the fellow eye, the highest improvement was observed in group 1 (Fig. 1), which received the lowest number of BM-MSCs. Specifically, when compared to the baseline, the BCVA in group 1 improved at M2, 5, 7, and 8, reaching statistically significant improvements at M7 ($p = 0.04$) and M8 ($p = 0.02$) (Figure 7). [45]

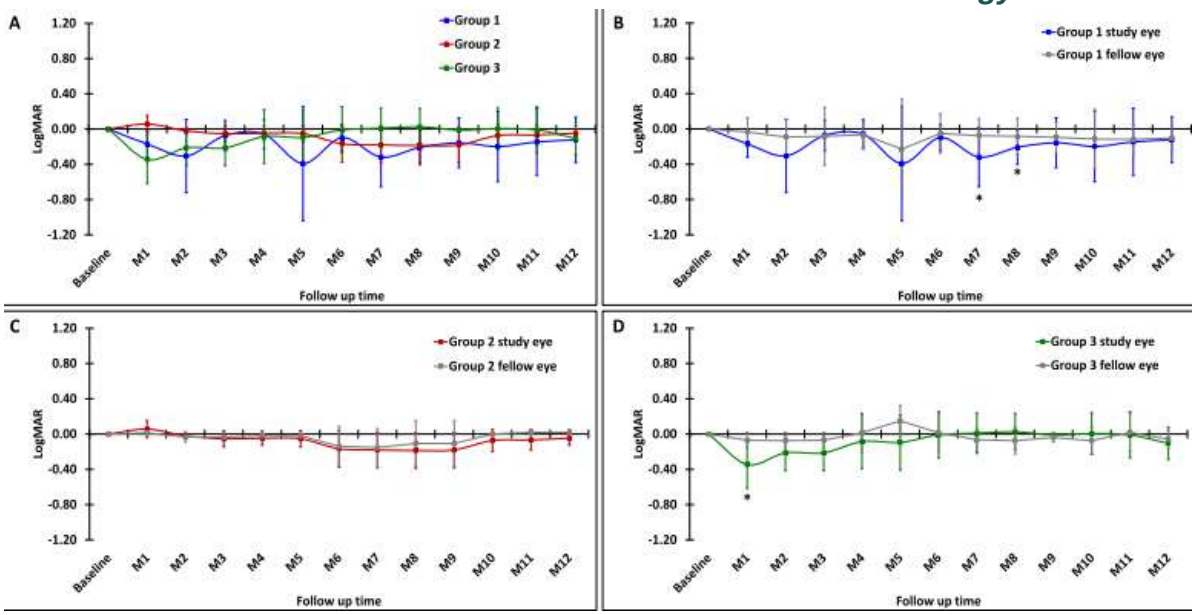


Figure 7: Best corrected visual acuity (BCVA) after the intravitreal BM-MSC injection.

a The comparison of the BCVA in the study eye among groups (blue, red, and green lines indicate groups 1, 2, and 3, respectively). The comparison of the BCVA between the study eye (gray line) and fellow eye of groups 1 (b), 2 (c), and 3 (d). Data represent mean of study participants from each group; group 1:n=7, group 2:n=3, and group 3:n=4 (except for M12: n=3). Error bars indicate the SD of cells and flare value in each group. Asterisks indicate the statistical significance at p < 0.05

Oner A et al. (2016) in another RCT evaluated subretinal adipose tissue-derived MSC (ADMSC) implantation in patients with advanced RP. This single center, prospective phase I RCT in Erciyes University, Turkey included 11 patients with end-stage RP (irreversible vision loss due to RP) who received subretinal implantation of adipose tissue derived MSCs. The mean age of the subjects was 38.2 years (age range 26–57 years). The study was performed according to Helsinki Declaration, and approved by the Institutional Review Board, and the Review Board of Stem Cell Application Ministry of Health in accordance with the regulation in their country. All patients had a total visual field defect and five of them only had light perception. The BCVA in the study population was 20/2000. All patients had undetectable electroretinography (ERG). Patients were included if they had: 1) a diagnosis of hereditary retinal dystrophy classified clinically as RP; 2) an Early Treatment Diabetic Retinopathy Study BCVA worse than 20/200; 3) a visual field less than 20 degrees, considered as legally blind; 4) decreased electroretinography (ERG) recordings; and 5) were aged older than 18 years. The ADMSCs obtained from the adipose tissue of a single donor were used for all patients in this study to eliminate donor-based differences. Subcutaneous adipose tissue was carried to the laboratory in a transfer solution. Adipose tissue derived mesenchymal stem cell (ADMSCs) were then harvested and cryopreserved until use. Before the appointed surgery date, sufficient cryopreserved vials were thawed to provide the required dose for administration. The frozen ADMSCs were thawed and cultured under the same conditions. ADMSCs were recovered, washed with PBS and trypsin/EDTA, and then resuspended in saline solution and transferred to the surgery room in a temperature-controlled bag within one hour.

The total injection volume was $2.47x10^6 \pm 0.11/150$ µl per patient for this study. The procedure for ADMSC preparation was performed under good manufacturing practice (GMP) conditions in the Genome and Stem Cell Center of our University. All of the donation, manufacturing, and testing procedures were carried out according to GMP protocols authorized by the Ministry of Health in their country. For release testing, ADMSCs were assessed for cell appearance, viability, identification, purity, content, and potency. In addition, ADMSCs were screened for contamination. ADMSCs were subjected to flow cytometry analyses for confirmation that ADMSCs maintain their phenotypic characteristics in vitro. Immunophenotyping characterization of ADMSCs was performed with antibodies against the following combination of human antigens: CD11b, CD19, CD34, CD44, CD45, CD73, CD90, and CD105. All patients received a routine 23-gauge pars plana vitrectomy operation with retrobulbar anesthesia under sterile conditions. Subretinal ADMSCs were injected at a concentration of $2.47 \times 10^6 \pm 0.11/150$ µl with a 41-gauge needle. The worst eye of the patient was operated on and, after total vitrectomy with a 23 gauge, ADMSCs were injected subretinally.

Patients were evaluated at day 1, at weeks 1 to 4, and then once a month for 6 months, postoperatively. Best Corrected Visual Acuity (BCVA), anterior segment and fundus examination, color photography, and optical coherence tomography (OCT) were carried out at each visit. Fundus fluorescein angiography (FFA), perimetry, and ERG recordings were performed before treatment and at the end of month 6, and anytime if necessary, during the follow-up. The patients received topical steroid and antibiotic eye drops four times a day for 2 months. Low dose systemic cyclosporin A (2.5–3 mg/kg/day, twice daily) was used as an immunosuppressive agent for two months starting from 1 week before surgery.

There was no statistically significant difference in BCVA and ERG recordings from baseline. Only one patient experienced an improvement in visual acuity (from 20/2000 to 20/200), visual field, and ERG. Three patients mentioned that the light and some colors were brighter than before and there was a slight improvement in BCVA. The remaining seven patients had no BCVA improvement (five of them only had light perception before surgery).[43]

Siquiera et al. (2011) in another non-randomized trial evaluated the short-term (10 months) safety of a single intravitreal injection of autologous bone marrow–derived mononuclear cells (ABMSC) in patients with RP or cone–rod dystrophy. Patients were evaluated at the Retina and Vitreous Section of the Department of Ophthalmology, Otorhinolaryngology and Head and Neck Surgery, School of Medicine of Ribeira˜o Preto, Sao Paulo, Brazil between May 2009 and February 2010. This prospective, phase I, non-randomized, open-label study included five patients (three patients with retinitis pigmentosa and two patients with cone-rod dystrophy) and an Early Treatment Diabetic Retinopathy Study best-corrected visual acuity of 20/200 or worse. Patients were included if they had a 1) diagnosis of hereditary retinal dystrophy classified clinically as RP or cone–rod dystrophy and 2) Early Treatment Diabetic Retinopathy Study BCVA of 20/200 or worse. Exclusion criteria were 1) previous ocular surgery other than

cataract extraction; 2) presence of cataract or other media opacity that would prohibit high-quality ocular imaging or that would affect electroretinography (ERG) or visual field evaluation; 3) presence of other ophthalmic disease such as glaucoma or uveitis; 4) history of blood disorders such as leukaemia; 5) known allergy to fluorescein or ICG angiography; or 6) known coagulation abnormalities or current use of anticoagulative medication other than aspirin. If both eyes were eligible for treatment, the eye with worse visual acuity was included in the study. Evaluations including BCVA, full-field electroretinography, kinetic visual field (Goldman), fluorescein and indocyanine green angiography, and optical coherence tomography were performed at baseline and 1, 7, 13, 18, 22, and 40 weeks after intravitreal injection of 10 x 10^6 autologous bone marrow–derived mononuclear cells (0.1 mL) into one study eye of each patient.

They found a 1-line improvement in BCVA was observed in four out of five patients (80.0%) one week after injection and was maintained throughout follow-up. [3]

b) Visual field / perimetry

Ozmert E and Arslan U (2020) in the RCT conducted found the mean fundus perimetry deviation index (FPDI) was 8.0%, 11.4%, and 11.6%, respectively (p = 0.01; T0 < T1, T2) following subtenon WJMSC transplantation in patients with RP. Visual field sensitivity was measured by fundus perimetry deviation index (FDPI) and mean deviation (MD). Example of visual field finding from a patient is illustrated in figure 8. [42]

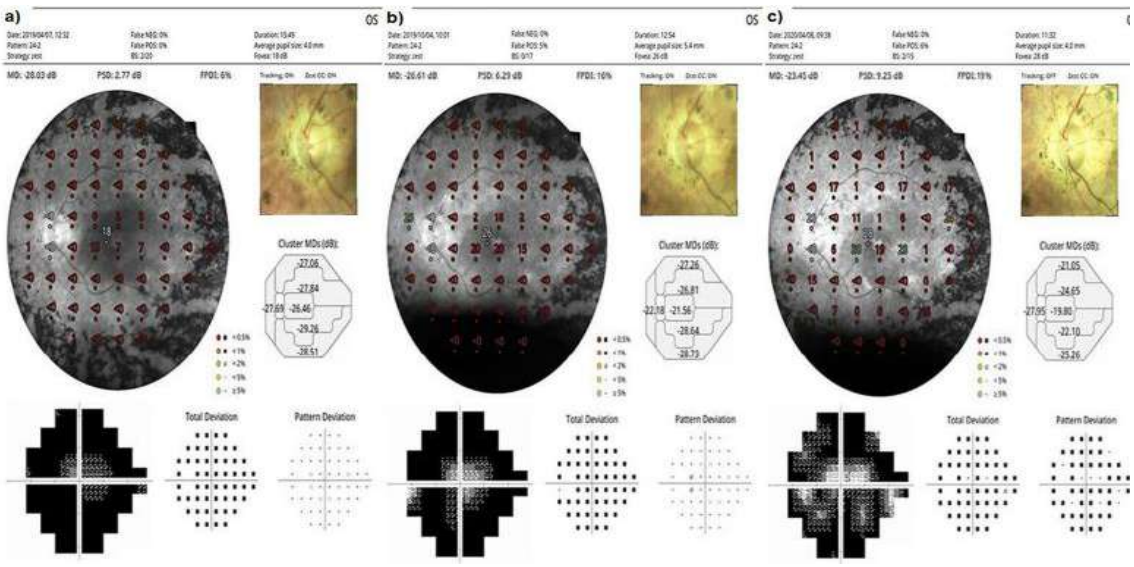


Figure 8: 'Visual field' enlargement according to study time points in eye treated with WJ-MSC, example from a patient (patient 2, left eye)
a: Before application, FDPI 6%, MD 28.03, b: at sixth month, FDPI 16%, MD 26.61 and, c: at twelve months: FDPI 19%, MD 23.45

Tueprakhon A et al. (2021) in the non-randomized trial assessing the efficacy of intravitreal injection of bone marrow-derived mesenchymal stem cells (BM-

MSCs among patients with advanced RP found the VF and CST were stable, indicating no remarkable disease progression. Eight out of 14 participants showed unremarkable VF changes between the baseline and at M12 (twelve months), while it was not able to be evaluated in the remaining six participants.[45]

Oner A et al. (2016) in another RCT evaluated subretinal adipose tissue-derived MSC implantation in 11 patients with advanced RP. One participant (Subject 9) was noted to have improvement in the visual field on Goldmann perimetry at 1-month follow-up examination, which appeared sustained at the final 6- months follow-up visit. The remaining patients did not show any improvement regarding the perimetry.[43]

Siquiera et al. (2011) in the non-randomized trial in Brazil evaluating intravitreal injection of 10 x 10^6 autologous bone marrow–derived mononuclear cells (0.1 ml) in five patients with RP or cone-rod dystrophy found no reduction in visual fields (with a Goldman Standard V5e stimulus) for any patient at any visit (longest at 40 weeks).[3]

c) Electroretinography (ERG) parameters

Ozmert E and Arslan U (2020) found the mean full-field flicker ERG parameters at T0, T1, and T2: ERG amplitudes were 2.4 mV, 5.0 mV, and 4.6 mV, respectively (p=0.01; T0 < T1, T2). Implicit time were 43.3 ms, 37.9 ms, and 38.6 ms, respectively (p=0.01; T0 > T1, T2). Flicker electroretinography is a non-invasive objective test that measures the electrical activity of the retina in response to a light stimulus. [42]

Kahraman & Oner (2020) in another RCT found the amplitudes of the P1 waves in the central areas (<2^0 and 2^0 to 5^0) showed significant improvement in multifocal ERG recordings at sixth month postoperatively. There were also significant increases in implicit times of P1 waves in the central areas (<2^0, 2^0 to 5^0, and 5^0 to 10^0) postoperatively.[41]

Park S et al. (2015) in the earlier RCT conducted in the US, evaluated autologous bone marrow (BM) CD34+ cell therapy for ischemic and degenerative retinal disorders involving six subjects, found full-field ERG showed no worsening after six months among the subjects. Among subjects with detectable full field ERG signal at baseline, there was no worsening of signal amplitude during the follow-up in the study eye. Clinical examination also showed no worsening during follow-up except among age-related macular degeneration subjects in whom mild progression of geographic atrophy was noted in both the study eye and contralateral eye at 6-month follow-up, concurrent with some possible decline on multifocal ERG and microperimetry. [40]

Oner A et al. (2016) in another RCT evaluated subretinal adipose tissue-derived MSC implantation in 11 patients with advanced retinitis pigmentosa. Ten subjects had flat unrecordable full-field ERG at baseline and at 6-month

follow-up in both eyes. There was a slight improvement in the ERG recordings of subject 9. [43]

Siquiera et al. (2011) in the non-randomized trial evaluating intravitreal injection of 10 x 10^6 autologous bone marrow–derived mononuclear cells in five patients with RP or cone-rod dystrophy found a total of three patients showed undetectable electroretinography responses at all study visits, while one patient demonstrated residual responses for dark-adapted standard flash stimulus (a wave amplitude approximately 35 mV), which remained recordable throughout follow-up, and one patient showed a small response (a wave amplitude approximately 20 mV) recordable only at weeks 7, 13, 22, and 40. Evaluations including full-field electroretinography, kinetic visual field (Goldman), fluorescein and indocyanine green angiography, and optical coherence tomography were performed at baseline and 1, 7, 13, 18, 22, and 40 weeks after intravitreal injection of cell therapy. No other changes were observed on optical coherence tomography or fluorescein and indocyanine green angiograms.[3]

5.2.2 Structural finding

Ozmert & Arslan et al (2020) in their trial found the mean of outer retinal thickness was 100.3µm, 119.1µm and 118.0µm, (p = 0.01; T0 < T1, T2). The mean horizontal ellipsoid zone width were 2.65 mm, 2.70 mm, and 2.69 mm respectively (p = 0.01; T0 < T1, T2). Ellipsoid zone width showed healthy photoreceptors, which was measured both horizontally and vertically. [42]

Park S et al. (2015) in their trial involving six subjects found cellular in vivo imaging using adaptive optics OCT showed changes suggestive of new cellular incorporation into the macula of the hereditary macular degeneration study eye.[40]

Tueprakhon A et al (2021) in their non-randomized trial found the central subfield thickness (CST) showed unremarkable changes, with average CST at the baseline of 172 ± 59.2 µm in the study eyes. The (CST) was demonstrated to remain stable throughout the study, i.e., M1 (178 ± 61.7 µm), M3 (178 ± 58.7 µm), M6 (176 ± 60.1 µm), and M12 (176 ± 59.8 µm).[45]

5.2.3 Characterization/phenotype of bone marrow or adipose tissue-derived mesenchymal stem cells

a) Bone marrow-derived mesenchymal stem cells (BMDSC)

Tueprakhon et al (2021) found the BM-MSCs from all participants exhibited spindle shaped-like cells. The stem cell phenotypes were in accordance with the International Society for Cellular Therapy (ISCT), such as adherence to the plastic culture vessel; expression of more than 95% of CD73, CD90, and CD105; and negative (less than 2%) for CD34. The trilineage differentiation ability to be adipocyte, osteocyte, and chondrocyte was confirmed in all samples. There was no microorganism or endotoxin contamination. The average cell viability was 92.12 ± 3.5.[45]

b) Adipose derived mesenchymal stem cells (ADMSC)

Oner A et al (2016) in the RCT evaluated 11 patients with advanced RP whom underwent injection of ADMSCs. The ADMSCs were positive for CD44, CD73, CD90, and CD105, and negative for CD11b, CD34, CD45, and HLA-DR. No evidence of bacterial or fungal contamination was observed in the cells which were tested before release. Cell viability evaluated by trypan blue exclusion was >90.3 ± 0.5% before cell transplantation. For immunophenotypic characterization of ADMSCs, culture-expanded cells at the third passage were examined for surface protein expression using flow cytometry. [43]

5.2.4 Vision-Related Quality of Life

Siqueira RC et al. (2015) in another RCT evaluated quality of life in patients with RP submitted to intravitreal use of bone marrow-derived stem cells (Reticell clinical trial phase II). The study included 20 patients with RP submitted to intravitreal use of bone marrow-derived stem cells.The study was conducted in a single center (Hospital das Clinicas, Medical School Ribeirao Preto- Sao Paulo Brazil). Patients were evaluated at the Retina and Vitreous Section of the Department of Ophthalmology, Otorhinolaryngology and Head and Neck Surgery, School of Medicine of Ribeirão Preto, between April 2012 and July 2013. Patients were included if they had: 1) a diagnosis of hereditary retinal dystrophy classified clinically as RP or cone–rod dystrophy, and 2) Early Treatment Diabetic Retinopathy Study BCVA of 20/200 (or worse) or visual field less than 20 degrees, considered legally blind. If both eyes were eligible for treatment, the eye with worse visual acuity was included in the study. Bone marrow (10 ml) was harvested from the posterior iliac crest and mononuclear cells were separated by Ficoll–Hypaque gradient centrifugation and suspended in buffered saline containing 5% human albumin at a concentration of 1×10^7 cells/ml. The final product demonstrated absence of microbial contamination. The final 0.1 ml of cell suspension used for the intravitreal injection contained 0.92×10^4 to 2.91×10^4 (mean: 1.68×10^4) bone marrow–derived hematopoietic stem cells (CD34+). Autologous (freshly isolated) bone marrow–derived mononuclear cells were injected into the vitreous cavity using a 27-gauge needle inserted through the inferotemporal pars plana 3.0 mm to 3.5 mm posterior to the limbus. The sham stem cell injection control procedure involved anaesthetizing the contralateral eye in a manner identical to that used for stem cell intravitreal injection.

They evaluated the vision-related quality of life (VRQOL) of patients using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25). The NEI-VFQ evaluated the patients' subjective visual function. The NEI-VFQ-25 gives an overall score, as well as 12 subscale scores: general health, general vision, near vision, distance vision, driving, peripheral vision, colour vision, ocular pain, vision-associated role limitations, dependency, social functioning, and mental health. The questionnaire comprises five-point scale ratings that were transformed into percentages (0% to 100%). Patients were scheduled to answer the questionnaire before treatment, three and 12 months after treatment.

All patients completed the survey as scheduled. They found statistically significant improvement ($p<0.05$) in the quality of life of patients at 3 months after treatment, whereas by the 12th month there was no statistically significant difference from baseline. Figure 9 illustrates the behaviour of quality of life of the patients based on the replies to the survey three to twelve months after treatment. Figure 10 shows a line representing the average of all patients, more clearly revealing the significant improvement by the third month after treatment.[44]

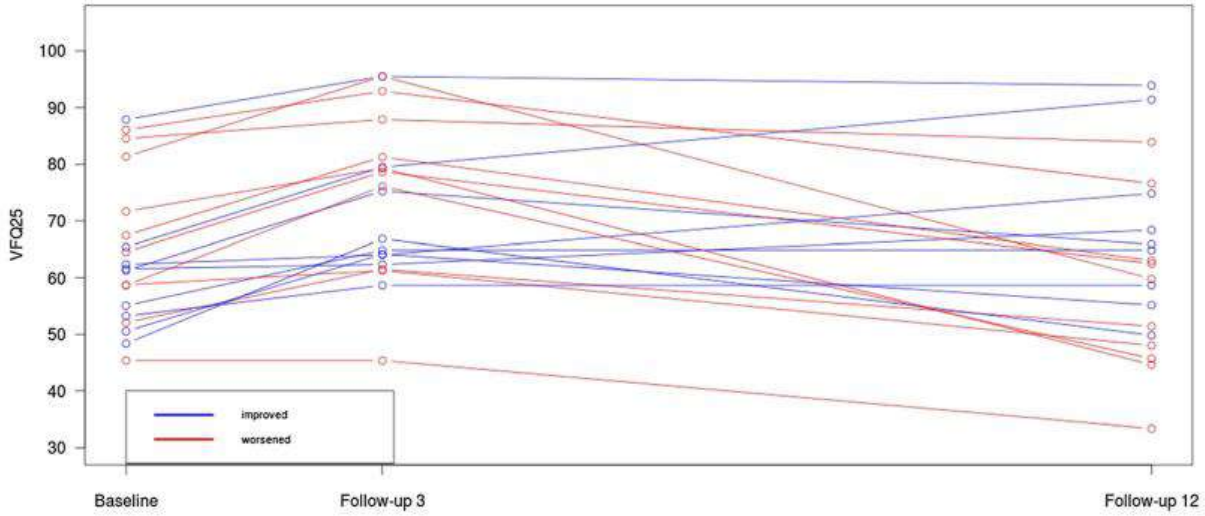


Figure 9: Quality of life of all study population following treatment

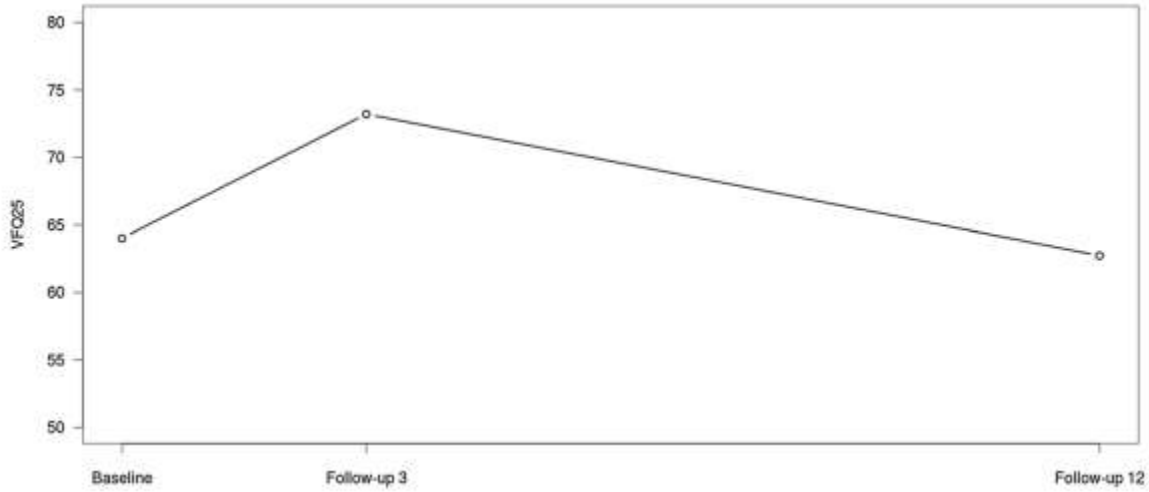


Figure 10: Average quality of life of the study population following treatment

Tueprakhon et al. (2021) also found subjectively, most participants experienced improvements in the QOL during the 12-month period after the BM-MSC injection. Seven out of 14 (50%) participants described a stable vision, five (35.7%) participants could see better in dim light, five (35.7%) could see light better than the fellow eye, three (21.4%) could see some colors, and four (28.6%) could perform daily activities better, such as walking to the bathroom at night, using the cell phone, watching TV, and riding the bicycle.[45]

5.3 SAFETY

There were eight studies retrieved on the safety of MSC in the management of RP, consisted of three RCT, three non-randomized trial and one case report.

Currently, the only stem cell products that are FDA-approved for use in the US consist of blood-forming stem cells (hematopoietic progenitor cells) that are derived from umbilical cord blood. These products are approved for use in patients with hematopoietic system disorders but they are not approved for other uses.[47]

Park SS et al (2015) explored the safety and feasibility of intravitreal autologous CD34+ bone marrow (BM) cells as potential therapy for ischemic or degenerative retinal conditions. This prospective study enrolled six subjects (six eyes) with irreversible vision loss from retinal vascular occlusion, age related macular degeneration or retinitis pigmentosa. The CD34+ cells were isolated from the mononuclear cellular fraction of the BM aspirate. All subjects tolerated the BM aspiration and intravitreal injection of CD34+ cells and completed the six months follow up without any adverse event except for grade 1 local pain immediately following BM aspiration. Overall, the therapy was well tolerated with no intraocular inflammation or hyperproliferation. Intravitreal autologous BM CD34+ cell therapy was well tolerated in eyes with ischemic or degenerative retinal conditions.[40]

Ozmert E and Arslan (2020) in their RCT found no ocular or systemic adverse events related to the surgical methods and/or WJ-MSCs among the study population during the one year follow-up period. [42]

Kahraman & Oner (2020) in another prospective, single center RCT evaluating suprachoroidal umbilical cord derived mesenchymal stem cell (UC-MSC) implantation in patients with retinitis pigmentosa (RP) involving 124 eyes of 82 RP patients found none of them had any serious systemic or ocular complications. One patient reported to have transient vision loss in the treated eye lasted for a few minutes at third day of surgery. Ocular examination revealed similar findings to preoperative test, systemic and neurological examination were within normal limits. Slight deterioration in the VF test at first month was experienced and recovered at the sixth month of visit. [41]

Siqueira RC et al. (2011) in another non-randomized trial evaluated short term (ten month) safety of a single intravitreal injection of autologous bone marrow derived mononuclear cells in five patients with RP or cone-rod dystrophy. This non-randomized trial included three patients with RP and two patients with cone-rod dystrophy and an Early Treatment Diabetic Retinopathy Study BCVA of 20/200 or worse. Overall, no adverse events associated with the Intravitreal injection of autologous bone marrow derived mononuclear cells injection was observed. [3]

Tueprakhon A et al. (2021) in a non-randomized trial conducted in Thailand evaluated 14 participants with advanced RP following intravitreal injection of

bone marrow-derived mesenchymal stem cells (BM-MSCs). The immediate adverse events (AE) were recorded during 24h after the injection. The short-term AEs and efficacy were examined daily for the first 7 days, then once weekly for up to 4 weeks, and then monthly for a period of 12 months. They found during the 12-month period, several mild and transient AEs were observed. An increase in IOP in all groups (4.40 ± 2.07 mmHg in group 1; 6 ± 4.24 mmHg in group 2; and 9 ± 0 mmHg in group 3) were observed 1hour post-intravitreal injection. However, the IOP returned to the baseline values on the first day (D1) and remained stable throughout the course of the study. During the first week post-injection, two participants (14.28%) complained of mild pain in the study eye, one (7.14%) reported feeling pressure, two (14.28%) with redness, and four with mild irritation in the study eye. All symptoms subsided spontaneously within 1 week without treatment. In the course of 12 months, no participant experienced a sudden decline in the BCVA or VF.

They followed 12 participants beyond the study period, ranging from 1.5 to 7 years, and observed one severe but manageable AE at year 3. Diffuse vitreous hemorrhage, which obscured fundus details was reported in a patient following which pars plana vitrectomy was performed to remove the vitreous hemorrhage and intraoperatively, thick fibrous membrane was observed along the vitreous base. Another mild AE observed was minimal IOL subluxation in both eyes. However, according to the author it was difficult to exactly determine whether these AEs were caused by the intervention, the BM-MSC or following the progression of the disease.[45]

Oner A et al (2016) in the RCT involving 11 patients with end-stage RP found all 11 patients completed the 6-month follow-up. They found none of them had systemic complications. Five patients had no ocular complications. One of the patients experienced **choroidal neovascular membrane (**CNM) at the implantation site and received an intravitreal anti-vascular endothelial growth factor drug once. Five patients had **epiretinal membrane** around the transplantation area and at the periphery, and received a second vitrectomy and silicon oil injection. They found no evidence of adverse proliferation, rejection, or serious ocular or systemic safety issues related to the implanted stem cells.[43]

Kim JY et al. (2016) reported an epiretinal membrane (ERM) formation after intravitreal autologous stem cell implantation in a patient with RP in Korea. This was a retrospective case report of a patient with RP who underwent vitrectomy for epiretinal membrane following intravitreal autologous stem cell implantation. The case was a 71-year-old female patient with RP attending ophthalmic evaluation after intravitreal autologous stem cell injection, with presenting BCVA of 20/100 (OD, right eye) and 20/200 (OS, left eye). Four months prior to that, she underwent intravitreal autologous stem cell injection for both eyes at another hospital. Earlier, at the age of 66-years, this patient presented with visual disturbance in both eyes, with BCVA of 20/40 (OD, right eye) and 20/33 (OS, left eye) during presentation. After observation for 4 years, her visual acuity was decreased to 20/100 (OD, right eye) and 20/50 (OS, left eye). Subsequently she underwent intravitreal autologous stem cell injection on both

eyes at another hospital (USA) in November 2014. On examination at the current presentation (post stem cell implantation), they found new thick epiretinal membrane (ERM) with extensive macular pucker on her left eye, following which she underwent pars plana vitrectomy and membranectomy. After biopsy, many CD34-positive stem cells were detected in the ERM specimen. [17] level III

5.4 ECONOMIC EVALUATION / FINANCIAL IMPLICATION

There was no retrievable evidence on the cost-effectiveness of MSC in the management of patients with RP or retinal degenerative diseases.

Mesenchymal stem cells can be derived from umbilical cord, bone marrow, or adipose tissue with different procedures such as umbilical cord separation of Wharton jelly collection, bone marrow harvesting and liposuction.[48] In Malaysia, the complete breakdown of cost of activities entailed in the testing, harvesting, isolation and storage of mesenchymal stem cells was not able to be retrieved fully. However, it is quoted that a treatment of mesenchymal stem cells may cost MYR60,000 to MYR80,000 consisting of 100 million cells.[48] Based on current local practice as informed by clinical experts, two patients with retinitis pigmentosa have received retinal mesenchymal stem cell injection in Malaysia and were subjected to out-of-pocket payment of RM20,000 to RM30,000 per procedure (unpublished data, 2022). Treatment of one injection of mesenchymal stem cell for RP seems to be beneficial and safe until follow up of one year, usually at <10 million cells per injection.[42] Post stem cell injection medications include guttae steroids and antibiotics. 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.[50] Computed from this, the cost implication will be approximately MYR 7,860,000 to MYR 10,480,000 per year.

5.5 ORGANISATIONAL

Definition and properties of MSCs after in vitro expansion has been reached by the International Society for Cellular Therapy (ISCT) a specific immunophenotype, ex vivo plastic-adherent growth, and multilineage differentiation, defined as the minimal prerequisites needed.[50]

The ICST highlighted minimal criteria that should be demonstrated before a cell can be considered or referred to as an MSC include (1) Tissue culture plastic adherent; (2) Positive (≥95%) for surface antigen markers CD105, CD90, and CD73 while also negative (≤2%) for CD45 (pan-leukocyte), CD34 (hematopoietic and endothelial cells), CD14 or CD11b (monocytes and macrophages), CD79α or CD19 (B cells), and HLA-DR; and (3) Capable of differentiation to adipocytes, chondroblasts, and osteoblasts. [51]

Methods used for human MSC isolation, expansion, characterization for tissue repair, and using BM-derived MSCs were addressed in the Human Bone Marrow and Adipose Tissue Mesenchymal Stem Cells: A User's Guide. The production of MSCs for clinical intervention needs to comply with good manufacturing practice (GMP) to ensure the final delivery of a safe, reproducible, and efficient ''celldrug.'' All steps of the process must be defined, from the source for isolation to culture methods, to the procedures, materials and methods used for cell culture, and quality controls. Even if MSCs are expandable from virtually all tissues, to date the preferred source remains the BM. Hundreds of millions MSCs can be expanded in vitro starting from 10 to 20 ml of BM aspirate, although cell yield may vary depending on age and condition of the donor and on the expansion techniques. Adipose tissue may represent an important alternative to easily obtain a large number of MSCs, in addition to source from other tissues such as trabecular bone, cord blood, or amniotic membrane. [50]

The parameters of the culture process must be optimized to reach GMP goals; the first critical parameter is the plating density, which could be involved in the maintenance of early progenitors. Additionally, the time in culture may also change the quality of MSCs. In humans, after 3 weeks and 12–15 population doublings, MSCs decrease their proliferation rate and progressively loose their multipotency.[50]

Academic and industrial laboratories using clinical-grade MSCs should follow guidelines of the regulatory agencies and use equipment, reagents and supplies, established procedures, and strict safety measures. In the US, the GMP hMSC production is regulated by FDA CFR Title 21, part 1271, subpart D, sections 145-320, focusing on current good tissue practice requirements which provide exemptions, maintenance of quality, personnel, procedures, facilities, environmental control, equipment, supplies, recovery, process controls, process changes, process validation, labeling controls, storage, shipment, records, tracking, and complaint file (USFDA). In the European Union, the GMP production is regulated under the European Regulation No. 1394/2007. [31]

For release testing, ADMSCs were assessed for cell appearance, viability, identification, purity, content, and potency. In addition, ADMSCs were screened for contamination. ADMSCs were subjected to flow cytometry analyses for confirmation that ADMSCs maintain their phenotypic characteristics in vitro.[41]

In Malaysia, standards have been established to promote the standardization of procedures and practices in collection, processing, storage and infusion of haemopoietic stem cells (HSC) and therapeutic cells among the transplant centers in line with the National Organ, Tissue and Cell Transplantation Policy. The guideline represents an update on the laboratory framework to support stem cell therapy from the point of collection, processing, storage, handling and infusion of the products to ensure patients' safety. The application of these standards shall not be limited to only HSC transplant and lymphocyte infusion, other **therapeutic cells therapy namely mesenchymal stem cells** collection,

processing, storage and infusion shall also follow the requirements of these standards.[52]

Apart from these standards, the laboratory shall comply with relevant international and local regulatory requirements such as Good Tissue Practice Guideline, published by National Pharmaceutical Regulatory Agency (NPRA). Thus, compliances to these Standards do not itself confer immunity from legal. Therefore, this document should be read in conjunction with relevant MOH legislative and guidelines document such as current Good Tissue Practice Guideline and guidance document and guidelines for registration of cell and gene therapy products (CGTPs) in Malaysia. These standards only focus on the use of internationally established transplant procedures and processes. Those which are still under the investigational list will be addressed in the standards prepared by the National Ethics and Research Committee.[52]

The source of MSCs and delivery route are fundamental clinician decisions. Among those MSCs, BM-MSC is the most commonly used, with the longest track record, source of human MSCs.[45]

There are several administration routes of MSCs that had been validated. Intravenous is among the easiest and the least invasive route. This method is most common for MSC delivery. However, this route requires a large number of MSCs since MSCs could circulate to various organs and be trapped within the small capillaries. Therefore, this route might not be suitable for retinitis pigmentosa. Subretinal transplantation would deliver the cells directly under the retina in an immunoprivileged site, but the procedure is more complex and invasive. Moreover, this route is restricted with the number and volume of MSC product. Intravitreal transplantation of MSCs could overcome the volume restriction and the procedure is less invasive. Another mode of injection, subtenon has been shown to be safe and efficacious since this cavity is hypovascular and the secreted growth factors could pass through the choroid to the subretinal space.[45]

Approach to stem cell therapy is to revive and regenerate the affected cells in the retina by introducing stem cells that have a paracrine trophic effect, which is potentially possible using BMSCs.[24] If these stem cells can be delivered intravitreally without adverse effects, the ease of such route of administration would be highly desired. Unlike vitrectomy surgery for subretinal administration of cells that requires hospital admission and significant recovery time from surgery, intravitreal injection of cells can be performed in the clinic, with minimal recovery time.[24]

Among cell injection sites, the **subretinal space is particularly advantageous** as it is maintained as an immune privileged site by the connections between the RPE layer. It has been said that if the blood-retinal barrier is preserved during surgery, immunosuppressive drugs are not necessary. Thus, the success of subretinal transplantation depends on maintenance of RPE integrity. Moreover, both ESCs and MSCs have negligible immunogenicity, reducing the chance of rejection. In contrast, there may be a disruption of the blood-retinal barrier by

subretinal injection; the balance of the subretinal microenvironment may be broken and immunosuppression will be necessary until recovery of the barrier.[43]

The eye has numerous advantages for developing stem cell therapies as all tissues of the eye are surgically accessible, and transplanted cells can be monitored. Moreover, the ocular immune privilege might greatly simplify immunosuppressive treatment after transplantation. Immunosuppression is still controversial and there is no established standard immunosuppressive therapy protocol after stem cell therapy.[43]

Quality control standards of the stem cell products must be maintained to minimize the AEs that could appear.[45]

5.6 ETHICAL

BMSCs are usually harvested from adult tissue. Thus, there are no ethical issues. For autologous use, the need for systemic immunosuppression is avoided. These adult stem cells are multi-potent and have more limited capacity to differentiate and divide when compared to embryonic and induced pluripotent stem cells. [24]

Since the MSCs exhibit the lower potential of differentiation compared to Retinal Progenitor Cells (RPCs), Embryonic Stem Cells (ESCs), and induced pluripotent stem cells (iPSCs), this stem cell type has a lower risk of differentiating into undesired tissues, teratoma formation, immune rejection (even from allogeneic sources), and ethical concerns to its use.[45]

5.7 LIMITATION

Our review has several limitations. Although there was no restriction in language during the search, only English full text articles were included in the report. Very few RCT and no head-to-head comparison trial available assessing the effectiveness of MSC in the treatment of patients with RP with varying source of cellulr therapy, method of delivery and amount delivered. Many of the studies involved limited or small study population, with lack of long-term data on the measure of effectiveness in the included studies. Heterogeneity of outcomes measured limiting quantitative summary of results. Most of sthe studies were followed up to one year, hence sustain or long-term improvement in visual acquity following the intervention need to be ascertained. Studies included involved mainly patients with RP, hence limiting generalization of the study finding to wider patients with degenerative retinal disease. Comparing effectiveness of MSC in different stages of the disease with larger number of patients would be useful. One of outcome measurement tool, visual field testing has the limitation in that it is subjective, and relies on patients' cooperation and experience with the test. Another more objective test such as microperimetry has been said to be more reliable to evaluate central VF. Included studies with high risk of bias may affect methodological quality of this review. Lack of local

data on cost and utility of the interventions and comparator in the population of interest prohibit the generation of local cost-utility analysis.

6.0 CONCLUSION

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 was 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 was 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 was 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.

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).

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.

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.

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APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 2: SEARCH STRATEGY

Ovid MEDLINE® In-Process & Other Non-indexed Citations and Ovid MEDLINE® 1946 to present		
1	mesenchymal stem cell.tw.	12762
2	MSC.tw.	128078
3	mesenchymal stem cells.tw.	42857
4	retinal degenerative disease.tw.	301
5	retina degenerative disease.tw.	3
6	hereditary retinal dystrophies.tw.	121
7	retinitis pigmentosa.tw.	9991
8	best disease.tw.	922
9	Beatti's macula dystrophy.tw.	0
10	Beatti's macular dystrophy.tw.	0
11	cone rod dystrophy.tw.	845
12	age related macular degeneration.tw.	25185
13	ARMD.tw.	1470
14	1 or 2 or 3	158558
15	4 or 5 or 6	421
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 15	34391
17	14 and 16	1002
18	Limit 17 (human and English)	362

OTHER DATABASES	
EBM Reviews – Cochrane Central Registered of Controlled Trials	Similar MeSH, keywords, limits used as per MEDLINE search
EBM Reviews – Database of Abstracts of Review of Effects	
EBM Reviews – Cochrane database of systematic reviews	
EBM Reviews – Health Technology Assessment	
NHS economic evaluation database	
PubMed	Similar MeSH, keywords, limits used as per MEDLINE search
INAHTA	
US FDA	

APPENDIX 3: EVIDENCE TABLE

Only available upon request.

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