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Is mesenchymal stem cell transplantation able to decrease the number of relapses in patients with multiple sclerosis?

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not mesenchymal stem cell therapy decreased the number of relapses in patients with multiple sclerosis.

STUDY DESIGN: Review of three randomized controlled trials from 2006-2016.

DATA SOURCES: Two randomized control trials and one case series were found searching PubMed. The randomized control trials compared the number of relapses of patients undergoing stem cell therapy against placebo and anti-inflammatory treatment (IV methylprednisolone and oral prednisone). The case series compared the number of relapses patients experienced before and after stem cell therapy.

OUTCOMES MEASURED: Clinical outcomes included the number of relapses patients experienced measured by onset of new neurological symptoms or by the presence of new gadolinium enhancing lesions (GELs) on MRI.

RESULTS: Li J, Zhang D, Geng T, et al. demonstrated that recurrence frequency was significantly different between the two groups ($p < 0.038$).[5] After dichotamization of the relapse data, it was found that for every two patients treated with human umbilical cord derived mesenchymal stem cells therapy for 6 weeks, 2 or more relapses were prevented when compared to steroid therapy (NNT = 2). Llufriu S, Sepulveda M, Blanco Y, et al. found a decrease in mean number of GEL between the BM-MSC group and placebo group (-2.78 ± 5.89 vs 3 ± 5.36, $p = 0.075$).[6] The relapse frequency data was evaluated as NNT and found that for every patient with multiple sclerosis treated with bone marrow derived stem cells for 12 months, no additional relapses will be prevented when compared to the placebo group (NNT = 0). Lu Z, Zhao H, Xu J, Zhang Z, Zhang X, et al. study suggested that HUC-MSC reduced relapse rate in MS patients by 36.4% at 18 months post treatment compared to before treatment (1.2 ± 0.5 vs 3.3 ± 0.7, $p < 0.05$).[7]

CONCLUSIONS: The results of two RCTs and one case studies showed a decrease in the number of relapses patients with MS experienced after being treated with MSCs compared to steroids, placebo, and before therapy.

KEY WORDS: Multiple Sclerosis, mesenchymal stem cell therapy

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disease effecting the central nervous system (CNS). It is characterized by chronic inflammation, demyelination, gliosis (scarring), and neuronal loss.[1] Those affected by MS experience episodes of weakness, numbness and tingling in their upper extremities along with loss of voluntary control of their limbs along with visual symptoms and incontinence issues. Patients may experience periods where they recover partial neuronal function but ultimately progress to permanent disabilities.[2] The prevalence of MS worldwide is 0.1-0.2%.[2] It affects approximately 2.5 million people worldwide with 350,000 cases reported in the US alone.[2] MS is a chronic disabling disease present throughout the world.

The etiology of MS is not completely understood. Current evidence suggests a genetic susceptibility to the disease based on twin studies and family history. MS also has an autoimmune association with HLA-DR2 (human leukocyte antigen) and alleles of *IL2RA* (the interleukin-2 receptor alpha gene) and *IL7RA* (the interleukin-7 receptor alpha gene).[2] While the etiology is unclear, current treatment options are used to reduce inflammation and prevent new flare ups. Acute episodes are treated with steroids (methylprednisolone, prednisone, or dexamethasone) to reduce inflammation.[2] Current first line recommendations for relapse prevention include interferon β-1a, interferon β-1b, glatiramer acetate, fingolimod, teriflunomide, or dimethyl fumarate.[2] If patients continue to have disease activity then providers may consider using natalizumab, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, or mitoxanate.[2] While these therapies aim to relieve symptoms and prevent relapse there is yet to be a definitive curative treatment.

While patients may find relief from these medications, the cost of treatment is very expensive. The annual cost for relapse prevention medications listed above range from $51,158

to $ 63,806 annually.[3] On top of drug costs, MS patients are 3.5 times as likely to be hospitalized, twice as likely to have at least 1 emergency room visit and 2.4 times as likely to have at least 1 visit for physical, occupational, or speech therapy. Not only do they seek care more frequently than the average patient but they also spend more money on medical services. In comparing patients with MS to non-MS patients, it was found that on average they spend on $4,110 on inpatient services compared to $836, $1,693 vs. $259 for radiology services, $432 vs. $189 for ER services, and $849 vs. $310 for office visits in a one-year period.[4] These are only the costs patients experience for one year and this is a life-long progressively disabling condition. Patients with MS have more medical visits and expenses than the average patient.

There is no current cure for multiple sclerosis. The above medications are expensive and do not alter the course of the condition. Mesenchymal stem cell therapy is a relatively new area of research in treating MS and may be helpful in preventing relapses in affected patients. This paper reviews two randomized control trials and a case series in evaluating if stem cells are a new potential therapy as a treatment option for people suffering from MS.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not mesenchymal stem cell therapy decreased the number of relapses in patients with multiple sclerosis.

METHODS

Two randomized control trials and one case series are included in this review. The population consisted of males and females ages 18 and older with multiple sclerosis. Li J, Zhang D, Geng T, et al. compared the number of relapses between a control group receiving steroid treatment and the experimental group which received stem cell therapy. Both groups received the same treatment schedule of IV methylprednisolone for 6 weeks but the experimental group

received human umbilical cord derived mesenchymal stem cells (HUC-MSC) therapy three times a week in addition to steroids.[5] The number of relapses were then compared between the two groups.[5] Llufriu S, Sepulveda M, Blanco Y, et al study contained two randomized groups that received either bone marrow derived mesenchymal stem cells (BM-MSC) IV for 6 months or placebo. The treatment was reversed at 6 months and patients were followed for an additional year. The authors compared the two groups at baseline, 6 months, and 1 year.[6] Lu Z, Zhao H, Xu J, Zhang Z, Zhang X, et al compared the relapse frequency in the same patient population before and 18 months after a series of five injections of HUC-MSC.[7]

The studies were found searching PubMed for key words: multiple sclerosis, mesenchymal stem cells. Articles were chosen based on their relevance to the proposed clinical question and were selected only if they studied patient oriented evidence that matters (POEMs). Articles were published in English in peer reviewed journals between 2006 and 2016. Participants that were included in the studies were relapse-remitting multiple sclerosis (RRMS) or secondary-progressive multiple sclerosis (SPMS)[5,6,7], EDSS scores between 3.0 to 8.0[6], and age between 18 and 65[7]. Those excluded were patients with significant cardiac/renal/liver failure[5], active or chronic infection[5,6,7], or autoimmune condition unrelated to MS[7]. The statistics reported in this review include numbers needed to treat (NNT), confidence intervals, chi-squares, mean difference, and p-values. See Table 1 for demographics and inclusion/exclusion criteria.

Table 1 – Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Li[5] (2014)	RCT	23	25-55	-RRMS or SPMS - Mean EDSS of 5.0 -deterioration of $\geq$ 1.0 on	-treated with cytotoxic medications in the past 3 months	0	Human umbilical cord-derived mesenchymal stem cell therapy at the

				EDSS in past year -≥ 2 attacks in the last 2 years	-significant cardiac, renal, or hepatic failure -active infection -severe cognitive decline -unable to understand and sign the informed consent		same time as anti-inflammatory treatment
Llufriu[6] (2014)	RCT	9	23-48	-RRMS not responding therapy for a year -ages 18 to 50 years -disease duration of 2 to 10 years -EDSS scores 3.0 to 6.5.	-Active or chronic infection -treatment with any immunosuppressive therapy within the previous 3 months or interferon-beta, glatiramer acetate or corticosteroids within 30 days prior to randomization.	1	Bone marrow derived mesenchymal stem cells
Lu[7] (2013)	Case Series	8	18-59	-SPMS -Ages 18-65 -Duration of disease > 4 years -EDSS score 3.0 to 8.0 -Failure to respond to the MS therapy	-Systemic active disease -Autoimmune condition unrelated to MS or allergies; -Pregnant or possibly pregnant; -HIV (+), Tumor marker (+), brain tumor or BP ≥ 200 mmHg/110 mmHg	0	intrathecal intravenous injections of human umbilical cord-derived stem cells

OUTCOMES MEASURED

Clinical outcomes included the number of relapses patients experienced measured by onset of new neurological symptoms or by the presence of new gadolinium enhancing lesions (GELs) on MRI.

RESULTS

Li J, Zhang D, Geng T, et al. had an experimental group consisting of 13 patients with an average age of 42 years and a control group of 10 patients with an average age of 39 years. All patients had either RRMS or SPMSS. The experimental group had an average EDSS score of 7.0 and the control group had an average score of 6.0. All patients were treated with IV methylprednisolone for 5 days followed by an oral prednisone taper for 2 weeks until they reached the maintenance dosage (5mg daily). The experimental group received HUC-MSCs once every 2 weeks 3 consecutive times. The authors used a chi-square to demonstrate that gender and type of MS had no significant effect between groups ($p = 0.968$). A chi-square was also performed on recurrence frequency data which found a significant decrease in relapse frequency between the two groups ($p < 0.038$).[5] The study suggests that using HUC-MSCs with steroid therapy decreased relapses when compared to steroids alone.

This review further investigated the incidence of relapses by dichotomizing the data found in Table 5 (Group x Relapse Incidence Crosstab) from Li J, Zhang D, Geng T, et al. Success was defined as one relapse or less and failure was considered if a patient had more than one relapse after treatment. This data was then constructed into a 2x2 table to calculate the control event rate (CER), experimental event rate (EER), relative and absolute risk ratio (RRR), absolute risk ratio (ABR), and numbers needed to treat (NNT). The results are summarized in Table 2 below.

Table 2: Efficacy of HUC-MSC in Reducing Relapses Compared to Steroids

Study	CER	EER	RRR	ABR	NNT
Li[5]	0.20	0.77	2.85	0.57	2

Llufriu S, Sepulveda M, Blanco Y, et al. had a total of nine participants in their study, four of which were randomized into the placebo group and five which received the BM-MSCs.

The experimental group received 6 months of BM-MSC therapy and then the treatment was reversed for the next six months. Patients were assessed at 1, 3, 6, 7, 9, and 12 months after randomization. No difference was found in the demographics or gadolinium enhancing lesions at baseline (4.75 $\pm$ 7.6 vs 4.6 $\pm$ 9.7, p = 1.0). At six months, the mean difference in cumulative GEL was found to be difference when comparing the data at a 95% confidence interval (CI) (1.53, 95% CI 0.53-4.42 vs 6.15, 95% CI 2.19-17.28, p = 0.064). At the end of the study there was also a decrease in mean number of GEL between the BM-MSC group and placebo group (-2.78 $\pm$ 5.89 vs 3 $\pm$ 5.36, p = 0.075). Four patients experienced relapses during the placebo phase. One patient assigned to the placebo group withdrew consent after having five relapses within the first three months. Three patients experienced relapses during the BM-MSC treatment period.[6] While the study showed a decrease none of the results were statistically significant.

This review dichotomized the data in Figure 2 (relapses and gadolinium-enhancing lesions during the study) from Llufriu S, Sepulveda M, Blanco Y, et al. The number of relapses were counted in placebo and MSC treatment groups. A 2x2 table was constructed comparing before and after treatment with success defined as 1 relapse or less. Patient one withdrew from treatment after having 3 relapses and his data was counted as a failure for both the placebo and control groups. A 2x2 table was constructed and used to calculate CER, EER, RRR, ABR, and NNT reported below in Table 3.

Table 3: Efficacy of BM-MSC in Reducing Relapses Compared to Placebo

Study	CER	EER	RRR	ABR	NNT
Llufriu[6]	0.78	0.78	0	0	0

Lu Z, Zhao H, Xu J, Zhang Z, Zhang X, et al. recruited eight patients with SPMS to receive intrathecal IV injections of HUC-MSCs. The authors used brain and spinal MRI to

evaluate any decrease in volume or number of lesions before and after treatment as well as any a neurological assessment to detect any new neurological symptoms. The authors noted that the GEL lesion volume was lower 12 months after treatment and that two patients had a decrease in the number of lesions. The decreased GELs and reported symptoms were analyzed by using a mean difference to compare the same group at baseline and after treatment. Their results suggested that the relapse rate was reduced by 36.4% at 18 months post treatment compared to before treatment (1.2 ± 0.5 vs 3.3 ± 0.7, $p < 0.05$).[7] The number of relapses before and after treatment are summarized in Table 4 below.

Table 4: Efficacy of HUC-MSC in Reducing Relapses Before and After Treatment

Study	Relapses Before HUC-MSC	Relapses After HUC-MSC	Mean Relapses Before HUC-MSC	Mean Relapses After HUC-MSC	P-value	Relapse Frequency
Lu7	25	9	3.3 ± 0.7	1.2 ± 0.5	0.05	36.4%

DISCUSSION

Stem cell therapy is a promising new area of research for multiple chronic nervous disorders. Stem cells can be harvested from the bone marrow of healthy donors (BM-MSC) or from umbilical cord blood (HUS-MSC). Patients are treated with a preparative regiment to suppress the patient's immune system. Immunosuppression with cyclosporine or tacrolimus is used to prevent graph versus host disease.[8] Stem cells are used in this manner to currently provide curative treatments for leukemias, myelodysplasia, and severe aplastic anemia.[8] Umbilical cord stem cells are associated with less graft versus host disease, less HLA restriction, and less likely to be contaminated with herpes virus compared to other forms of stem cells.[9] HUS-MSCs are preferred over BM-MSC due to more availability and less risk of graft versus

host disease. Many clinical trials are being undertaken in other neuronal conditions such as ALS, spinal cord injury, epilepsy, Parkinson's disease, and Alzheimer's disease.[9] Stem cells are currently being studied as a new therapy in the treatment of progressive degenerative neurological diseases.

Stem cell therapy is not without its own risks. Most studies report very little side effects and demonstrate a good safety profile for the drug. Out of the three studies in this review none reported any adverse reactions to the therapy. Herberts, Kwa, and Hermsen[10] reviewed adverse reactions to stem cell therapy and found the following: rejection of cells, susceptibility to disease, toxicity, neoplasm formation, disease transmission, and reactivation of latent viruses. The most concerning of which is tumor formation. They followed a report of a 13-year-old boy developing a brain tumor of non-host origin four years after transplant. This is thought be due to the resemblance of stem cells to cancer cells with a long-life span, apoptosis resistance, and ability to replicate for long periods of time.[10] The largest concern with stem cell therapy is neoplasm formation which may be a future area of research in the long-term safety profile of this novel therapy.

In the United States, the government has authorized research for using existing embryonic stem cells but restricts federal funding for developing new stem cell lines. Stem cell research raises concerns on the ethical limits of science and human life. A team of scientists, health care providers, lawyers, and sociologists must balance the medical benefits with the ethical dilemmas of stem cell therapy.[10] Other limitations surrounding stem cell therapy include not being in clinical phases and not being a FDA approved therapy. Therefore, stem cell therapy is not readily available yet as a treatment option is still in preclinical research phases.

In the three articles reviewed each found that stem cells decreased relapse rates. Li J, Zhang D, Geng T, et al. demonstrated that recurrence frequency was significantly different between the two groups ($p < 0.038$).[5] Table 2 evaluated this data as NNT showing that for every two patients treated with human umbilical cord derived mesenchymal stem cell therapy for 6 weeks, 2 or more relapses were prevented when compared to the control group. This is a small treatment effect that could become more significant with a larger pool of patients. Llufriu S, Sepulveda M, Blanco Y, et al. found a nonsignificant decrease in mean number of GEL between the BM-MSC group and placebo group (-2.78 ± 5.89 vs 3 ± 5.36, $p = 0.075$).[6] Table 3 evaluated the number of relapses as a NNT; For every patient with multiple sclerosis treated with bone marrow derived stem cells for 12 months, no additional relapses will be prevented when compared to the placebo group. This may be due to the stringent criteria used to dichotomize the data; defining a success as one relapse or less. It is also due in part to the small sample size of nine patients. Lu Z, Zhao H, Xu J, Zhang Z, Zhang X, et al. found a reduction in relapse rate by 36.4% at 18 months post treatment compared to before treatment (1.2 ± 0.5 vs 3.3 ± 0.7, $p < 0.05$).[7] All three studies found a decrease in the number of relapses participants experienced after treatment with mesenchymal stem cells however one of the RCTs did not translate well as NNT and was not statistically significant.

This EBM review encountered difficulty in finding appropriate studies and each study found was limited by a small sample size. Only two RCTs and one case series were found using online databases for mesenchymal stem cell therapy giving limited the available data to be reviewed. Each article found had small sample sizes decreasing the generalizability of the results. More research is necessary to confirm the validity of these authors' results and a larger participant group is needed to help generalize the results. Furthermore, the articles followed

participants for about a year which is a short amount of time for a chronic condition such as MS. It is unknown how long the stem cells remain effective for or the frequency of treatments needed to prevent relapses and an area that needs future investigation. The case series lacks randomization, blinding, and a comparison group making it difficult to make any generalizations about the effectiveness of MSCs. Also, none of the studies compared biologic therapy to MSC therapy. The authors only compared MSC therapy to placebo, steroids, and no treatment. It is unknown if MSC therapy is superior to biologics in preventing relapses in MS patients. Further research is needed to address these issues.

CONCLUSION

The results of two RCTs and one case studies showed a decrease in the number of relapses patients with MS experienced after being treated with MSCs compared to steroids, placebo, and before therapy. However, in evaluating Llufriu et al's study as NNT, it was found that for every patient with multiple sclerosis treated with bone marrow derived stem cells for 12 months, no additional relapses will be prevented when compared to the placebo group. Each study suffered from having a very small group of participants making it difficult to generalize the results. Repeat research is warranted with larger population sizes to support the evidence found in this review. The case series data is limited due to a lack of randomization, blinds, and a control group. The only research that focused on POEM was performed in comparing MSC therapy to placebo and steroids. Steroid therapy is only used for relief of acute exacerbations of MS and not for relapse prevention. This does not demonstrate any advantage to current therapies to keep MS in remission and needs to be addressed before becoming a treatment option available to patients. This review suggests that further research is warranted to compare MSC therapy to biologic therapies such as interferon, fingolimod, or glatiramer acetate. Further research is

necessary to help evaluate the efficacy of MSC therapy as a viable treatment option for patients suffering from MS.

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