Vol 7 No 2 June 2022

BULETIN FARMATERA

E-ISSN: 2528-410X

Application of Autologous Mesenchymal Stem Cells in Various Diseases: A Systematic Review

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Abstract: The use of *mesenchymal stem cells* (MSCs) efforts to cure a wide variety of diseases have been increasingly carried out, and various clinical trials have been reported, both at stage 1 to level 4. This systematic literature study aims to find out what diseases have been treated using *autologous mesenchymal stem cells*. This study is a systematic literature study by conducting literature searches in national and international journals in the last five years, using the Google Scholar application using systematic study methods, with the help of prism diagrams and classification tables to make it easier to search. From the search results, 24 kinds of literature were obtained that were included in the inclusion criteria. The results of this study found that currently the use of MSCs as an alternative in the treatment of diseases has been very widely carried out in clinical trials, where a large part of the results of these studies indicate a good level of safety, and can provide improvements histologically and physiologically, although in some diseases more follow-up research must still be carried out to obtain consistent results.

Keywords: *Autologous, Mesenchymal stem cells*, MSCs,

INTRODUCTION

Mesenchymal Stem Cells (MSC) are stem cells that have not undergone differentiation into specific cells.[1] MSCs can be sourced from donors (others) referred to as allogenic mesenchymal stem cells, but can also be obtained from the patient's own body, known as *autologous mesenchymal stem cells*.[2] To obtain MSCs from within the human body, they can be produced from various sources such as the spinal cord, adipose tissue, placenta and peripheral blood.[3] Both Allogenic MSC and Autologous MSC s have been conducted in many clinical trials, both at level 1 to level IV in various fields of medical science, in a *systematic review* conducted by David *et all* concluded that the use of MSCs is considered safe and does not show any *adverse events* which are serious in the various clinical studies that have been carried out and shows a new hope in the field of treatment of various diseases with a cellular approach in various lines of medical science..[4] This study aims to determine the use of *autologous*

E-ISSN: 2528-410X

mesenchymal stem cells in various diseases by conducting a systematic literature search with the prism method.

METHODS

This research is a *systematic review* by conducting literature research using Google Scholar. Furthermore, the literature is collected and tabulated with a further systematic study using the prism method. The literature included in the inclusion criteria is to discuss stem cell therapy using *autologous mesenchymal stem cells* which are published in national and international scientific journals with a period between 2016 and 2021. Furthermore, the literature is compiled in a table and reviewed and summarized and discussed.

RESULTS

The use of MSCs in the therapy of various diseases is relatively new, but various studies and case reports have been widely reported around the world, and show excellent potential in overcoming various severe diseases, this can be seen in (figure 1), Some studies are still conducted at the preclinical stage, but many studies have also been conducted at the clinical trial stage on a wide variety of diseases as we can see in table 1.

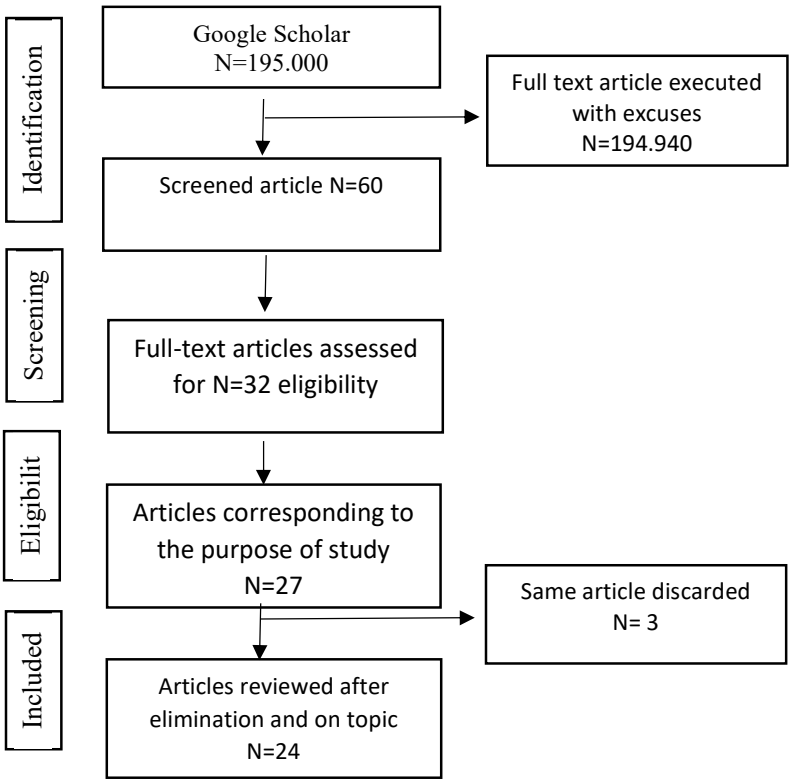

Figure 1. Prism diagram

E-ISSN: 2528-410X

Table 1. Literature search results

Author	Country	Year	Studies	N	Case	Results
Bhasin A. et al[5]	India	2017	Experimental	12	Chronic stroke	MSCs may act as "chaperones" or work through paracrine mechanisms leading to functional recovery post-stroke
Travis JB, et al[6]	USA	2017	Experimental	6	age-related diseases	These results suggest that it is feasible to obtain large numbers of high-quality autologous MSCs from the elderly population and establish personal stem cell banks that will allow serial infusions of "rejuvenated" MSCs for treating age-related diseases.
Carbone et al[7]	Italia	2021	Review Artikel	3142	Acute myocardial infarction	. 20 trials including 1437 patients showed a mean 7.2% LVEF increase while 14 trials including 1705 patients did not show any significant LVEF improvement.
Centeno C et al,[8]	USA	2017	Eksperimental studio	33	lumbar degenerative disc disease	Patients treated with autologous cultured MSCs for lower back pain with radicular symptoms in the setting of DDD reported minor adverse events and significant improvements in pain, function, and overall subjective

E-ISSN: 2528-410X

						improvement through 6 years of follow-up.
Hare JM,et al[9]	USA	217	RCT	37	Kardiomiopati	Clinical benefits of the magnitude shown here support the development of all-hMSCs for treating NIDCM
Jeong H, et al[10]	Korea	2017	A systematic review and Meta-analysis	950	Ischemic heart disease	The findings of this meta-analysis indicate that MSCs can be beneficial in improving heart function in the treatment of MI
Zhu Y, et al[11]	Cina	2017	eksperimental	6	Osteoartritis	The present study demonstrated that iMSC-Exos have a greater therapeutic effect on OA than SMMSC-Exos
Zheng H, et al[12]	Cina	2018	Systematic Review	8	Stroke	majority of the pre-clinical and clinical studies demonstrated statistically significant effects,
Yeltokova M et al[13]	Kazakhstan	2019	RCT	1	Diabetik retinopaty	The results of calculations could be used as diagnostic indicators in the correction of pathogenetic therapy.
Espinosa JML et al[14]	Spanyol	2016	RCT	13	Knee Osteoarthritis	MRI (WORMS protocol) showed that joint damage decreased only in the BM-MSC high-dose group, albeit slightly
Fu Y, et al[15]	Cina	2016	RCT	15	Neuromyelitis Optica	MSC infusion is safe, reduces relapse frequency, and mitigates

E-ISSN: 2528-410X

						neurological disability with neural structures in the optic nerve and spinal cord recovery in patients with NMOSD. The beneficial effect of MSC infusion on NMOSD was maintained, at least to some degree, throughout a 2-year observational period
Gao, et al[16]	Cina	2016	Review article	400	Immunomodulation	they show great promise in the treatment of many immune disorders, but the large variability in cell quality derived from different donors and tissues, inconsistent protocols, varying dosages and differing transfusion patterns can limit their therapeutic benefit
Zhang H, et al[17]	Cina	2016	Experimental	25	Tibial non-union	Our study demonstrates that using autologous bone marrow-derived mesenchymal stem cells as an add-on therapy to the Ilizarov procedure shows significant clinical benefit in the fixation of tibial non-union.
Ghoryani M, et al[18]	Iran	2018	Experimental	9	Rheumatoid arthritis	our data indicated that clinical symptoms were significantly

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E-ISSN: 2528-410X

						ameliorated following the intravenous injection of autologous bone marrow-derived MSCs into the patients with refractory RA
Honmou O, et al[19]	Jepang	2021	Experimental	13	Spinal cord injury	Our observations provide evidence supporting the feasibility, safety and functional improvements of infused MSCs in patients with SCI.
Lee SW, et al	Korea Selatan	2019	Experiment	12	Osteoarthritis	Intra-articular injection of autologous AD-MSCs provided satisfactory functional improvement and pain relief for patients with knee osteoarthritis in the outpatient setting, without causing adverse events at 6 months follow-up. A larger sample size and long-term follow-up are required
Bryon A et al[20]	USA	2018	RCT	65	Cardiomyopathy	Mesenchymal stem cell therapy is beneficial in DCM and ICM patients, despite variable effects on cardiac phenotypic outcomes.
Tsang KS, et al[21]	Cina	2017	RCT	9	Kronik stroke	Intravenous administration of autologous bone marrow-derived MSC is safe and has

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						the potential of improving neurological functions in chronic stroke patients with severe disabilities.
Zhang H, et al[17]	Cina	2016	RCT	25	Tibial Non-Union	Our study demonstrates that using autologous bone marrow-derived mesenchymal stem cells as an add-on therapy to the Ilizarov procedure shows significant clinical benefit in the fixation of tibial non-union
Whitehouse MR, et al	Inggris	2016	Prospective study	5	Osteoarthritis	undifferentiated MSCs could provide a safe way to augment avascular meniscal repair in some patients.
Vaquero, et al[22]	Spanyol	2017	RCT	10	Spinal Cord Injury	Administration of repeated doses of MSCs by subarachnoid route is a well-tolerated procedure that can achieve progressive and significant improvement in the quality of life of patients suffering incomplete SCI
Suk KI, et al[23]	Korea	2016	RCT	72	Alcoholic cirrhosis	Autologous BM-MSC transplantation safely improved histologic fibrosis and liver function in patients with alcoholic cirrhosis
Mehrabani et al[24]	Iran	2016	Case Report	1	Osteoarthritis	After intra-articular injection of 36×106

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						passage 2 of bone marrow-derived stem cells (BMSCs), the patient's functional status of the knee, the number of stairs she could climb, the pain on the visual analogue scale (VAS) and walking distance improved after two months post-transplantation
Saad A, et al[25]	USA	2017	Experimental	28	Renovaskular diesese	MSC infusion without main renal artery revascularization is associated with increased renal tissue oxygenation and cortical blood flow

From the results of the analysis using the table, the researcher described what diseases were the most studied as can be seen in figure 1.

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E-ISSN: 2528-410X

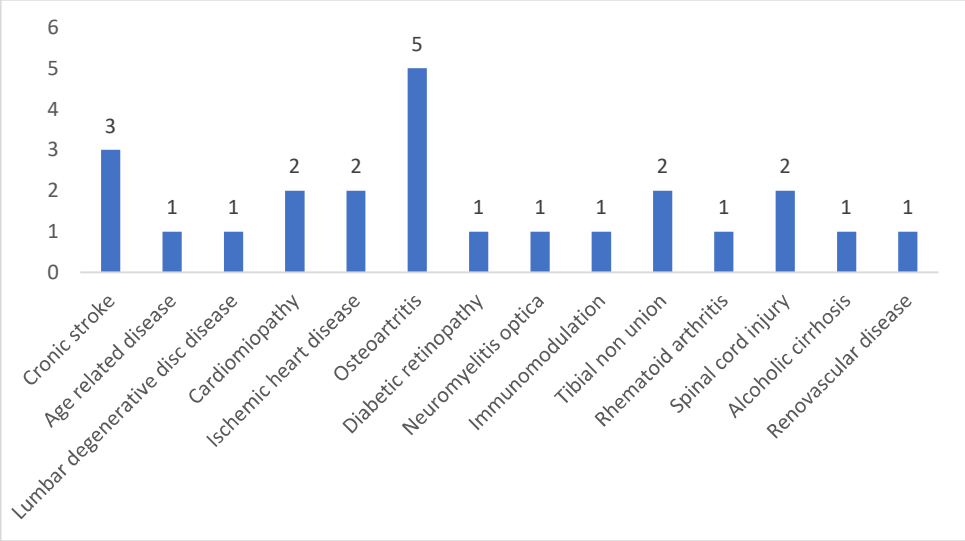

Figure 1. Number of studies by case

DISCUSSION

Osteoarthritis

Osteoarthritis (OA) is a degenerative and progressive joint disease that can involve one joint or many joints.[26] OA in the knee joint is a common movement disorder disease, which is characterized by the occurrence of degeneration of cartilage, remodelling of subchondral bones, the formation of *osteophyte* and inflammation of the synovial which affects the quality of life of the patient and requires large medical costs.[26] In addition to oral therapy and intra-articular injection that only reduces the appearance and improves joint function, there has been no proven treatment that can stop the progressivity of joint damage.[26]

Various surgical methods, including *microfracture and subchondral drilling* techniques, have been introduced as an effort to regenerate joint cartilage, but due to various complications and the low quality of cartilage regeneration, the risks and cost factors of joint replacement procedures are often things that still need to be considered..[26]

The use of stem cells in the treatment of osteoarthritis (OA) has been widely reported, while the *stem* cells used are MSCs isolated from bone marrow, muscle and adipose cells. In a clinical trial reported by *Brittberg et al,* it was explained that the use of autologous chondrocyte cultures can be used in improvements to deep cartilage defects in the knee joint. In this study, it was also explained that the use of MSCs can correct cartilage defects, regenerate cartilage tissue and reduce symptoms and signs that arise from OA. Applications used in OA are intra-articular injection of MSCs or inserting MSCs in the si nominal compartment. Another study conducted by Centeno *et al* reported that there was significant growth in cartilage and

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meniscus and decreased pain symptoms and improved joint mobility in OA patients at 24 weeks after injection of MSCs in the joints.[27]

Spinal cord injury

Spinal cord injury (SCI) is a serious central nervous system disorder and has been recognized as an important global health problem. SCI is most commonly caused by traffic accidents (38%), falls (>22%), trauma (13.5 %), sports injuries (9%) and other traumatic events.[28] However, non-traumatic conditions such as cancer, inflammation, infection or degenerative processes of the spinal cord, can also cause SCI.[28] This condition of damage triggers serious effects on sufferers, mental disorders, disorders in the ability to work, and social abilities. The main clinical manifestations of SCI include changes in somatic sensations, volunteer gout, urinary function, and systolic and diastolic functions.[28] The main damage to SCI is caused by local deformations of the spinal nerve that provoke the loss of nerve cells. Sete is the mechanism of damage that occurs, compression of the spinal nerve triggers the degeneration of neurons and damage to blood vessels. In this condition, the inflammatory stage is an important factor in the pathogenesis of SCI triggering the loss of neurons and *oligodendrocytes* with the consequent destruction of nerve tissue.[28] A condition that occurs after primary trauma is called secondary damage. Post-traumatic inflammatory reactions in which free radicals form, vascular ischemia, oedema, apoptosis, or genetic processes in dead cells cause secondary damage. The latest pharmacological therapy from SCI involves the use of high doses of corticosteroids, administered in the first 8 hours post-traumatic and continued for the next 1-2 days.[28] Stem cell therapy may be an effective treatment of SCI. Several preclinical studies have proven the ability of STEM SELL therapy to improve mobility.[28] Among the many methods of stem cell therapy, *Mesenchymal Stem Cells* (MSCs) appear to be the most interesting thing for SCI improvement. MSCs are cells that show the ability to differentiate into different types of various tissues such as cartilage, bone, fat and nerve tissue. MSCs show the potential to repair the damage to neural tissue that occurs after trauma, thanks to their ability to differentiate into nerve cells. So MSCs exhibit immunomodulatory and anti-inflammatory properties and can release inflammatory cytokines that reduce neural loss, thus providing hope for SCI management.[28]

Cardiomyopathy

Non-Ischemic Dilated Cardiomyopathy (NIDCM) is a progressive disorder that until now has not been cured, leading to a heart transplant. Cell-based therapies promise new therapeutic strategies under development, with great challenges and opportunities in the development of allogeneic therapies.[9]

The use of autologous or *allogenic* MSCs in cases of cardiomyopathy is considered quite safe and effective, a study conducted by Hare et al in 2017 involving 37 research

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subjects, and using the POSEIDON-DCM (Percutaneous Stem Cell Injection Delivery Effect on Neo myogenesis in Dilated Cardiomyopathy) showed positive things both in the level of safety and efficacy. In this study, observations were carried out for 12 months after MSCs induction and there were improvements in *immune biomarkers* and *computed tomography images*.[9] Likewise, the study conducted by Brayon where in this study compared the efficacy of the *transcardial delivery of mesenchymal stem cells* method in *ischemic* cardiomyopathy (ICM) and *dilated cardiomyopathy* (DCM) with the results of finding the same effectiveness .[20]

Chronic Stroke

Intravenous administration of MSCs' spinal cord proved safe and potential to treat neurological function disorders in chronic stroke patients with disabilities. MSCs bone marrow is recorded to regenerate *trophic factors*, stimulate growth, provide regulatory signals and *cytokines,* and can help trigger neuron regeneration and post-stroke neuron restoration through the mechanisms of neurogenesis, angiogenesis and synapse genesis. The study conducted by Bhasin et all of 12 patients who were given *autologous intravenous injection ex vivo stem cells* with *follow-up* for 4 years concluded that the procedure was considered quite safe, and showed signs of *recovery* from damaged nerve tissue.[5] Tsang et al who conducted a study of patients experiencing intracerebral haemorrhage with neurological disorders for one year found that intravenous administration of *autologous bone marrow-derived* MSCs was safe and had the potential to improve neurological function in chronic receipts with a severe disability.[21]

Other Disease Disorders

In this sub-topic, the authors cited the findings of publications related to the use of MSCs in various cases of disease which in literature studies had a presentation of findings of less than 2% as shown in graph 1. The source of MSCs, although derived from the elderly remains potential and has the same quality as MSCs derived from a young age, for use in the therapy of diseases caused by ageing.[6] A review article on the use of stem cells in cases found that MSC therapy still gets dubious results and more research is needed to prove the improvement of Left Ventricular Ejection Fraction post *stem cell* therapy.[7] The use of MSCs in lower back pain patients in one article showed minimal *adverse events* and resulted in improvements in pain degree values, functional assessment and subjective assessment of post-evaluation patients for 6 years involving 33 patients with degenerative disc disease (DDD) as the cause of lower back pain.[8] A meta-analysis conducted by Joeng et all discussing the use of MSCs in *Ischemic* heart disease by looking at 950 patients from 14 *randomized placebo-controlled trials* with evaluation for 6 months after MSC therapy, drew the conclusion that MSCs indicated to have benefits in improving heart function in *Miocard*

E-ISSN: 2528-410X

Infarction therapy (MI), but its efficacy still requires more trials with diverse methods.[10] In the case of stroke, the benefits of using MSCs are still debated, and some articles conclude the ability to regenerate nerve cells after MSCs therapy. However, in other articles, there is a gap in the results of the pre-clinical and clinical research conducted in several studies.[12,5,21] Case reports observing the level of security of MSC users in type 1 diabetes mellitus patients with retinopathy complications showed a low immunological response associated with post-transplantation security levels of MSCs.[13] In the case of knee osteoarthritis, in a *multicenter randomized control clinical trial* involving 30 patients evaluated for 12 months, the use of MSCs given in conjunction *with hyaluronic acid* by intra-articular injection method was considered quite safe clinically and provided clinical improvement in *knee osteoarthritis* patients..[14] A study conducted by Fu et al on 15 patients with *neuromyelitis optical spectrum disorder* who were given MSC infusion with follow-up for 12 months showed a level of safety, as well as clinical improvement of patients after administration of IV MSCs.[15] Gao *et al* made observations on the immunomodulation of MSCs and gained the ability of MSCs in the presence of the influence of MSCs as immunomodulation and gave new hope to cell therapy in the case of immunology.[16] The use of MSCs as supportive therapy in *mal union tibial fracture* with the Ilizarov method showed satisfactory results on the improvement of the tibia bone. [17] The use of MSCs in recurrent cases of *rheumatoid arthritis* showed improvement clinically, although immunologically it has not shown significant results.[18] In one study conducted by Suk et al on 72 patients who were confirmed to have alcoholic cirrhosis, where patients were divided into 3 groups, namely the control group, the group that received one injection of the hepatisarterial k using *bone marrow* MSC s (BM-MSC s) and twice received BM-MSC s injection with levels of $5x10^7$, the patient was evaluated for 12 months, the results showed a good level of safety as well as histologically and physiologically improved liver.[23] The use of MSCs infusion in patients with the renovascular disease after a follow-up for three months after autologous MSC s infusion showed a good level of safety, and it was also found that there was an increase in *renal tissue oxygenation and cortical blood flow*.[25]

CONCLUSIONS

From the results of a systematic literature search, it can be concluded that currently the use of MSCs as an alternative in the treatment of diseases has been very much carried out in clinical trials, where a large part of the results of the study indicates a good level of safety, and can provide histologically and physiological improvements, although in some diseases more follow-up research must still be carried out to obtain results that consistent.

E-ISSN: 2528-410X

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