Send Orders for Reprints to reprints@benthamscience.net

Current Stem Cell Research & Therapy, 2023, *18*, 779-786

REVIEW ARTICLE

Review of the Published Literature Confirms the Safety of Intravenous Infusion of Mesenchymal Stem Cells

Amir Barmada[1], Joshua Sharan[1], Nicolas Band[1], Tobias Rumschlag[1], Arwah Yaqub[1], Eliana Liebman[1] and Chadwick Prodromos[1,*]

[1]*The Foundation for Orthopaedics and Regenerative Medicine, Glenview, IL, USA*

Abstract: ***Background*:** Mesenchymal stem cells (MSCs) have been shown to decrease inflammation and enhance healing due to their immunomodulatory properties and secretion of growth factors. Intravenous infusion is the most common delivery route of MSCs, and it is used for the treatment of a wide variety of conditions, with established efficacy.

***Objective*:** This review will analyze the safety of intravenous infusion of MSCs and determine the incidence of any possible resultant Serious Adverse Events (SAEs).

***Methods*:** Using PubMed, we searched the scientific literature to identify SAEs related to intravenous infusion of MSCs. We performed disease-specific searches and a general adverse event search.

***Results*:** A total of 70 studies were included in this review. Thousands of infusions were administered and only two SAEs were identified from the same study. The SAEs were two upper extremity thromboembolisms in patients with preexisting renal disease.

***Conclusion*:** Properly performed intravenous infusion of MSCs is very safe, with a near absence of reported serious adverse events associated with its use.

ARTICLEHISTORY

Received: March 18, 2022
Revised: June 21, 2022
Accepted: June 28, 2022

DOI:
10.2174/1574888X17666220823092202

Keywords: Mesenchymal stem cell, intravenous infusion, inflammation, serious adverse events, rheumatoid arthritis, stem cell treatment.

1. INTRODUCTION

Mesenchymal stem cells (MSCs) have been shown to decrease inflammation and enhance healing due to their immunomodulatory properties and secretion of growth factors [1-4]. Since MSCs have outstanding homing abilities, the cells can localize to areas of inflammation or tissue damage [1, 2]. Intravenous infusion is the most common delivery route of MSCs, and it is used for the treatment of a wide variety of conditions, with established efficacy [5-11]. However, safety is of paramount importance. This review will analyze the safety of intravenous infusion of MSCs and determine the incidence of any possible resultant serious adverse events (SAEs).

Minor self-limited side effects can occur with intravenous infusion of any substance. Side effects include lethargy, fatigue, phlebitis, and localized skin irritation [12-14]. These side effects are not the focus of our review since they are not serious or related to MSCs, and they can occur with intravenous infusion of any substance.

*Address correspondence to this author at the Foundation for Orthopaedics and Regenerative Medicine, Glenview, IL, USA; Tel: +18476996810; E-mail: research@ismoc.net

In a previous study, we demonstrated the absence of SAEs related to intra-articular injection of autologous MSCs [15]. In addition, many clinical trials have demonstrated the safety of intrathecal injection of MSCs [16-23]. We hypothesized that this literature review would also demonstrate the safety of intravenous administration of MSCs.

2. MATERIALS AND METHODS

Using PubMed, we searched the scientific literature to identify SAEs related to intravenous infusion of MSCs. We performed disease-specific searches and a general adverse event search. The list of diseases included multiple sclerosis (MS), rheumatoid arthritis (RA), amyotrophic lateral sclerosis (ALS), ankylosing spondylitis, autism, cerebral palsy, idiopathic pulmonary fibrosis, Crohn's disease, ulcerative colitis, lupus, multiple system atrophy, and traumatic brain injury. Specifically searching for clinical trials, each disease was crossed referenced with the term "Mesenchymal stem cell". In order to identify any additional SAEs, we searched for serious adverse events using the terms "Human mesenchymal stem cell" and "serious adverse event".

We included clinical trials that used intravenous MSC infusion and noted SAEs related to the stem cell treatment. We excluded reviews, discussions, pre-clinical studies, and pro-

1574-888X/23 $65.00+.00

tocols. We excluded studies in which MSC treatment was combined with alternative therapies or medications. In addition, we excluded patients that had multi-system organ failure, malignancies, or pre-cancerous lesions/conditions at baseline. We reviewed titles and abstracts for all studies, and the full text was reviewed for articles that met our inclusion criteria.

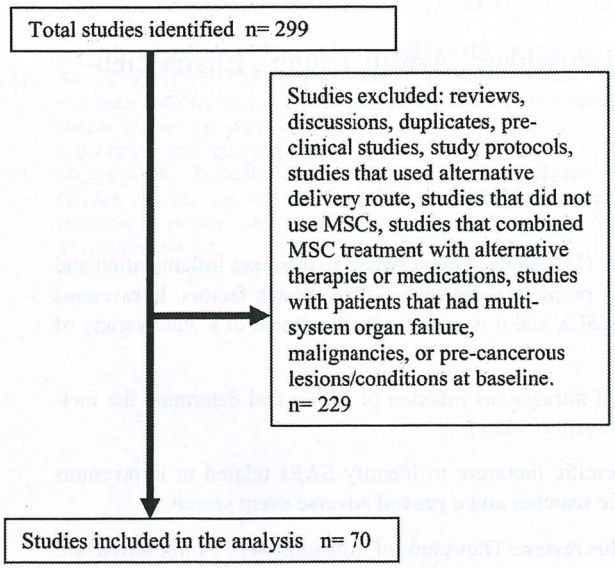

Fig. (1). Intravenous MSC study selection process.

3. RESULTS

A total of 299 articles were identified using our search criteria. 229 articles were excluded based on our exclusion criteria, leaving 70 studies included in this review. Our selection process is shown in Fig. (**1**). The included studies were for the following conditions: MS, RA, lupus, acute respiratory distress syndrome/Covid-19, Crohn's disease, stroke, idiopathic pulmonary fibrosis, frailty, multiple system atrophy, sepsis, diabetes and diabetes-related complications, epidermolysis bullosa, cerebral palsy, tuberculosis, FLNA associated respiratory failure, chronic lung allograft dysfunction, ALS, neuromyelitis optica spectrum disorder, autoimmune liver cirrhosis, psoriasis vulgaris and psoriatic arthritis, allograft rejection after renal transplantation, cardiomyopathy, autosomal dominant polycystic kidney disease, chronic kidney disease, bronchiolitis obliterans, spinocerebellar ataxia, autism, traumatic brain injury, acute myocardial infarction, spinal cord injury, a chronic obstructive pulmonary disorder, and ankylosing spondylitis. A detailed summary of included studies is shown in Table **1**.

Thousands of infusions were administered and only two SAEs were identified, both from the same study. The SAEs were two upper extremity thromboembolisms in patients with renal disease [78].

4. DISCUSSION

To our knowledge, this is the first review that specifically evaluates the safety of intravenous infusion of autologous

Table 1. Included studies summary.

Author/Year	Condition	Cell Type	Dose (millions)	# of Treated Patients	Follow up (months)	MSCs Related SAEs
Connick *et al.* (2012) [5]	MS	Autologous BM-MSCs	1.1- 2/kg	10	5.8–10.2	none
Li *et al.* (2014) [6]	MS	Allogeneic UC-MSCs	4/kg	13	12	none
Llufriu *et al.* (2014) [24]	MS	Autologous BM-MSCs	1–2/kg	8	12	none
Cohen *et al.* (2018) [25]	MS	Autologous BM-MSCs	1–2/kg	24	6	none
Fernández *et al.* (2018) [26]	MS	Autologous AD-MSCs	1 or 4/kg	19	12	none
Riordan *et al.* (2018) [27]	MS	Allogeneic UC-MSCs	20	20	12	none
Petrou *et al.* (2020) [28]	MS	Autologous BM-MSCs	1/kg	16	14	none
Karussis *et al.* (2010) [29]	MS/ALS	Autologous BM-MSCs	23.4-24.5	48	25	none
Odinak *et al.* (2011) [30]	MS	Autologous BM-MSCs	2/kg	8	12	none
Lublin *et al.* (2014) [31]	MS	Allogeneic P-MSCs	150or 600	12	12	none
Wang *et al.* (2013) [32]	RA	Allogeneic UC-MSCs	40	136	8	none
Liang *et al.* (2012) [33]	RA	Allogeneic UC-MSCs	1/kg	4	36	none
Wang *et al.* (2019) [34]	RA	Allogeneic UC-MSCs	40	64	36	none
Ghoryani *et al.* (2020) [35]	RA	Autologous BM-MSCs	1/kg	13	12	none
Yang *et al.* (2018) [36]	RA	Allogeneic UC-MSCs	1/kg	52	12	none

(Table 1) Contd....

Author/Year	Condition	Cell Type	Dose (millions)	# of Treated Patients	Follow up (months)	MSCs Related SAEs
Park *et al.* (2018) [37]	RA	Allogeneic UC-MSCs	25, 50, or 100	9	1	none
Ghoryani *et al.* (2019) [38]	RA	Autologous BM-MSCs	1/kg	9	12	none
Gu *et al.* (2014) [7]	Lupus	Allogeneic UC-MSCs or BM-MSCs	1/kg	81	12	none
Liang *et al.* (2010) [8]	Lupus	Allogeneic BM-MSCs	1/kg	15	36	none
Sun *et al.* (2009) [9]	Lupus	Allogeneic BM-MSCs	1/kg	4	18	none
Wang *et al.* (2014) [39]	Lupus	Allogeneic UC-MSCs	1/kg	40	12	none
Wang *et al.* (2013) [40]	Lupus	Allogeneic UC-MSCs or BM-MSCs	1/kg	87	48	none
Yang *et al.* (2014) [41]	Lupus	Allogeneic UC-MSCs	30	20	12	none
Wang *et al.* (2012) [42]	Lupus	Allogeneic UC-MSCs or BM-MSCs	1/kg	58	48	none
Hashemian *et al.* (2021) [43]	ARDS/Covid-19	Allogeneic UC-MSCs or P-MScs	200	11	2	none
Meng *et al.* (2020) [44]	Covid-19	Allogeneic UC-MSCs	30	9	1	none
Wilson *et al.* (2015) [45]	ARDS/Covid-19	Allogeneic BM-MSCs	1, 5, or 10/kg	9	2	none
Zheng *et al.* (2014) [46]	ARDS/Covid-19	Allogeneic AD-MSCs	1/kg	6	1	none
Lanzoni *et al.* (2021) [47]	ARDS/Covid-19	Allogeneic UC-MSCs	100	12	1	none
Yip *et al.* (2020) [48]	ARDS/Covid-19	Allogeneic UC-MSCs	1, 5, or 10/kg	9	1	none
Zhang *et al.* (2018) [10]	Crohn's disease	Allogeneic UC-MSCs	1/kg	37	12	none
Duijvestein *et al.* (2010) [49]	Crohn's disease	Autologous BM-MSCs	1-2/kg	10	3	none
Dhere *et al.* (2016) [50]	Crohn's disease	Autologous BM-MSCs	2, 5, or 10/kg	12	2	none
Chung *et al.* (2021) [51]	Stroke	Autologous BM-MSCs	1/kg	39	3	none
Levy *et al.* (2019) [52]	Stroke	Allogeneic BM-MSCs	0.5, 1, or 1.5/kg	36	12	none
Fang *et al.* (2019) [53]	Stroke	Autologous BM-MSCs	2.5/kg	9	48	none
Glassberg *et al.* (2017) [54]	IPF	Allogeneic BM-MSCs	20, 100, or 200	9	15	none
Averyanov *et al.* (2020) [55]	IPF	Allogeneic BM-MSCs	200	8	12	none
Chambers *et al.* (2014) [56]	IPF	Allogeneic P-MSCs	1 or 2/kg	8	6	none
Tompkins *et al.* (2017) [57]	Frailty	Allogeneic BM-MSCs	100 or 200	20	12	none
Golpanian *et al.* (2017) [58]	Frailty	Allogeneic BM-MSCs	20, 100, or 200	15	12	none
Lee *et al.* (2008) [59]	MSA	Autologous BM-MSCs	40	11	12	none
Lee *et al.* (2012) [60]	MSA	Autologous BM-MSCs	40	14	12	none
He *et al.* (2018) [61]	Sepsis	Allogeneic UC-MSCs	1, 2, or 3/kg	15	18	none
McIntyre *et al.* (2018) [62]	Sepsis	Allogeneic BM-MSCs	0.3, 1, or 3/kg	9	12	none
Skyler *et al.* (2015) [63]	Type 2 diabetes	Allogeneic BM-MSCs	0.3, 1, or 2/kg	45	3	none
Packham *et al.* (2016) [64]	Diabetic nephropathy	Allogeneic BM-MSCs	150 or 300	20	15	none

(Table 1) Contd....

Author/Year	Condition	Cell Type	Dose (millions)	# of Treated Patients	Follow up (months)	MSCs Related SAEs
Lee *et al.* (2021) [65]	Epidermolysis bullosa	Allogeneic UC-MSCs	1-3/kg	6	24	none
Rashidghamat *et al.* (2020) [66]	Epidermolysis bullosa	Allogeneic BM-MSCs	2-4/kg	9	12	none
Gu *et al.* (2020) [11]	Cerebral palsy	Allogeneic UC-MSCs	50	20	12	none
Huang *et al.* (2018) [67]	Cerebral palsy	Allogeneic UC-MSCs	50	27	24	none
Skrahin *et al.* (2014) [68]	Tuberculosis	Autologous BM-MSCs	1/kg	30	6	none
Pelizzo *et al.* (2020) [69]	FLNA associated respiratory failure	Allogeneic BM-MSCs	1/kg	1	9	none
Chambers *et al.* (2017) [70]	Chronic lung allograft dysfunction	Allogeneic BM-MSCs	2/kg	10	12	none
Rushkevich *et al.* (2015) [71]	ALS	Autologous BM-MSCs	1/kg	10	12	none
Fu *et al.* (2016) [72]	Neuromyelitis optica spectrum disorder	Autologous BM-MSCs	100	15	24	none
Liang *et al.* (2017) [73]	Autoimmune liver cirrhosis	Allogeneic UC-MSCs or BM-MSCs	1/kg	26	70	none
De Jesus *et al.* (2016) [74]	Psoriasis vulgaris and psoriatic arthritis	Autologous AD-MSCs	0.5-3.1/kg	2	12	none
Reinders *et al.* (2013) [75]	Allograft rejection after renal transplantation	Autologous BM-MSCs	1-2/kg	6	6	none
Butler *et al.* (2017) [76]	Cardiomyopathy	Allogeneic BM-MSCs	1.5/kg	22	3	none
Makhlough *et al.* (2017) [77]	Autosomal dominant polycystic kidney disease	Autologous BM-MSCs	2/kg	6	12	none
Wu *et al.* (2017) [78]	Chronic kidney disease	Allogeneic UC-MSCs	1/kg	2	UK	Two SAEs
Chen *et al.* (2019) [79]	Broncholitis obliterans	Allogeneic BM-MSCs	1/kg	32	3	none
Jin *et al.* (2013) [80]	Spinocerebellar ataxia	Allogeneic UC-MSCs	UK	16	12	none
Lv *et al.* (2013) [81]	Autism	Allogeneic UC-MSCs	1/kg	23	6	none
Wang *et al.* (2017) [82]	Traumatic brain injury	Autologous BM-MSCs	20-40	10	6	none
Chullikana *et al.* (2015) [83]	Acute myocardial infarction	Allogeneic BM-MSCs	2/kg	10	24	none
Ra *et al.* (2011) [84]	Spinal cord injury	Autologous AD-MSCs	400	8	3	none
Weiss *et al.* (2013) [85]	Chronic obstructive pulmonary disorder	Allogeneic BM-MSCs	100	31	24	none
Wang *et al.* (2014) [86]	Ankylosing spondylitis	Allogeneic BM-MSCs	1/kg	31	5	none

BM-MSCs: bone marrow-derived mesenchymal stem cells, UC-MSCs: umbilical cord-derived mesenchymal stem cells, AD-MSCs: adipose-derived mesenchymal stem cells, P-MSCs: placenta-derived mesenchymal stem cells. MS: multiple sclerosis, ALS: amyotrophic lateral sclerosis, RA: rheumatoid arthritis, ARDS: acute respiratory distress syndrome, IPF: idiopathic pulmonary fibrosis, MSA: multiple system atrophy, UK: unknown.

and allogeneic MSCs for the treatment of various conditions. This review demonstrates that intravenous infusion of MSCs, when properly performed, is very safe for the treatment of various conditions. In the 70 included studies, thousands of infusions were performed and only one study reported MSC-related SAEs, which were upper extremity thromboembolisms. These occurred in two patients with preexisting renal disease who received intravenous infusions of umbilical cord-derived MSCs [78]. It is known that renal disease results in a hypercoagulable state. In Urine, the loss of antithrombin-III, an anticoagulation factor, limits the anticoagulation cascade and increases the likelihood of developing thromboembolism [87]. Although it is unknown whether this directly occurred due to MSC treatment, it does raise concern for providing intravenous administration of MSCs in patients with preexisting hypercoagulable states. Taking a baby (81mg) Aspirin on the morning of treatment or the morning of a long travel day before treatment can reduce the risk of thromboembolism in such patients.

A weakness of our study is that we depend on reported adverse events from the authors of the included studies. Therefore, it is possible that there could be additional adverse events that were not reported. Our paper included 70 studies, with thousands of infusions. In addition, it included studies that used MSCs derived from various tissues, both autologous and allogeneic, including but not limited to bone marrow, adipose tissue, and umbilical cord. We believe the near absence of SAEs satisfactorily establishes that intravenous infusion of MSCs is extremely safe.

CONCLUSION

Properly performed intravenous infusion of MSCs is very safe, with a near absence of reported serious adverse events associated with its use.

LIST OF ABBREVIATIONS

ALS	=	Amyotrophic Lateral Sclerosis
MS	=	Multiple Sclerosis
MSCs	=	Mesenchymal Stem Cells
RA	=	Rheumatoid Arthritis
SAEs	=	Serious Adverse Events

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Lin W, Xu L, Zwingenberger S, Gibon E, Goodman SB, Li G. Mesenchymal stem cells homing to improve bone healing. J Orthop Translat 2017; 9: 19-27. http://dx.doi.org/10.1016/j.jot.2017.03.002 PMID: 29662796

[2] Fu X, Liu G, Halim A, Ju Y, Luo Q, Song AG. Mesenchymal stem cell migration and tissue repair. Cells 2019; 8(8): 784. http://dx.doi.org/10.3390/cells8080784 PMID: 31357692

[3] Murphy MB, Moncivais K, Caplan AI. Mesenchymal stem cells: Environmentally responsive therapeutics for regenerative medicine. Exp Mol Med 2013; 45(11): e54. http://dx.doi.org/10.1038/emm.2013.94 PMID: 24232253

[4] Wang L, Li Y, Xu M, *et al.* Regulation of inflammatory cytokine storms by mesenchymal stem cells. Front Immunol 2021; 12: 726909. http://dx.doi.org/10.3389/fimmu.2021.726909 PMID: 34394132

[5] Connick P, Kolappan M, Crawley C, *et al.* Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: An open-label phase 2a proof-of-concept study. Lancet Neurol 2012; 11(2): 150-6. http://dx.doi.org/10.1016/S1474-4422(11)70305-2 PMID: 22236384

[6] Li JF, Zhang DJ, Geng T, *et al.* The potential of human umbilical cord-derived mesenchymal stem cells as a novel cellular therapy for multiple sclerosis. Cell Transplant 2014; 23 Suppl 1: 113-22. http://dx.doi.org/10.3727/096368914X685005 PMID: 25385295

[7] Gu F, Wang D, Zhang H, *et al.* Allogeneic mesenchymal stem cell transplantation for lupus nephritis patients refractory to conventional therapy. Clin Rheumatol 2014; 33(11): 1611-9. http://dx.doi.org/10.1007/s10067-014-2754-4 PMID: 25119864

[8] Liang J, Zhang H, Hua B, *et al.* Allogenic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: A pilot clinical study. Ann Rheum Dis 2010; 69(8): 1423-9. http://dx.doi.org/10.1136/ard.2009.123463 PMID: 20650877

[9] Sun L, Akiyama K, Zhang H, *et al.* Mesenchymal stem cell transplantation reverses multiorgan dysfunction in systemic lupus erythematosus mice and humans. Stem Cells 2009; 27(6): 1421-32. http://dx.doi.org/10.1002/stem.68 PMID: 19489103

[10] Zhang J, Lv S, Liu X, Song B, Shi L. Umbilical cord mesenchymal stem cell treatment for crohn's disease: A randomized controlled clinical trial. Gut Liver 2018; 12(1): 73-8. http://dx.doi.org/10.5009/gnl17035 PMID: 28873511

[11] Gu J, Huang L, Zhang C, *et al.* Therapeutic evidence of umbilical cord-derived mesenchymal stem cell transplantation for cerebral palsy: A randomized, controlled trial. Stem Cell Res Ther 2020; 11(1): 43. http://dx.doi.org/10.1186/s13287-019-1545-x PMID: 32014055

[12] Guo Y, Tian X, Wang X, Xiao Z. Adverse effects of immunoglobulin therapy. Front Immunol 2018; 9: 1299. http://dx.doi.org/10.3389/fimmu.2018.01299 PMID: 29951056

[13] Padayatty SJ, Sun AY, Chen Q, Espey MG, Drisko J, Levine M. Vitamin C: Intravenous use by complementary and alternative medicine practitioners and adverse effects. PLoS One 2010; 5(7): e11414. http://dx.doi.org/10.1371/journal.pone.0011414 PMID: 20628650

[14] Froessler B, Gajic T, Dekker G, Hodyl NA. Treatment of iron deficiency and iron deficiency anemia with intravenous ferric carboxymaltose in pregnancy. Arch Gynecol Obstet 2018; 298(1): 75-82. http://dx.doi.org/10.1007/s00404-018-4782-9 PMID: 29740690

[15] Prodromos C, Rumschlag T. Administration of autologous mesenchymal cells for the treatment of arthritis. Curr Stem Cell Res Ther 2021; 16(8): 931-8. http://dx.doi.org/10.2174/1574888X16666210224145104 PMID: 33655846

[16] Siwek T, Jezierska-Woźniak K, Maksymowicz S, *et al.* Repeat administration of bone marrow-derived mesenchymal stem cells for treatment of amyotrophic lateral sclerosis. Med Sci Monit 2020; 26: e927484. http://dx.doi.org/10.12659/MSM.927484 PMID: 33301428

[17] Oh KW, Moon C, Kim HY, *et al.* Phase I trial of repeated intrathecal autologous bone marrow-derived mesenchymal stromal cells in amyotrophic lateral sclerosis. Stem Cells Transl Med 2015; 4(6): 590-7. http://dx.doi.org/10.5966/sctm.2014-0212 PMID: 25934946

[18] Mohyeddin Bonab M, Ali Sahraian M, Aghsaie A, *et al.* Autologous mesenchymal stem cell therapy in progressive multiple sclerosis: An open label study. Curr Stem Cell Res Ther 2012; 7(6): 407-14. http://dx.doi.org/10.2174/157488812804484648 PMID: 23061813

[19] Tian C, Wang X, Wang X, *et al.* Autologous bone marrow mesenchymal stem cell therapy in the subacute stage of traumatic brain injury by lumbar puncture. Exp Clin Transplant 2013; 11(2): 176-81.
http://dx.doi.org/10.6002/ect.2012.0053 PMID: 22891928

[20] Sharifzadeh N, Ghasemi A, Tavakol Afshari J, *et al.* Intrathecal autologous bone marrow stem cell therapy in children with autism: A randomized controlled trial. Asia-Pac Psychiatry 2021; 13(2): e12445.
http://dx.doi.org/10.1111/appy.12445 PMID: 33150703

[21] Dahbour S, Jamali F, Alhattab D, *et al.* Mesenchymal stem cells and conditioned media in the treatment of multiple sclerosis patients: Clinical, ophthalmological and radiological assessments of safety and efficacy. CNS Neurosci Ther 2017; 23(11): 866-74.
http://dx.doi.org/10.1111/cns.12759 PMID: 28961381

[22] Barczewska M, Maksymowicz S, Zdolińska-Malinowska I, Siwek T, Grudniak M. Umbilical cord mesenchymal stem cells in amyotrophic lateral sclerosis: An original study. Stem Cell Rev Rep 2020; 16(5): 922-32.
http://dx.doi.org/10.1007/s12015-020-10016-7 PMID: 32725316

[23] Oh KW, Noh MY, Kwon MS, *et al.* Repeated intrathecal mesenchymal stem cells for amyotrophic lateral sclerosis. Ann Neurol 2018; 84(3): 361-73.
http://dx.doi.org/10.1002/ana.25302 PMID: 30048006

[24] Llufriu S, Sepúlveda M, Blanco Y, *et al.* Randomized placebo-controlled phase II trial of autologous mesenchymal stem cells in multiple sclerosis. PLoS One 2014; 9(12): e113936.
http://dx.doi.org/10.1371/journal.pone.0113936 PMID: 25436769

[25] Cohen JA, Imrey PB, Planchon SM, *et al.* Pilot trial of intravenous autologous culture-expanded mesenchymal stem cell transplantation in multiple sclerosis. Mult Scler 2018; 24(4): 501-11.
http://dx.doi.org/10.1177/1352458517703802 PMID: 28381130

[26] Fernández O, Izquierdo G, Fernández V, *et al.* Research Group Study EudraCT 2008-004015-35. Adipose-derived mesenchymal stem cells (AdMSC) for the treatment of secondary-progressive multiple sclerosis: A triple blinded, placebo controlled, randomized phase I/II safety and feasibility study. PLoS One 2018; 13(5): e0195891.
http://dx.doi.org/10.1371/journal.pone.0195891 PMID: 29768414

[27] Riordan NH, Morales I, Fernández G, *et al.* Clinical feasibility of umbilical cord tissue-derived mesenchymal stem cells in the treatment of multiple sclerosis. J Transl Med 2018; 16(1): 57.
http://dx.doi.org/10.1186/s12967-018-1433-7 PMID: 29523171

[28] Petrou P, Kassis I, Levin N, *et al.* Beneficial effects of autologous mesenchymal stem cell transplantation in active progressive multiple sclerosis. Brain 2020; 143(12): 3574-88.
http://dx.doi.org/10.1093/brain/awaa333 PMID: 33253391

[29] Karussis D, Karageorgiou C, Vaknin-Dembinsky A, *et al.* Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis. Arch Neurol 2010; 67(10): 1187-94.
http://dx.doi.org/10.1001/archneurol.2010.248 PMID: 20937945

[30] Odinak MM, Bisaga GN, Novitskiĭ AV, *et al.* Transplantation of mesenchymal stem cells in multiple sclerosis. Zh Nevrol Psikhiatr Im S S Korsakova 2011; 111(2 Pt 2): 72-6.

[31] Lublin FD, Bowen JD, Huddlestone J, *et al.* Human placenta-derived cells (PDA-001) for the treatment of adults with multiple sclerosis: A randomized, placebo-controlled, multiple-dose study. Mult Scler Relat Disord 2014; 3(6): 696-704.
http://dx.doi.org/10.1016/j.msard.2014.08.002 PMID: 25891548

[32] Wang L, Wang L, Cong X, *et al.* Human umbilical cord mesenchymal stem cell therapy for patients with active rheumatoid arthritis: Safety and efficacy. Stem Cells Dev 2013; 22(24): 3192-202.
http://dx.doi.org/10.1089/scd.2013.0023 PMID: 23941289

[33] Liang J, Li X, Zhang H, *et al.* Allogeneic mesenchymal stem cells transplantation in patients with refractory RA. Clin Rheumatol 2012; 31(1): 157-61.
http://dx.doi.org/10.1007/s10067-011-1816-0 PMID: 21837432

[34] Wang L, Huang S, Li S, *et al.* Efficacy and safety of umbilical cord mesenchymal stem cell therapy for rheumatoid arthritis patients: A prospective phase I/II study. Drug Des Devel Ther 2019; 13: 4331-40.
http://dx.doi.org/10.2147/DDDT.S225613 PMID: 31908418

[35] Ghoryani M, Shariati-Sarabi Z, Tavakkol-Afshari J, Mohammadi M. The sufficient immunoregulatory effect of autologous bone marrow-derived mesenchymal stem cell transplantation on regulatory T cells in patients with refractory rheumatoid arthritis. J Immunol Res 2020; 2020: 1-8.
http://dx.doi.org/10.1155/2020/3562753 PMID: 32411794

[36] Yang Y, He X, Zhao R, *et al.* Serum IFN-γ levels predict the therapeutic effect of mesenchymal stem cell transplantation in active rheumatoid arthritis. J Transl Med 2018; 16(1): 165.
http://dx.doi.org/10.1186/s12967-018-1541-4 PMID: 29903026

[37] Park EH, Lim H, Lee S, *et al.* Intravenous infusion of umbilical cord blood-derived mesenchymal stem cells in rheumatoid arthritis: A phase ia clinical trial. Stem Cells Transl Med 2018; 7(9): 636-42.
http://dx.doi.org/10.1002/sctm.18-0031 PMID: 30112846

[38] Ghoryani M, Shariati-Sarabi Z, Tavakkol-Afshari J, Ghasemi A, Poursamimi J, Mohammadi M. Amelioration of clinical symptoms of patients with refractory rheumatoid arthritis following treatment with autologous bone marrow-derived mesenchymal stem cells: A successful clinical trial in Iran. Biomed Pharmacother 2019; 109: 1834-40.
http://dx.doi.org/10.1016/j.biopha.2018.11.056 PMID: 30551438

[39] Wang D, Li J, Zhang Y, *et al.* Umbilical cord mesenchymal stem cell transplantation in active and refractory systemic lupus erythematosus: A multicenter clinical study. Arthritis Res Ther 2014; 16(2): R79.
http://dx.doi.org/10.1186/ar4520 PMID: 24661633

[40] Wang D, Zhang H, Liang J, *et al.* Allogeneic mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus: 4 years of experience. Cell Transplant 2013; 22(12): 2267-77.
http://dx.doi.org/10.3727/096368911X582769c PMID: 24388428

[41] Yang GX, Pan LP, Zhou QY, *et al.* Therapeutic effects of umbilical cord mesenchymal stem cells transplantation on systemic lupus erythematosus. Sichuan Da Xue Xue Bao Yi Xue Ban 2014; 45(2): 338-41.

[42] Wang D, Akiyama K, Zhang H, *et al.* Double allogenic mesenchymal stem cells transplantations could not enhance therapeutic effect compared with single transplantation in systemic lupus erythematosus. Clin Dev Immunol 2012; 2012: 1-7.
http://dx.doi.org/10.1155/2012/273291 PMID: 22829849

[43] Hashemian SMR, Aliannejad R, Zarrabi M, *et al.* Mesenchymal stem cells derived from perinatal tissues for treatment of critically ill COVID-19-induced ARDS patients: A case series. Stem Cell Res Ther 2021; 12(1): 91.
http://dx.doi.org/10.1186/s13287-021-02165-4 PMID: 33514427

[44] Meng F, Xu R, Wang S, *et al.* Human umbilical cord-derived mesenchymal stem cell therapy in patients with COVID-19: A phase 1 clinical trial. Signal Transduct Target Ther 2020; 5(1): 172.
http://dx.doi.org/10.1038/s41392-020-00286-5 PMID: 32855385

[45] Wilson JG, Liu KD, Zhuo H, *et al.* Mesenchymal stem (stromal) cells for treatment of ARDS: A phase 1 clinical trial. Lancet Respir Med 2015; 3(1): 24-32.
http://dx.doi.org/10.1016/S2213-2600(14)70291-7
PMID: 25529339

[46] Zheng G, Huang L, Tong H, *et al.* Treatment of acute respiratory distress syndrome with allogeneic adipose-derived mesenchymal stem cells: A randomized, placebo-controlled pilot study. Respir Res 2014; 15(1): 39.
http://dx.doi.org/10.1186/1465-9921-15-39 PMID: 24708472

[47] Lanzoni G, Linetsky E, Correa D, *et al.* Umbilical cord mesenchymal stem cells for COVID-19 acute respiratory distress syndrome: A double-blind, phase 1/2a, randomized controlled trial. Stem Cells Transl Med 2021; 10(5): 660-73.
http://dx.doi.org/10.1002/sctm.20-0472 PMID: 33400390

[48] Yip HK, Fang WF, Li YC, *et al.* Human umbilical cord-derived mesenchymal stem cells for acute respiratory distress syndrome. Crit Care Med 2020; 48(5): e391-9.
http://dx.doi.org/10.1097/CCM.0000000000004285
PMID: 32187077

[49] Duijvestein M, Vos ACW, Roelofs H, *et al.* Autologous bone marrow-derived mesenchymal stromal cell treatment for refractory luminal Crohn's disease: Results of a phase I study. Gut 2010; 59(12): 1662-9.
http://dx.doi.org/10.1136/gut.2010.215152 PMID: 20921206

[50] Dhere T, Copland I, Garcia M, *et al.* The safety of autologous and metabolically fit bone marrow mesenchymal stromal cells in medically refractory Crohn's disease - a phase 1 trial with three doses. Aliment Pharmacol Ther 2016; 44(5): 471-81.
http://dx.doi.org/10.1111/apt.13717 PMID: 27385373

[51] Chung JW, Chang WH, Bang OY, *et al.* Efficacy and safety of intravenous mesenchymal stem cells for ischemic stroke. Neurology 2021; 96(7): e1012-23.
http://dx.doi.org/10.1212/WNL.0000000000011440
PMID: 33472925

[52] Levy ML, Crawford JR, Dib N, Verkh L, Tankovich N, Cramer SC. Phase I/II study of safety and preliminary efficacy of intravenous allogeneic mesenchymal stem cells in chronic stroke. Stroke 2019; 50(10): 2835-41.
http://dx.doi.org/10.1161/STROKEAHA.119.026318
PMID: 31495331

[53] Fang J, Guo Y, Tan S, *et al.* Autologous endothelial progenitor cells transplantation for acute ischemic stroke: A 4-year follow-up study. Stem Cells Transl Med 2019; 8(1): 14-21.
http://dx.doi.org/10.1002/sctm.18-0012 PMID: 30156755

[54] Glassberg MK, Minkiewicz J, Toonkel RL, *et al.* Allogeneic human mesenchymal stem cells in patients with idiopathic pulmonary fibrosis *via* intravenous delivery (AETHER). Chest 2017; 151(5): 971-81.
http://dx.doi.org/10.1016/j.chest.2016.10.061 PMID: 27890713

[55] Averyanov A, Koroleva I, Konoplyannikov M, *et al.* First-in-human high-cumulative-dose stem cell therapy in idiopathic pulmonary fibrosis with rapid lung function decline. Stem Cells Transl Med 2020; 9(1): 6-16.
http://dx.doi.org/10.1002/sctm.19-0037 PMID: 31613055

[56] Chambers DC, Enever D, Ilic N, *et al.* A phase 1b study of placenta-derived mesenchymal stromal cells in patients with idiopathic pulmonary fibrosis. Respirology 2014; 19(7): 1013-8.
http://dx.doi.org/10.1111/resp.12343 PMID: 25039426

[57] Tompkins BA, DiFede DL, Khan A, *et al.* Allogeneic mesenchymal stem cells ameliorate aging frailty: A phase II randomized, double-blind, placebo-controlled clinical trial. J Gerontol A Biol Sci Med Sci 2017; 72(11): 1513-22.
http://dx.doi.org/10.1093/gerona/glx137 PMID: 28977399

[58] Golpanian S, DiFede DL, Khan A, *et al.* Allogeneic human mesenchymal stem cell infusions for aging frailty. J Gerontol A Biol Sci Med Sci 2017; 72(11): 1505-12.
http://dx.doi.org/10.1093/gerona/glx056 PMID: 28444181

[59] Lee PH, Kim JW, Bang OY, Ahn YH, Joo IS, Huh K. Autologous mesenchymal stem cell therapy delays the progression of neurological deficits in patients with multiple system atrophy. Clin Pharmacol Ther 2008; 83(5): 723-30.
http://dx.doi.org/10.1038/sj.clpt.6100386 PMID: 17898702

[60] Lee PH, Lee JE, Kim HS, *et al.* A randomized trial of mesenchymal stem cells in multiple system atrophy. Ann Neurol 2012; 72(1): 32-40.
http://dx.doi.org/10.1002/ana.23612 PMID: 22829267

[61] He X, Ai S, Guo W, *et al.* Umbilical cord-derived mesenchymal stem (stromal) cells for treatment of severe sepsis: Aphase 1 clinical trial. Transl Res 2018; 199: 52-61.
http://dx.doi.org/10.1016/j.trsl.2018.04.006 PMID: 30044959

[62] McIntyre LA, Stewart DJ, Mei SHJ, *et al.* Cellular immunotherapy for septic shock. A phase I clinical trial. Am J Respir Crit Care Med 2018; 197(3): 337-47.
http://dx.doi.org/10.1164/rccm.201705-1006OC PMID: 28960096

[63] Skyler JS, Fonseca VA, Segal KR, Rosenstock J. Allogeneic mesenchymal precursor cells in type 2 diabetes: A randomized, placebo-controlled, dose-escalation safety and tolerability pilot study. Diabetes Care 2015; 38(9): 1742-9.
http://dx.doi.org/10.2337/dc14-2830 PMID: 26153271

[64] Packham DK, Fraser IR, Kerr PG, Segal KR. Allogeneic Mesenchymal Precursor Cells (MPC) in diabetic nephropathy: A randomized, placebo-controlled, dose escalation study. EBioMedicine 2016; 12: 263-9.
http://dx.doi.org/10.1016/j.ebiom.2016.09.011 PMID: 27743903

[65] Lee SE, Lee SJ, Kim SE, *et al.* Intravenous allogeneic umbilical cord blood–derived mesenchymal stem cell therapy in recessive dystrophic epidermolysis bullosa patients. JCI Insight 2021; 6(2): e143606.
http://dx.doi.org/10.1172/jci.insight.143606 PMID: 33491668

[66] Rashidghamat E, Kadiyirire T, Ayis S, *et al.* Phase I/II open-label trial of intravenous allogeneic mesenchymal stromal cell therapy in adults with recessive dystrophic epidermolysis bullosa. J Am Acad Dermatol 2020; 83(2): 447-54.
http://dx.doi.org/10.1016/j.jaad.2019.11.038 PMID: 31786163

[67] Huang L, Zhang C, Gu J, *et al.* A randomized, placebo-controlled trial of human umbilical cord blood mesenchymal stem cell infusion for children with cerebral palsy. Cell Transplant 2018; 27(2): 325-34.
http://dx.doi.org/10.1177/0963689717729379 PMID: 29637820

[68] Skrahin A, Ahmed RK, Ferrara G, *et al.* Autologous mesenchymal stromal cell infusion as adjunct treatment in patients with multidrug and extensively drug-resistant tuberculosis: An open-label phase 1 safety trial. Lancet Respir Med 2014; 2(2): 108-22.
http://dx.doi.org/10.1016/S2213-2600(13)70234-0 PMID: 24503266

[69] Pelizzo G, Avanzini MA, Lenta E, *et al.* Allogeneic mesenchymal stromal cells: Novel therapeutic option for mutated FLNA-associated respiratory failure in the pediatric setting. Pediatr Pulmonol 2020; 55(1): 190-7.
http://dx.doi.org/10.1002/ppul.24497 PMID: 31468740

[70] Chambers DC, Enever D, Lawrence S, *et al.* Mesenchymal stromal cell therapy for chronic lung allograft dysfunction: Results of a first-in-man study. Stem Cells Transl Med 2017; 6(4): 1152-7.
http://dx.doi.org/10.1002/sctm.16-0372 PMID: 28186707

[71] Rushkevich YN, Kosmacheva SM, Zabrodets GV, *et al.* The use of autologous mesenchymal stem cells for cell therapy of patients with amyotrophic lateral sclerosis in Belarus. Bull Exp Biol Med 2015; 159(4): 576-81.
http://dx.doi.org/10.1007/s10517-015-3017-3 PMID: 26395626

[72] Fu Y, Yan Y, Qi Y, *et al.* Impact of autologous mesenchymal stem cell infusion on neuromyelitis optica spectrum disorder: A pilot, 2-year observational study. CNS Neurosci Ther 2016; 22(8): 677-85.
http://dx.doi.org/10.1111/cns.12559 PMID: 27219819

[73] Liang J, Zhang H, Zhao C, *et al.* Effects of allogeneic mesenchymal stem cell transplantation in the treatment of liver cirrhosis caused by autoimmune diseases. Int J Rheum Dis 2017; 20(9): 1219-26.
http://dx.doi.org/10.1111/1756-185X.13015 PMID: 28217916

[74] De Jesus MM, Santiago JS, Trinidad CV, *et al.* Autologous adipose-derived mesenchymal stromal cells for the treatment of psoriasis vulgaris and psoriatic arthritis: A case report. Cell Transplant 2016; 25(11): 2063-9.
http://dx.doi.org/10.3727/096368916X691998 PMID: 27301844

[75] Reinders MEJ, de Fijter JW, Roelofs H, *et al.* Autologous bone marrow-derived mesenchymal stromal cells for the treatment of allograft rejection after renal transplantation: Results of a phase I study. Stem Cells Transl Med 2013; 2(2): 107-11.
http://dx.doi.org/10.5966/sctm.2012-0114 PMID: 23349326

[76] Butler J, Epstein SE, Greene SJ, *et al.* Intravenous allogeneic mesenchymal stem cells for nonischemic cardiomyopathy. Circ Res 2017; 120(2): 332-40.
http://dx.doi.org/10.1161/CIRCRESAHA.116.309717
PMID: 27856497

[77] Makhlough A, Shekarchian S, Moghadasali R, *et al.* Safety and tolerability of autologous bone marrow mesenchymal stromal cells in ADPKD patients. Stem Cell Res Ther 2017; 8(1): 116.
http://dx.doi.org/10.1186/s13287-017-0557-7 PMID: 28535817

[78] Wu Z, Zhang S, Zhou L, *et al.* Thromboembolism induced by umbilical cord mesenchymal stem cell infusion: A report of two cases and literature review. Transplant Proc 2017; 49(7): 1656-8.
http://dx.doi.org/10.1016/j.transproceed.2017.03.078
PMID: 28838459

[79] Chen S, Zhao K, Lin R, *et al.* The efficacy of mesenchymal stem cells in bronchiolitis obliterans syndrome after allogeneic HSCT: A multicenter prospective cohort study. EBioMedicine 2019; 49: 213-22.
http://dx.doi.org/10.1016/j.ebiom.2019.09.039 PMID: 31668569

[80] Jin JL, Liu Z, Lu ZJ, *et al.* Safety and efficacy of umbilical cord mesenchymal stem cell therapy in hereditary spinocerebellar ataxia. Curr Neurovasc Res 2013; 10(1): 11-20.
http://dx.doi.org/10.2174/15672021380480593 6 PMID: 23151076

[81] Lv YT, Zhang Y, Liu M, *et al.* Transplantation of human cord blood mononuclear cells and umbilical cord-derived mesenchymal stem cells in autism. J Transl Med 2013; 11(1): 196.
http://dx.doi.org/10.1186/1479-5876-11-196 PMID: 23978163

[82] Wang Z, Luo Y, Chen L, Liang W. Safety of neural stem cell transplantation in patients with severe traumatic brain injury. Exp Ther Med 2017; 13(6): 3613-8.
http://dx.doi.org/10.3892/etm.2017.4423 PMID: 28588689

[83] Chullikana A, Majumdar AS, Gottipamula S, *et al.* Randomized, double-blind, phase I/II study of intravenous allogeneic mesenchymal stromal cells in acute myocardial infarction. Cytotherapy 2015; 17(3): 250-61.
http://dx.doi.org/10.1016/j.jcyt.2014.10.009 PMID: 25484310

[84] Ra JC, Shin IS, Kim SH, *et al.* Safety of intravenous infusion of human adipose tissue-derived mesenchymal stem cells in animals and humans. Stem Cells Dev 2011; 20(8): 1297-308.
http://dx.doi.org/10.1089/scd.2010.0466 PMID: 21303266

[85] Weiss DJ, Casaburi R, Flannery R, LeRoux-Williams M, Tashkin DP. A placebo-controlled, randomized trial of mesenchymal stem cells in COPD. Chest 2013; 143(6): 1590-8.
http://dx.doi.org/10.1378/chest.12-2094 PMID: 23172272

[86] Wang P, Li Y, Huang L, *et al.* Effects and safety of allogenic mesenchymal stem cell intravenous infusion in active ankylosing spondylitis patients who failed NSAIDs: A 20-week clinical trial. Cell Transplant 2014; 23(10): 1293-303.
http://dx.doi.org/10.3727/096368913X667727 PMID: 23711393

[87] Lu Z, Wang F, Liang M. *SerpinC1* /Antithrombin III in kidney-related diseases. Clin Sci (Lond) 2017; 131(9): 823-31.
http://dx.doi.org/10.1042/CS20160669 PMID: 28424376