Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Current Research in Translational Medicine 68 (2020) 105–110

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

General review

Mesenchymal stem cells in the fight against viruses: Face to face with the invisible enemy

Aleen Sleem, Fatima Saleh*

Department of Medical Laboratory Sciences, Faculty of Health Sciences, Beirut Arab University, Lebanon

ARTICLE INFO

Article history:
Received 7 April 2020
Accepted 23 April 2020
Available online 1 May 2020

Keywords:
Mesenchymal stem cells (MSCs)
Clinical trials
HIV
Hepatitis B virus
COVID-19

ABSTRACT

The relative ease of isolation of mesenchymal stem cells (MSCs) from different tissues coupled with their culture expansion in vitro and their differentiation capacity to mesodermal, endodermal and ectodermal lineages have made these cells attractive for a large number of therapeutic applications. In recent years, there has been remarkable progress in the utilization of MSCs in diverse clinical indications both in animal models and human clinical trials. However, the potential of MSCs to control or treat viral diseases is still in its infancy. In this study, we report quantitative data on the MSC-based clinical trials over the last ten years as they appear on the online database of clinical research studies from US National Institutes of Health. In particular, we provide comprehensive review of either completed or ongoing clinical trials using MSCs for virus-associated diseases focusing on HIV, hepatitis B virus and COVID-19 virus.

Contents

1. Introduction

Stem cell-based therapies currently hold great promise to treat a large number of diseases including cardiovascular diseases [1]; neurodegenerative diseases [2]; muscular degenerative disorders [3]; haematopoietic and immune system disorders [4]; liver injuries [5]; metabolic disorders [6]; cancers [7] and much more diseases in the human body that might take advantage of stem cell therapy. Mesenchymal stem or stromal cells (MSCs) in particular are a heterogeneous population of non-hematopoietic stem cells [8]. According to the minimal criteria set by the International Society for Cellular Therapy (ISCT), MSCs are characterized by their adherence to plastic; in vitro differentiation into osteoblasts, adipocytes and chondroblasts; expression of cell surface markers of CD105, CD73, CD44 and CD90 and lack of expression of CD45, CD34, CD11b, CD14, CD79a and HLA-DR [9]. Their multipotential differentiation ability combined with their relative ease of isolation and expansion in vitro have captured the attention of scientists worldwide as an appealing candidate for a wide range of therapeutic applications [10]. Despite initially harvested from the bone marrow, MSCs can now be derived from multiple sources such as adipose tissue, placenta, umbilical cord, dental pulp, skin and others [11]. Given all of the above, the therapeutic use of MSCs for many diseases has been substantially explored which is obvious through the increasing numbers of preclinical and clinical trials of MSC-based products that has risen exponentially over the last 10 years.

During the past decade, research in the field of stem cells has expanded significantly and many trials have been carried out to

* Corresponding author at: Department of Medical Laboratory Technology, Faculty of Health Sciences, Beirut Arab University, P.O. Box: 11 5020, Beirut, Lebanon.
E-mail address: f.saleh@bau.edu.lb (F. Saleh).

http://dx.doi.org/10.1016/j.retram.2020.04.003
2452-3186/

exploit the ability of MSCs to treat diseases including musculoskeletal, cardiovascular, neurodegenerative and metabolic diseases [12]. However, comparatively, there is less work done in exploring their therapeutic potential in infectious diseases. Even less is known regarding the utility of MSC for the treatment of viral infections.

The emergence of new viruses such as the novel coronavirus disease (COVID-19) virus pose serious threats to public health [13]. Due to the current absence of drugs or vaccines to treat infected patients with COVID-19; scientist are interested in moving from conventional to safe and effective MSC-based therapies owing to their immunomodulatory and tissue-repair properties [14]. This review will address the development of MSC clinical trials over the last 10 years with in-depth exploration of MSC-based therapies in viral diseases such as HIV, hepatitis and COVID-19.

2. Therapeutic applications of MSCs in the last decade

Data were extracted from ClinicalTrials.gov (NIH, Bethesda, Maryland, USA) using the term “mesenchymal” for trials registered between 1st of January 2010 and 4th of March 2020 yielding 923 trials of MSC-based interventions for investigation of their therapeutic potential. The highest activity is found in east Asia (32.6 %) mainly China; followed by North America (19.2 % with 18.4 % in the United States) and Europe coming in third place with 18.1 % as shown in Fig. 1C. Currently, China conducts almost 22.5 % of all MSC-based trials registered. That is not surprising as the Chinese government has invested a substantial amount of money which is around 3 billion yuan (460 million dollars) to support stem cell and translational research in its twelfth Five-year plan (2011–2015). Moreover, China’s latest thirteen’s Five-year plan for biotechnology that was released in 2016 sets stem cells as one of the key research tasks to be supported.

The total number of registered trials increased linearly from 2010 to 2012, and almost tripled during this period (Fig. 1A). However, there was a dramatic drop in 2013 followed by slow increase to reach 110 trials in 2015 after which they appear to have plateaued between 2016 and 2018, then the number of new trials seems to pick up in 2019.

The clinical trials were then divided into 8 groups by disease classification and the remainder was designated as others. Based on disease categories, nervous system diseases is the largest group which accounts for 18.1 % of all trials. The second most common condition for MSC trials is musculoskeletal diseases (154 trials) accounting for 16.7 % of MSC trials including 88 for osteoarthritis. Combined with MSC trials for cardiovascular diseases (121 trials), these three categories make almost half of the ongoing clinical trials (48 %). On the other hand, MSC-based therapies for infectious diseases comprises only 2.7 % of all trials with only 13 trials studying MSCs and their therapeutic applications in viral diseases.

3. MSCs to prevent or treat viral diseases

3.1. MSCs and human immunodeficiency virus (HIV)

Since HIV was discovered in 1983, researchers worldwide are still haunting an effective treatment for HIV infections [15,16]. HIV pathogenesis is characterized by selective and progressive loss of CD4 T cells, leading to immunodeficiency in HIV-infected patients [17]. Highly active anti-retroviral therapy, referred to as HAART, is very effective in suppressing plasma HIV viral load leading to significant immune restoration and subsequently reduction in morbidity and mortality in chronic HIV-infected patients [18,19]. However, there is a group of patients known as nonimmune responders (NIRs) who fail to reverse the immunodeficiency despite the full viral suppression making them susceptible to opportunistic infections and thus lower life expectancies as compared to those of immune responders [20]. Therefore, treating HIV-infected HAART-treated NIRs patients has become a daunting challenge and alternative treatment options are required. In the

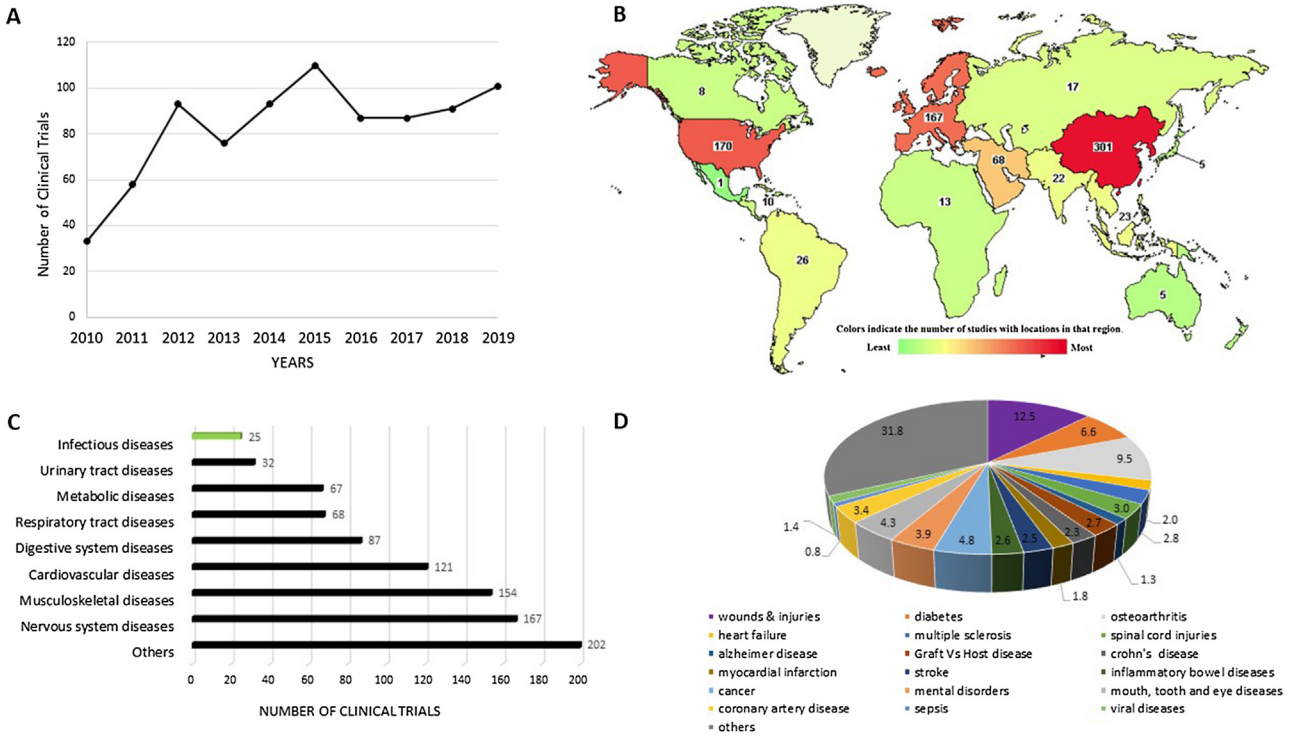

Fig. 1. Number of registered MSC-based clinical trials collected from clinicaltrial.gov from 2010 to March 2020 with the term "mesenchymal" listing 923 trials (A). Distribution of MSC-based clinical trials around the world (B). Number (C) and percentage (D) of MSC clinical trials by disease classification.

last decade, stem cell-based therapy provided a glimmer of hope for patients living with HIV. In fact, it was the hematopoietic stem cells (HSCs) that took center stage after the so called 'Berlin patient' was functionally cured from HIV after HSC transplantation with donor cells not expressing the C—C chemokine receptor type 5 (CCR5) which is essential for the HIV entry process [21]. Nearly a decade after the first case of sustained HIV remission in the 'Berlin patient' was announced, Gupta and collaborators reported the second case named 'London patient' who similarly underwent HSC transplantation with cells lacking CCR5 [22]. However, using allogeneic HSCs in HIV-infected patients is not without its limitations. Strong immunogenicity and occurrence of graft-versus-host disease (GvHD) remain at the forefront of concern when using this allogenic HSC transplantation [23]. Unlike HSCs, hypoimmunogenicity and unique immunosuppressive properties of MSCs have made them attractive candidates for treatment of HIV-infected individuals [24].

An interesting pilot study was conducted by Zhang and colleagues in 2013 to assess the safety and efficacy of umbilical cord MSCs (UC-MSCs) in HIV-infected NIR patients [25]. UC-MSC therapy was clinically and biologically tolerated by all patients with no recognized adverse effects throughout the trial under the registration number NCT01213186 [26]. Moreover, UC-MSC transfusion induced a significant elevation in CD4 T-cell numbers

Table 1
Ongoing clinical trials on the use of Mesenchymal stem cells in the treatment of virus infections.

	Title	Virus	Patients	Aims	Phase	Start date	Trial number	Location	Refs
1	Treatment with Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19)	Corona Virus Disease 2019 (COVID-19)	90	to assess treatment with three intravenous doses of MSCs $4.0*10^7$ cells per time) compared with placebo, all of them receive the conventional treatment	I/II	2020	NCT04288102	China	47
2	Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With 2019 Novel Coronavirus	Corona Virus Disease 2019 (COVID-19)	20	to inspect the safety and efficiency of Mesenchymal Stem Cells (MSCs) therapy for pneumonia patients infected with 2019-nCoV.	I	2020	NCT04252118	China	46
3	A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia	Corona Virus Disease 2019 (COVID-19)	30	to explore the safety and efficiency of aerosol inhalation of the exosomes derived from allogenic adipose mesenchymal stem cells (MSCs-Exo) in the treatment of severe patients hospitalized with novel coronavirus pneumonia (NCP)	I	2020	NCT04276987	China	48
4	Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Novel Coronavirus Severe Pneumonia	Corona Virus Disease 2019 (COVID-19)	48	to inspect the safety and efficiency of Human Umbilical Cord Mesenchymal Stem Cells (UC-MSCs) therapy for severe pneumonia patients infected with 2019-nCoV.	N.A.	2020	NCT04273646	China	44
5	Umbilical Cord(UC)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019-novel Coronavirus (nCOV) Pneumonia	Corona Virus Disease 2019 (COVID-19)	10	To assess safety and efficacy of UC-MSCs Treatment for Serious Pneumonia and Critical Pneumonia Caused by the 2019-nCOV	II	2020	NCT04269525	China	45
6	Treatment With MSC in HIV-infected Patients With Controlled Viremia and Immunological Discordant Response	Human Immunodeficiency Virus	5	to Assess the Safety and Efficiency of the Treatment With Allogenic Adult Mesenchymal Stem Cells From Adipose Tissue Expanded, in HIV-infected Patients With Controlled Viremia and Immunological Discordant Response	I/II	2017	NCT02290041	Spain	27
7	Umbilical Cord Mesenchymal Stem Cells for Immune Reconstitution in HIV-infected Patients	Human Immunodeficiency Virus	72	to learn what dose of transfused MSC reduces the level of activation of CD8 cells in people infected with HIV.	II	2013	NCT01213186	China	26
8	Clinical Study of Human Umbilical cord Mesenchymal Stem Cells (19#iSCLife®-LC) in the Treatment of Decompensated Hepatitis b Cirrhosis	Hepatitis B Virus	20	to evaluate the effectiveness and safety of human umbilical Mesenchymal stem cells in patients with hepatitis B cirrhosis	I	2018	NCT03826433	China	
9	Trial of Mesenchymal Stem Cell Transplantation in Decompensated Liver Cirrhosis	Hepatitis B & C Viruses	200	to investigate the safety and efficacy of mesenchymal stem cells in hepatitis B and C related liver cirrhosis patients	N.A.	2017	NCT03209986	China	40
10	Mesenchymal Stem Cells Transplantation for Liver Cirrhosis Due to HCV Hepatitis	Hepatitis C virus	5	To study the efficacy of Adipose Tissue Derived Autologous Repeated Mesenchymal Stem Cells Transplantation Via Hepatic Artery and Peripheral Vein in Patients With Liver Cirrhosis Due to HCV Hepatitis	I/II	2016	NCT02705742	Turkey	
11	Umbilical Cord Mesenchymal Stem Cells Transplantation Combined With Plasma Exchange for Patients With Liver Failure	Hepatitis B Virus	120	to investigate safety and efficacy of human umbilical cord mesenchymal stem cells (UC-MSCs) transplantation combined with plasma exchange (PE) for patients with liver failure caused by hepatitis B virus	I/II	2012	NCT01724398	China	38
12	Allogeneic Bone Marrow Mesenchymal Stem Cells Transplantation in Patients With Liver Failure Caused by Hepatitis B Virus (HBV)	Hepatitis B Virus	120		II	2011	NCT01322906	China	37
13	MSC for Treatment of CMV Infection	cytomegalovirus (CMV)	120	to evaluate the efficacy of mesenchymal stem cells (MSC) in the treatment of refractory cytomegalovirus (CMV) infection after allogeneic hematopoietic stem cell transplantation (allo-HSCT).	Phase	2014		China	

and reduction in proinflammatory cytokines levels [25]. However, the mechanisms by which UC-MSC treatment reduced the overactivation of the immune system in NIRs are still far from clear. A phase I/II clinical trial (NCT02290041) is also evaluating the safety and efficiency of intravenous infusion of allogenic adipose-derived MSCs (AD-MSCs) in HIV-infected patients with discordant immunologic and virologic responses to HAART [27] (see Table 1).

Although HAART has been very successful in suppressing HIV replication and improving clinical outcomes, it cannot eliminate latent HIV reservoirs and thus fails to cure HIV infection [28]. Therefore, there is an increasing need to develop novel strategies to reactivate latent HIV reservoirs and subsequently enhance their clearance. An in vitro study using latent HIV-infected cell lines reported a novel role for MSCs and MSC-secretome in HIV-1 latency-reactivation through PI3K and NFκB signaling pathways [29]. However, further research is needed to understand the efficacy of MSCs in reactivation of HIV-1 within reservoir micro-environments in vivo.

3.2. MSCs and hepatitis B virus (HBV)

Chronic infection with Hepatitis B virus (HBV) is a serious life-threatening condition affecting 260 million humans which is more than 3 % of the word population and causing more than 880,000 deaths annually due to liver failure or hepatocellular carcinoma [30]. HBV-related acute-on-chronic liver failure (HBV-ACLF) is observed in populations with chronic HBV infections and associated with high mortality rates due to limited treatment options [31]. Current therapies available are nucleos(t)ide analogues that help in reducing cirrhosis and liver-related mortality by suppressing HBV replication, but cannot eliminate the virus [32]. Interferon-α treatment can clear HBV in a low number of patients but its use is limited by severe side effects [33]. Besides, Artificial Liver Support System (ALSS) therapy has been developed and widely employed for the treatment of patients with HBV-ACLF; however, it is mainly used as a bridge to liver transplantation which is the only highly efficient therapy for HBV-ACLF patients poorly-responding to standard medical treatment [34]. Nevertheless, Liver transplantation is limited because of rapid disease progression and organ scarcity [34,35].

In the era of regenerative medicine, MSCs have emerged as a novel approach for HBV-ACLF treatment due to their ability to home to damaged tissues, hypoimmunogenicity that allows allogenic transplantation, anti-inflammatory effects and their differentiation capacity into functional hepatocyte-like cells [36,37]. An study by Peng and colleagues investigated the therapeutic effects of single transfusion of culture expanded autologous Bone marrow (BM)-MSCs in HBV-associated liver failure patients [38]. BM-MSC transplantation was proven safe for those patients with short term efficacy as measured by improvement of albumin, total bilirubin, prothrombin time and Model for End-Stage Liver Disease (MELD) scores compared to the control group [38]. However, the MSC therapy could not markedly improve the clinical laboratory measurements in a long-term follow-up, which could be explained by the slow proliferation of autologous MSCs derived from hepatitis B patients thus delaying timely intervention [38].

Regarding clinical application of MSCs in HBV-infected patients, there are actually four trials registered at clinicaltrials.gov in the last decade, as shown in Table 1, with each one of them employing allogenic MSCs instead of autologous. Lin and colleagues reported the findings of a prospective, phase II, randomized controlled trial (NCT01322906) showing that allogeneic BM-MSC infusion was safe with no serious adverse effects in patients with HBV-ACLF [39]. Moreover, MSC infusions improved hepatic function as total bilirubin and MELD scores and decreased the incidence or severity of infections and death, which could be due to the immunomodulatory properties of MSCs [39]. In another recent clinical study (NCT01724398) conducted by Xu et al. to determine the safety and efficacy of UC-MSC transplantation combined with plasma exchange (PE) therapy for HBV-ACLF patients, results showed that the combined treatment was safe which was in agreement with a similar study by Li et al. [40,41]. However; the short-term prognosis was not markedly improved as compared with single treatment [40]. Currently, two randomized controlled trials (NCT03209986; NCT03109236) are in the process of recruiting to determine the potential clinical benefits of MSC-based therapy for treatment of patients with hepatitis B related liver cirrhosis [42,43].

Despite all the evidence of the MSCs therapeutic abilities in HBV infection suppression, these results are non-conclusive and thus further studies are required specifically to understand the outcomes of the long-term use of MSCs to treat HBV-ACLF and all the mechanisms involved in liver regeneration.

3.3. MSCs and COVID-19

Coronaviruses are members of large viral family causing mild respiratory diseases to severe fatal infections such as Severe Acute Respiratory Syndrome (SARS) that emerged firstly in China in 2002/2003, Middle East Respiratory Syndrome (MERS) that emerged initially in Saudi Arabia in 2012, and recently the emergence of the novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and that has grown to be a global pandemic since patients were first detected in China, in December 2019 [13]. At present, there are no available anitviral drugs or vaccines to treat patients with COVID-19. The mainstay of medical management is currenlty symptomatic treatment, with care and support to the vital organ functions for seriously ill patients [44]. Therefore, there is a pressing need for an effective therapeutic approach for COVID-19 patients especially the critical cases.

A study by Huang et al. [44] have shown that COVID-19 infected patients had high circulating levels of proinflammatory cytokines with ICU-admitted patients showing elevated GCSF, IP10, MCP1, MIP1A, and TNFα levels when compatrd to non-admitted patients [44]. This indicates a cytokine storm in the lungs which is often associated with a flood of immune cell responses and subsequently pulmonary inflammation and extensive lung damage which might lead to death [44]. Hence, the key to COVID-19 treatment is to avoid the cytokine storm and thereby supress the super-inflammatory immunological response induced by SARS-CoV-2 thus reducing the lung injury, coupled with repair and regeneration of the lung tissue structure and function [45,46].

Owing to their anti-inflammatory, immunomodulatory and homing properties as well as regenerative potential, MSCs have attracted the attention of many scientists as a cell-based therapy for the treatment for COVID-19. A recent pilot study by Leng et al. [46] issued in the Chinese Clinical Trial Registry (ChiCTR2000029990) has shown the effectiveness of MSCs in seven patients suffering from COVID-19 pneumonia in Beijing Hospital, China [46]. Two to four days after intravenous injection of MSCs; symptoms of fever, weakness and shortness of breath disappeared in the seven patients with significant improvement in the pulmonary function [46]. Leng and colleagues also reported a sharp decline in the major inflammatory marker C-reactive protein as well as pro-inflammatory cytokine TNF-α and a remarkable increase in the anti-inflammatory IL-10 in the MSC treated patinets [46]. Thus, the intravenous infusion of MSCs was found to be safe and successful in reversing the virus-induced cytokine storm and enhancing endogenous lung repair by improving the local pulmonary microenvironment [46]. Herein, this pilot study has

yielded encouraging data paving the way for more trials on MSCs as a therapeutic approach to patients with COVID-19.

As of 5 March 2020, five clinical trials have shown up on Clinicaltrials.gov studying the safety and efficacy of MSCs in treatment of patients infected with COVID-19 as shown in Table 1, all of which are being undertaken in China. Two ongoing trials are using Human UC-MSC therapy that were infused intravenously at a concentration of 0.5×10^6 cells /kg body weight (NCT04273646) and 3.3×10^7 cells /50 ml (NCT04269525), respectively [47,48]. Another Phase I clinical trial (NCT04252118), where a total of three doses of MSCs (3.0×10^7 cells) were administered, confirmed their safety in COVID-19 patients [49]. A parallel phase I/II study (NCT04288102) is also assessing the safety and efficiency of 3 doses of intravenously administered MSCs(4.0×10^7 cells per dose) at days 0, 3 and 6 [50]. Moreover, a newly registered trial (NCT04276987) is intending to investigate the safety and efficacy of aerosol inhalation of allogenic AD-MSCs-derived exosomes in patients with COVID-19 Pneumonia [51]. The use of MSC-Exosomes as an alternative to parent MSCs will offer considerable advantages. One advantage is their ability to migrate efficiently to the target site because of their nanosized dimensions without getting physically trapped in microvasculature [52]. Moreover, with MSC exosomes, a higher 'dose' is quite guaranteed to the injured target tissue unlike their counterpart cells whose dose quickly decreases after infusion [53].

3.4. Conclusion & future perspectives

Among all types of stem cells, MSCs remain the most commonly used in cell therapy as they are free from ethical concerns with low risk of teratoma formation. Moreover, their immunomodulatory, anti-inflammatory, regenerative capacity as well as homing abilities to damaged tissues have made MSCs a very popular candidate for preclinical and human clinical trials as shown in this review for patients with viral diseases. However, the limitations of these MSC-based therapies should never be underestimated. First, the heterogeneity of MSCs is a serious concern which might explain discrepancies in research results. Also, recent literature has shown increasing evidence that MSCs may not be immunologically silent as assumed previously. Therefore, there might be need for more research studies to determine ways to isolate the "immune privileged" subpopulations from the heterogeneous pool of MSCs for clinical applications. Another approach to avoid these limitations is the use of cell-free therapeutic strategies such as MSC-exosomes that will provide considerable benefits over their parent cells especially that the efficacy of MSC therapy appears to derive from the paracrine activity.

Due to the limited studies of MSCs on virus-associated diseases and because most of these investigations are still in the early clinical phases, their efficacy cannot be concluded at this time. Therefore, well-designed, randomized controlled trials with larger sample size are needed to validate MSC safety and therapeutic outcomes at both short and long-term follow up.

References

[1] Lalu MM, Mazzarello S, Zlepnig J, Dong YYR, Montroy J, McIntyre L, et al. Safety and efficacy of adult stem cell therapy for acute myocardial infarction and ischemic heart failure (SafeCell heart): a systematic review and meta-analysis. STEM CELLS Trans Med [Internet] 2018;7(12)857–66, doi:http://dx.doi.org/10.1002/sctm.18-0120 Dec 1 [cited 2020 Mar 30] Available from:.

[2] Volkman R, Offen D. Concise review: mesenchymal stem cells in neurodegenerative diseases. Stem cells, Vol. 35. Wiley-Blackwell; 2017. p. 1867–80.

[3] Wilschut KJ, Ling VB, Bernstein HS. Concise review: stem cell therapy for muscular dystrophies. Stem Cells Transl Med 2012;1(November (11)):833–42.

[4] Ra JC, Kang SK, Shin IS, Park HG, Joo SA, Kim JG, et al. Stem cell treatment for patients with autoimmune disease by systemic infusion of culture-expanded autologous adipose tissue derived mesenchymal stem cells. J Trans Med BioMed Central 2011;9:1–11.

[5] Boyd A, Newsome P, Lu WY. The role of stem cells in liver injury and repair. Expert Rev Gastroenterol Hepatol 2019;13(July (7)):623–31.

[6] Solis MA, Moreno Velásquez I, Correa R, Huang LLH. Stem cells as a potential therapy for diabetes mellitus: a call-to-action in Latin America. Diabetology and metabolic syndrome, Vol. 11. BioMed Central Ltd.; 2019. p. 1–13.

[7] Zhang C-L-L, Huang T, Wu B-L-L, He W-X-X, Liu D. Stem cells in cancer ty: opportunities and challenges. Oncotarget [Internet] 2017;8(43)75756–66. . Sep 26 [cited 2018 Jun 8] Available from: http://www.ncbi.nlm.nih.gov/pubmed/29088907.

[8] Phinney DG. Functional heterogeneity of mesenchymal stem cells: Implications for cell therapy. J Cell Biochem 2012;113:2806–12.

[9] Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini FC, Krause DS, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006;8(August (4)):315–7.

[10] Ullah I, Subbarao RB, Rho GJ. Human mesenchymal stem cells - current trends and future prospective. Bioscience reports, Vol. 35. Portland Press Ltd; 2015.

[11] Hass R, Kasper C, Böhm S, Jacobs R. Different populations and sources of human mesenchymal stem cells (MSC): a comparison of adult and neonatal tissue-derived MSC. Cell Commun Signal 2011;9:.

[12] Wang J, Chen Z, Sun M, Xu H, Gao Y, Liu J, et al. Characterization and therapeutic applications of mesenchymal stem cells for regenerative medicine. Tissue and cell, Vol. 64. Elsevier Ltd; 2020. p. 101330.

[13] Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E. A novel coronavirus emerging in China — key questions for impact assessment. N Engl J Med [Internet] 2020;382(8)692–4, doi:http://dx.doi.org/10.1056/NEJMp2000929 Feb 20 [cited 2020 Mar 30] Available from:.

[14] Fedson DS, Opal SM, Rordam OM. Hiding in plain sight: an approach to treating patients with severe COVID-19 infection. mBio [Internet] 2020;11(2). . Mar 20 [cited 2020 Mar 30] Available from: http://www.ncbi.nlm.nih.gov/pubmed/32198163.

[15] Barré-Sinoussi F, Chermann Jc, Rey F, Nugeyre Mt, Chamaret S, Gruest J, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science 1983;220(May(4599)):868–71.

[16] Schmid S. The discovery of HIV-1. Nat Res 2019;2018(November (28)).

[17] Okoye AA, Picker LJ. CD4+ T-Cell depletion in hiv infection: mechanisms of immunological failure. Immunol Rev 2013;254(July (1)):54–64.

[18] Rachlis AR, Zarowny DP. Guidelines for antiretroviral therapy for HIV infection. Canadian HIV trials network antiretroviral working group. CMAJ 1998;158(4) 496–505 1998/06/17.

[19] Brechtl JR, Breitbart W, Galietta M, Krivo S, Rosenfeld B. The use of highly active antiretroviral therapy (HAART) in patients with advanced HIV infection: Impact on medical, palliative care, and quality of life outcomes. J Pain Symptom Manage 2001;21(1):41–51.

[20] Shete A, Dhayarkar S, Sangale S, Medhe U, Panchal N, Rahane G, et al. Incomplete functional T-cell reconstitution in immunological non-responders at one year after initiation of antiretroviral therapy possibly predisposes them to infectious diseases. Int J Infect Dis 2019;81(April (1)):114–22.

[21] Hutter G, Nowak D, Mossner M, Ganepola S, Müß A, Allers K, et al. Long-term control of HIV by CCR5 delta32/delta32 stem-cell transplantation. N Engl J Med 2009;360(February (7)):692–8.

[22] Gupta RK, Abdul-Jawad S, McCoy LE, Mok HP, Peppa D, Salgado M, et al. HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation. Nature, Vol. 568. Nature Publishing Group; 2019. p. 244–8.

[23] Stelljes M, Strothotte R, Pauels HG, Poremba C, Milse M, Specht C, et al. Graft-versus-host disease after allogeneic hematopoietic stem cell transplantation induces a CD8+ T cell-mediated graft-versus-tumor effect that is independent of the recognition of alloantigenic tumor targets. Blood 2004;104(August (4)):1210–6.

[24] Allam O, Samarani S, Ahmad A. Mesenchymal stem cell therapy in HIV-infected HAART-treated nonimmune responders restores immune competence. AIDS [Internet] 2013;27(8)1349–52. . May 15 [cited 2020 Mar 30] Available from: http://journals.lww.com/00002030-201305150-00019.

[25] Zhang Z, Fu J, Xu X, Wang S, Xu R, Zhao M, et al. Safety and immunological responses to human mesenchymal stem cell therapy in difficult-to-treat HIV-1-infected patients. AIDS 2013;27(May (8)):1283–93.

[26] Umbilical cord mesenchymal stem cells for immune reconstitution in HIV-infected patients - full text view - ClinicalTrials.gOv [Internet]. [cited 2020 Mar 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT01213186.

[27] Treatment with MSC in HIV-infected patients with controlled viremia and immunological discordant response - full text view - ClinicalTrials.gOv [Internet]. [cited 2020 Mar 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT02290041.

[28] Shan L, Siliciano RF. From reactivation of latent HIV-1 to elimination of the latent reservoir: the presence of multiple barriers to viral eradication. BioEssays 2013;35(June (6)):544–52.

[29] Chandra PK, Gerlach SL, Wu C, Khurana N, Swientoniewski LT, Abdel-Mageed AB, et al. Mesenchymal stem cells are attracted to latent HIV-1-infected cells and enable virus reactivation via a non-canonical PI3K-NFκB signaling pathway. Sci Rep 2018;8(December (1)):1–17.

[30] Michler T, Kosinska AD, Festag J, Bunse T, Su J, Ringelhan M, et al. Knockdown of virus antigen expression increases therapeutic vaccine efficacy in high-titer hepatitis B virus carrier mice. Gastroenterology 2020(January (28)).

[31] Wu T, Li J, Shao L, Xin J, Jiang L, Zhou Q, et al. Development of diagnostic criteria and a prognostic score for hepatitis B virus-related acute-on-chronic liver failure. Gut 2017;67(September (12)).
[32] Kao JH, Berg T. Nucleos(t)ide analogues in patients with chronic hepatitis B: to stop or not to stop? Gut, Vol. 68. BMJ Publishing Group; 2019. p. 2105–6.
[33] Gehring AJ, Protzer U. Targeting innate and adaptive immune responses to cure chronic HBV infection. Gastroenterology 2019;156(January (2)):325–37.
[34] LL X, XW X, KZ H, YL Z, LJ Z, LJ L. Artificial liver support system improves short-term outcomes of patients with HBV-associated acute-on-chronic liver failure: a propensity score analysis. Biomed Res Int 2019;2019:.
[35] Huang K, Ji F, Xie Z, Wu D, Xu X, Gao H, et al. Artificial liver support system therapy in acute-on-chronic hepatitis B liver failure: classification and regression tree analysis. Sci Rep 2019;9(December (1)):1–10.
[36] Chen Z, Kuang Q, Lao XJ, Yang J, Huang W, Zhou D. Differentiation of UC-MSCs into hepatocyte-like cellsin partially hepatectomized model rats. Exp Ther Med 2016;12(September (3)):1775–9.
[37] Chen B, Wang Y-H, Qian J-Q, Wu D-B, Chen E-Q, Tang H. Human mesenchymal stem cells for hepatitis B virus-related acute-on-chronic liver failure. Eur J Gastroenterol Hepatol [Internet] 2018;30(10)1224–9. . Oct 1 [cited 2020 Apr 11] Available from: http://journals.lww.com/00042737-201810000-00017.
[38] Peng L, ying Xie D, Lin BL, Liu J, peng Zhu H, Xie C, et al. Autologous bone marrow mesenchymal stem cell transplantation in liver failure patients caused by hepatitis B: short-term and long-term outcomes. Hepatology 2011;54(September (3)):820–8.
[39] Lin BL, Chen JF, Qiu WH, Wang KW, Xie DY, Chen XY, et al. Allogeneic bone marrow–derived mesenchymal stromal cells for hepatitis B virus–related acute-on-chronic liver failure: a randomized controlled trial. Hepatology [Internet] 2017;66(1)209–19, doi:http://dx.doi.org/10.1002/hep.29189 Jul 1 [cited 2020 Mar 30] Available from:.
[40] Xu WX, He HL, Pan SW, et al. Combination treatments of plasma exchange and umbilical cord-derived mesenchymal stem cell transplantation for patients with hepatitis B virus-related acute-on-chronic liver failure: a clinical trial in China. Stem Cells Int 2019;2019:.
[41] Li M, Sun J, Li J, Shi Z, Xu J, Lu B, et al. Clinical observation on the treatment of acute liver failure by combined non-biological artificial liver. Exp Ther Med 2016;12(December (6)):3873–6.
[42] Trial of mesenchymal stem cell transplantation in decompensated liver cirrhosis - full text view - ClinicalTrials.gOv [Internet]. . . [cited 2020 Mar 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT03209986.
[43] Autologous endothelial progenitor cell therapy for reversal of liver cirrhosis - full text view - ClinicalTrials.gOv [Internet]. . . [cited 2020 Mar 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT03109236.
[44] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395 (February (10223)):497–506.
[45] Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents [Internet] 2020;34(2). . [cited 2020 Apr 11] Available from: http://www.ncbi.nlm.nih.gov/pubmed/32171193.
[46] Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, et al. Transplantation of ACE2-mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis 2020;11(March (2)):216.
[47] Study of human umbilical cord mesenchymal stem cells in the treatment of novel coronavirus severe pneumonia - full text view - ClinicalTrials.gov [Internet]. . . [cited 2020 Mar 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT04273646.
[48] Umbilical cord(UC)-Derived mesenchymal stem cells(MSCs) treatment for the 2019-novel coronavirus(nCOV) pneumonia - full text view - ClinicalTrials.gov [Internet]. . . [cited 2020 Mar 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT04269525.
[49] Mesenchymal stem cell treatment for pneumonia patients infected with 2019 novel coronavirus - full text view - ClinicalTrials.gov [Internet]. . . [cited 2020 Mar 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT04252118.
[50] Treatment with mesenchymal stem cells for severe corona virus disease 2019 (COVID-19) - full text view - ClinicalTrials.gov [Internet]. [cited 2020 Mar 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT04288102.
[51] A pilot clinical study on inhalation of mesenchymal stem cells exosomes treating severe novel coronavirus pneumonia - full text view - ClinicalTrials.gov [Internet]. . . [cited 2020 Mar 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT04276987.
[52] Mendt M, Rezvani K, Shpall E. Mesenchymal stem cell-derived exosomes for clinical use. Bone marrow transplantation, Vol. 54. Nature Publishing Group; 2019. p. 789–92.
[53] Phinney DG, Pittenger MF. Concise review: MSC-derived exosomes for cell-free therapy. Stem Cells [Internet] 2017;35(4)851–8, doi:http://dx.doi.org/10.1002/stem.2575 Apr 1 [cited 2017 Nov 9] Available from:.