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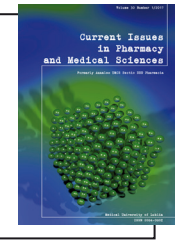

Application of mesenchymal stem cells in paediatrics

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ABSTRACT

Mesenchymal stem cells (MSC) were described by Friedenstein in the 1970s as being a group of bone marrow non-hematopoietic cells that are the source of fibroblasts. Since then, knowledge about the therapeutic potential of MSCs has significantly increased. MSCs are currently used for the treatment of many diseases, both in adults and children. MSCs are used successfully in the case of autoimmune diseases, including rheumatic diseases, diabetes mellitus type 1, gastroenterological and neurological diseases. Moreover, treatment of such organ disorders as damage or hypoxia through application of MSC therapy has shown to be satisfactory. In addition, there are some types of congenital disorders, including osteogenesis imperfecta and Spinal Muscular Atrophy, that may be treated with cellular therapy. Most studies showed no other adverse effects than fever. Our study is an analysis that particularly focuses on the registered trials and results of MSCs application to under 18 patients with acute, chronic, recurrent, resistance and corticosteroids types of Graft-versus-Host Disease (GvHD). Stem cells currently play an important role in the treatment of many diseases. Long-term studies conducted on animals have shown that cell therapy is both effective and safe. The number of indications for use of these cells in the course of treatment of people is constantly increasing. The results of subsequent studies provide important data justifying the application of MSCs in the course of treatment of many diseases whose treatment is ineffective when utilizing other approaches.

Abbreviations

CD – Cluster of Differentiation
CD – Crohn's Disease
CK18 – cytokeratin 18
GvHD – Graft-versus-Host Disease
HbA1c – Glycosylated Haemoglobin
HSCT – hematopoietic cells transplantation
IL – *Interleukin*
IL-2Rα – Alpha receptor for IL-2
ISCT – International Society for Cellular Therapy
MMP-9 – Matrix Metallopeptidase
MSCs – Mesenchymal stem cells
OI – osteogenesis imperfecta
POI – premature ovarian insufficiency
SCA – spinocerebellar ataxia
SCK 18F – soluble fragments of cytokeratin 18
TGF-β1 – Transforming growth factor beta
TNFR1 – Tumour Necrosis Factor Receptor 1
TNF-α – Tumour Necrosis Factor α
VSELs – very small embryonic-like stem cells

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INTRODUCTION

Mesenchymal stem cells (MSCs) were described in the 1970s as being a group of bone marrow non-hematopoietic cells which were the source of fibroblasts [15]. In the following years it has been shown that these cells can differentiate into osteoblasts and chondroblasts. In the 1990s, Caplan introduced the term 'mesenchymal stem cells' (MSCs) to denote such cells [7]. At that time it was suggested that they may have significant therapeutic importance, however, medical application of MSC would required further knowledge and testing. Between 1999 and 2001, the discovery of the surface antigens which characterize these cells took place, and flow cytometry characteristics was used to distinguish the MSCs population from other stem cells [4]. Presently, according to the International Society for Cellular Therapy (ISCT), MSCs should adhere to plastic in standard rearing conditions. In addition, they should express the CD73,

CD90 and CD105 antigens, CD73, CD90, but not the CD34, CD45 and CD14 antigens. MSCs should also be capable of self-renewal, as well as differentiation in osteoblasts, adipocytes and chondroblasts. Furthermore, they should facilitate the implantation of hematopoietic cells and exhibit immunomodulatory qualities [5,12]. Cells having the above characteristics are currently used for the treatment of many diseases, both in adults and children. In recent years, there have been number of reports about the effectiveness of mesenchymal stem cells in the treatment of congenital, inflammatory, infectious, autoimmune, degenerative diseases and cancer [5, 19,47]. Numerous clinical trials using the MSCs in the treatment of various medical conditions have been conducted [46]. In our work, we analyzed the results of application of mesenchymal stem cells in the treatment of patients under the age of 18.

The present research used the data obtained from the publications available in the following databases: PubMed, EBSCO, Scopus, and the page www.clinicaltrials.gov. The search-terms were "mesenchymal stem cells", "paediatric", "children". The analysis uses the original articles and overviews describing the results of the application of the MSCs in the treatment of various diseases in children. Out of many publications, a number of randomly selected articles describes the comparable effectiveness of therapy in given diseases.

In the compilation, we included 617 trials involving mesenchymal stem cell therapy, including 113 trials concerning children aged 0 to 17 which were registered on the 25th of June 2017. Moreover, of the trials reported upon, 13 trials were registered in Europe, 1 in Central America, 14 in North America, 4 in South America, 14 in the United States, 53 in East Asia and 3 in Africa [46].

MESENCHYMAL STEM CELLS IN THE GRAFT-VERSUS-HOST DISEASE

Available literature deals with the results of the application of the MSCs in the treatment of Graft-versus-Host Disease (GvHD) in acute, chronic, recurrent and resistance to corticosteroids type. Currently, about 20 studies on the prevention or treatment of GvHD after HSCT in patients with different malignancies such as leukaemia or neuroblastoma are registered [46]. The results of the tests carried out so far, show that the application of the MSC in the treatment of GvHD is satisfactory. The research conducted by Wernicke *et al*. presents a meta-analysis of literature describing the results of the treatment of Graft-versus-Host Disease and describes the two cases of MSC infusion in children [44]. The authors found that MSC infusion treatment applied in children with GvHD was confirmed to be both safe and effective. In addition, the results of the treatment in children were shown to be more beneficial than in adults [22,44]. Similarly, the work of Introna *et al*. (2014) describes the results of MSC treatment received by 15 children and 16 adults with steroid resistant and refractory GvHD of II, III and IV degree. The effectiveness of the treatment was better in the case of paediatric patients. No side effects were documented during and immediately after MSC infusion [22]. Safety application of mesenchymal stem cells from third-party donor is also described in the work of Prasad *et al*. [36]. In this study, patients received MSC contained in the product called 'Prochymal'. This study included 12 children with III or IV degree of GvHD resistance to other treatments. The results of the study indicate a rather high effectiveness of MSC when used in GvHD [36]. The efficiency and safety of mesenchymal stem cells contained in Prochymal, was also described by Kurtzberg *et al*. in 2014. They treated 75 patients (whose average age was 8) suffering from GvHD affecting the gastrointestinal tract, the skin and/or liver. The post-treatment assessment showed satisfactory results in most patients (total or partial remission at day +28 was 66.7% for GVHD grade B, 76.2% for grade C, and 53.3% for grade D). Patients, whose initial respond to the treatment was poor, received additional doses of the cells, which produced good final results [27]. The volume and number of the infusion of MSC in GvHD is still being discussed in literature. The need for bulk applications of MSC was indicated by the study of Ball *et al*. in 2013. In this study, the authors describe a group of 37 paediatric patients who received several infusions of mesenchymal stem cells in the course of treatment of steroid-resistant GvHD. Based on the data obtained, the authors suggested that repeated infusions of MSC are more efficient than a single administration of the cells [3]. In addition, the authors noticed better results in groups of patients who received MSC infusions during a shorter time after being diagnosed for various forms of skin GvHD, rather than in the case of liver or gastrointestinal tract GvHD. No adverse reactions arising from the administration of MSC from unrelated donors to the recipient were observed. The authors also indicated the importance of the growth response of T cells in viral and fungal infections in patients after transplantation of mesenchymal stem cells. This plays a vital role in the prognosis of immunocompromised patients [3].

The effectiveness of treatment of chronic GvHD with MSC infusion in patients under the age of 18 is particularly described in literature. In the study of Krenska *et al*., two patients aged 17 and 16 were diagnosed with GvHD of skin and eye tissues. Cellular therapy was commenced after 420 and 330 days from the diagnosis of GvHD. Complete remission was observed in the first patient, while in the second one only a temporary improvement of skin condition was noticed [26].

Each year brings new evidence concerning the MSC treatment of GvHD of different degrees and locations. From perusal, it must be pointed out that the GvHD preventive treatment should be initiated as early as possible, even before the HSC transplantation itself [6].

So far, a simultaneous administration of MSCT from HSCT is applied only as a way to increase the chance of transplant adoption. Thus, a number of ongoing trials aim not only at the prevention of GvHD, but also at the increase of the chance for successful engraftment in various haematological malignancies. In 2009, the results of treatment with co-transplantation MSC with HSCTs in two patients were described. Both were diagnosed with aplastic anaemia after the first and second transplant rejection [13]. However, 2 years after the transplantation of the two cell lines, an

observation was conducted and indicated no reasons for any re-treatment [13].

MESENCHYMAL STEM CELLS IN THE AUTOIMMUNE DISEASES

Autoimmune diseases constitute another group of diseases in which mesenchymal stem cells have found application. The treatment of these disorders takes advantage of the immunomodulatory effects of stem cells, their impact on T lymphocytes and the production of anti-inflammatory cytokines in the place of action. Mesenchymal stem cells can be administered locally, for example, inside a damaged joint, or systemically, because they have the ability to chemotaxis to the place of damage [35,40]. Currently, a few clinical studies have been registered that involve the treatment of rheumatic diseases in patients under the age of 18. In these studies, MSC are used for the treatment of systemic sclerosis, rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus, lupus nephritis and another type of nephrotic syndrome. So far, literature does not refer sufficiently to the results of these therapies. In a study conducted by Sun *et al*., the authors described a group of young adults aged 20 and 23, and two children aged 16 and 17 all suffering from Systemic Lupus Erythematosus with renal involvement who had previously been treated with immunosuppressive drugs (cyclophosphamide, prednisone). These patients received mesenchymal stem cells derived from their family members. All patients showed autoimmune disease remission and hence, presented a case for the discontinuation or reduction of the administered immunosuppressive drugs. Neither duration of the treatment nor patient observation period (from 12 to 18 months) indicated correlation with the appearance of serious side effects [38]. In this study, as in another study by Sun *et al*., the authors noted a disorder in the structure and functioning of the own MSCs of patients suffering from Systemic Lupus Erythematosus [38,39]. In a study of Liang *et al*., among the 15 patients were three children aged 12, 16 and 17. The patients received 1 × 106 cells/kg body weight in a single donation. During the treatment and during the observation period (lasting from 3 to 36 months), no serious toxicity was observed, and the patients remained in remission of autoimmune disease [30].

A distinct type of autoimmune disease is type 1 diabetes (the main type of diabetes observed in children). Trials applying MSCT treatment in type 1 diabetes provide promising data. Currently, 5 trials of 1 and 2 phase have been registered. These involve treatment with MSC on diabetics under the age of 18. The data provided in the study of Hu *et al*. include 29 patients. Herein, 15 out of these patients received MSC from the Wharton's jelly at the age of 17.6 ± 8.7. In this study, 24 months after the end of the MSC treatment, the patients maintained lower levels of glycosylated haemoglobin (HbA1c) and higher levels of C peptide, when compared to a group receiving a traditional treatment or placebo [21]. The success of the treatment demonstrates that the MSC treatment in type 1 diabetes is effective [21].

Crohn's Disease (CD) is another condition of combined pathogenesis requiring continuous immunosuppressive treatment. Although MSC have been used in the treatment of CD patients for a number of years, there is little data confirming their effectiveness in the treatment of children [11]. Still, some individual studies included patients under the age of 18. In 2011, Ciccocioppo described the results of fistula topical MSC administrations in the course of the treatment of 12 CD patients. Among the patients there was a child aged 16 [10]. As a result of the treatment, a significant improvement of the patients' condition was achieved (including closure of fistulae). What is more, no toxic side effects associated with the use of MSC were observed [10]. The effect exerted by the MSC on tissues damaged in Crohn's disease is associated not only with the immunosuppressant action of the MSC, but also with the ability to proliferate and differentiate into cells of various tissues types such as myocytes or fibroblasts, and for the ability to induce the repair of damaged tissues. This comes about because MSC influences the increase of angiogenesis, ensuring proper blood supply of regenerated tissue. The myogenic properties of MSC are used both for the treatment of children after the plasticity of anus and in the case of Duchenne Muscular Dystrophy. In this cases, it is recommended to perform the reconstruction of correctly constructed and correctly functioning myocytes. Mesenchymal stem cells also induce myogenesis and have regenerated the anal sphincter of patients with faecal incontinence [46].

MESENCHYMAL STEM CELLS IN REGENERATIVE MEDICINE

The ability of mesenchymal stem cells to differentiate into fibroblast, chondroblasts, osteoblasts and cells of neural tissue is used in the regenerative medicine to treat skin injuries, skin ulcers, burn injuries and Epidermolysis bullosa and androgenetic alopecia [46]. Furthermore, MSCs are used to regenerate bone tissue and cartilage, as well as the nervous system organs. In addition, the multidirectional action of mesenchymal stem cells leads to a more rapid regeneration of damaged organs and the inhibition of the progress of degenerative changes, as well as the prevention of some irreversible effects like organ fibrosis [5,17,33]. The application of mesenchymal stem cells in infantile osteoarticular diseases include congenital disorders of bone formation such as osteogenesis imperfecta (OI) and acquired damage to the bone and cartilage [16,34]. In 2005, scientists described intrauterine administration of mesenchymal stem cells in a 32 week old foetus diagnosed with osteogenesis imperfecta. At the age of 2 years, normal growth and psychomotor development have been achieved [29]. In 2014, Götherström *et al*. described the medical history of the same child and another baby who also received a MSC in utero. These patients had additional MSC infusions after birth, respectively, at the age of 8 years and 2 months (first patient), and 19 months and 11 days (second patient). The follow-up examination performed several years later indicated that the treatment of OI with MSC is safe and effective. It prevents the formation of pathological fractures, extends and improves the quality of life for OI patients. For comparison, the authors also presented a patient with the same genetic mutation who was born with complications related to numerous fractures in utero, and also with

malformation of the musculoskeletal system. The patient co-received vitamin D3, calcium and bisphosphonates. Unfortunately, he died at the age of 5 months as a result of respiratory failure associated with pneumonia [18].

The osteogenic and chondrogenic properties of mesenchymal stem cells have been harnessed to rebuild the alveolar bones and teeth in the occurrence of congenital lip and palate and articular cartilage defects [20]. Moreover, the repair of damaged cartilage using MSC infusion in young adults has been described. The success demonstrated may give rise to the implementation of this method in children [43]. On-going trials include the regeneration of bone and cartilages after fracture, osteonecrosis and osteodysplasia [2,46].

The ability of mesenchymal stem cells to stimulate the regeneration and prevention of chronic idiopathic myelofibrosis is also used for the prophylactics and treatment of respiratory diseases, including bronchopulmonary dysplasia of premature, lung injury after Parquot poisoning, as well as chronic liver disease. In the publication of Chang *et al*., the authors described the results of the phase 1 clinical trial involving 9 patients born in the 23rd-29th week of pregnancy with birth weight varying from 500 to 1250 g. All these patients required reactive oxygen therapy. At the time of 5 to 14 days after birth, all these neonates received a single intratracheal dose of mesenchymal stem cells. The assessment performed 3 days after the transplantation indicated a tendency for the improvement of the respiratory index in the newborns. The observation conducted until the 84th day after the MSC infusion indicated the reduction of risk of bronchopulmonary dysplasia development. Moreover, the children treated with MSC, when compared to children treated in the standard way, required a shorter time of tracheal intubation and steroid medication. Furthermore, in the course of treatment, there were no toxicity or differences in the condition of the patients depending on the dose of MSC [8]. The regenerative effect of MSC on the respiratory system is also used in the treatment of adults and children over 16 years of age suffering from the emphysema associated with different congenital and acquired diseases of the respiratory system [46].

MESENCHYMAL STEM CELLS IN ORGAN'S FIBROSIS

Gastroenterological clinical trials of MSC application include the treatment of viral liver disease. Herein, the infusion of mesenchymal stem cells has prevented chronic idiopathic fibrosis and improved liver regeneration in cases of toxic liver damage and in cases of HCV, HBV and CMV infected patients. In addition, the mesenchymal stem cells have been used to treat haemophilia and familial hypercholesterolemia due to their ability to differentiate into the hepatocytes and endothelial cells responsible for the production of coagulation factors [46].

MESENCHYMAL STEM CELLS IN NEUROLOGICAL DISORDERS

Mesenchymal stem cells have the ability to stimulate the cell proliferation of neural tissue through the secretion of growth factors, through anti-inflammatory activity, and through differentiation into neurons and glial cells [41]. The last in nerve cells is induced by the presence of yet unknown factors present in the cerebrospinal fluid [14]. These properties of mesenchymal stem cells are used in the treatment of congenital and acquired neurological disorders. In addition, the stimulation of angiogenesis improves the recovery after ischemic stroke or myocardial infarction [41]. However, significant improvement of motor and sensory function has been observed only in a small percentage of analysed patients [34]. Herein, the inhibition of the progression of the disease and the improvement in the maintenance of balance due to MSC administration was observed in adult patients with spinocerebellar ataxia (SCA), and in children with hereditary ataxia [23]. In children with autism, several authors observed a partial improvement after transplantation of mononuclear cells derived from their umbilical cord blood, together with the mesenchymal stem cells obtained from the Wharton's jelly [31]. The mechanism of the action of MSC in this disorder is associated with the probable improvement of brain blood circulation and the action of the immunomodulatory agent. The cells present in the cord blood, including CD34+ cells, also require angiogenesis, which is of importance for the enhancement of blood supply to the brain [31].

Currently, additional clinical trials are being carried out. Their aim is to ascertain whether MSC therapy is effective in the treatment of brain leukodystrophy in children aged 4 and over, autism in children between 3 and 12 years of age, damage to the spinal cord in children over 2, congenital ataxia, hypoxic ischemic encephalopathy, haemorrhage IV degree, encephalopathy associated with ischemia and hypoxia of the brain, as well as cerebral palsy [1,9,46]. From 2016 on, MSC therapy has been utilized in treating the autosomal recessive disease of motor neuron and Spinal Muscular Atrophy. Herein, the results of the intracerebroventricular administration of autologous umbilical cord blood cells into a 16 months old child suffering from hypoxic/ischemic brain injury after cardiac arrest at the age of 9 months has demonstrated the effectiveness of the application of these cells in neurological disorders [24]. The child has indicated slow, but significant improvements in cognitive functions and motor activities after 6 months after transplantation [24]. In 2010, the work of San *et al*. presented the results of cord blood cell transplantation in 184 children with neurological disorders. The majority of the cases were of cerebral palsy. Among the analyzed patients, 3 had anaphylactic reactions related to transplantation, in other children there were no complications observed [38]. Of note, there is a registered trial of a case of brain death due to diffuse axonal injury wherein the aim of the trial is to document the possibility of the reversal of the necrosis through MSC therapy [46].

MESENCHYMAL STEM CELLS IN CARDIOMYOPATHY

The angiogenic and antifibrogenic action of MSC is also used for the treatment of cardiac diseases such as cardiomyopathy and hypoplastic left heart syndrome in infants aged over 28 days [46]. So far, the results of the treatment of

these conditions are satisfactory [37]. In the 2011 study of Lacis *et al*., the authors described one case of a 4 months old baby with dilated cardiomyopathy whose ejection fraction increased by 41% 4 months after the cord blood cell transplantation [28].

MESENCHYMAL STEM CELLS IN OVARIAN INSUFFICIENCY

In reproductive medicine, it is suggested that MSC may be applied in the course of the treatment of Premature Ovarian Insufficiency (POI). Currently, there is no available treatment for POI. It has been put forward that since there are very small embryonic-like stem cells (VSELs) found in the ovary, their regeneration may be used for the affected ovary. In the reported trials, ovarian function was stimulated by the injection of MSCs triggering the secretion of trophic factors [42,46].

ADVERSE EFFECTS OF MSC APPLICATION

Despite the many known potential therapeutic benefits of mesenchymal stem cells which allow for their wide application, scientist are still of two minds with regard to the safety of MSC cell therapy. Several authors have mentioned reactions of fever or anaphylaxis, but there are several articles describing other more adverse effects such as pulmonary embolism and infarct of the lung, as well as tumorigenesis after MSC transplantation [45]. For example, iIn the study of Jung *et al*., the authors described patients with multiple pulmonary artery embolism and infarct of the right lung after the fifth intravenous administration of autologous adipose tissue derived from stem cell therapy used for cervical herniated intervertebral disc [25]. What is more, infections are also described as adverse effects of MSC application in a single trial of sepsis treatment. In contrast, in the work of Mei *et al*., MSCs have shown to have beneficial effects on experimental sepsis, possibly via paracrine mechanisms, suggesting that immunomodulatory cell therapy may be an effective adjunctive treatment to reduce sepsis-related morbidity and mortality [32].

CONCLUSION

Present studies have shown that stem cells, including mesenchymal stem cells, play important roles in the treatment of many diseases. Long-term studies on animals have revealed that cell therapy is safe, thus, stem cell therapy is now successfully used in the treatment of people. With time, the applications of stem cell therapy have been extended, but both the manner and the number of infusions still need to be studied.

The authors declare that they have no conflict of interest.

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