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THERAPEUTIC APPROACHES ON THE HUMAN MESENCHYMAL STEM CELLS – A REVIEW

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ABSTRACT

The mesenchymal stem cells (mesenchymal stem cells – MSCs) are thoroughly researched and explored by the regenerative medicine and tissular engineering, due to their immunosuppressive and renewal properties, replacement and regeneration of the injured or dead tissues. They differentiate into osteoblasts, adipocytes, and chondroblasts during standard *in vitro* differentiation parameters (according to the International Society for Cellular Therapy). The known sources of mesenchymal stem cells are: the bone marrow, the fatty tissue, the umbilical cord, the amniotic fluid, the placental tissue, the dental pulp. There are numerous clinical studies that research the mesenchymal stem cells therapeutically, aiming to cure many diseases, such as the autoimmune ones, or the inflammatory pathologies and the post - transplant complications. It is customary that, post excision and prelevation, these cells are cultivated by means of various lab methods, and then used directly, as they are, or preserved frozen and banked for shorter or longer periods of time before their usage. The mesenchymal stem cells derived from the umbilical cord are valuable in the cure of numerous diseases, due to the fact that, along with their biological anti-inflammatory and immunomodulator properties, they do not imply any ethical matters and are easily prelevated by non-invasive methods, at birth. Regarding the MSCs-based therapy, the clinical trials proved to be safe and well accepted by their host-organism. For a certain therapeutic effect, one should consider stability, reproductibility, capacity to preserve their biological properties post-manipulation and potential freezing, as well as their migration to the injured or inflamed tissues. Only few MSCs products were authorized to be marketed, which represents merely a small fraction compared to the conventional chemical and the biological drugs.
This current scientific approach will be continued with further studies on the banking procedures and regulations regarding the use of the MSCs in Romania, EU, and worldwide.

INTRODUCTION

The stem cells underwent an unprecedented development, correlated to the current scientific and technologic trends. The mesenchymal stem cells (mesenchymal stem cells – MSC) are thoroughly researched and explored by the regenerative medicine and by the tissular engineering, due to their immunosuppressive and renewal properties, replacement and regeneration of injured or dead tissues (Nasadyuk, 2016).
Known as stromal mesenchymal cells, they are part of the adult body in various sources, as well as in perinatal tissues. MSCs are characterized by a low immunogenity, are able to migrate to the altered tissue, manifest a paracrine activity as a trophic and an immunomodulator, they undergo differentiation into specialized cells, and

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do not form tumors. There are numerous clinical studies that use some cell therapies based on the mesenchymal stem cells, aiming to cure several diseases, such as the autoimmune ones, or the inflammatory pathologies and their post - transplant complications. It is customary that post - excision and prelevation, these cells are cultivated using various methods, and then used directly, as they are, or preserved frozen and banked for shorter or longer periods of time before usage. For a certain therapeutic effect, one should consider stability, reproductibility, capacity to preserve their biological properties post-manipulation and potential freezing, as well as their migration to the injured or inflamed tissues. The MSCs should be handled, grown, tested and banked in authorized institutions that meet the required criteria and conditions to facilitate their use in human patients, regarding that they are substances of human origin (SOHO) (Ch et al., 2023; Gimble et al., 2007).

The mesenchymal stem cells derived from the umbilical cord are used in the cure of numerous diseases, due to the fact that, along with their biological anti-inflammatory and immunomodulator properties, they do not imply any ethical matters and are easily prelevated by non-invasive methods, at birth. Neither the mother, nor the offspring are in jeopardy. Therefore, they are preferred to any other sources of MSCs (Mebarki et al., 2021).

The known sources of mesenchymal stem cells are: the bone marrow, the fatty tissue, the umbilical cord, the amniotic fluid, the placental tissue, the dental pulp.

The umbilical cord as a source of mesenchymal stem cells is collected at birth, by means of non-invasive methods. The obtained MSCs display a low immunogenicity – a low expression of the main histocompatibility complex (type I and type II), a higher self-renewal property to MSCs obtained from other sources, a low oncogenic potential, and may differentiate into several cellular types.

Mesenchymal stem cells are one of the best sources for the regenerative medicine due to their self-renewal and differentiation capacity, and for the lack of ethical issues.

ISCT (International Society for Cellular Therapy) defines the MSCs as it follows: adherent to plastic surfaces, maintained in standard cultures; they express the differentiation clusters CD105, CD73 and CD90; they differentiate into osteoblasts, adipocytes, and chondroblasts during standard *in vitro* differentiation parameters. In 2016, ISCT added the factors that induce the immunomodulation as an extra standard.

This present scientific contribution relies on the study of scientific papers and databases issued in this complex domain. The clinical studies that were consulted (CellTrials.org) and the platforms, web sites, on line data bases, such as ClinicalTrials.gov provided new and valuable information. The rules and regulations from Romania and from the EU on the matter of cells and tissues, and for the advanced therapies represented a valuable source (Advanced Therapy Medicinal Products – ATMP).

Worldwide tendencies regarding the umbilical cord MSCs

The mesenchymal stem cells obtained from the umbilical cord served for various therapeutic trials during the last decades. The most clinical trials of this type were in phase I or II, in order to evince their fesability, safety, efficiency, and very few reached phase III.

According to the data available on CellTrials.org on the advanced mesenchymal stem cells collected from various sources, the number of clinical trials increased from 100 to 150 per year, mainly by 50%, during 2011 to 2017 (A Policy Audit on Fertility, 2018).

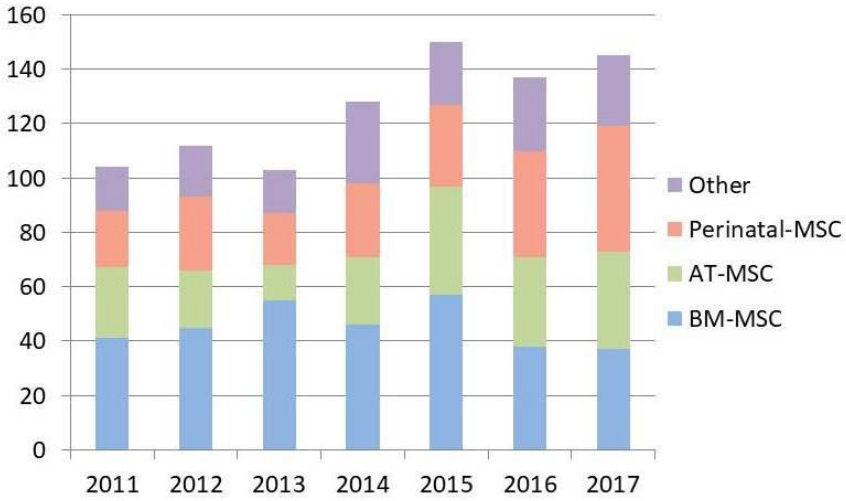

Figure 1. Number of clinical studies using mesenchymal stem cells during 2011 – 2017 (perinatal – MSCs, AT-MSC (adipose tissues), BM-MSCs (bone marrow) (Counting Keywords is not Compiling Clinical Trials: Mesenchymal, 2018)

In the begining, the bone marrow MSCs prevaled, although the umbilical cord MSCs gradually grew from 20% to 30% (Figure 1) (Counting Keywords is not Compiling Clinical Trials: Mesenchymal, 2018).
By the year 2021, there were issued over 464 clinical studies on mesenchymal stem cells from the umbilical cord and 151 trials on umbilical cord MSCs combined with other sources of perinatal tissues. During 2015 – 2020, the clinical trials on the mesenchymal stem cells from the umbilical cord tissues annually increased by four times, and, compared to the trials on umbilical cord blood, they surpassed the latter during the previous years.
During the COVID-19 Pandemic, the umbilical cord tissue turned into a source of MSCs. The number of clinical trials increased by 20%, in an attempt to cure the medical emergencies in SARS-CoV-2 pateints, mainly the cytokine storm (Verter et al., 2020).
Mid year 2020, there were registered 111 clinical studies on cellular therapies that aimed to cure COVID-19 (Figure 2). Among those, 48% involved MSCs from the perinatal tissues (umbilical cord tissue, umbilical cord blood or placenta) (Verter et al., 2020).

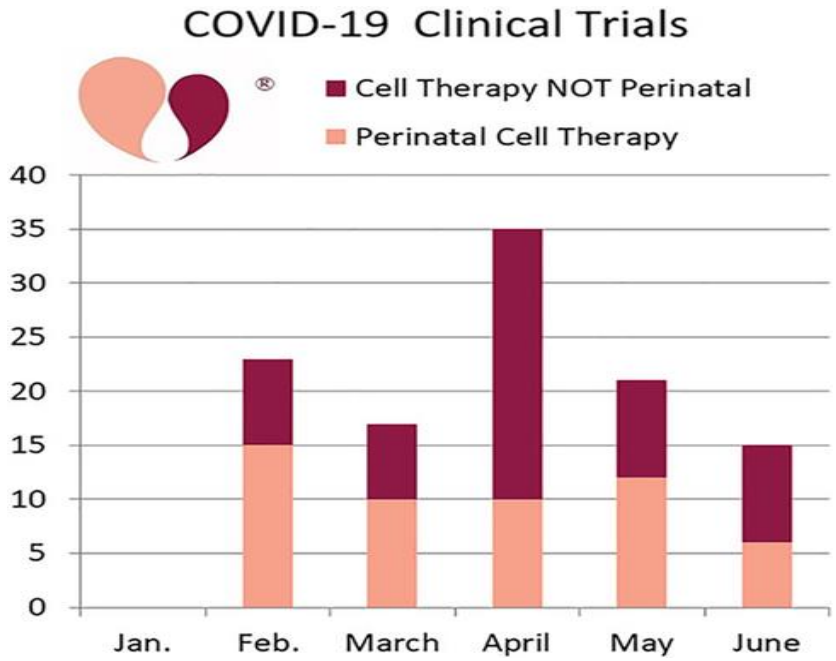

Figure 2. Clinical trials on cell therapies aiming to cure COVID-19 (Counting Keywords is not Compiling Clinical Trials: Mesenchymal, 2018)

There is a rising trend of an augmented use of the MSCs from the umbilical cord tissue in clinical trials compared to the umbilical cord blood (Cumulative Trials Advanced Cell Therapy through end of 2021, 2022).

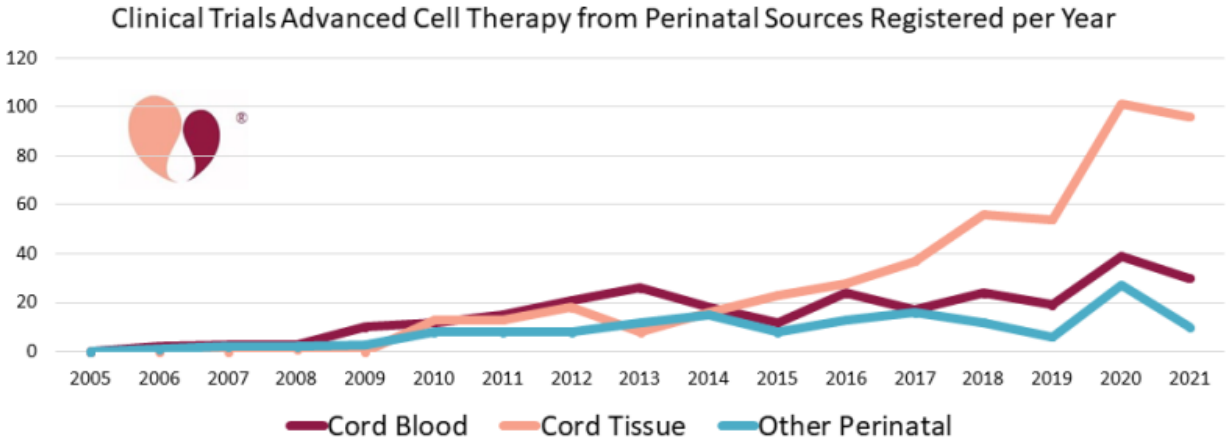

Figure 3. The shift of the umbilical cord tissue MSCs use in clinical trials (https://clinicaltrials.gov)

By the year 2020, there were issued more than 1200 clinical trials based on MSCs from various sources on the ClinicalTrials.gov web page, most of them tested the bone marrow or the fatty tissue MSCs (Figure 3) (https://clinicaltrials.gov).

Over 4000 review articles were published during the last two decades. Their topic was related to various sources MSCs' research, including the umbilical cord MSCs, according to PubMed.
The umbilical cord mesenchymal cells are a promising source for the bone regeneration in the treatment of the osseous defects.
The research evinced the MSCs osteogenic differentiation, that may be influenced by means of chemical or physical factors (Ansari et al., 2018).
The osseous defects can be corrected surgically. Grafts can be used, as well (either autogenous, or allografts and xenografts), or implants, all coming with a risk, to a certain extent.
The MSCs are mesenchymal progenitors of the osteoblast lineage, enhancing the osteogenesis. The osteoblasts differentiated from the MSCs may be of use in the cure of the osseous defects.
During the bone regeneration, the inflammatory factors activate and boost the MSCs, that migrate to the injured region, with a major role in the bone fractures' healing. The possible infections may sometimes cause a progressive bone damage and a loss of bone tissue. In case of infection or of inflammation, the MSCs interact with the immune system's cells and interfere with the immunomodulation process (Gu et al., 2022; Friedenstein et al., 1968).
The MSCs have a major role in the prevention/suppression of graft-against-host. They decrease the grafting process of the hematopoietic stem cells. The grafting time is significantly reduced (Wu et al., 2013).
Due to their immunosuppressant activity, the MSCs are researched during the clinical trials for the immune diseases, such as the rheumatoid arthritis. This is the most common autoimmune disease. To improve patients' life quality, there is a continuous search for the best solutions to replace the conventional therapies (El-Jawhari et al., 2014).
The umbilical cord MSCs clinical trials combined with the conventional treatment displayed the absence of side effects and the decrease of the blood alpha necrosis factor. The therapeutic effects lasted a total of six months, therefore requiring repeated MSCs infusions (Wang et al., 2013a).
The umbilical cord MSCs infusions in *Lupus eritematosus* patients were beneficial. A health improvement was clearly evinced. In some patients, a new MSC infusion was required six months after the first one (Wang et al., 2013).
More than 1500 patients suffering from Crohn disease were subjected to MSCs therapy within several clinical trials. The treatment proved to be safe. There were many improvements, mainly in the patients' resistant to the anti-cytokines' therapy (Nasadyuk, 2014).
MSCs capacity to differentiate into cardiomyocytes and endothelial cells, as well as the secretion of some growth factors by means of their paracrine activity, justify their use in the treatment of the cardiovascular diseases, such as the myocardial infarction, the cardiomyopathy, the heart arrhythmia, and the coronary disease. Within the clinical trials on patients suffering from heart failure, the MSCs therapy joining the conventional treatment proved to be efficient in the cellular and in the vascular regeneration, the main effects being the stimulation of the vascularization process and the decrease of fibrosis (Kim et al., 2016; Zhao et al., 2015; Santos Nascimento et al., 2014).
There are two main causes of a cerebrovascular accident: a clogged artery (an ischemic stroke) or a damaged blood vessel (a hemorrhage). The most cases of strokes are the ischemic strokes. The hemorrhagic accidents may be caused by the high arterial blood pressure and by the aneurysms. In addition to the conventional therapies, to the medication and the speech therapy, the MSCs cure is beneficial in case of a stroke. Expressing their paracrine effect (the release of growth factors), the MSCs are angiogenic, releasing the vascular endotelial growth factor (VEGF) (Singh et al., 2020).
The mesenchymal stem cells decrease the inflammation and the ischemic lessions. Moreover, they are considered neuroprotectors as they release neurotrophic factors and improve vascular activity. They provide a neuronal microenvironment by means of the exosome release and the secretion of bioactive neurotrophic factors (Zhang et al., 2020; Zhou et al., 2019).
There was primarily considered that the MSCs would replace the injured cells. Nevertheless, they fuel the endogenous repair processes, releasing trophic factors, such as: the vascular endothelial growth factor (VEGF), IGF (the insulin-like growth factor), BDNF (the brain-derived neurotrophic factor), and growth factors that enhance the regeneration (Singh et al., 2020).
The experimental trials evinced that the umbilical cord MSCs may develop into hepatocyte-like cells, expressing the hepatic markers.
A clinical trial in which the antiviral and the hepatoprotective medication was combined with the MSCs displayed the lack of side effects and the higher serum albumin level (Xue et al., 2015).
Many clinical trials search the cure for some neurologic diseases by means of the umbilical cord MSCs. Their differentiation into neuronal cells was not possible in vivo until present time, although their paracrine effect increased the neuroprotection and the release of some neurotrophic factors (Nasadyuk, 2016).
The clinical trials on ASD (Autism Spectrum Disorder) aim to highlight their therapeutic efficiency and beneficial role, once the safe usage has been already tested. ASD triggers some neural and immune disorders, therefore the MSCs represent the ideal therapeutic tool, by immunomodulation, neuroprotection, neurogenesis and the genesis of synapses (Gesundheit et al., 2015).
There were ran numerous clinical trials aiming to cure the autism until present day, and there was an improvement in social behaviour, whilst the severe side effects lacked (Sun et al., 2021a; Sun et al., 2018b).

The MSCs may differentiate into several cell lines. They have a major role in the immunomodulation process. All the above highlight their therapeutic potential in the ovarian function improvement and of the ovarian stock, as well, by means of their paracrine path. The MSCs migrate directly to the affected ovary and survive in that zone. They activate the primer folicles, enhance the ovarian function and may decrease the ovarian cell apoptosis, particularly in the presence of collagen (Esfandyari et al., 2020; Zhao et al., 2015).
The pre-clinical trials evinced that the MSCs are effective and safe in the cure of lung diseases, they resume the affected lung's function and integrity, and recover the lung alveoli (O'Reily et al., 2017).

CONCLUSION

The mesenchymal stem cells are one of the best sources for the regenerative medicine due to their self-renewal and differentiation capacity. Regarding the MSCs-based therapy, the clinical trials proved they are safe and well accepted by their host-organism.
The mesenchymal stem cells derived from the umbilical cord are used in the cure of numerous diseases, due to the fact that, along with their biological anti-inflammatory and immunomodulator properties, they do not imply any ethical matters and are easily prelevated by non-invasive methods, at birth.
The umbilical cord MSCs' various biological roles recommend their use in the translational medicine, in an attempt to apply and capitalize the latest available scientific findings in the conventional medicine, to give access to many novel therapies that might heal several medical conditions impossible to treat at present.
The mesenchymal stem cells from the umbilical cord tissue, collected at birth, display certain advantages compared to those prelevated from the bone marrow or the fatty tissue.
The umbilical cord mesenchymal stem cells are considered ATMPs (advanced therapy medicinal products), manipulated to change their biological characteristiscs, used to cure, diagnose or prevent certain diseases.
Only few MSCs products were authorized to be marketed, which represents only a small fraction compared to the conventional chemical and biological drugs.

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