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Implementation of experimental cellular (cellular-genetic) therapies on the example of eye diseases

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ABSTRACT

The development of technology and a modern research approach in the 21st century has enabled access to new therapies in many fields of medicine and nanotechnology. Work on the use of cellular therapies is carried out in leading centers around the world. According to the "clinicaltraial.gov" service, it is estimated that there are about 5.5 thousand clinical trials using stem cells. The classification of stem cells is based on their potential to differentiate into other cells, tissues, organs or the whole organism. In cell therapy 3 groups of stem cells are used: Pluripotent Stem Cells (PSC), multipotent and unipotent, which have two common features: the ability to self-revalue, that is, to divide and to differentiate in many directions. To date, there are no objective, randomized clinical trials that would clearly determine the efficacy and safety of the cell therapy used in ophthalmic diseases. Hope is given by gene therapies such as the recently approved Luxturna™ gene therapy used in hereditary retinal degeneration caused by mutations in the RPE65 gene. Research is currently underway on experimental cell therapies to treat the following diseases of the optic system: glaucoma, retinopathy, age-related macular degeneration (AMD), optic nerve atrophy, retinal pigmentation (RP) and Stargardt's disease. Stem cell-based medical therapies are a promising and rapidly developing method of innovative treatment, especially for conditions that were previously considered incurable. The use of experimental cellular gene therapies in diseases of the visual organ gives hope to both patients and scientists, but the age of regenerative medicine has yet to come.

Key words: cellular therapies; stem cell; eye diseases

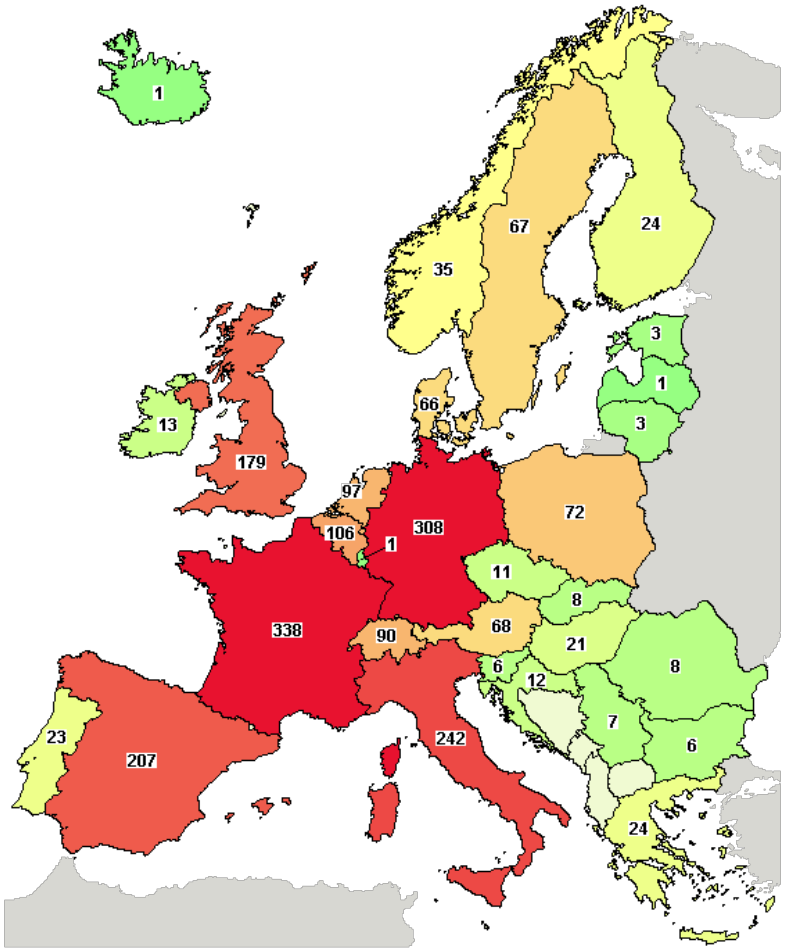
INTRODUCTION

The development of technology and a modern research approach in the 21st century has enabled access to new therapies in many fields of medicine and nanotechnology. Currently, research is underway all over the world, which could provide potential solutions to many problems related to incurable diseases or irreversible changes in the human body. The rapidly developing regenerative medicine, which includes stem cell therapies, is very successful [1,2].

The history of the use of stem cells for therapeutic purposes begins in 1981, when colonies of mice, embryonic stem cells, later known as ES cells (Embryonic Stem Cells), were first isolated worldwide. This event was recognized in the world of science by

awarding the Nobel Prize in Physiology or Medicine to Martin Evans, Mario Capecchi and Olivier Smithies in 2007 for discovering "the principles of introducing certain gene modifications in mice by means of embryonic stem cells" [3]. In the following years stem cells were obtained from human embryos in 1998, from primates in 2001 and from rats in 2008 [4].

Currently, work on the use of cellular therapies is carried out in leading centers around the world. According to the "clinicaltraial.gov" service, it is estimated that there are about 5.5 thousand clinical trials conducted with the use of stem cells. The country where the most research is conducted (about 2700) is the United States, while in Europe, research on the use of cellular therapies is half as much (about 1200). The largest number of research projects is respectively: in France - 338, Germany - 308, Italy - 242, Spain - 207 and the United Kingdom - 179. In Poland there are about 72 clinical trials using stem cells, which is presented in Figure 1 [5, entry 01.06.2020].



Cellular therapy plays an important role in medicine, especially in haematology [6,7], dermatology [8], orthopaedics [9,10], neurodegenerative diseases [11,12], immunology [13] and ophthalmology, which are highly expected [14,15,16].

LEGAL REGULATIONS CONCERNING CELL THERAPY IN POLAND

Although the origins of stem cell research took place as early as the 1960s, until now their use as a public therapy has been limited by appropriate regulations and restrictions. Legislative work is still ongoing and still under discussion. The restrictions related to the legal application of cellular therapies are burdened with data deficits in its various phases. Currently, only cellular therapies are carried out in two areas: haematology for haematopoietic cell transplantation and skin renewal procedures using connective tissue cells. In other fields of medicine, they are still at the stage of experimental research [17].

In view of the current legislation on the treatment and use of medicinal products in advanced therapy, there are also separate legal acts on the use of stem cells. They include these:

- European Parliament directives and regulations (e.g. 2004/23/WE)[18];
- European Commission directives (e.g. 2006/17/WE; 2006/86/WE; 2015/565; 2009/120/WE) [19,20,21,22];
- Regulations of the Minister of Health of Poland (e.g. Rozporządzenie Ministra Zdrowia z dnia 29 września 2016r. w sprawie szczegółowych warunków pobierania, przechowywania i przeszczepiania komórek, tkanek; Rozporządzenie Ministra Zdrowia z dnia 29 czerwca 2011r. w sprawie wzoru wniosku o wydanie zgody na wytwarzanie produktów leczniczych terapii zaawansowanej i narządów Dz.U. poz. 1674) [23];
- Laws of the Polish Parliament (e.g. Ustawa z dnia 23 marca 2017r. o zmianie ustawy o pobieraniu, przechowywaniu i przeszczepianiu komórek, tkanek i narządów Dz.U.2017 poz. 798; Ustawa z dnia 24 lutego 2017r.o zmianie ustawy o zawodach lekarza i lekarza dentysty oraz ustawy o pobieraniu, przechowywaniu i przeszczepianiu komórek, tkanek i narządów Dz.U. 2017 poz. 767 [24,25].

In Poland, legal acts are based on permits from the Ministry of Health to receive and use stem cells for therapeutic purposes. Moreover, the Ministry regulates the status of stem cells, but unfortunately, it no longer refers to long-term procedures, i.e. preparation of therapeutically competent cells. However, it is possible to treat stem cells, according to the law, as an Advanced-therapy medicinal product (ATMP). Then they are subject to the regulations of both the Chief Pharmaceutical Inspectorate and the regulations: The

European Medicines Agency (EMA) and its Committee for Advanced Therapies (CAT) [26,27,17].

Moreover, in Poland, the condition for experimental cell therapy is to obtain the consent of local Bioethics Committees. Unfortunately, this often involves a rashly positive opinion without elementary knowledge about the therapy itself and lack of information about meeting the basic criteria of the research center. There are still doubts about charging patients for experimental cellular therapies. According to Polish law, such studies whose therapeutic outcome is doubtful should be free of charge. The research should be financed from grants, grants and research programs, and not from the patients concerned [28].

Therefore, the use of experimental cellular therapies as a routine therapy in the treatment of many diseases becomes realistic. However, it still needs to be further developed in the future.

TYPES OF STEM CELLS USED IN EXPERIMENTAL CELL THERAPY IN OPHTHALMOLOGY

The classification of stem cells is based on their potential to differentiate into other cells, tissues, organs or the whole body. In cell therapy 3 groups of stem cells are used: PSC (Pluripotent Stem Cells), multipotent and unipotent, which have two common attributes: the ability to self-revalue, i.e. to divide and to differentiate in many directions [29].

A characteristic feature of PSC is their ability to differentiate to almost all cell types in the body. However, they are not able to produce structures outside the germ, i.e., the placenta and the entire body. Since they can regenerate infinitely, they are capable of generating almost unlimited amounts of differentiated retinal tissues. The breakthrough was the receipt of Induced Pluripotent Stem Cells (IPSC) by Shinya Yamanak's team, which ended with the 2012 Nobel Prize [30]. The most commonly used stem cells in the therapy of cellular visual diseases are two types of PSC - human embryonic stem cells (hESC) and induced pluripotent stem cells (iPSC) [31]. However, in Poland induced stem cells are not used in experimental therapies [28].

However, multipotent stem cells are those that can differentiate into different cell types, coming from one of the three germ leaves. An example are hematopoietic stem cells, which can transform into several types of blood cells in the bone marrow. In addition to hematopoietic cells, of a multipotential nature, MSC (mesenchymal stem

cells) is currently the most frequently studied and used in cell therapy [32,33,34,35]. MSC can be isolated from bone marrow, peripheral blood, adipose tissue, cord blood, umbilical cord (Wharton jelly), amniotic fluid, placenta, dental pulp, periodontal ligaments, smooth, skeletal and cardiac muscles, liver, spleen, testis, menstrual blood, pancreas, periosteum, synovial membrane, dermis, barrel bone and lungs [36,37]. However, studies have shown that MSC, isolated from the umbilical cord, are not able to differentiate towards retinal nerve cells, and thus to treat eye disorders.

On the other hand, unipotent stem cells differentiate into cells of one type of tissue. This group includes corneal stem cells, which are used in the treatment of corneal epithelial damage, and stem cells taken from the skin [28]. Epidermal stem cells help to treat difficult-healing wounds, extensive skin burns and ulcers [38,39].

APPLICATION OF EXPERIMENTAL CELLULAR-GENE THERAPIES IN DISEASES OF THE VISUAL ORGAN

Stem cell treatments save people around the world. Experimental cell therapies are also used in ophthalmology to create new, alternative and sometimes unique treatments. However, as of today, there are no objective, randomized clinical trials that would clearly determine the effectiveness and safety of the applied cell therapy in ophthalmic diseases. Hope is given by gene therapies such as the recently approved Luxturna™ gene therapy used in hereditary retinal degeneration caused by mutations in the RPE65 gene [40].

Research is currently underway on experimental cell therapies to treat the following diseases of the optic system: glaucoma, retinopathy, age-related macular degeneration (AMD), optic nerve atrophy, retinal dye degeneration (RP), and Stargardt disease. Moreover, safety data from several clinical studies concern only phase I/II of retinal stem cell transplantation [41,42]. Two stem cell-based therapies are currently being developed, i.e. the strategy of transient dosing using multi-cent stem cells or eye progenitor cells and the strategy of permanent implantation using retinal photoreceptors derived from pluripotent stem cells and/or retinal pigment epithelial cells (RPE) [43].

Experimental phase I and II studies with therapeutic effect in AMD have already been observed using two types of stem cells, but not of ocular origin, but of umbilical cord origin (identifier NCT02895815) and neural progenitor cells from the fetus' brain (identifier NCT01632527). It seems surprising that the research related to the strategy of transient dosing seems to be completed quickly, despite their safe use. Clinical trials are continued, but with the use of ocular stem cells, i.e. retinal progenitor cells (RPC)

(identifier NCT03073733) and cells similar to them (identifier NCT02464436) [42]. In the case of the strategy of permanent implantation, the researchers, after numerous observations, reconstructed fully mature and functional RPE cells from both IPSC and ESC for cell therapy purposes. There is also evidence of the beneficial effect of adult RPE stem cells (RPESC). The results of these studies are promising, but they are certainly challenging [44]. Similarly, the use of RPE cell suspension from ESC is in phase I/IIa of clinical trials in patients with AMD and Stargardt disease [45,46]. In addition, studies are underway using RPE derived from hESC (identifier NCT02286089) in the USA and Israel, where cells are administered as a suspension in an ophthalmic balanced salt solution [42]. However, prior to the commercial application of cellular therapy for sight diseases, or for tissue regeneration, there is a need to develop at least one in vitro test to predict the effectiveness of stem cell RPE. To this end, efforts to verify RPE cells from both ESC and IPSC are still ongoing [47,48].

In ophthalmology, fetal retinal progenitor cells (fRPC) are also transplanted in experimental treatment of RP and AMD. Currently the research is in phase I/II. The most important focus is on regenerative photoreceptor therapies in AMD and hereditary retinal dystrophies (RP and Stargardt disease) [49,50]. Moreover, in view of recent developments, the aim is to use CD34+ cells isolated from the bone marrow to treat vision loss due to various retinal disorders. These include hereditary or age-related macular degeneration, pigmented retinitis, retinal vein obstruction and diabetic retinopathy. The Phase I study in patients treated with CD34+ cells has been completed with the expected result, therefore this method will be continued in Phase II of clinical trials [51,52].

The improvement in the quality of vision in experimental cellular therapies is only the beginning of the iceberg, noted in the literature to varying degrees. The main difficulty in the use of cell therapies is that the disease process may affect many types of retinal cells or form in one cell and then affect the adjacent ones.

DANGER OF CELLULAR THERAPIES IN OPHTHALMOLOGY

On April 28, 2020, the Committee for Advanced Therapies (CAT) of the European Medicines Agency (EMA) published its position on the use of unproven cell-based therapy. The communication indicates the existence of potential risks, resulting from the use of unproven cell-based therapies in the treatment of cancer, cardiovascular

diseases, autism spectrum, cerebral palsy, muscular dystrophy, as well as changes leading to the loss of vision by therapists [53].

In addition to the risk of unconfirmed cellular therapies in ophthalmology (glaucoma development, haemorrhage to the vitreous body, intra- and subretinal space, tractional and transient retinal detachment, vitreous-retinal proliferation, epithelial membrane, lens displacement), studies indicate the risk of potential complications from the very moment of stem cell administration [54]. In order to achieve this, less invasive procedures are performed, introducing appropriate procedures, e.g. administration to the vitreous glandular, which should not damage the retina. Literature data indicate that as a result of experimental cellular therapies the following side effects are observed: epithelial membrane formation, intraocular pressure increase and tractional retinal detachment [55,56,57].

As the pluripotent stem cells injected into the vitreous body can be transformed into myofibroblast-like cells, they can also contribute to the complications associated with vision loss. Therefore, it is very important to monitor the patient after the procedure. Moreover, there is a need to supervise the clinics offering cell therapy and to educate patients by specialized medical staff. Regulatory authorities are also essential to protect patients, while supporting relevant research and innovation [54].

SUMMARY

Stem cell-based medical therapies are a promising and rapidly developing method of innovative treatment, especially for conditions that were previously considered incurable. However, this new therapeutic strategy requires long-term monitoring of the risks associated with the effect of treatment and the occurrence of side effects before it is approved for routine use in patients. Wide optimism at this stage of the study is therefore not justified. Literature data clearly show that commercial use of stem cells in ophthalmology raises some concerns, mainly related to delayed side effects and therapeutic success. The use of experimental cell-genetic therapies in diseases of the visual organ gives hope to both patients and scientists, but the era of regenerative medicine has yet to come.

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