Adult stem cells in cardiovascular medicine: historical overview and ethical issues

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Abstract. The regenerative capacity of adult tissues depends on tissue-specific stem-cell populations that maintain stable numbers by self-renewal and possess the ability to differentiate into distinct cell lineages. Adult stem cells are found in children, as well as in adults. Regeneration and renewal in adult mammalian tissues has been studied in several compartments such as the hematopoietic, endothelial, mammary, intestinal, neural, skin, muscle, and hair-follicle tissues. Regenerative medicine places emphasis on cell-based therapy, particularly stem cells, to repair or replace damaged tissues/organs, and is a topic of major current interest. While the use of adult stem cells in research and therapy does not require the destruction of an embryo, the use of embryonic stem cells is much more controversial. Even the performance of clinical trials with adult stem cells, however, have important ethical implications. This review, after a brief historical overview, concisely examines the findings of clinical trials in cardiovascular medicine and focuses principally on the ethical issues.

Key words: adult stem cells, randomised controlled trials, heart diseases, ethical issues in cardiovascular medicine

Abbreviations: randomised controlled trials (RCTs), congestive heart failure (CHF), acute myocardial infarction (AMI), ischaemic heart disease (IHD), ischemic heart failure (IHF), primary angioplasty (PCI), coronary artery bypass graft (CABG), New York Heart Association (NYHA) class, Canadian Cardiovascular Society (CCS) angina grade, left ventricular ejection fraction (LVEF), left ventricular end-systolic volumes (LVESV), therapeutic misconception (TM).

Historical overview

In 1868, Ernst Haeckel (1834-1919), an illustrious German biologist and one of the greatest morphologists of the 19th century, used for the first time the term "Stammzelle"- that is "stem cell" - to describe the unicellular organism from which multicellular organisms would be developed (1). The term "stem cell" was taken up by Haeckel in his book Anthropogenie (2) but the concept was clarified in the 3rd edition of the same book (3) in which the German scientist attributed to 'Stammzelle' or 'Cytula' a double meaning, both as a unicellular progenitor of all multicellular organisms and as a fertilized egg from which all the cells of an animal or human organism develop. The new term was also introduced to point out that the fertilized egg cell was different from the original egg cell, chemically, morphologically and physiologically. Haeckel noted that the stem cell 'is partly of fatherly and partly of motherly origin; and we will now no longer find it astonishing if the child, who develops from this stem cell, inherits individual characteristics from both parents' (4)

In the late 19th century, August Weismann (1834-1914) elaborated the theory of the continuity of the 'germ plasm' ('Keimplasma'). 'Germinal plasma',

segregated in the nucleus of germ cells (egg cells and spermatozoa) since the early stages of embryonic development, transmitted hereditary characters from one generation to the next (5). Following the debate on this theory, the term stem cell was used to indicate an embryonic cell capable of giving rise to specialized cells.

To verify Weismann's theory, two great embryologists of the time, Theodor Boveri (1862-1915) and Valentin Haecker (1864-1927) conducted studies in animal embryos to identify the earliest germ cells that presumably carry germ-plasm.

Both Haecker and Boveri called 'stem cell' ('Stammzelle'), the common precursor cell of the primordial germ cells and of the primordial somatic cells (6,7). According to Boveri, in the very early stages of the embryo development, a stem cell is divided into two daughter cells, one of which retains the stem cell features and the other gives rise to somatic cell precursors. So, in 1892, Boveri adopted Haeckel's term of 'Stammzelle' highlighting also a stem cell's capacity for self-renewal as well as for differentiation into specific types of somatic cells or germ cells (7).

In the same years, the concept of "stem cells" also spread in other areas of bio-medical research. In 1896 Artur Pappenheim (1870-1916), one of the leaders in modern haematology, researcher at Virchow's Pathological Institute in Berlin, in his studies of hematopoiesis attributed the name of "stem cell" to the common progenitor cell of the red and white blood cell lineages (8). Moreover, he believed that the stem cell was an embryonic cell capable of giving rise to diverse cell types, from germ cells to tissues of the entire body (9). The unitarian model of hematopoiesis, which proposed a stem cell as the common precursor of the entire blood system, was supported, in the early 1900s, by other eminent researchers, including Wera Dantschakoff (1879-), Alexander Maximow (1874-1928) and Ernst Neumann (1834-1918), professor of pathology of Königsberg (10-12).

Thus, the concept of stem cells was born in Germany in the late nineteenth century within the context of important embryological questions such as the theory of the continuity of the germ plasm and the hematopoiesis.

Characteristics of adult stem cells

Adult stem cells are undifferentiated cells that are found in many different tissues in juvenile as well as adult animals and humans. They can give rise to both cells like themselves and to differentiated cells (13-15). The regenerative capacity of adult tissues depends on tissue-specific stem-cell populations that maintain stable numbers by self-renewal and possess the ability to differentiate into distinct cell lineages.

Scientists have discovered adult stem cells in bone marrow more than 50 years ago and cell transplantation has been developed clinically for over 40 years in patients with haematological malignancies, e.g. haematopoietic stem cell transplantation in patients with leukemia. Later, the blood stem cells have been used in transplants for patients with several other diseases.

In later years, researchers have found adult stem cells in many more tissues than they once thought possible. By the 1990s, several studies had confirmed that nerve cells in the brain can also be regenerated from endogenous stem cells. So it has been hypothesized that adult stem cells of different tissues could lead to treatments for numerous conditions that range from type 1 diabetes, to cardiovascular diseases, to neurological diseases.

However, the adult cell-based therapies for the treatment of these conditions, such as heart disease, have only been possible since 2002.

Findings from clinical trials: a brief précis

Most pre-clinical and clinical studies in cardiovascular regenerative medicine have analyzed the treatment with different types of stem cells of acute myocardial infarction (AMI), chronic ischaemic heart disease and congestive heart failure (CHF).

Stem cells and acute myocardial infarction

Over the past 2 decades, randomised controlled trials (RCTs) have tested the use of autologous bone marrow-derived cells as a treatment to the repair and regeneration of damaged vascular and cardiac tissue

after AMI. Systematic reviews and meta-analysis on cell therapies for patients with AMI suggested that cell therapy does not appear to have beneficial effects (16-17). In agreement with these data, an updated systematic review analysed data from a total of 41 RCTs with over 2700 patients treated with autologous adult bone marrow stem cells as a therapy for AMI. Cochrane's review concluded that there is insufficient evidence for a beneficial effect of cell therapy for individuals with AMI, as most of the results were obtained from small trials that showed no relevant clinical differences (18). The authors believe that there is currently insufficient evidence to suggest that cell therapy reduces mortality and morbidity beyond standard therapy. Larger clinical trials are required to more concretely evaluate the efficacy of cell-based therapies post-AMI.

Stem cells, chronic ischaemic heart disease and congestive heart failure

Ischaemic heart disease (IHD) is very widespread throughout the world and individuals with CHF are increasing (19). The use of stem cells is a promising method for the treatment of chronic IHD and CHF but it is an experimental therapy used in clinical trials that is not part of standard clinical practice. Currently, patients with these diseases are treated with pharmacological therapy and, whenever possible, with primary angioplasty (PCI) or with heart surgery (or coronary artery bypass graft - CABG) (20) to make the heart's revascularisation. Revascularisation has reduced the death rate associated with heart disease and heart failure, but in some patients, symptoms persist even after revascularisation. Recently, on these patients, whether or not they also undergo revascularisation, a new bone marrow stem/progenitor cells treatment was studied.

The mechanism of action of such therapies remains unclear. Therefore, in the last years, a large number of RCTs has been performed producing results that require further evaluation. Early trials and systematic reviews have demonstrated that cell therapy may result in some improvements over conventional therapy (21-24). In following systematic reviews it was observed that cell therapy may reduce the risk of mortality in the long-term in people with chronic IHD and CHF and that there are no major adverse events associated with the treatment (25-26). Some evidence suggests that cell therapies have a beneficial effect on people with IHD and heart failure (27-28). A systematic review, that included 38 randomised controlled trials with 1907 participants (1114 cell therapy, 793 controls), described that treatment with bone marrow-derived cells administered to people with chronic IHD or CHF, can lead to a reduction in deaths in participants followed for at least 12 months (29). However, the same authors considered the quality of evidence as low and the results have to be confirmed in larger, subsequent randomized clinical trials.

A recent meta-analysis shows that stem cell transplantation is a effective and safe treatment which improves some indices of cardiac function (NYHA class, CCS grade, LVESV and LVEF) but does not reduce mortality in patients with IHF(30). However, it is necessary to verify the data with further well-designed clinical trials.

Ethical issues

In addition to the requirements commonly required to make a clinical trial ethical (choice of study design and endpoints to optimize the response to the clinical question; selection of participants using appropriate scientific criteria, protection of privacy and guarantee of dissemination of results, review and approval of research by independent individuals, etc.), the complex procedure used in stem cell trials requires particular attention to the evaluation of the risk-benefit ratio and informed consent.

Evaluation of the risk-benefit ratio

Role of uncertainty

All international documents on ethics in clinical research are based on the principle that risks for recruited persons must be fewer than the intended benefits (31).

The most predictable risks are those related to the psychological distress of undergoing multiple invasive procedures, to the uncertainty of the arm where the

participants are randomized and to the possibility of receiving ineffective treatment (32).

The potential physical and psychological risks must be minimized and justified from the potential benefit for the participants.

But, in the application of innovative techniques such as regenerative medicine, risks and benefits are always characterized by uncertainty that arises also from some peculiarities of stem cells, such as:

- Self-renewal and differentiation of stem cells are difficult to control and often lead to heterogeneous results.
- Stem cells represent a completely novel product, requiring the assays that ensure the purity, stability, safety, and validity of the final product. Concerning safety issues, transplantation studies with human cells inserted in animals cannot with precision predict the immune or other metabolic responses in patients. Hence, preclinical evidence of safety is of utmost importance as stem cells can also cause tumors or ectopic tissue formation.
- Stem cells require careful monitoring of the patient since, once transplanted, they persist for many years in the body (33).

Therefore, the extent of uncertainty is related to the tests already carried out and the type of stem cells used (34-35). The complex mechanism of the action of stem cells, the inherent risks to the invasive procedures and often the lack of correspondence between animal models and humans, tend to increase uncertainty in regenerative medicine trials when compared to those traditional pharmaceuticals (34-36).

Potential benefits for participants, science and society

In a clinical trial it is important to minimize the risks and increase the individual benefits and those benefits that pertain to science and society, in order to obtain a favorable risk- benefit ratio. The aim of a clinical trial is to be useful to both the individual and to society by improving scientific knowledge. New knowledge is obtained with large randomized trials and not with small and often uncontrolled studies. In addition, to improve knowledge it is important to stimulate preclinical studies related to clinical outcome. This is called "reciprocal value" and guarantees that trial promotes further research, even though no beneficial results are observed (37). It is also very important that the negative results of the trials are published[33] and that outcome measures are used in future trials to facilitate the comparison of the results.

Informed consent

Informed consent is at present a needed condition both for therapy and research. Modern informed consent results from fundamental principles expressed in the Nuremberg Code: the value of a person's autonomy and the respect due to persons. It is necessary to protect the decision-making autonomy of trial participants by formulating an adequate informed consent, which pays particular attention to four essential aspects: disclosure of information, understanding information, decision aids, voluntariness (38-39).

- *Disclosure of information*: As with all innovative procedures, even in stem cell applications, the disclosure of information to participants on the risks and benefits of the study is critical because of the high uncertainty. Disclosure is only clear when standardized procedures that present known risks are used.
- *Understanding information:* Another critical aspect is to understand the information provided. In fact, participants in these trials may misunderstand the purpose, the risks, and the potential benefits and often do not appreciate important differences between research and treatment, a phenomenon called "therapeutic misconception" (TM).[40] TM exists when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial (40-41). The risk of TM could be further increased by the application of invasive interventions (42) and by the promise of regeneration, which creates high expectations especially in patients with advanced or termi-

nal disease. Some scholars believe that the TM is favored by the often recurring consideration that researchers, as they are also medical doctors, carry out their research for therapeutic purposes. This belief could facilitate the exploitation of the participants (43). Additionally, older participants as well as those with a lower grade of education are more inclined to TM. For this, attention needs to be paid to the linguistic aspects, giving written and oral information which is clear and easy to understand, in order to avoid confusion. For example, terms such as cell therapy could generate TM (44). In addition, to enhance the participant's understanding, it is important to repeat the information in different ways, also using face-to-face communication and audiovisual information.

- *Decision aids:* It is difficult to make patients understand risks, benefits and uncertainties especially as the estimate of the individual risk / benefit ratio is often unknown. It is important to implement a shared decision-making process using aids such as pamphlets, videos or web-based tools. There is growing evidence that decision aids may improve congruent choices (45). Comorbidities and older age of participants could reduce decision making.
- *Voluntariness:* To provide informed consent, trial participants must have in-depth knowledge of the purpose, methods, risks, benefits and alternatives to research. Full awareness of all the information acquired allows individuals to make rational and free decisions about their enrollment in a clinical trial consistent with their interests.

Discussion

Adult stem cell therapy opens new perspectives for the treatment of many pathologies, including cardiovascular diseases.

In the past twenty years, researchers have studied the efficacy and safety of various adult stem cell populations in many clinical trials. Although initial results were encouraging, subsequent large-scale randomized trials have highlighted modest benefits in patients receiving this therapy. The reasons for these differences are largely due to variations in trial methodology, such as the differences in the choice of cell source, cellular concentration, timing of delivery and clinical conditions of the examined patients. And last but not least to the lack of standardized protocols (46). The results from recent studies show that it is necessary to adhere to rigorous standards in conducting future stem cell clinical trials.

Furthermore, there are great uncertainties about the mechanisms of action at the base of cellular therapy in cardiac diseases. In the first studies it was hypothesized that stem cells had the ability to produce new heart tissue or develop blood vessels. Instead, preclinical studies suggest that these cells release cardioprotective paracrine factors that activate endogenous pathways resulting in myocardial repair (47,48). It has been hypothesized that cardio-protective paracrine factors produced by stem cells are enclosed in extracellular membrane vesicles, such as exosomes and microsomes, which transfer RNA, microRNA, proteins, lipids to perform cardioprotection. The hypothesis that vesicles can replace stem cells in therapy is very interesting from a clinical and commercial point of view, but must be confirmed by further studies (49,50).

The research done on adult stem cells has been relatively free of serious ethical issues but the realization of clinical trials, indispensable to raise relevant evidence on long-term safety and efficacy of stem cells therapies, is scientifically and ethically challenging (51).

Indeed, due to the complexity of the procedures and the possible use of stem cells in the field of regenerative medicine, it is considerably more difficult to construct protocols for randomized controlled trials on cell therapy compared to the trials that evaluate the effectiveness of traditional pharmaceuticals, surgical procedures or medical devices. Moreover, as this is a rapidly expanding field, preclinical knowledge is rather scarce and animal models may not be good predictors of what happens in humans (52,36). It is also important to emphasize the economic interests that gravitate around the use of stem cells. The great public interest and the pressure exerted by companies on researchers and desperate patients induce hyper acceler-

ated translation of interventions in the clinic (53,54). Often, to concretize in a short time the expected results, no major clinical trials are funded, that are long lasting and costly and necessary to have sure responses (55).

Therefore, the progress of clinical trials is conditioned and patients may take unnecessary risks.

Conclusion

Future research should focus on developing new strategies to follow stem cells post-delivery, in order to improve the knowledge of their molecular mechanisms. Further studies are still needed to clarify if stem cell regenerative therapy is clinically efficacious and can be routinely utilized in clinical practice. To that end larger studies that use clinically meaningful endpoints should be conducted. In addition, in clinical trials efforts must be concentrated to minimize risks, obtain appropriate informed consent, reduce the likelihood of the therapeutic misconception and facilitate a good translation from research to clinical practice. As clinical research is increasingly sophisticated and interactions between different actors increase, the ethics of clinical trials becomes increasingly complex.

These observations are also valid for randomized controlled trials using different types of stem cells and are applicable to other medical fields, in addition to cardiovascular medicine.

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