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ESC report

The consensus of the task force of the European Society of Cardiology concerning the clinical investigation of the use of autologous adult stem cells for repair of the heart

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A task force has been established by the European Society of Cardiology to investigate the role of progenitor/stem cell therapy in the treatment of cardiovascular disease. This article is the consensus of this group, of what clinical studies are needed in this field, and the challenges to be addressed in the translation of progenitor/stem cell biology to repair of the heart.

Introduction

In theory, cell therapy can be used to repair damaged or aged organs. However, medicine is awaiting definitive proof that organ repair using stem cells is possible. To achieve this, the most promising cell types are embryonic stem cells and autologous stem/progenitor cells (either native or engineered). Clinical evidence concerning translation of basic biological research in stem cells to restore the function of any organ is advanced in the heart. This is probably related to the simplicity in which the heart can be accessed and the relative ease with which quantitative change in function can be measured. Several problems have been identified in translational research in the heart: (i) the type of cells to be used (including the preparatory methodology, the time at which cells are given to the heart, the route by which they are given, the number of cells, the volume to be given, and optimisation of the cells); (ii) outcome measurement; (iii) original organisational problems; (iv) funding.

The European Society of Cardiology established a task force on stem cells and repair of the heart, which suggests that the immediate future of this science is the use of autologous bone marrow stem/progenitor cells, or skeletal myoblasts in repairing the acute or chronically damaged myocardium. Repair of the arterial and venous wall is also possible, but clinical translation in this field is far behind repair of the myocardium. The isolation, expansion, and application of resident cardiac stem cells may hold therapeutic promise for the future.

A danger that must be avoided is that stem cells will be delivered and advocated as a therapy, without definitive proof of efficacy.

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What has been achieved so far?

Autologous bone marrow cells

So far, several small trials of autologous bone marrow derived cells have been published in peer-reviewed journals. All demonstrate an improvement in function in patients with acute myocardial infarction (AMI) or chronic myocardial ischaemia treated by autologous bone marrow derived cells.

Autologous muscle cells

With respect to other types of autologous stem cells, work using the skeletal myoblast should be recognised. After a decade of work, robust experimental studies have consistently shown, in small and large animal models of myocardial infarction, that in-scar transplantation of skeletal myoblasts resulted in their differentiation in myotubes and improved left ventricular function. The early phase I trials have clearly shown the feasibility of the technique and revealed a potential risk of arrhythmias. Although, the intrinsic arrhythmogenic nature of the target scars still makes it difficult to establish conclusively a cause-and-effect relationship between these events and myoblast engraftment. A large multi-centre, randomized, placebo-controlled, double-blind study (MAGIC) is currently under way and its results should clarify the pending safety and efficacy issues associated with skeletal myoblasts. Parallel bench work is optimizing the benefits of the procedure, primarily through the enhancement of cell survival following transplantation.

Research problems that remain

The trials of bone marrow cells so far, have used the pragmatic approach of injecting a fixed volume of bone marrow-derived mononuclear cells (10 mL being the maximum that can be delivered at one injection into the coronary artery with less directly intramyocardial). The number of cells, as well as, the types of subpopulation has clearly varied. Ideally, a dose response would be helpful. However, injecting autologous stem cells applies a systems biology to a damaged organ which has undergone a myriad of changes. It is not similar to the injection of a defined, single molecular species that can be profiled accurately in relation to a receptor or enzyme. The practicality of assessing clinical efficacy in stem cell biology probably excludes the application of traditional preclinical pharmacology.

Whether one cell type has the beneficial effect in man, or many cell types talking to each other, is not known. To test all possible combinations of bone marrow cell types, number of cells, time of injection after damage, and frequency of injection, all via different routes in animal models and then in man, is obviously of great scientific interest. However, it would take the best part of a century. A pragmatic approach to demonstrate clinical efficacy is needed.

Future therapeutic targets

Over the next few years, we believe that the target diseases for myocardial repair should be (i) AMI; (ii) chronic myocardial ischaemia; (iii) cardiomyopathy.

The ethics of proceeding with more clinical studies

So far, the infusion of autologous bone marrow stem cells into the coronary artery appears to be safe. There have been several hundreds of patients treated in this way, out of which no unexpected deaths have occurred when autologous bone marrow stem cells have been used. These questions therefore arise:

- Should more clinical studies be attempted?
- Should clinical studies be undertaken before an understanding of mechanisms of myocardial repair using autologous stem cells is understood from animals and human studies? If this is so, what animal experiments would stop or encourage future work on stem cells and repair of the heart?
- Should imaging studies demonstrate the anatomical fate of autologous stem cells in the heart in observational studies, before further clinical trials are undertaken? Does an imaging agent exist that does not affect the function or movement of these cells?

We believe that safety of the procedure is the primary consideration in determining whether future clinical trials should be undertaken. This, combined with an indication of potential efficacy in the given disease, is all that is needed to encourage future clinical studies. The understanding of any other mechanism of action of any therapeutic in the cardiovascular system is always provisional. We are still trying to understand how aspirin and beta-blockers work. No matter what animal experiments are undertaken, the mechanisms that may be deduced from those animal experiments may not be the actual mechanism pertaining to benefit in the human clinical situation. Indeed, all mechanisms involved may never be known. We believe that sufficient animal experiments have been performed in this area to allow clinical studies to continue. However, clearly animal models are of value, particularly, as the use of large animal models may be useful in addressing some of the mechanistic questions. However, diseases of the myocardium cause a very high incidence of mortality and morbidity in the world and it is the role of academic medicine to translate novel science for the treatment of ischaemic heart disease.

What studies are needed?

We believe that the use of autologous stem/progenitor cell therapy is not at a stage to be used in routine clinical practice.

We believe that it is timely to perform the following studies that should be designed on the basis of the published data:

(i) Further large, double-blind, randomized, controlled trials for the use of autologous bone marrow cells in the treatment of AMI. The patient population should be all those presenting within 12 h of AMI and treated with immediate revascularisation, be it primary angioplasty or fibrinolysis.

(ii) A double-blind, randomized, controlled trial for the use of autologous bone marrow cells in the treatment of myocardial infarction in those patients presenting late ($>$12 h) or who fail to respond to therapy

(candidates for 'rescue' angioplasty). Although, these groups may represent a small proportion of all patients with AMI, their prognosis remains poor.

(iii) Double-blind, randomised, controlled trials for the use of autologous bone marrow cells or skeletal myoblasts in the treatment of heart failure secondary to ischaemic heart disease. At some stage, the role of autologous stem/progenitor cells in the treatment of cardiomyopathies (in particular, dilated cardiomyopathy) will need to be examined.

(iv) A series of well-designed small studies to address safety or mechanism to test specific hypotheses (e.g. studies with labelled cells or to investigate paracrine or autocrine mechanisms). Such hypotheses would have arisen from basic science experiments.

(v) Studies to confirm the risk/benefit ratio of the use of cytokines alone (e.g. granulocyte colony stimulating factor) or in conjunction with stem/progenitor cell therapy.

Ultimately, endpoints for studies should focus on robust clinical outcomes, as well as, MACE (major adverse cardiac advents), subjective benefit, and economic gain. Outcome measures for future trials should be standardized so that comparisons can be made. In all of these studies, questions concerning optimal timing of delivery, number of cells delivered, and the route of delivery (e.g. at the time of bypass surgery or by percutaneous techniques) will need addressing. However, preliminary data from several pilot studies exist, suggesting that at least in the first two groups above an intracoronary route using cells, harvested from a bone marrow aspirate, may be efficacious. It should also be noted that outcome studies in this field will need to recruit in the region of 1000 patients to provide enough statistical power to be meaningful. Such studies should be multicentre and ideally pan-Europe. It is not until the results of such studies are available, that the role of autologous cells as a treatment could be considered. Until we are able to perform large outcome studies, surrogate endpoints need to be agreed. So far, studies of AMI have used ejection fraction as a primary endpoint. Considerable debate exists over the most accurate measure of this modality. Clearly, investigators must choose a method of assessing such primary endpoints, which in their hands, has the minimum intra- and inter-observer variability, until a consensus can be reached over the ultimate method.

Biology and regulation of translation

Careful attention should be given to the processing of autologous stem/progenitor cells. To derive meaningful comparative data from the trials, standardisation of this procedure is crucial. Currently, this is best achieved in specialized centres producing GLP-grade cell preparations i.e. certified haematology laboratories.

The regulatory bodies should work in partnership with the profession to set standards and requirements for translation to clinical practice.

What studies are not needed?

An increasing number of small, uncontrolled studies have been published using autologous bone marrow derived cells in the clinical setting. The initiation of similar small studies should be avoided as they are unlikely to add anything new to the field.

Unique considerations for stem cell repair of the heart

There is no intellectual property associated with autologous bone marrow cells themselves, which constrains the pharmaceutical industry from supporting early stage research. It is therefore, the duty of doctors themselves to demonstrate whether or not this treatment is efficacious. The situation is without precedence in the cardiovascular system. It would be a tragedy for the treatment of patients with myocardial ischaemia and for healthcare costs, if efficacy of this treatment were not fully explored, and an expensive patented cellular treatment (perhaps which would not have been as efficacious as autologous cells) were brought into use in the future.

The task force of the European Society of Cardiology on stem cell repair of the heart intends to review the situation of clinical trials, and publish position papers from time to time indicating its consensus on necessary future studies.