

A Note on Clinical Trials for Stem Cell Therapies

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The rapid advance of stem cell clinical trials for a broad spectrum of conditions warrants an update of the review by Trounson [1]. There has been a rapid surge in clinical trials involving stem cell therapies over the last two to three years and those trials are establishing the clinical pathways for an emergent new medicine. These early trials are showing roles for stem cells both in replacing damaged tissue as well as in providing extracellular factors that can promote endogenous cellular salvage and replenishment.

There are many studies involving autologous therapies and some allogenic therapies, based on the recovery of mobilized bone marrow cells, including mesenchymal stem cells (MSCs) and adipose derived stem cells that also include the stromal or adherent cell type that has an MSC phenotype. Human umbilical cord blood cells have been used in a large number of trials for paraplegia, ataxia, multiple sclerosis, amyotrophic lateral sclerosis, cerebrovascular disease, multiple system atrophy, motor neuron disease, among other indications, without severe immunological response [2].

A significant proportion of clinical studies that are underway involve bone marrow and cord blood stem cells for blood and immune disorders [3] and cancers. Several of those are now considered applicable for patient treatments beyond the need for regulated clinical trials.

We have chosen to concentrate on the emerging therapeutics that broadly involves a wide range of cell types in clinical trials registered on the National Institutes of Health's clinical trials web site. MSCs are a stromal cell type and the current definition of MSCs includes plastic adherence in cell culture, specific surface antigen expression (CD105(+)/CD90(+)/CD73(+), CD34(-)/CD45(-)/CD11b(-) or CD14(-)/CD19(-) or CD79 α (-)/HLA-DR1(-)), and multi-lineage in vitro differentiation potential (osteogenic, chondrogenic, and adipogenic) [4].

The majority of which are in Phase I (safety studies), Phase II (proof of concept for efficacy in human patients), or a mixture of Phase I/II studies. This includes bone and cartilage repair, cell types into which MSCs readily differentiate, and immune conditions such as graft versus host disease and autoimmune conditions that utilize the MSC's immune suppressive properties.

Expectations for patient benefits are high in these therapeutic applications. Nevertheless, there are many prospective applications where the mechanism of action is not obvious and some concerns have been expressed about the likelihood of long-term benefit of these applications. In the case of allogenic MSCs, delivery to an inflamed site can result in gain of immune potency with accelerated damage due to a heightened immunemediated inflammatory response.

Clinical trials on the use of stem cells are underway for a wide variety of conditions and there is an emphasis on the use of bone marrow, hematopoietic (mobilized and recovered in blood and umbilical cord blood) and mesenchymal stem cells. While safety has been consistently demonstrated, particularly with autologous transplants, sustained curative benefit has not been consistently obtained [5].

Allogenic transplants generally have major issues for continual immunosuppression to prevent rejection of grafted cells. In some cases, the benefit of cell therapy is through unidentified trophic effects of transient grafted cells. Nevertheless, progress for therapeutic benefit for patients is increasing and there is clear merit for using stem cells as delivery vehicles for correcting genetic mutations that cause severe disease phenotypes.

Increasingly, new stem cell types are being explored and both neural and pluripotent stem cells (embryonic stem cells) are under study in early Phase I/II trials. It is too early to predict the outcome of these trials at present but early observations of patients indicate that they do appear to be safe.

Recent studies using induced pluripotent stem cells (iPSCs) have shown sizeable genetic and epigenetic abnormalities in these cells and there is now a clear need to determine the biological significance of those changes before iPSCs are taken to clinical trials [6].

A strong indication of the confidence in the cell therapy field is the increasing participation of the large pharmaceutical companies in stem cell therapies [7]. Strong funding from organizations such as the Californian Institute for Regenerative Medicine and their collaborating partners worldwide is likely to rapidly expand new clinical trials in the next few years.

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