Placental Cell Therapy for the Treatment of Muscle Trauma and Postoperative Stress in Hip Fracture Patients: From Preclinical Models to Clinical Phase III

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INTRODUCTION:

Despite modern hip arthroplasty techniques, which would allow total weight bearing, mobility is critical and difficult to achieve in hip fracture patients. This is due to the second hit of the surgical procedure after the suffered trauma and the additional muscle injury needed for joint exposition in the frail patients. To date, there is no effective therapy to address skeletal muscle injuries and surgery related stress. Our studies have explored therapies with mesenchymal stromal cells (MSC) for skeletal muscle injuries and transferred this therapy from preclinical experiments to the patient.

METHODS:

First, we established an animal model, mimicking a clinically relevant crush trauma of the soleus muscle, and tested several applications of autologous MSC transplantation. Following this, we tested the efficacy of an allogeneic approach in the same trauma model, using human placenta-derived mesenchymal like adherent stromal cells (PLX-PAD). We then translated this therapy into the clinics by using acute iatrogenic muscle damage after total hip arthroplasty (THA) as a model system and conducted a prospective, randomized, double blind, placebo-controlled phase I/II study. 20 patients undergoing THA via lateral approach were included and received a transplantation of $300x10^6$ (300M), $150x10^6$ (150M) PLX-PAD or placebo into the injured gluteus medius muscles (GM).

RESULTS:

Preclinical experiments showed improved muscle healing with increased force generation after autologous and allogeneic MSC therapy versus placebo. Patients of the phase I/II study were followed for 2 years. No relevant AEs have been observed during this period. The primary efficacy endpoint, change of GM strength after 6 months, showed a significant increase in the 150M group ($p=0.0067$) compared to placebo, which was accompanied by an increase in muscle volume ($p = 0.004$). The change of strength and volume in the 300M group showed a similar pattern as in the 150M group but was not statistically significant. Histology indicated faster healing after PLX-PAD therapy. Interestingly, our biomarker studies showed a reduction of the postoperative immunological stress reaction due to the cell therapy.

Based on these results we designed a phase III study (The HIPGEN study) treating hip fracture arthroplasty patients (N=240) with an intramuscular injection of 150M PLX cells to improve muscle healing, mobility and mortality. Our consortium received funding from the European Union Horizon 2020 program (Grant No 779293) and has recently finalized enrolment patients in 20 sites in Germany, England, Denmark, Israel and the US (EudraCT Number: 2017-005165-49). Partners are among others the universities of Charité, Oxford, Odense, the Biotech company Pluristem and the International Osteoporosis Foundation. The patients are followed for function, biomechanics, quality of life, lean muscle volume and with accompanying immunological biomarker studies. We further look into the mechanisms of action by a broad spectrum of in vitro experiments on the effect of PLX cells on muscle cells of healthy donors and HIPGEN patients.

DISCUSSION AND CONCLUSION:

In summary, our data showed consistent positive results of MSC therapy for skeletal muscle regeneration in different preclinical application modes and finally in patients, where we are currently conducting the first phase III study using allogeneic cell therapy in hip fracture patients. Treatment with allogeneic cells could be a game changer not only in the treatment of the analyzed injuries but also for other traumatic or iatrogenically induced muscle injuries. Particularly hip fracture patients are promising candidates for the seen benefits of placental cell therapy.