Information about Stem Cell Therapy in Orthopedics

1. General information about stem cell therapy

In the first decade of the 21st century, more than 17,000 scientific articles involving 2,724 cell therapy clinical trials were published (Culm-Seymour *et al.*, 2012). These results include 323,000 patients treated with more than 675,000 cell therapy units. This number of cell therapy products represent a distinct healthcare sector among other well established medical products; the sector, which is very safe and often very effective in the treatment of various diseases with the potential to significantly improve health worldwide (Mason and Manzotti, 2010).

There are currently many ongoing cell therapy clinical trials for treatment of various diseases. There are more than 23,000 cell therapy trials registered (status up to April 1, 2013) in a public database of clinical trials (www.clinicaltrials.gov). Approximately 4,500 of them are focused on the use of stem cells for the treatment of a variety of diseases. Most of these clinical trials are in Phase I- safety studies, Phase II - proof of concept for efficacy in human patients or represent a combination of Phase I/II studies. Regarding source of the cells, a similar ratio of the number of autologous (the donor and recipient are the same individual) and allogeneic (the donor and recipient are different individuals) trials is found within the cell therapy clinical trials. Most clinical trials are ongoing in the United States, Europe and Asia. Roughly 1 million patients have been treated with their own stem cells since the mid-1980s in the United States (New York Stem Cell Summit 2012).

2. The use of stem cells in orthopedics

Recent ongoing clinical studies are focused on the use of stem cells in the treatment of many diseases, including stroke, type 2 diabetes, multiple sclerosis, amyotrophic lateral sclerosis or osteoarthritis. There is a growing body of research regarding stem cells for the treatment of osteoarthritis. Stem cells have the immunomodulatory and anti-inflammatory properties, they are able to differentiate into specialized cells of the connective tissue and can contribute to the regeneration of joint cartilage, thus supporting their potential in the treatment of osteoarthritis. Treatment with stem cells from adipose and connective tissue of the lipoaspirate, typically obtained from the abdomen and buttocks, supports regeneration of connective tissue, including the synovial tissue, in which it leads to the formation of intra-articular fluid supporting cartilage with necessary growth factors. In order to replace or renew lost or damaged cells, stem cells are usually applied to the affected area directly associated with the damaged tissue. Thus, inflammatory response is inhibited and regeneration, repair and regrowth of healthy tissue is supported. There are currently several ongoing clinical trials focused on the stem cell therapy of cartilage diseases, including osteoarthritis (see **Table 1**).

The most frequently used source of stem cells in clinical trials is bone marrow or adipose and connective tissue. The use of adipose and connective tissue has many advantages. Stem cells from adipose tissue – fat can be easily obtained by liposuction under local anesthesia without the risk of thrombosis or introduction of infection into the bone marrow, resulting in sepsis or osteomyelitis. Unlike bone marrow stem cells, adipose-derived stem cells do not require cultivation in the laboratory and are ready for use immediately. In addition, the adipose tissue contains unique populations of cells that suppress the inflammatory responses, and thus further contribute to regeneration and create optimal environment for adaptation of stem cells that support regeneration and repair of damaged cells and tissues. Furthermore, adipose stem cells are plentiful and lipoaspirate contains approximately 500-1000 times higher amount of stem cells compared to the same volume of the bone marrow (Aust *et al.*, 2004).

Recently, several articles in scientific journals have described stem cell therapy of the cartilage defects or osteoarthritis. These publications present the results of clinical status of a total of 559 patients. Altogether, they emphasize safety and clinical effect of stem cell treatment, see **Table 2**. The results show significant reduction of pain, improvement of joint function and better quality of life in patients with articular cartilage disease or knee and hip osteoarthritis (Wakitani *et al.*, 2002, Wakitani *et al.*, 2004, Wakitani *et al.*, 2007, Haleem *et al.*, 2010, Nejadnik *et al.*, 2010, Saw *et al.*, 2011, Kasemkijwattana *et al.*, 2011, Emadedin *et al.* 2012, Pak *et al.*, 2012, Koh *et al.*, 2012, Koh *et al.*, 2013). The study that involved 339 patients reported 60% improvement in patients with osteoarthritis of the knee and 65% improvement in patients with osteoarthritis of the hip one year after stem cells application (Centeno *et al.*, 2010, Centeno *et al.*, 2011). The results of clinical trial focused on the adipose-derived stem cell therapy at Sydney's Royal North Shore Hospital in Australia show that the anti-inflammatory effects are almost immediate. Regarding pain and improved function, benefits can be seen within 10 days and reduction of pain ranges from 30 to 100 percent. The regeneration of cartilage (Wakitani *et al.*, 2002, Wakitani *et al.*, 2004, Wakitani *et al.*, 2007, Haleem *et al.*, 2010, Centeno *et al.*, 2010, Centeno *et al.*, 2011, Saw *et al.*, 2011, Emadedin *et al.* 2012, Pak *et al.*, 2012, Koh *et al.*, 2013), increase in cartilage thickness, extension of the repair tissue over the subchondral bone and a considerable decrease in the size of edematous subchondral patches (Emadedin *et al.*, 2012) were seen by the magnetic resonance imaging and arthroscopy. Improvement of clinical symptoms, including reduction of pain and walking without limp persisted at several years' follow-up (usually 2 to 11 years) after the application of stem cells (Wakitani *et al.*, 2004). Therefore, stem cell therapy may lead to the regeneration of cartilage as well as connective tissues that nourish the cartilage. Articular cartilage thus becomes more resistant and qualitatively better. Currently, it is not certainly clear, whether the patient treated with stem cells will be permanently healed. Clinical research of this procedure is still at the beginning, but the safety and clinical effect of stem cell therapy in the 1-4 years' follow-up is clear. However, in patients with severe damage or loss of articular cartilage (i.e., arthritis stage IV), especially of the large joints (knee, hip), the breakthrough results of stem cell treatment are not expected. Nevertheless, also in such heavily damaged cartilages, stem cell therapy can at least partially and temporarily help to reduce the pain and other clinical manifestations of arthritis. These patients are then usually candidates for artificial joint replacement. On the other hand, patients with earlier stages of osteoarthritis (grades II and III) can experience a complete recovery and long-term improvement in the follow-up of 5 years or more after stem cell therapy.

The risks of stem cell therapy are minimal. Use in humans has been shown to be completely safe with the injection of bone marrow- or adipose tissue-derived stem cells (Wakitani *et al.*, 2011, Kasemkijwattana *et al.*, 2010, Centeno *et al.*, 2011, Emadedin *et al.* 2012, Rodriguez *et al.*, 2012, Koh *et al.*, 2013). Only some people experience modest discomfort in the area of liposuction and minimal pain at the site of stem cell application that usually subside within 24 hours. In one study, although no hematopoietic or biological abnormalities were noted, one of the patients with rheumatoid arthritis reported facial flushing, fever and myalgia. These symptoms resolved spontaneously and could be due to other disease rather than administration of stem cells (Rodriguez *et al.*, 2012). However, adverse events have to be observed also in the longer-term follow-up. Very importantly, there were no adverse events, no infection and no cancer associated with the area of stem cell application in the follow-up of 2-11 years (Centeno *et al.*, 2010, Centeno *et al.*, 2011, Wakitani *et al.*, 2011, Emadedin *et al.* 2012, Rodriguez *et al.*, 2012).

Experience of the International Consortium for Cell Therapy and Immunotherapy (ICCTI) www.iccti.eu that associates more than 50 world-renowned experts in the field of cell therapy, also shows that the treatment of osteoarthritis with autologous stem cells derived from adipose and connective tissue leads to a very significant improvement of health. It involves the group of more than 1100 patients with osteoarthritis of the large joints from the Czech Republic, U.S.A., Lithuania, and Slovakia in whom more than 1800 joints were treated. Importantly, in neither case severe adverse events or side effect associated with the treatment were observed; in neither case (median follow-up of 2 years and 3 months) infectious complications, the occurrence of cancer or autoimmune disease were reported (Michalek *et al.*, 2014, STEMSO conference, Freeport, Grand Bahama, Bahamas; Michalek et al. 2015 Cell Transplantation, in press).

Table 1: Overview of ongoing clinical trials focused on the stem cell therapy of cartilage diseases and osteoarthritis of the knee or hip

Source of stem cells	Type of stem cells	Trial phase	No. of patients	Country	Reference
Bone marrow	autologous	0	50	France	NCT01159899
		I	50	Norway	NCT00885729
		I	6	Iran	NCT00850187
		I	20	Brazil	NCT01325103
		I/II	15	Spain	NCT01227694
		I/II	12	Spain	NCT01183728
		I/II	10	India	NCT01152125
		I/II	20	China	NCT01446640
		II	40	Belgium	NCT01429012
		II	50	Malaysia	NCT01459640
		II	40	Iran	NCT01504464
		II/III	25	Egypt	NCT00891501
	allogeneic	I	12	U.S.	NCT01061099
		I/II	30	Spain	NCT01586312
Umbilical cord blood	allogeneic	I/II	150	China	NCT01547091
		I/II	12	U.S.	NCT01733186
		III	104	Korea	NCT01041001
		III	103	Korea	NCT01626677
Peripheral blood	autologous	Not defined	50	Malaysia	NCT01076673
Adipose tissue	autologous	I	18	France, Germany	NCT01585857
		I	15	Korea	NCT01624779
		I/II	30	Spain	NCT01399749
		I/II	18	Korea	NCT01300598
		I/II	8	Korea	NCT01643681
		I/II	15	Korea	NCT01643655
		I/II	15	Korea	NCT01769872
		II	40	Australia	ACTRN12611001046998
		II/III	60	Australia	ACTRN12611000274976
Not specified	allogeneic	II	60	India	NCT01453738
		II	72	Malaysia	NCT01448434

Table 2: Overview of publications focused on the stem cell therapy of cartilage diseases and osteoarthritis of the knee or hip

Source of stem cells	Type of stem cells	No. of patients	Improvement (method used)	Serious adverse events	Country	Reference
Bone marrow	autologous	24	Yes (arthroscopy, histology)	No	Japan	Wakitani *et al.*,2002
		2	Yes (arthroscopy)	No	Japan	Wakitani *et al.*, 2004
		3	Yes (arthroscopy, histology)	No	Japan	Wakitani *et al.*, 2007
		41	Not defined – study focused on safety	No	Japan	Wakitani *et al.*, 2011
		339	Yes (Likert scale, Functional Rating Index, Visual Analog scale, MRI)	No	U.S.A.	Centeno *et al.*, 2010, Centeno *et al.*, 2011
		5	Yes (Lysholm score, Revised Hospital for Special Surgery Knee score, MRI)	No	Egypt	Haleem *et al.*, 2010
		2	Yes (Knee and Osteoarthritis Outcome Score, International Knee Documentation Committee Score)	No	Thailand	Kasemkijwattana *et al.*, 2011
		72	Yes (Short-Form Health Survey)	No	Singapore	Nejadnik *et al.*, 2010
Peripheral blood – progenitor cells	autologous	5	Yes (arthroscopy, histology)	No	Malaysia	Saw *et al.*, 2011
Adipose and connective tissue	autologous	4	Yes (Visual Analog scale, Harris Hip Score, MRI)	No	South Korea	Pak *et al.*, 2012
		6	Yes (MRI)	No	Iran	Emadedin *et al.*, 2012
		13	Not defined – study focused on safety of stem cells application	1 patient - facial flushing, fever and myalgia	U.S., Panama	Rodriguez *et al.*, 2012
		25	Yes (Lysholm score, Tegner activity scale, Visual Analog scale)	No	South Korea	Koh *et al.*, 2012
		18	Yes (Western Ontario and McMaster Universities Osteoarthritis Index, Lysholm Score, Visual Analog scale, MRI)	No	South Korea	Koh *et al.*, 2013
		1128	Yes (KOOS/HOOS modified score, X-ray, MRI)	No	Czech Republic, USA, Slovakia, Lithuania	Michalek *et al.*, 2015

MRI – Magnetic Resonance Imaging

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