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The Current State of Clinical Cell Transplantation Trials in Iran: A Survey in 2011

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ABSTRACT

Context: Recently, stem cell research has gained great public interest and different cell-based clinical trials have started in Iran. The objective of this study was to provide an overview of clinical cell transplantation researches in Iran, which has assumed a leadership role in the Middle East.

Evidence Acquisitions: To evaluate the state of clinical cell transplantation researches in Iran, we conducted a literature review on December 1, 2011 using PubMed, IranMedex, US NIH registry for clinical trials and Iranian registry of clinical trials (IRCT).We used "Cell", "Cells", "Cell Transplantation", and "Iran" as keywords to identify stem cell related research articles or projects. Publications were then examined manually to exclude those that did not use stem cells in a clinical setting or did not report original research. Hard copy of all related articles were used to extract the following data: the year of publication, journal's name, number of authors, cell type, processing method, subject, and study design.

Results: Twenty one articles and 33 registered trials were related to clinical application of cellular products. Except for 6 articles, the others were multicenteral. The main subject of articles was cardiovascular diseases (23.52%) and for registered clinical trials this was osteoarticular disorders (24.24%). Bone marrow derived mesenchymal stem cells (BM-MSC) and mononuclear cells (BM-MNC) were the most frequent cell types in these trials. From 12 completed trials only 4 have been reported in medical journals.

Conclusions: By comparison with basic stem cell research, the current status of cell transplantation trials in Iran is not optimal. Joined multicenteral research, establishment of national regulations, sharing of facility and staff, international collaborations and bridging the gap between basic and clinical research may improve quality and quantity of clinical cell transplantation research in Iran.

Keywords: Clinical Trial; Stem Cells; Therapy; Transplantation

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Implication for health policy/practice/research/medical education:
This article is recommended for basic and clinical scientists interested in translational and clinical cell transplantation trials. It is also suggested for health authorities and regulatory bodies.

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1. Context

Cell-based therapies have grown dramatically in power and scope during the recent years. Once limited to blood and BM transplantation, these therapies now encompass tissue repair and regeneration, metabolic support, gene replacement, and immune effector functions, with established and investigational clinical applications in disorders affecting nearly every tissue (1). Transplantation activities in Iran started in 1935, when the first corneal transplantation was performed, followed by kidney (1968), bone marrow (1991), liver and heart (1993), lung (2000) and pancreas (2006) (2). Although, Hematopoietic Stem Cell Transplantation (HSCT)started in 1991, the history of novel cell-based therapies is less than 10 years (3, 4). Iran's government has actively promoted science and technology in an attempt to enhance the country's global status (5). In 2005, the Ministry of Health and Tehran University of Medical Sciences jointly developed a set of guidelines regarding research on gametes and embryos which permitted the use of human embryos for stem cell research and therapy under certain circumstances (6). Based on a recent report, stem cell clinical trials in the Middle East have more than quadrupled to over 400 registered clinical trials in January 2010. Countries such as Saudi Arabia and Qatar have founded nascent programs while Iran is more established in the field (7). In the recent decade, stem cell research has become one of the most important and dynamic fields of biomedical research. The annual number of articles devoted to stem cell research has increased by more than seven-folds during the last 16 years (8). Quantification of scientific productivity of a country can reflect its research status in a specific field and may affect the decision-making process by research policy makers (9, 10). Recently, two reports tried to describe the status of stem cell research in Iran (11, 12). One of them reported on the clinical aspect of stem cell research, focusing on NIH-registered clinical trials. This report only reflected part of the actual work in this field, because there are some other published trials that have not been registered in clinical trial registries. The intention of this paper is to provide an overview of registered and published clinical cell transplantation researches in Iran, which has assumed a leadership role in the Middle East. In the current study, cell preparation methods, GMP compliance and quality testing are reviewed.

2. Evidence Acquisitions

The authors conducted a literature review of publications on December 1, 2011 using PubMed (www.ncbi.nlm.nih.gov) as international and IranMedex (http://www.iranmedex.com) as a national database. To investigate the status of ongoing or unpublished researches, US NIH registry for clinical trials (http://www.clinicaltrials.gov) and Iranian registry of clinical trials (IRCT- http://www.irct.ir) were included. IranMedex is a local database, which consists of 231 journals and 72791 articles at the time of study. It covers all publications of Iranian biomedical journals registered and indexed in Iran's ministry of health. IRCT is a primary registry in the WHO Registry Network that has been set up with help from the Ministry of Health and Medical Education (MOHME) and is hosted by Tehran University of Medical Sciences (TUMS). We used "Cell", "Cells", "Cell Transplantation", and "Iran" as keywords to identify stem cell related research articles or clinical trials. Publications were then examined manually to exclude those that did not use stem cells in a clinical setting or did not report original research. HSCT for hematological disorders and malignancies were also excluded. Hard copies of all related articles were used to extract the following data: the year of publication, journal's name, number of authors, authors' affiliation, subject, cell type, cell processing method, and quality testing.

3. Results

The PubMed search resulted in 17 articles related to clinical cell transplantation. In IranMedex, only 4 articles were related to the research topic. The average number of authors per article was 8.90 and the average of affiliation was 3.90 per article. All authors were Iranian and only in 2 articles a foreign country was used as a second affiliation. Except for 6 articles, the others were multicenteral. The main subject of articles was cardiovascular disease (23.52%), followed by liver disease (17.64%), neurological disorders (17.64%), skin lesions (11.76%), oral pathologies (11.76%) and other conditions (17.64%) (*Table 1*). The most frequent cell types for these trials were BM-MSC (41.17%) and BM-MNC (17.64%) respectively. In 6 articles, the cell products had been manufactured in GMP facilities (i.e. a cleanroom) which were affiliated to the Brain and Spinal Injury Repair Research Center (TUMS) and the Royan institute. Autologous human serum had been used as a substitute for fetal bovine sera (FBS) for culturing Schwann cells and BM-MSCs in 3 articles. The country of origin for FBS was not identified in published articles. Microbiological studies should be performed routinely during different steps of cell manufacturing, however only 7 articles reported doing these tests. The most frequent cell transplant solution was normal saline supplemented with 1% human serum albumin. Other transplant solutions were: autologous serum, autologous plasma, medium 199 and melanocyte growth medium (MGM-M2). *Table 1* represents detailed informationabout the published articles in PubMed. From the 33 registered clinical trials, 8 were registered in the IRCT website and 25 in the US NIH registry (*Table 2*). The main condition was osteoarticular disorders (26.67%) followed by liver disease (16.67%), diabetes (13.33%), cardiovascular diseases (13.33%), skin lesions (13.33%), neurological disorders (10%), and other conditions (6.67%). In 2 trials, adult BM-MSCs and fetal hematopoietic stem cells were used as allograft transplants (NCT00515307 and IRCT138811071414N10). Differentiated

BM-MSCs were considered in 2 trials (NCT00515307 and IRCT201107221696N3). From 18 published trials, only 4 had been previously registered.

4. Conclusions

While cell-based therapies are the clinical standard of care for a few conditions, such as HSCT for hematological disorders and epithelial cell transplantation for burns

Table 1. PubMed Indexed Articles That are Related to Clinical Cell Transplantation (up to Dec 1, 2011)

Journal Name, y	No. Of Authors	1st Author	No. of Affiliations	Correspondence	Cell Type	Condition	No. of Cases	Citation	IF (2010)
Arch Iran Med, 2007	9	TUMS [1]	3	TUMS	BM-MSC	Liver disorder	4	83	0.87
Iran J Immunol, 2007	8	TUMS	4	TUMS	BM-MSC	Multiple Sclerosis	10	51	0.058
Arch Iran Med, 2007	16	TUMS	3	TUMS	BM-MSC	Myocardial Infarction	8	37	0.87
CurrNeurovasc Res, 2007	13	TUMS	2	Royan	CD 133+	Myocardial Infarction	18	33	3.047
World J Gastroenterol, 2007	9	TUMS	3	Royan	CD34+	liver disorder	4	70	2.24
NeurosciLett, 2008	9	TUMS	4	TUMS	Schwann Cell	Spinal cord injury	4	33	2.055
Oral Surg Oral Med [1], 2008	6	SBMU [2]	5	SBMU	BM-MSC	Sinus augmentation	6	41	N/A
Oral Surg Oral Med, 2009	7	SBMU	5	SBMU	BM-MSC	Alveolar cleft	2	10	N/A
Cytotherapy, 2010	13	TUMS	5	Royan	BM-MNC	limb ischemia	15	1	3.55
Arch Dermatol Res, 2010	7	Royan [3]	4	Royan	Epidermal	Viteligo	10	1	2.011
Cornea, 2010	10	SBMU	3	Royan	Limbal SC	Limbal cell deficiency	8	7	1.76
Cytotherapy, 2011	6	MUMS [4]	4	MUMS	BM –TNC [5]	Wound	8	2	3.55
Int J Rheum Dis, 2011	5	TUMS	2	TUMS	BM-MSC	Osteoartritis	4	3	0.205
Pediatr transplant, 2011	6	TUMS	2	TUMS	BM-MSC	Cardiomyopathy	1	2	1.873
Arch Iran Med, 2011	13	SUMS [6]	11	Royan	CD133+/ BM-MNC	Liver disorder	6	5	0.87
Cell tissue bank, 2011	11	TUMS	7	TUMS	Pancreatic Islets	Diabetes	2	0	1.157
J Neurosurg spine, 2011	9	TUMS	7	TUMS	Schwann Cell	Spinal cord injury	33	1	2.73

[1] Oral Surg Oral Med Oral Pathol Oral Radiol Endod
[2] Shahid Beheshti Medical University
[3] Royan Institute
[4] Mashhad University of Medical Sciences
[5] Bone Marrow Total Nucleated Cell
[6] Shiraz University of Medical Sciences

Table 2. Registered Clinical Trials (up to Dec 2011)

Registration Number, y	Status	Data Registry Website	Sponsor(s)	Cell type	Condition	Route of Administration	Phase	No. of Case	Study Design
NCT00476060, 2007	Unknown	US-NIH	TUMS	BM-MSC	Cirrhosis	Intravenous	II	36	R[1]/PA[2]/DB[3]
NCT00515307, 2007	Completed	US-NIH	TUMS	BM-MSC	Hyperchole-sterolemia	Portal vein	I	1	SGA[4]/OL[5]
NCT00550498, 2007	Completed	US-NIH	TUMS	BM-MSC	Behcet's Retinitis	In-vitreal	I	5	SGA/OL
NCT00420134, 2007	Completed	US-NIH	SBMU[6]-TMU[7]	BM-MSC	Cirrhosis	Portal vein	I/II	30	R/SGA/SB[8]
NCT00550524, 2007	Enrolling participant	US-NIH	TUMS	BM-MSC	Osteoartritis	Intra-articular	I	5	SGA/OL
NCT00631865, 2008	completed	US-NIH	Royan	Melanocyte	Vitiligo	Intra-epidermal	III	100	SGA/OL
NCT00677404, 2008	completed	US-NIH	TUMS-Royan	BM-MNC	lower limb ischemia	Intramuscular	I/II	20	SGA/OL
NCT00713934, 2008	completed	US-NIH	Royan, SUMS	BM-MNC/CD133+	Cirrhosis	Portal vein	I/II	7	R/PA/SB
NCT00736307, 2008	completed	US-NIH	Royan	Limbal Stem Cell	Limbal Stem Cell Defi-ciency	In site	I/II	10	SGA/OL
IRCT138804091267N19, 2009	Recruitment com-plete	IRCT	SBMU	BM-MSC	Diabetic nephropathy	Intravenous	I	10	SGA/OL
NCT00850187, 2009	completed	US-NIH	Royan-TUMS	BM-MSC	Osteoarthritis	Intra-articular	I	6	SGA/OL
IRCT138810271414N8, 2010	Recruitment com-plete	IRCT	TUMS	BM-MSC	Type1 Diabetes	intravenous	?	20	SGA/OL
IRCT138811071414N10, 2010	Recruitment com-plete	IRCT	TUMS	FHSC[9]	Type1 Diabetes	intravenous	?	18	SGA/OL
IRCT201008174586N1, 2010	Recruitment com-plete	IRCT	TUMS	BM-MNC	Diabetic foot	Intramuscular	?	20	R/PA/SB
IRCT138812133487N1, 2010	Recruitment com-plete	IRCT	IUMS[10]-Royan	Fibrocyte	Diabetic wounds	Dressing	I	20	SGA/DB
IRCT138902081159N2, 2010	Recruiting partici-pants	IRCT	IUMS	Fibroblasts	Atrophic scars	In site	?	20	R/PA/SB
IRCT138902113799N2, 2010	Recruitment com-plete	IRCT	TUMS	BM-MSC/CD133+	MI	Intra-myocardial	?	9	SGA/OL
IRCT138903131605N10, 2010	Recruitment com-plete	IRCT	SUMS	Epithelial cell	Hypopigmentation	In site	?	20	R/PA/OL
NCT01115634, 2010	completed	US-NIH	Royan	Fibroblast	Facial Deformities	In site	II/III	40	R/PA/DB
NCT01120925, 2010	Recruiting partici-pants	US-NIH	Royan -TUMS	BM-MNC/CD133+	Cirrhosis	Portal vein	I/II	30	R/PA/DB
NCT01187654, 2010	Recruiting partici-pants	US-NIH	Royan	BM-MNC/CD133+	MI	PCI[11]	II/III	100	R/PA/SB

NCT01167751, 2010	Recruiting participants	US-NIH	Royan	BM-MNC/CD133+	MI	Intra-myocardial	III	105	R/PA/SB
NCT01198080, 2010	Recruiting participants	US-NIH	Royan	CD133+	Osteonecrosis	In site	I	10	SGA/OL
NCT01206179, 2010	completed	US-NIH	Royan	BM-MSC	Non Union	In site	I	6	SGA/OL
NCT01207193, 2010	completed	US-NIH	Royan	BM-MSC	Bone cyst	In site	I	6	SGA/OL
NCT01207661, 2010	completed	US-NIH	Royan	BM-MSC	Osteoarthritis	Intra-articular	I	6	SGA/OL
NCT01210950, 2010	Recruiting participants	US-NIH	Royan	BM-MSC	Leg Length Inequality	callus center	I	6	SGA/OL
IRCT201107221696N3, 2011	Recruiting participants	IRCT	Shafa[12]	BM-MSC	ALS	Intra-spinal	II	20	SGA/OL
NCT01377870, 2011	Recruiting participants	US-NIH	Royan	BM-MSC	Multiple Sclerosis	Intravenous	I/II	30	R/DB
NCT01404663, 2011	Recruiting participants	US-NIH	Royan	CD133	Cerebral Palsy	Intrathecal	I	8	SGA/OL
NCT01436058, 2011	completed	US-NIH	Royan	BM-MSC	Osteoarthritis	Intra-articular	I	6	SGA/OL
NCT01454336, 2011	Recruiting participants	US-NIH	Royan-TUMS	BM-MSC	Liver Fibrosis	Portal vein	I	3	SGA/OL
NCT01480414, 2011	Recruiting participants	US-NIH	Royan	BM-MNC	Ischemic Ulcer	Intramuscular	I/II	10	R/PA/OL

[1] Randomized
[2] Double blind
[3] Parallel assignment
[4] Single group assignment
[5] Open label
[6] Shahid Beheshti Medical University
[7] Tarbiat Modares University
[8] Single blind
[9] Fetal Hematopoietic Stem Cell
[10] Isfahan University of Medical Sciences
[11] Percutaneous coronary intervention
[12] Shafa Neuroscience Research Center (Khatamol-Anbia Hospital)

and corneal disorders, many years of preclinical and clinical research will be required to bring novel stem-cell based therapies to the bedside (13). Recently, stem cell researches have found great public interest in Iran and different cell therapy projects have started in the country (4). The number of Iranian published papers in ISI scientific journals have dramatically increased from 15 papers in 2004 to 145 in 2011 (12). The current study revealed that despite rapid growth of basic stem cell research in Iran a small number of publications were related to their clinical applications. This may be due to many factors such as: complexity of cell manufacturing for clinical application, inappropriate facilities, insufficient human and financial recourses, safety concerns, lack of legislation and validated pre-clinical studies. The gap between basic scientists and clinicians is another obstacle in the way of clinical and translational stem cell research. To bridge this gap, we need someone with a medical background and basic science experience that is familiar with GMP rules and quality management system. In this model of collaboration the responsibility of each party has to be well defined and overlaps minimized. As seen in *Tables 1* and *2*, the most frequent cell type is BM-MSC. The safety and biological properties of MSC rapidly led to the investigation of their use in cell-based therapy by the middle of the 1990s. More than 260 clinical trials related to MSCs have been registered with the US NIH registry. Thus it is not surprising that these are the cells of interest in clinical trials (14). There are different protocols for isolation and expansion of BM-MSC in published trials, therefore, it is difficult to compare and contrast study outcomes. To address this problem, in 2006, the International Society for Cellular Therapy (ISCT) proposed minimal criteria to define human MSC for both laboratory-based scientific investigations and pre-clinical studies (15). In the current study, none of the published trials fulfilled these criteria for MSC characterization. Although these minimal criteria are intended for research purposes, it can be used to standardize different cell preparation protocols. Except for 3 articles, FBS have been used as serum supplements in culture protocols. When applicable, animal-derived reagents should be replaced by animal-free products. Human platelet lysate, autologous serum and pooled human serum have been suggested by different studies as alternatives to FBS (1, 16-19). Another animal derived reagent that has been applied for cell detachment is Trypsin. TrypLE (Invitrogen) and TrypZean (Sigma-aldrich) have been suggested as two animal origin-free alternatives for porcine Trypsin (20). We have successfully utilized TrypLE for dissociation of BM-MSC, Adipose tissue derived MSC and Schwann cell and recommend it for clinical grade cell preparation (unpublished data). If animal products cannot be replaced, they should be sourced in a controlled and documented manner and from animals bred and raised in captivity in countries or geographic regions that have appropriate national health status, disease prevention, and control systems (The United States Pharmacopeial Convention 2008). According to the current European law and FDA regulations, cell-based products should be manufactured under principles of GMP when they are used in phase I studies (21). Only 6 articles noted that cell preparations had been performed in a clean room facility. It should be considered that establishment and maintenance of a clean room is a complex procedure that needs technical expertise and considerable financial support. Therefore, collaboration with an existing GMP facility may be more cost-effective for centers with limited resources (22). The final cell product to be administered, as well as the production process and materials used, should be subjected to quality control testing. Based on FDA recommendation these tests include, but are not limited to, microbiological testing (including sterility, mycoplasma, and adventitious viral agent testing) to ensure safety and assessments of other product characteristics such as identity, purity (including endotoxin), viability, and potency (FDA: Guidance for Human Somatic Cell Therapy and Gene Therapy 1998). Only 7 articles reported performing microbiological testing for the final product and during processing. Endotoxin was tested just in one article for pancreatic islet transplants. In 2009, Iranian Deputy of Research and Technology - MOHME, announced that all clinical trials that are conducted in Iran should have registration with IRCT. Based on this regulation, unregistered trials cannot be published in Iranian biomedical journals and will not receive financial support. In addition, the member journals of the International Committee of Medical Journal Editors (ICMJE) require, as a condition of consideration for publication, registration in a public trials registry (http://www.icmje.org). In spite of these statements, only 4 articles have been registered in clinical trial registries. In this study, the average number of authors and affiliations per article were 8.90 and 3.90 respectively. Collaboration with a well-established laboratory may provide a mechanism for newer and less well-known researchers to network within the stem cell research community. It has been proposed that the number of authors on a paper increases the citation rate simply due to increased self-citation (7). Although there was not any international collaboration, most of the publications were multi-institutional. Prior studies on stem cell research in the Middle East suggest that international collaborations resulted in stem cell publications with a higher citation rate than articles published by a single nation from the region (23). Another research has established that articles with authors from multiple countries were cited twice as frequently as publications authored by scientists working at a single institution or within a single country. Although citation rate is not the best way to measure quality, but it is the simplest quantitative measure of publication quality that is used across disciplines and across national contexts (7); (*Table 1*). We also found that 64.70% of pub-

lished articles have been affiliated to TUMS (based on first author's affiliation). On the other hand, mostregistered clinical trials had been sponsored by the Royan institute and TUMS respectively. TUMS with the largest network of research in the medical sciences is now managing more than 90 research centers. According to formal national reports, more than one third of science production in Iran takes place in this university alone (http://publicrelations.tums.ac.ir). Royan Institute is a public non-profit organization established in 1991 as a research institute for reproductive biomedicine and infertility treatments. In 1998,the Ministry of Health approved this institute as a cell based research center and its cell therapy center was founded in 2009 (http://www.royaninstitute.org).

The present study describes the status of clinical cell transplantation research in Iran. The authors suggest that more comprehensive studies should be conducted to make a detailed map of stem cell research in this country. The growing trend towards stem cell research and transplantation in this country will open new horizons for treatment of incurable diseases. However, this raises safety and ethical concerns that necessitate strict supervision by regulatory agencies. To reduce these concerns, Iranian council of stem cell technology was established in 2008. Its main goal is the promotion of clinical and translational stem cell researches in order to improve public health. The authors suggest that this council should play an active role in regulation of cell therapies. This can be achieved by collaboration with other regulatory bodies (such as Food and Drug Organization) and preparation of national guidelines for clinical cell transplantation. Financial limitations and sanctions are the main barriers against stem cell research and therapy in Iran. Sanctions increase purchasing cost and time because they prevent the direct purchasing of materials and equipment from the main suppliers that are located in foreign countries. On the other hand, clinical grade cell manufacturing needs clinical grade reagents, specialized instruments, strict quality testing, and proper facilities (i.e. a cleanroom). Therefore, the primary costs of cell transplantation are higher than other conventional therapies. To perform a cost-effective procedure, stem cell research priorities should be set by research centers, paying attention to health system priorities. In conclusion, joined multicenter research, international collaborations, establishment of national regulations, well designed preclinical studies, adhering to international standards, sharing of facilities and staff, and bridging the gap between basic and clinical research may improve quality and quantity of clinical cell transplantation research in Iran.

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Authors' Contribution

Study concept and Idea: Aghayan HR, Larijani B. Literature review: Arjmand B, Heshmat R. Data acquisition and analysis: Heshmat R and Arjmand B. Drafting of the manuscript: Ajmand B, Aghayan HR, and Abbas Norouzi-Javidan. Critical revision of the manuscript: Soleimani M and Larijani B. Review of submitted manuscript: All authors. Final approval on behalf of all authors: Aghayan HR.

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