ORTHOPEDIC (OA & INJURIES)

1. ORTHOPEDIC (OA & INJURIES) PROTOCOL

A. Clinical Response: Patients may experience improvements in function and quality of life parameters. This could include improvements as measured by:

- Review of Medical History
- Review of Medication History
- Complete physical exam (including vital signs of sitting blood pressure, temperature, and heart rate)
- Serum or urine pregnancy test (for women of childbearing age)
- Visual Analog Scale
- Patient questionnaire
  - WOMAC for knee or hip
  - WOOS for shoulder
  - AOS for Ankle
- Laboratory determinations (urinalysis, hematology and biochemistry)

B. Objective: To provide the patient with a treatment that stimulates his / her immune system, promote cellular regeneration and improve symptoms associated with Orthopedic (OA & Injuries). The endovascular/intravenous Ad-SVF Containing Adult Stem Cell Procedure should serve to compliment the patient's current treatment regimen or to promote healing when current treatment is not responding.

2. PRELIMINARIES

A. Background: Osteoarthritis (OA) is a condition associated with failure of the diarthrodial joint. It is not a disease of only the cartilage but instead the synovial joint in which all the tissues are affected including: subchondral bone, synovium, meniscus, ligaments, and cartilage. OA is the most common joint disease in humans. According to Harrison's, over 1,000,000 people have impaired walking capabilities due to OA at hips or knees.

B. Causes of Orthopedic (OA & Injuries)**:** OA and other orthopedic injuries caused by some kind of trauma like:

- ***Synovitis***- inflammation of the synovial membrane
- ***Capsulitis***- inflammation of the fibrous joint capsule
- ***Articular cartilage and bone fracture***
- ***Ligament tears***
- ***Severe Injuries***

Osteoarthritis: Results from severe injuries or injuries not treated correctly and causes the progressive loss of cartilage. It is characterized by seeing a change in walking ability, reduced activity, decrease in mobility and visibly swollen joints [1]. Joint pain should be treated soon after it occurs to prevent the joint pain from worsening and converting into things like tears and later on arthritis [1].

C. Treatment Options: Current treatment emphasizes on reducing pain, maintaining mobility and minimizing disability. Regardless, there are no therapies available that have the potential of regenerating the affected tissue [3]

3. AD-SVF CONTAINING ADULT STEM CELLS TREATMENT OPTION

A. Ad-SVF Containing Adult Stem Cells Procedure

- ***Initial patient evaluation***: A physician reviews the medical information, lab work, and diagnostic imaging provided by the patient in order to determine the stage of the medical condition and any other secondary conditions.

- ***Pre-op Evaluation / post-op medical consultation***: A medical specialist to the specific condition to be treated provides a medical consultation at the location where the procedure will be performed. During pre-op evaluation informed consent is obtained from all patients and medical records are updated, including patient's most recent physical exam, most up-to-date lab results and imaging studies. Physician then performs surgical risk assessment.

- ***Harvesting of adipose tissue***: Adipose tissue acquisition can be summarized as three step process:

    - ***Application of anesthetic / injection of tumescent solution***

    - ***Waiting time***

    - ***Acquisition of adipose tissue:*** An area of the body with sufficient adipose tissue is selected; this is usually the periumbilical area. With the patient supine, the physician infiltrates a small amount of local anesthetic. A tissue sample is then obtained using 60 cc syringe(s) to aspirate 50 to 100 cc of adipose tissue. Immediately following lipo-aspiration, adipose tissue sample is processed (minimally manipulated) to separate stem cells for use as graft.

- ***Preparation of Platelet Rich Plasma (PRP)***: Using a standard phlebotomy technique the patient's own blood sample is obtained. After collection of whole blood, sample is centrifuged to obtain PRP aliquot. The regenerative potential of PRP is based on the release of growth factors / cytokines upon platelet rupture. PRP also enhances stem cell proliferation.

- ***Autologous implant of Ad-SVF***: The stem cells obtained from the adipose tissue sample and the PRP are applied to the patient using appropriate protocol for their condition. Autologous Ad-SVF containing adult stem cells suspended in PRP and injected intra-articular.

B. Risks: There are possibilities for unwanted effects related to the local anesthesia, harvesting procedure, and injection of stem cells. Even with the most established protocol, adequate technique, and careful administration; a medical team may encounter uncontrollable events. Although there is no guarantee of perfect results, excellent results can be attained. The surgeon provides services in the most responsible, professional and diligent manner, always considering that surgeries imply risks. The risks of complications of adipose tissue harvesting and stem cell infusion are very low. Possible risks include but are not limited to:

- Pain at site of injections
- Bleeding at injection site
- Malaise
- Low-grade fever
- Hot flashes
- Itching at injection site
- Vascular spasm or obstruction
- Bruising
- Nerve or muscle injury
- Allergic reaction
- Dizziness
- Nausea
- Vomiting

C. Benefits: Recent studies have focused on the use of adult stem cells for disorders such as osteoarthritis. Mesenchymal stem cells (MSCs) are non-hematopoietic, multipotent progenitor cells, which can be isolated from various human adult tissues. The potential to form cells of chondrogenic lineage has indicated the potential of these cells in cases of osteoarthritis [2]. In recent years, MSCs have been shown to possess broad range of regenerative capabilities, modulating disease progression repairing cartilage lesions so closely associated with osteoarthritis [1].

D. Follow-up plan:

- ***3 month after Ad-SVF implant:*** Patients will be seen by physician for evaluation including:
  - Patient Status
  - Review of Medical History
  - Review of Medication History
  - Complete physical exam (including vital signs of sitting blood pressure, temperature, and heart rate)
  - Visual Analog Scale
  - Patient questionnaire

- ***6 months after Ad-SVF implant:*** Patients will be seen by referring physician for evaluation including:
  - Patient Status
  - Review of Medical History
  - Review of Medication History
  - Complete physical exam (including vital signs of sitting blood pressure, temperature, and heart rate)
  - Visual Analog Scale
  - Patient questionnaire

ORTHOPEDIC – Physician Schedule of Events

	Baseline Evaluation and Data Review	**Study Intervention**	**Three month Follow-up**	**Six-month Follow-upError! Bookmark not defined.**
	Visit 1	***Visit 2***	***Visit 3***	***Visit 4***
Informed Consent	X			
Adverse Event Review/Status	X	X	X	X
Medical History Review	X		X	X
Medication History Review	X		X	X
Physical examination including vital signs	X	X	X	X
Pregnancy test[1]	X			
Laboratory determinations	X		X	X
Questionnaire	X		X	X
Visual Analogue Scale (VAS)	X		X	X
Liposuction and ASC isolation		X		
Adipose-derived stem cell implantation		X		

[1] For female patients of childbearing age.

ORTHOPEDIC – Adult Stem Cells Schedule of Events

1. **Initial Patient Evaluation:** A physician reviews the medical information, lab work, and diagnostic imaging provided by the patient in order to determine the stage of the medical condition and any other secondary conditions.

   A. Pre-Examination:
   - You will have a physical exam, which will include measuring your blood pressure, temperature and heart rate (vital signs).
   - Your doctor will discuss your medical history and any medications that you are taking.
   - Your doctor will assess how well you can perform your daily activities
   - If needed, you will have a urine or blood pregnancy test.
   - Blood will be taken.

   B. Additional Tests: should be done during or soon after this visit
   - Visual Analog Scale
   - Patient questionnaire:
     - WOMAC for knee or hip
     - WOOS for shoulder
     - AOS for Ankle
   - Laboratory determinations (urinalysis, hematology and biochemistry)
   - Provide liposuction instructions to the patient

   C. Review Results: After your doctor has reviewed the results of these tests, he or she will assess whether you are a good candidate for stem cell therapy. If you decide to obtain this therapy you will sign a consent form. A medical specialist to the specific condition to be treated provides a medical consultation at the location where the procedure will be performed. During pre-op evaluation informed consent is obtained from all patients and medical records are updated, including patient's most recent physical exam, most up-to-date lab results and imaging studies. Physician then performs surgical risk assessment.

1. **Pre-Operation / Stem Cell Procedure:**

   A. Two Weeks Before Procedure:

   - No Aspirin or medicines that contain aspirin or Ibuprofen since it interferes with normal blood clotting.
   - You may take Tylenol or generic forms of this drug.
   - Discuss with your primary physician to discontinue anticoagulant drugs at least 1 week before the procedure.
   - Please discontinue all herbal medications as many have side effects that could complicate a surgical procedure by inhibiting blood clotting, affecting blood pressure, or interfering with anesthetics.
   - Please discontinue all diet pills whether prescription, over-the-counter or herbal.

- NO SMOKING because nicotine reduces blood flow to the skin and can cause significant complications during healing.
- Purchase a compressive garment to wear after the lipoaspiration procedure.

B. Morning of the Procedure:

- Have a light breakfast.
- Take your regular prescribed medications
- Wear comfortable, loose-fitting clothes that do not have to be put on over your head.

2. Stem Cell Procedure:

A. Preparation & Harvesting of Adipose Tissue:

- ***Application of anesthetic / injection of tumescent solution***
- ***Waiting time (~15 – 20 minutes)***
- ***Acquisition of adipose tissue:*** An area of the body with sufficient adipose tissue is selected; this is usually the periumbilical area. With the patient supine, the physician infiltrates a small amount of local anesthetic. Immediately following lipo-aspiration, adipose tissue sample is processed (minimally manipulated) to separate stem cells for use as graft.

B. Autologous implant of Ad-SVF: To do the implant procedure, the cells are directly injected intra-articularly into the affected joint(s). You will be closely monitored throughout the procedure.

3. Recommended Post-Operation / Stem Cell Therapy Schedule:

A. Post-Op Medical Instruction - **(Please follow these instructions closely!)**

- ***Post-op medication*** will be given to you the day of your surgery. They will consist of an antibiotic and a painkiller:
  - *Antibiotic*: Cephalexin/Cipro, please take as directed beginning the day after surgery
  - *Painkiller:* Please take as directed and only as needed for pain

    * If you are unable to take any of these medications, please contact your patient coordinator so we can arrange for other medications.
- ***Resume previous medication*** as directed by the physician
- ***Report any symptoms of feeling unwell***: dizziness, changes in heart rate, pain, or fever. Patients should be seen promptly by an physician for full evaluation should any of the above symptoms be encountered.
- It is recommended that the ***patient have a companion stay with him or her*** for at least 24 hours after discharge.

- You should ***expect some of blood-tinged anesthetic solution to drain from the incision sites*** during the first 24 to 48 hours. This will vary from patient to patient. Maxi-pads are recommended for bandages over your incision sites. You may take a shower 24 hours after the procedure.
- ***Compressive garments should be worn*** 24 hours a day for the first week and 12 hours a day for the second week.
- ***Do not shower for the first 24 hours***. ***Do not submerge yourself in any water*** (i.e. taking a bath or swimming) for the 1st week.
- ***If you experience nausea or vomiting it is probably due to the medication***. Please try to take it with food. If it persists, please contact our office.
- ***Diet-meals are not restricted.***
- ***Drink plenty of clear fluids***. We recommend 8 glasses of water or fruit juice every day.
- ***Do not drink any alcohol*** for 48 hours and limit alcohol intake for the first week.

B. <u>Post-Op Medical Consultation Schedule: 3 months & 6 months</u>

- Patient Status
- Review of Medical History
- Review of Medication History
- Complete physical exam (including vital signs of sitting blood pressure, temperature, and heart rate)
- Visual Analog Scale
- Patient questionnaire

Your doctor will contact you by phone within the first week to follow up then future follow up visits will be arranged through your patient coordinator. If you need assistance before do not hesitate to contact us.

ORTHOPEDIC – Supporting Studies

J Biomed Mater Res A. 2013 Jul 27. doi: 10.1002/jbm.a.34896. [Epub ahead of print]

Adipose-derived mesenchymal stem cells for cartilage tissue engineering: State-of-the-art in in vivo studies.

Veronesi F, Maglio M, Tschon M, Aldini NN, Fini M.

Source
Laboratory of Preclinical and Surgical Studies, Rizzoli Orthopaedic Institute (IOR), 40136, Bologna, Italy.

Abstract
Several therapeutic approaches have been developed to address hyaline cartilage regeneration, but to date, there is no universal procedure to promote the restoration of mechanical and functional properties of native cartilage, which is one of the most important challenges in orthopedic surgery. For cartilage tissue engineering, adult mesenchymal stem cells (MSCs) are considered as an alternative cell source to chondrocytes. Since little is known about adipose-derived mesenchymal stem cell (ADSC) cartilage regeneration potential, the aim of this review was to give an overview of in vivo studies about the chondrogenic potential and regeneration ability of culture-expanded ADSCs when implanted in heterotopic sites or in osteoarthritic and osteochondral defects. The review compares the different studies in terms of number of implanted cells and animals, cell harvesting sites, in vitro expansion and chondrogenic induction conditions, length of experimental time, defect dimensions, used scaffolds and post-explant analyses of the cartilage regeneration. Despite variability of the in vivo protocols, it seems that good cartilage formation and regeneration were obtained with chondrogenically predifferentiated ADSCs (1 × 107 cells for heterotopic cartilage formation and 1 × 106 cells/scaffold for cartilage defect regeneration) and polymeric scaffolds, even if many other aspects need to be clarified in future studies. © 2013 Wiley Periodicals, Inc. J Biomed Mater Res Part A, 2013.

ORTHOPEDIC – Supporting Studies

Knee Surg Sports Traumatol Arthrosc. 2013 Dec 11. [Epub ahead of print]

Clinical results and second-look arthroscopic findings after treatment with adipose-derived stem cells for knee osteoarthritis.

Koh YG, Choi YJ, Kwon SK, Kim YS, Yeo JE.

Abstract
PURPOSE:
In the present study, the clinical outcomes and second-look arthroscopic findings of intra-articular injection of stem cells with arthroscopic lavage for treatment of elderly patients with knee osteoarthritis (OA) were evaluated.

METHODS:
Stem cell injections combined with arthroscopic lavage were administered to 30 elderly patients (≥65 years) with knee OA. Subcutaneous adipose tissue was harvested from both buttocks by liposuction. After stromal vascular fractions were isolated, a mean of 4.04 × 106 stem cells (9.7 % of 4.16 × 107 stromal vascular fraction cells) were prepared and injected in the selected knees of patients after arthroscopic lavage. Outcome measures included the Knee Injury and Osteoarthritis Outcome Scores, visual analog scale, and Lysholm score at preoperative and 3-, 12-, and 2-year follow-up visits. Sixteen patients underwent second-look arthroscopy.

RESULTS:
Almost all patients showed significant improvement in all clinical outcomes at the final follow-up examination. All clinical results significantly improved at 2-year follow-up compared to 12-month follow-up ($P < 0.05$). Among elderly patients aged >65 years, only five patients demonstrated worsening of Kellgren-Lawrence grade. On second-look arthroscopy, 87.5 % of elderly patients (14/16) improved or maintained cartilage status at least 2 years postoperatively. Moreover, none of the patients underwent total knee arthroplasty during this 2-year period.

CONCLUSION:
Adipose-derived stem cell therapy for elderly patients with knee OA was effective in cartilage healing, reducing pain, and improving function. Therefore, adipose-derived stem cell treatment appears to be a good option for OA treatment in elderly patients.
LEVEL OF EVIDENCE:

Therapeutic case series study, Level IV.

PMID: 24326779 [PubMed - as supplied by publisher]

ORTHOPEDIC – Supporting Studies

J Shoulder Elbow Surg. 2012 Feb;21(2):278-94. doi: 10.1016/j.jse.2011.11.015.

Cell- and gene-based approaches to tendon regeneration.

Nixon AJ, Watts AE, Schnabel LV.

Source
Comparative Orthopaedics Laboratory, College of Veterinary Medicine, Cornell University, Ithaca, New York 14853, USA. ajn1@cornell.edu

Abstract
Repair of rotator cuff tears in experimental models has been significantly improved by the use of enhanced biologic approaches, including platelet-rich plasma, bone marrow aspirate, growth factor supplements, and cell- and gene-modified cell therapy. Despite added complexity, cell-based therapies form an important part of enhanced repair, and combinations of carrier vehicles, growth factors, and implanted cells provide the best opportunity for robust repair. Bone marrow-derived mesenchymal stem cells provide a stimulus for repair in flexor tendons, but application in rotator cuff repair has not shown universally positive results. The use of scaffolds such as platelet-rich plasma, fibrin, and synthetic vehicles and the use of gene priming for stem cell differentiation and local anabolic and anti-inflammatory impact have both provided essential components for enhanced tendon and tendon-to-bone repair in rotator cuff disruption. Application of these research techniques in human rotator cuff injury has generally been limited to autologous platelet-rich plasma, bone marrow concentrate, or bone marrow aspirates combined with scaffold materials. Cultured mesenchymal progenitor therapy and gene-enhanced function have not yet reached clinical trials in humans. Research in several animal species indicates that the concept of gene-primed stem cells, particularly embryonic stem cells, combined with effective culture conditions, transduction with long-term integrating vectors carrying anabolic growth factors, and development of cells conditioned by use of RNA interference gene therapy to resist matrix metalloproteinase degradation, may constitute potential advances in rotator cuff repair. This review summarizes cell- and gene-enhanced cell research for tendon repair and provides future directions for rotator cuff repair using biologic composites.

PMID: 22244071 [PubMed - indexed for MEDLINE]

ORTHOPEDIC – Supporting Studies

Biochem Biophys Res Commun. 2013 Nov 1;440(4):786-91. doi: 10.1016/j.bbrc.2013.10.012. Epub 2013 Oct 14.

Chondrogenic potential of stem cells derived from adipose tissue: A powerful pharmacological tool.

Roux C, Pisani DF, Yahia HB, Djedaini M, Beranger GE, Chambard JC, Ambrosetti D, Michiels JF, Breuil V, Ailhaud G, Euller-Ziegler L, Amri EZ.

Source
University Nice Sophia Antipolis, iBV, UMR 7277, 06100 Nice, France; CNRS, iBV, UMR 7277, 06100 Nice, France; Inserm, iBV, U1091, 06100 Nice, France; Service de Rhumatologie, Hospital l'Archet 1 CHU, 06200 Nice, France.

Abstract
Chondrogenesis has been widely investigated in vitro using bone marrow-derived mesenchymal stromal cells (BM-MSCs) or primary chondrocytes. However, their use raises some issues partially circumvented by the availability of Adipose tissue-derived MSCs. Herein; we characterized the chondrogenic potential of human Multipotent Adipose-Derived Stem (hMADS) cells, and their potential use as pharmacological tool. hMADS cells are able to synthesize matrix proteins including COMP, Aggrecan and type II Collagen. Furthermore, hMADS cells express BMP receptors in a similar manner to BM-MSC, and BMP6 treatment of differentiated cells prevents expression of the hypertrophic marker type X Collagen. We tested whether IL-1β and nicotine could impact chondrocyte differentiation. As expected, IL-1β induced ADAMTS-4 gene expression and modulated negatively chondrogenesis while these effects were reverted in the presence of the IL-1 receptor antagonist. Nicotine, at concentrations similar to those observed in blood of smokers, exhibited a dose dependent increase of Aggrecan expression, suggesting an unexpected protective effect of the drug under these conditions. Therefore, hMADS cells represent a valuable tool for the analysis of in vitro chondrocyte differentiation and to screen for potentially interesting pharmacological drugs.

KEYWORDS:

Chondrocyte, Differentiation, hBM-MSC, hMADS

PMID: 24134848 [PubMed - in process]

ORTHOPEDIC – Supporting Studies

See 1 citation found by title matching your search:
BMC Vet Res. 2013 Jul 2;9:131. doi: 10.1186/1746-6148-9-131.

Controlled, blinded force platform analysis of the effect of intraarticular injection of autologous adipose-derived mesenchymal stem cells associated to PRGF-Endoret in osteoarthritic dogs.

Vilar JM, Morales M, Santana A, Spinella G, Rubio M, Cuervo B, Cugat R, Carrillo JM.

Source
Department of Animal Pathology, Faculty of Veterinary Medicine, Universidad de Las Palmas de Gran Canaria, Trasmontaña S/N, Arucas 35413 Las Palmas, Spain. jvilar@dpat.ulpgc.es

Abstract
BACKGROUND:
Adipose-derived mesenchymal stem cell (ADMSC) therapy in regenerative medicine is a rapidly growing area of research and is currently also being used to treat osteoarthritis (OA). Force platform analysis has been consistently used to verify the efficacy of different therapeutic strategies for the treatment of OA in dogs, but never with AD-MSC.The aim of this study was to use a force platform to measure the efficacy of intraarticular ADMSC administration for limb function improvement in dogs with severe OA.

RESULTS:
Eight lame dogs with severe hip OA and a control group of 5 sound dogs were used for this study. Results were statistically analyzed to detect a significant increase in peak vertical force (PVF) and vertical impulse (VI) in treated dogs. Mean values of PVF and VI were significantly improved after treatment of the OA groups, reaching 53.02% and 14.84% of body weight, respectively, at day 180, compared with only 43.56% and 12.16% at day 0.

CONCLUSION:
This study objectively demonstrated that intraarticular ADMSC therapy resulted in reduced lameness due to OA.

PMID: 23819757 [PubMed - in process] PMCID: PMC3716942

ORTHOPEDIC – Supporting Studies

Z Orthop Unfall. 2012 Jun;150(3):280-9. doi: 10.1055/s-0031-1298387. Epub 2012 Jun 21.

[Evidence-based therapy for cartilage lesions in the knee - regenerative treatment options].

[Article in German]
Proffen B, von Keudell A, Vavken P.

Source
Department of Orthopedic Surgery, Children's Hospital Boston, Massachusetts, United States.

Abstract
BACKGROUND:
The treatment of cartilage defects has seen a shift from replacement to regeneration in the last few years. The rationale behind this development is the improvement in the quality-of-care for the growing segment of young patients who are prone to arthroplasty complications because of their specific characteristics - young age, high level of activity, high demand for functionality. These days, two of the most popular regenerative treatments are microfracture and autologous chondrocyte implantation (ACI). Although these new options show promising results, no final algorithm for the treatment of cartilage lesions has been established as yet.

MATERIALS AND METHODS:
The objective of this review is to describe and compare these two treatment options and to present an evidence-based treatment algorithm for focal cartilage defects.

RESULTS:
Microfracture is a cost-effective, arthroscopic one-stage procedure, in which by drilling of the subchondral plate, mesenchymal stem cells from the bone marrow migrate into the defect and rebuild the cartilage. ACI is a two-stage procedure in which first chondrocytes are harvested, expanded in cell culture and in a second open procedure reimplanted into the cartilage defect. Microfracture is usually used for focal cartilage defects < 4 cm2, the treated defect size of the ACI seems to have a wider range. The effectiveness of these two treatments has been shown in long-term longitudinal studies, where microfracture showed improvement in up to 95 % of patients, whereas 92 % of the patients in a 2-9 year period of follow-up after ACI showed improvements, respectively. The successful outcome of the treatment depends on multiple factors such as the location of the defect, cell differentiation and proliferation, concomitant problems, and the age of the patient. Associated complications and disadvantages of the two different applications are, for the microfracture patient, a poor tissue differentation or a formation of an intra-lesional osteophyte, and for the ACI patient, periosteal hypertrophy and the need for two procedures in ACI. Only a few studies provide detailed and evidence-based information on a comparative assessment. These studies, however, are showing widely similar clinical outcomes but better histological results for ACI, which are likely to translate into better long-term outcomes.

CONCLUSIONS:
Although evidence-based studies comparing microfracture and ACI have not found significant differences in the clinical outcome, the literature does show that choosing the treatment based on the size and characteristics of the osteochondral lesion might be beneficial. The American Association of Orthopedic Surgeons suggest that contained lesions < 4 cm2 should be treated by microfracture, lesions bigger than that by ACI.

Georg Thieme Verlag KG Stuttgart · New York.

PMID: 22723070 [PubMed - indexed for MEDLINE]

ORTHOPEDIC – Supporting Studies

Curr Stem Cell Res Ther. 2012 Sep;7(5):319-28.

Isolation and phenotypic characterisation of stem cells from late stage osteoarthritic mesenchymal tissues.

Labusca L, Zugun-Eloae F, Shaw G, Botez P, Barry F, Mashayekhi K.

Source
Systems Bioinformatics and Modelling GMBH, Frankfurt, Germany. drlluminita@yahoo.com

Abstract
INTRODUCTION:
Osteoarthritis (OA) represents an increasing health issue worldwide. Regenerative medicine (RM) has raised the hope for introducing revolutionary therapies in clinical practice. Detection of autologus cell sources can improve accessibility to RM strategies.

OBJECTIVES:
To assess the presence and biological potential of mesehchymal stem cells in three tissues (subchondral bone, synovial layer, periarticular adipose tissue) in late stages osteoarthritic patients.

MATERIAL AND METHODS:
Samples were collected from subjects undergoing total knee replacement (TKR). MSCs were isolated and cultured in complete αMEM with β FGF. Cell morphology and growth potential was assessed. Flow cytometry was used for detection of several relevant cell surface markers. Quantitative and qualitative assessment of differentiation potential towards three mesenchymal lineages (osteogenesis adipogenesis chondrogenesis) was performed. Time lapse life cell imaging of nondiferentiated cells over 24 hours period was used to determine cell kinetics.

RESULTS:
Mesenchymal cells derived from all donors and tissue types showed morphology, growth and surface cell markers associated with stemness. All cell types underwent differentiation toward three mesenchymal lineages with significant differences between tissues of origin, not between donors. Cell kinetics, as derived from life imaging records, was variable with tissue of origin, significant higher for adipose derived MSCS.

CONCLUSION:
Human late stage OA mesenchymal tissues, contain progenitors with proliferative and differentiation potential of MSCs. These populations can be used for research and autologus regenerative therapies. Further comparative studies with age matched non OA samples has the potential of contributing to deepening knowledge about disease occurrence and progression.

PMID: 22480416 [PubMed - indexed for MEDLINE]

ORTHOPEDIC – Supporting Studies

Science. 2013 Aug 30;341(6149):1240104. doi: 10.1126/science.1240104.

Nuclear lamin-A scales with tissue stiffness and enhances matrix-directed differentiation.

Swift J, Ivanovska IL, Buxboim A, Harada T, Dingal PC, Pinter J, Pajerowski JD, Spinler KR, Shin JW, Tewari M, Rehfeldt F, Speicher DW, Discher DE.

Source
Molecular and Cell Biophysics Laboratory, University of Pennsylvania, Philadelphia, PA 19104, USA.

Abstract
Tissues can be soft like fat, which bears little stress, or stiff like bone, which sustains high stress, but whether there is a systematic relationship between tissue mechanics and differentiation is unknown. Here, proteomics analyses revealed that levels of the nucleoskeletal protein lamin-A scaled with tissue elasticity, E, as did levels of collagens in the extracellular matrix that determine E. Stem cell differentiation into fat on soft matrix was enhanced by low lamin-A levels, whereas differentiation into bone on stiff matrix was enhanced by high lamin-A levels. Matrix stiffness directly influenced lamin-A protein levels, and, although lamin-A transcription was regulated by the vitamin A/retinoic acid (RA) pathway with broad roles in development, nuclear entry of RA receptors was modulated by lamin-A protein. Tissue stiffness and stress thus increase lamin-A levels, which stabilize the nucleus while also contributing to lineage determination.
Comment in

Mechanotransduction: Lamin A for tension relief. [Nat Rev Mol Cell Biol. 2013]

Cell biology. Strength under tension. [Science. 2013]

ORTHOPEDIC – Supporting Studies

Rheumatology (Oxford). 2012 Oct;51(10):1757-64. Epub 2012 Jun 19.

Intra-articular adipose-derived mesenchymal stem cells from rheumatoid arthritis patients maintain the function of chondrogenic differentiation.

Skalska U, Kontny E, Prochorec-Sobieszek M, Maśliński W.

Source
Department of Immunology and Pathophysiology, Institute ofRheumatology, Warsaw, Poland. urszula.skalska@ir.ids.pl

Abstract
OBJECTIVES:
To evaluate the chondrogenic potential, phenotype and percentage of IA adipose-derived mesenchymal stem cells (ADSCs) from RA patients in comparison with OA patients. The effect of TNF treatment on ADSC differentiation was also examined.

METHODS:
Adipose tissue was obtained from RA and OA patients. ADSCs were isolated and cultured until passage 4. After that period, the phenotype and percentage of these cells were analysed by flow cytometry. Passage 4 cells were cultured in chondrogenic medium with or without TNF. After 3 weeks of differentiation the expression of Sox9, aggrecan (Acan) and collagen 2a (Col2a) mRNA was assessed by RT-PCR and GAG deposition by alcian blue staining.

RESULTS:
The phenotype and percentage of ADSCs were similar in both RA and OA. The results of alcian blue staining showed effective chondrogenesis in RA and OA ADSCs. TNF inhibited GAG deposition in both RA and OA samples similarly. Sox9, Acan and Col2a mRNA expression was significantly increased in chondrogenic-medium-treated cells ($P<0.05$) and decreased after TNF exposure ($P<0.01$). No statistically significant differences between RA and OA were observed.

CONCLUSION:
ADSCs from RA and OA patients are similar with regard to their phenotype, percentage in IA tissue and chondrogenic potential, which is reduced after exposure to TNF.

PMID: 22718867 [PubMed - indexed for MEDLINE]

ORTHOPEDIC – Supporting Studies

Arthritis Rheum. 2003 Dec;48(12):3464-74.

Stem cell therapy in a caprine model of osteoarthritis.

Murphy JM, Fink DJ, Hunziker EB, Barry FP.

Source
Osiris Therapeutics, Baltimore, Maryland 21231, USA.

Abstract
OBJECTIVE:
To explore the role that implanted mesenchymal stem cells may play in tissue repair or regeneration of the injured joint, by delivery of an autologous preparation of stem cells to caprine knee joints following induction of osteoarthritis (OA).

METHODS:
Adult stem cells were isolated from caprine bone marrow, expanded in culture, and transduced to express green fluorescent protein. OA was induced unilaterally in the knee joint of donor animals by complete excision of the medial meniscus and resection of the anterior cruciate ligament. After 6 weeks, a single dose of 10 million autologous cells suspended in a dilute solution of sodium hyaluronan was delivered to the injured knee by direct intraarticular injection. Control animals received sodium hyaluronan alone.

RESULTS:
In cell-treated joints, there was evidence of marked regeneration of the medial meniscus, and implanted cells were detected in the newly formed tissue. Degeneration of the articular cartilage, osteophytic remodeling, and subchondral sclerosis were reduced in cell-treated joints compared with joints treated with vehicle alone without cells. There was no evidence of repair of the ligament in any of the joints.

CONCLUSION:
Local delivery of adult mesenchymal stem cells to injured joints stimulates regeneration of meniscal tissue and retards the progressive destruction normally seen in this model of OA.

PMID: 14673997 [PubMed - indexed for MEDLINE]

ORTHOPEDIC – Supporting Studies

Stem Cell Res Ther. 2012 Feb 22;3(1):7. doi: 10.1186/scrt98.

Stem cell- and growth factor-based regenerative therapies for avascular necrosis of the femoral head.

Rackwitz L, Eden L, Reppenhagen S, Reichert JC, Jakob F, Walles H, Pullig O, Tuan RS, Rudert M, Nöth U.

Source
Orthopaedic Center for Musculoskeletal Research, Department of Orthopaedic Surgery König-Ludwig-Haus, Julius-Maximilians-University Würzburg, Brettreichstrasse 11, 97074 Würzburg, Germany.

Abstract
Avascular necrosis (AVN) of the femoral head is a debilitating disease of multifactorial genesis, predominately affects young patients, and often leads to the development of secondary osteoarthritis. The evolving field of regenerative medicine offers promising treatment strategies using cells, biomaterial scaffolds, and bioactive factors, which might improve clinical outcome. Early stages of AVN with preserved structural integrity of the subchondral plate are accessible to retrograde surgical procedures, such as core decompression to reduce the intraosseous pressure and to induce bone remodeling. The additive application of concentrated bone marrow aspirates, ex vivo expanded mesenchymal stem cells, and osteogenic or angiogenic growth factors (or both) holds great potential to improve bone regeneration. In contrast, advanced stages of AVN with collapsed subchondral bone require an osteochondral reconstruction to preserve the physiological joint function. Analogously to strategies for osteochondral reconstruction in the knee, anterograde surgical techniques, such as osteochondral transplantation (mosaicplasty), matrix-based autologous chondrocyte implantation, or the use of acellular scaffolds alone, might preserve joint function and reduce the need for hip replacement. This review summarizes recent experimental accomplishments and initial clinical findings in the field of regenerative medicine which apply cells, growth factors, and matrices to address the clinical problem of AVN.

PMID: 22356811 [PubMed - indexed for MEDLINE] PMCID: PMC3340551

ORTHOPEDIC – Supporting Studies

Mol Biol Rep. 2012 May;39(5):5683-9. doi: 10.1007/s11033-011-1376-z. Epub 2011 Dec 20.

Mesenchymal stem cell-based treatment for cartilage defects in osteoarthritis.

Qi Y, Feng G, Yan W.

Source
Department of Orthopedic Surgery, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, 310009, China.

Abstract
Osteoarthritis (OA) is a common disorder and the restoration of the diseased articular cartilage in patients with OA is still a challenge for researchers and clinicians. Currently, a variety of experimental strategies have investigated whether mesenchymal stem cells (MSCs) instead of chondrocytes can be used for the regeneration and maintenance of articular cartilage in OA. MSCs can modulate the immune response of individuals and positively influence the microenvironment of the stem cells already present in the diseased tissue. Through direct cell-cell interaction or the secretion of various factors, MSCs can initiate endogenous regenerative activities in the OA joint. Targeted gene-modified MSC-based therapy might further enhance the cartilage regeneration in OA. Conventionally, delivery of MSCs was attained by graft of engineered constructs derived from cell-seeded scaffolds. However, intra-articular MSCs transplantation without scaffolds is a more attractive option for OA treatment. This article briefly summarizes the current knowledge about MSC-based therapy for prevention or treatment of OA, discussing the direct intra-articular injection of MSCs for the treatment of OA in animal models and in clinical applications, as well as potential future strategies for OA treatment.

PMID: 22183306 [PubMed - indexed for MEDLINE]

ORTHOPEDIC – Supporting Studies

Med Hypotheses. 2012 Sep;79(3):420-1. doi: 10.1016/j.mehy.2012.05.024. Epub 2012 Jun 1.

Mesenchymal stem cell sheet encapsulated cartilage debris provides great potential for cartilage defects repair in osteoarthritis.

Qi Y, Yan W.

Abstract
The restoration of the degenerated articular cartilage in patients with osteoarthritis (OA) is still a challenge for researchers and clinicians. Drug interventions and surgical treatments have been widely attempted for cartilage regeneration in OA. However, the results were largely unsatisfactory. Autologous chondrocyte implantation (ACI) or matrix-induced autologous chondrocyte implantation (MACI) offers potential for the regeneration of cartilage over the long-term. However, due to the limitations and disadvantages of ACI, alternative therapies for cartilage regeneration are in need. The availability of large quantities of mesenchymal stem cells (MSCs) and the multilineage differentiation, especially their chondrogenic differentiation property, have made MSCs the most promising cell source for cartilage regeneration. In addition, MSCs have been shown the ability to undergo site-specific differentiation. MSCs can be obtained as MSC sheets using the temperature-responsive culture dish method. The MSC sheet can provide amounts of cells and extracellular matrix, which might provide the continuity between the implant and host cartilage, thus improving integrative cartilage repair. Moreover, OA is associated with progressive and often severe inflammation. MSCs not only have the ability to contribute structurally to tissue repair, but also possess potent immunomodulatory and anti-inflammatory effects. Taken together, these properties make MSC sheet promising candidate for cartilage repair in OA. We hypothesize that MSC sheet encapsulated cartilage debris can efficiently promote cartilage repair in OA patients. Chondrocytes can be obtained and cultured from small cartilage debris in vitro. Therefore, the chondrocytes may grow from the debris in cartilage defect and improve cartilage regeneration. MSC sheet provide amounts of cells, ECM and protein for cartilage regeneration and integration, and may play some roles of periosteum. The operation of MSC sheet encapsulated cartilage debris for cartilage repair is simple and practical. Moreover, the cell sheet/cartilage debris constructs can be easily shaped based on the size and shape of cartilage defects. The new method might have great potential in treating cartilage defects clinically, especially for OA patients.

PMID: 22658361 [PubMed - indexed for MEDLINE]

ORTHOPEDIC – Supporting Studies

Arch Iran Med. 2012 Jul;15(7):422-8. doi: 012157/AIM.0010.

Intra-articular injection of autologous mesenchymal stem cells in six patients with knee osteoarthritis.

Emadedin M, Aghdami N, Taghiyar L, Fazeli R, Moghadasali R, Jahangir S, Farjad R, Baghaban Eslaminejad M.

Source
Department of Regenerative Biomedicine and Cell Therapy, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran.

Abstract
BACKGROUND:
Osteoarthritis (OA) is a progressive disorder of the joints caused by gradual loss of articular cartilage, which naturally possesses a limited regenerative capacity. In the present study, the potential of intra-articular injection of mesenchymal stem cells (MSCs) has been evaluated in six osteoarthritic patients.

METHODS:
Six female volunteers, average age of 54.56 years, with radiologic evidence of knee OA that required joint replacement surgery were selected for this study. About 50 ml bone marrow was aspirated from each patient and taken to the cell laboratory, where MSCs were isolated and characterized in terms of some surface markers. About 20-24 × 10(6) passaged-2 cells were prepared and tested for microbial contamination prior to intra-articular injection.

RESULTS:
During a one-year follow-up period, we found no local or systemic adverse events. All patients were partly satisfied with the results of the study. Pain, functional status of the knee, and walking distance tended to be improved up to six months post-injection, after which pain appeared to be slightly increased and patients' walking abilities slightly decreased. Comparison of magnetic resonance images (MRI) at baseline and six months post-stem cell injection displayed an increase in cartilage thickness, extension of the repair tissue over the subchondral bone and a considerable decrease in the size of edematous subchondral patches in three out of six patients.

CONCLUSION:
The results indicated satisfactory effects of intra-articular injection of MSCs in patients with knee OA.

PMID: 22724879 [PubMed - indexed for MEDLINE]

ORTHOPEDIC – Supporting Studies

Cells Tissues Organs. 2012;196(3):231-40. doi: 10.1159/000334400. Epub 2012 Mar 20.

Differences in surface marker expression and chondrogenic potential among various tissue-derived mesenchymal cells from elderly patients with osteoarthritis.

Alegre-Aguarón E, Desportes P, García-Álvarez F, Castiella T, Larrad L, Martínez-Lorenzo MJ.
Source

Instituto Aragonés de Ciencias de la Salud, Zaragoza, España.
Abstract

Mesenchymal stem cells (MSCs) are self-renewing, multipotent cells that could potentially be used to repair injured cartilage in diseases such as osteoarthritis (OA). In this study we used bone marrow, adipose tissue from articular and subcutaneous locations, and synovial fluid samples from 18 patients with knee OA to find a suitable alternative source for the isolation of MSCs with high chondrogenic potential. MSCs from all tissues analysed had a fibroblastic morphology, but their rates of proliferation varied. Subcutaneous fat-derived MSCs proliferated faster than bone marrow- and Hoffa's fat pad-derived MSCs, while synovial fluid-derived MSCs grew more slowly. CD36 and CD54 expression was similar across all groups of MSCs with several minor differences. High expression of these surface markers in subcutaneous fat-derived MSCs was correlated with poor differentiation into hyaline cartilage. Synovial fluid-derived MSCs presented a relatively small chondrogenic differentiation capacity while Hoffa's fat pad-derived MSCs had strong chondrogenic potential. In conclusion, MSCs from elderly patients with OA may still display significant chondrogenic potential, depending on their origin.

PMID: 22947769 [PubMed - indexed for MEDLINE]

ORTHOPEDIC – Supporting Studies

Arthroscopy. 2013 Apr;29(4):748-55. doi: 10.1016/j.arthro.2012.11.017. Epub 2013 Jan 29.

Mesenchymal stem cell injections improve symptoms of knee osteoarthritis.

Koh YG, Jo SB, Kwon OR, Suh DS, Lee SW, Park SH, Choi YJ.

Source
Center for Stem Cell & Arthritis Research, Department of Orthopedic Surgery, Yonsei Sarang Hospital, Seoul, South Korea.

Abstract
PURPOSE:
The purpose of this study was to evaluate the clinical and imaging results of patients who received intra-articular injections of autologous mesenchymal stem cells for the treatment of knee osteoarthritis.

METHODS:
The study group comprised 18 patients (6 men and 12 women), among whom the mean age was 54.6 years (range, 41 to 69 years). In each patient the adipose synovium was harvested from the inner side of the infrapatellar fat pad by skin incision extension at the arthroscopic lateral portal site after the patient underwent arthroscopic debridement. After stem cells were isolated, a mean of 1.18 × 10(6) stem cells (range, 0.3 × 10(6) to 2.7 × 10(6) stem cells) were prepared with approximately 3.0 mL of platelet-rich plasma (with a mean of 1.28 × 10(6) platelets per microliter) and injected into the selected knees of patients. Clinical outcome was evaluated with the Western Ontario and McMaster Universities Osteoarthritis Index, the Lysholm score, and the visual analog scale (VAS) for grading knee pain. We also compared magnetic resonance imaging (MRI) data collected both preoperatively and at the final follow-up.

RESULTS:
Western Ontario and McMaster Universities Osteoarthritis Index scores decreased significantly ($P < .001$) from 49.9 points preoperatively to 30.3 points at the final follow-up (mean follow-up, 24.3 months; range, 24 to 26 months). Lysholm scores also improved significantly ($P < .001$) by the last follow-up visit, increasing from a mean preoperative value of 40.1 points to 73.4 points by the end of the study. Likewise, changes in VAS scores throughout the follow-up period were also significant ($P = .005$); the mean VAS score decreased from 4.8 preoperatively to 2.0 at the last follow-up visit. Radiography showed that, at the final follow-up point, the whole-organ MRI score had significantly improved from 60.0 points to 48.3 points ($P < .001$). Particularly notable was the change in cartilage whole-organ MRI score, which improved from 28.3 points to 21.7 points ($P < .001$). Further analysis showed that improvements in clinical and MRI results were positively related to the number of stem cells injected.

CONCLUSIONS:
The results of our study are encouraging and show that intra-articular injection of infrapatellar fat pad-derived mesenchymal stem cells is effective for reducing pain and improving knee function in patients being treated for knee osteoarthritis.

LEVEL OF EVIDENCE:
Level IV, therapeutic case series.

PMID: 23375182 [PubMed - indexed for MEDLINE]

ORTHOPEDIC – Supporting Studies

Arthritis Rheum. 2013 May;65(5):1271-81. doi: 10.1002/art.37908.

Adipose-derived mesenchymal stem cells exert antiinflammatory effects on chondrocytes and synoviocytes from osteoarthritis patients through prostaglandin E2.

Manferdini C, Maumus M, Gabusi E, Piacentini A, Filardo G, Peyrafitte JA, Jorgensen C, Bourin P, Fleury-Cappellesso S, Facchini A, Noël D, Lisignoli G.

Source
Istituto Ortopedico Rizzoli, Bologna, Italy.

Abstract
OBJECTIVE:
To examine the effect of different sources of good manufacturing practice clinical grade adipose-derived mesenchymal stem cells (AD-MSCs) on inflammatory factors in osteoarthritic (OA) chondrocytes and synoviocytes.

METHODS:
AD-MSCs from infrapatellar Hoffa fat, subcutaneous (SC) hip fat, and SC abdominal fat were cocultured in Transwells with chondrocytes or synoviocytes. Inflammatory factors (interleukin-1β [IL-1β], tumor necrosis factor α, IL-6, CXCL1/growth-related oncogene α, CXCL8/IL-8, CCL2/monocyte chemotactic protein 1, CCL3/macrophage inflammatory protein 1α, and CCL5/RANTES) were evaluated by quantitative reverse transcription-polymerase chain reaction or multiplex bead-based immunoassay. The role of different immunomodulators was analyzed.

RESULTS:
All the inflammatory factors analyzed were down-modulated at the messenger RNA or protein level independently by all 3 AD-MSC sources or by allogeneic AD-MSCs used in coculture with chondrocytes or synoviocytes. Inflammatory factor down-modulation was observed only when AD-MSCs were cocultured with chondrocytes or synoviocytes that produced high levels of inflammatory factors, but no effect was observed in cells that produced low levels of those factors, thus highlighting a dependence of the AD-MSC effect on existing inflammation. The immunomodulators IL-10, IL-1 receptor antagonist, fibroblast growth factor 2, indoleamine 2,3-dioxygenase 1, and galectin 1 were not involved in AD-MSC effects, whereas the cyclooxygenase 2 (COX-2)/prostaglandin E2 (PGE2) pathway exerted a role in the mechanism of antiinflammatory AD-MSC action.

CONCLUSION:
The antiinflammatory effects of AD-MSCs are probably not dependent on AD-MSC adipose tissue sources and donors but rather on the inflammatory status of OA chondrocytes and synoviocytes. AD-MSCs seem to be able to sense and respond to the local environment. Even though a combination of different molecules may be involved in AD-MSC effects, the COX-2/PGE2 pathway may play a role, suggesting that AD-MSCs may be useful for therapies in osteoarticular diseases.

PMID: 23613363 [PubMed - indexed for MEDLINE]

ORTHOPEDIC – Supporting Studies

J Indian Med Assoc. 2010 Sep;108(9):583-5.

The new avenues in the management of osteo-arthritis of knee--stem cells.

Varma HS, Dadarya B, Vidyarthi A.

Source
Department of Orthopaedics, NSCB Medical College, Jabalpur 482001.

Abstract
Osteo-arthritis is the most common degenerative joint disease. Recently, the regenerative potential of mesenchymal stem cells (MSCs) has been under intense investigation because of their ability for self renewal and differentiation to reconstitute muscle, cartilage or bone. In this study, 50 patients with mild to moderate osteo-arthritis knee were selected and divided in two groups (group A and group B). Group A received arthroscopic debridement alone and group B received buffy coat (mesenchymal stem cell concentrate) injection along with the arthroscopic debridement of the knee. On follow-up, patients were assessed on the basis of visual analogue scale (VAS) score and osteo-arthritis outcome score, to compare results in both groups against each other to determine the efficacy of arthroscopic injection of buffy coat in the management of osteo-arthritis. The results suggest that the technique used in the study considerably improved the overall osteo-arthritis outcome score, especially the quality of life within the studied follow-up period and at the end of the follow-up.

PMID: 21510531 [PubMed - indexed for MEDLINE]

ORTHOPEDIC – Supporting Studies

Int J Rheum Dis. 2011 May;14(2):211-5. doi: 10.1111/j.1756-185X.2011.01599.x. Epub 2011 Mar 4.

Mesenchymal stem cell therapy for knee osteoarthritis. Preliminary report of four patients.

Davatchi F, Abdollahi BS, Mohyeddin M, Shahram F, Nikbin B.

Source
Rheumatology Research Center, Tehran University of Medical Sciences, Shariati Hospital, Kargar Avenue, Tehran, Iran. fddh@davatchi.net

Abstract
BACKGROUND:
Osteoarthritis (OA) is a cartilage degenerative process, involving the immune system, producing local inflammatory reactions, with production of pro-inflammatory cytokines and metalloproteinases. No treatment is still available to improve or reverse the process. Stem cell therapy opened new horizons for treatment of many incurable diseases. Mesenchymal stem cells (MSCs) due to their multi-lineage potential, immunosuppressive activities, limited immunogenicity and relative ease of growth in culture, have attracted attentions for clinical use.

AIM:
The aim of this study was to examine whether MSC transplantation could reverse the OA process in the knee joint. The project was approved by the Tehran University of Medical Sciences Research Committee and Ethical Committee.

PATIENTS AND METHODS:
Four patients with knee osteoarthritis were selected for the study. They were aged 55, 57, 65 and 54 years, and had moderate to severe knee OA. After their signed written consent, 30 mL of bone marrow were taken and cultured for MSC growth. After having enough MSCs in culture (4-5 weeks) and taking in consideration all safety measures, cells were injected in one knee of each patient.

RESULTS:
The walking time for the pain to appear improved for three patients and remained unchanged for one. The number of stairs they could climb and the pain on visual analog scale improved for all of them. On physical examination, the improvement was mainly for crepitus. It was minor for the improvement of the range of motion.

CONCLUSION:
Results were encouraging, but not excellent. Improvement of the technique may improve the results.

PMID: 21518322 [PubMed - indexed for MEDLINE]

ORTHOPEDIC – Supporting Studies

Transplantation. 2013 Jun 27;95(12):1535-41. doi: 10.1097/TP.0b013e318291a2da.

Treatment of knee osteoarthritis with autologous mesenchymal stem cells: a pilot study.

Orozco L, Munar A, Soler R, Alberca M, Soler F, Huguet M, Sentís J, Sánchez A, García-Sancho J.

Source
Institut de Teràpia Regenerativa Tissular (ITRT), Centro Médico Teknon, Barcelona, Spain.

Abstract
BACKGROUND:
Osteoarthritis is the most prevalent joint disease and a frequent cause of joint pain, functional loss, and disability. Osteoarthritis often becomes chronic, and conventional treatments have demonstrated only modest clinical benefits without lesion reversal. Cell-based therapies have shown encouraging results in both animal studies and a few human case reports. We designed a pilot study to assess the feasibility and safety of osteoarthritis treatment with mesenchymal stromal cells (MSCs) in humans and to obtain early efficacy information for this treatment.

METHODS:
Twelve patients with chronic knee pain unresponsive to conservative treatments and radiologic evidence of osteoarthritis were treated with autologous expanded bone marrow MSCs by intra-articular injection (40×10 cells). Clinical outcomes were followed for 1 year and included evaluations of pain, disability, and quality of life. Articular cartilage quality was assessed by quantitative magnetic resonance imaging T2 mapping.

RESULTS:
Feasibility and safety were confirmed, and strong indications of clinical efficacy were identified. Patients exhibited rapid and progressive improvement of algofunctional indices that approached 65% to 78% by 1 year. This outcome compares favorably with the results of conventional treatments. Additionally, quantification of cartilage quality by T2 relaxation measurements demonstrated a highly significant decrease of poor cartilage areas (on average, 27%), with improvement of cartilage quality in 11 of the 12 patients.

CONCLUSIONS:
MSC therapy may be a valid alternative treatment for chronic knee osteoarthritis. The intervention is simple, does not require hospitalization or surgery, provides pain relief, and significantly improves cartilage quality.

PMID: 23680930 [PubMed - indexed for MEDLINE]

ORTHOPEDIC – References

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