Bone Marrow Concentrate: The Next Generation of Biologic Injectables for Osteoarthritis

Vishal Thakral D.O. M.S.

Western Annual Comp CME Day
Health Link Medical Center

- Los Angeles, California USA
- Our clinic offers non-surgical options for individuals experiencing pain from degenerative orthopedic conditions
- Vision/Action Personality Type
Common Treatments at Health Link Medical Center

- Hyaluronic Acid
- Platelet Rich Plasma (PRP)
- Bone Marrow Concentrate (BMC)
- Prolotherapy/Neural Prolotherapy
- Nerve Hydrodissections
- Ultrasound and/or Fluoroscopy Guided Injections

Our clinical and research interests: Orthobiologics
3 Generations of Biologic Injectables

• 1<sup>st</sup> Generation: Hyaluronic Acid
• 2<sup>nd</sup> Generation: Platelet Rich Plasma (PRP)*
• 3<sup>rd</sup> Generation: Regenerative Cells (i.e. stem cells, mesenchymal stem cell)*

*Autologous
HA effective in managing OA symptoms

- Successful in the treatment of painful OA of the knee.
- Benefits: safe, covered by insurance, activity encouraged
- Limits: temporary effect and best for early OA

The Revolution in Biologics

Major gap exists for treatment options between conservative treatment and surgery

PRP and Regenerative cells offer an important therapeutic treatment option
Platelet Rich Plasma

• What is PRP?
  – Platelet Rich Plasma (PRP) is a super concentration of platelet cells taken from your blood

• How does it work?
  – Platelet rich therapies allow for an opportunity to utilize the body’s own healing (growth) factors to improve the quality and speed of recovery from an injury.
What’s the problem and how does PRP work?

- Most MSK injuries involve anatomic areas with a low cell turnover rate
  - Joint spaces, ligaments, and cartilage have a naturally limited blood supply

- The imbalance of growth factor supply and demand **hinders the regenerative process**.

- Musculoskeletal injury and repair:
  - starts with formation of blood clot and degranulation of platelets
  - This releases GF and cytokines at the site
  - This microenvironment results in chemotaxis of inflammatory cells
  - Activations and proliferation of local progenitor cells
Osteoarthritis is characterized by an imbalance of anabolic and catabolic process in synovial joints, resulting in progressive cartilage damage.

PRP Properties:
- Increase anabolic effect on Chondrocytes
- Decrease catabolic effect in the inflammatory environment
PRP (second generation biologic) has demonstrated superior results when compared to HA (first generation biologic)


Beyond PRP

- PRP is likely just the tip of the iceberg in regenerative medicine
- Stem Cells are an emerging form of regenerative medicine
Different Stem Cell Types

- Stem Cells
  - Adult
  - Embryonic
  - iPSC
What is an adult stem cell?

• Adult Stem Cells or MSC’s secrete an array of cytokines and chemokines involved with immunomodulation, anti-inflammation, anti-apoptosis, proangiogenesis, proliferation, and chemoattraction.

• Can Orchestrate the process of differentiation with differentiated and undifferentiated cells
Proposed Mechanism of Action

- BMSC’s influence the MSC immune response (inhibiting T and B lymphocyte activation and proliferation) and promote healing
- Support hematopoiesis via production of stem cell factor (SCF), IL-6, lymphocyte inhibitory factor (LIF), granulocyte macrophage-colony stimulating factor (GM-CSF), G-CSF, or M-CSF
- Capable of homing to inflammation areas, via stromal derived factor-1 (SDF-1) up regulating CXCR4 receptors on the cell surface
- Its ability to differentiate into chondrocytes and cartilage provides theoretical evidence for use vs. adipose.
- Concentrating mimics the cell load of young patients

References:
Adult Stem Cell - MSC’s

- 2 main types of Adult MSC’s:
  - Adipose (ASC, SVF, AD-MSC)
    - Higher Concentration of MSC’s up to 2500x
    - Less studied
  - Bone Marrow (BM-MSC)
    - Lower concentrations of MSC’s
    - Extensively studied
Marrow Cellular Composition

• Surprisingly, few original papers on the subject
• Bone marrow cells are made up of erythroblasts, neutrophils, eosinophils, basophils, monoid cells (monocytes containing MSC’s and macrophages), lymphocytes, & plasma cells*


0.00003% osteoprogenitor cells
Derived from Mesenchymal cells
(1 out of 3 million cells)
Two Different Types of Bone Marrow Stem Cell Processes

- Same Day
  - Bone Marrow Nucleated Cell Isolation
    - The stem cell fraction of bone marrow is isolated via a centrifuge and re-injected the same day.

- Advanced
  - Bone Marrow Mesenchymal Stem Cell Culture
    - The stem cells themselves are isolated and cultured to greater numbers over a few weeks. This produces a “pure” population of stem cells which is different than the mix of cells produced by same day procedures.

Three Different Types of Fat Stem Cell Processes

- Same Day
  - Simple Adipose Graft
    - The fat is separated from the oil and liquid and the fat is injected (however the stem cells are still trapped in the fat and are not concentrated).

- Same Day
  - Stromal Vascular Fraction (SVF)
    - The fat is separated and then chemically digested to release the stem cell fraction, which is then concentrated.

- Advanced
  - Adipose Mesenchymal Stem Cell Culture
    - The stem cells are isolated and cultured to greater numbers over a few weeks. This produces a “pure” population of stem cells which is different than the mix of cells produced by same day procedures.
Regulatory

Current FDA Regulatory Status of Above
(Under Current Court Challenge)

Stem Cell Risk
All things being equal, the risk of a stem cell therapy increases as the source changes. The safest cells are your own. Stem cells from others can carry the good and bad of their genetic material. Embryonic cells can form tumors.
Cultured Vs Non-Cultured

- **“Two-step procedure”** which requires expansion of BMSCs in vitro to increase cells counts 100-10,000 fold over several weeks in culture*
  - considered advanced therapy medicinal products (ATMP’s) by the appropriate international and national regulatory bodies
- **“One-step procedure”** using either whole bone marrow aspirate (BMA) or bone marrow concentrate (BMC) at the lesion site without cell expansion and culturing
  - same day patient-side therapy with minimal cell manipulation
  - cells processed directly at point of care, eliminating need for a laboratory expansion and culturing phase; reducing costs, potential risks, and the need for a Good Manufacturing Practice (GMP) facility*


Adult Human Mesenchymal Stem Cells Delivered via Intra-Articular Injection to the Knee Following Partial Medial Meniscectomy

A Randomized, Double-Blind, Controlled Study

C. Thomas Vangsness Jr., MD, Jack Farr II, MD, Joel Boyd, MD, David T. Dellaero, MD, C. Randal Mills, PhD, and Michelle LeRoux-Williams, PhD

Investigation performed at the University of Southern California Orthopaedic Surgery Associates, Keck School of Medicine, Los Angeles, California, Unlimited Research, San Antonio, Texas, Triangle Orthopaedic Associates, Durham, North Carolina, Orthopaedic Center of Vero Beach, Vero Beach, Florida, Ortholndy, Indianapolis, Indiana, TRIA Orthopaedic Center, Bloomington Minnesota, and Greater Chesapeake Orthopaedic Associates, Baltimore, Maryland

Background: There are limited treatment options for tissue restoration and the prevention of degenerative changes in the knee. Stem cells have been a focus of intense preclinical research into tissue regeneration but limited clinical investigation. In a randomized, double-blind, controlled study, the safety of the intra-articular injection of human mesenchymal stem cells into the knee, the ability of mesenchymal stem cells to promote meniscus regeneration following partial meniscectomy, and the effects of mesenchymal stem cells on osteoarthritic changes in the knee were investigated.

Methods: A total of fifty-five patients at seven institutions underwent a partial medial meniscectomy. A single superolateral knee injection was given within seven to ten days after the meniscectomy. Patients were randomized to one of three treatment groups: Group A, in which patients received an injection of $50 \times 10^6$ allogeneic mesenchymal stem cells;
Results of Study

Results:
>15% increase in meniscal volume occurred in both Mesenchymal stem cell groups and not control group.

• One of the first double-blind, controlled studies to evaluate safety, regenerative effects, and clinical outcomes of human MSC’s via human knee intra-articular injection

• MSC’s have the potential to improve the overall condition of the knee joint.
Best Stem Cell Source?

• Comparing the chondrogenic potential in vivo of autogeneic mesenchymal stem cells derived from different tissues. Li et al. 2011
  – Bone marrow
  – Periosteum
  – Synovium
  – Adipose tissue
  – Muscle

• CONCLUSION: Bone marrow-MSCs have greater in vivo chondrogenic potential

• “Evaluation of adipose derived stromal vascular fraction or bone marrow-derived mesenchymal stem cells for treatment of osteoarthritis” Frisbie et. al 2009
  Journal of Orthopedic Research
  – Chemical, biochemical, histologic effects of SVF or BM-MSC
  – Middle carpal joint (Equine)
  – Evaluations included clinical, radiographic, synovial fluid, gross, histologic, histochemical, biochemical evaluations

• Result: Bone marrow showed greater improvement in synovial fluid effusion when compared to adipose derived SVF. (Overall – findings were not significant enough to use for treatment of Osteoarthritis)
Where is the Best Source for Marrow Stem Cells?

<table>
<thead>
<tr>
<th></th>
<th>Iliac Crest</th>
<th>Vertebral Body</th>
<th>Decorticated Vertebral Interbody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Number of MNC’s in 2ml</td>
<td>7 million</td>
<td>5 million</td>
<td>1 million</td>
</tr>
<tr>
<td>aspirate</td>
<td>to 9 million</td>
<td>to 7 million</td>
<td></td>
</tr>
</tbody>
</table>

*(Up to Liter Volume Possible)*  *(Volume Limited)*

* MNC – mono-nuclear cells
- Study looking at osteogenic progenitors in vertebral interbody fusion

- Romih, et al, “The Vertibral Interbody Grafting Site’s Low Concentration in Osteogenic Progenitors can Greatly Benefit from Addition of Iliac Crest Bone Marrow”, *European Spine Journal*; 14:645-648; 2005
Bone Marrow Aspiration (BMA)

- Developed in the early nineteenth century to diagnose marrow disorders
- Continues to be utilized when diagnosing leukemia, infections, types of anemia, and other blood disorders
- Complications, such as infections, serious bleeding, or breaking of the needle, are extremely rare.
- Considered a safe procedure with low risk of morbidity*

Bone Marrow Aspiration

- Avoid overuse of anesthetics due to cytotoxicity.*
- Ultrasound easily locates PSIS without radiation in cost effective manner*
- Pre-medicate with Tramadol & Valium*
- Automated power driver may reduce pain and procedure time

Cells collected from bone marrow aspirate

MSC’s isolated by lab

Bone Marrow Nucleated Cell Isolation
The stem cell fraction of bone marrow is isolated via a centrifuge and re-injected the same day.

Mesenchymal Stem Cells
Hematopoietic Stem Cells
Injected same day

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Health Link Medical Center
Cell Stacking Following Centrifugation

Illustration courtesy of Theodore Sand, Ph.D.
# Injection Ultrasound Technique: Visualization Critical

<table>
<thead>
<tr>
<th>Accuracy</th>
<th>US</th>
<th>Palpation</th>
<th>Fluoro</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH Joint</td>
<td>95%</td>
<td>79-83%</td>
<td></td>
</tr>
<tr>
<td>SA/SD Bursa</td>
<td>100%</td>
<td>63%</td>
<td>60%</td>
</tr>
<tr>
<td>AC joint</td>
<td>100%</td>
<td>40-67%</td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>96-100%</td>
<td>55-79%</td>
<td></td>
</tr>
<tr>
<td>BT sheath</td>
<td>100%</td>
<td>66.6%</td>
<td></td>
</tr>
<tr>
<td>PIP &amp; MCP jts</td>
<td>96%</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>Inf Arthritis Jt</td>
<td>83%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>GH Jt first try</td>
<td>94%</td>
<td>72%</td>
<td></td>
</tr>
</tbody>
</table>

- **Knee**
  - Improved accuracy Vs. anatomical guidance (95.8% versus 77.8%) with better patient clinical outcomes*

*Berkoff DJ, Miller LE, Block JE. Clinical utility of ultrasound guidance for intra-articular knee injections: a review. *Clinical interventions in aging*. 2012;7:89-95

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Who are our patients?

- Active Elderly
- Young Athletes
- Traumatically Injured
- Weekend Warriors
- Professional Athletes

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### What can be treated with Stem cells/PRP?

- **Osteoarthritis**: Knee, Shoulder, Hip, Hand, Foot/ankle
- **Tendon/Ligament**: full tears, partial tears, tendinosis
- **Accessory structures**: Knee meniscus, hip and shoulder Labrum, bursitis

<table>
<thead>
<tr>
<th>Shoulder</th>
<th>Knee</th>
<th>Hip</th>
<th>Foot/Ankle/Hand</th>
<th>Spine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotator Cuff (tear, tendinosis)</td>
<td>Osteoarthritis (PF, lateral, medial)</td>
<td>Osteoarthritis Hip Joint</td>
<td>Osteoarthritis (CMC, ankle joint)</td>
<td>Facet Joints</td>
</tr>
<tr>
<td>Osteoarthritis (glenohumeral, AC)</td>
<td>Meniscus tears</td>
<td>Labral Tears</td>
<td>Tendon (Achilles, deQuervain’s, Peroneal)</td>
<td>Disk (discogenic, Degenerative Disk Disease)</td>
</tr>
<tr>
<td>Glenoid Labrum</td>
<td>Tendon (patellar, quadriceps)</td>
<td>Muscle/Tendon injury (hamstring, quadriceps, hip flexors, gluteus, piriformis)</td>
<td>Ligament (ankle sprains, plantar fascia)</td>
<td>Ligaments</td>
</tr>
<tr>
<td>Biceps Tendon</td>
<td>Ligament (ACL, MCL, LCL)</td>
<td>Bursitis (greater trochanteric)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SI joint</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical Studies

• Prospective Study of 6 females who underwent injection of Bone marrow MSC’s for grade 4 knee OA.
  – 1 year follow up demonstrated decrease in mean pain on VAS, joint function and walking distance compared to baseline
  – All 6 patients were satisfied and had decreased pain
  – 3 out of 6 showed improvement on MRI in cartilage thickness, extension of repair tissue over subchondral bone, and decreased subchondral edema

MRI data

• Why did MRI cartilage thickness not correlate with clinical improvement in all patients?

• “The presence or absence of joint space narrowing . . . was not significantly associated with knee pain”!

OA & Cartilage, 1996
Why Is Knee OA Painful?

A Systematic Review Found that Pain Is:

- Strongly related to large Bone Marrow edema/lesions (seen on fluid-sensitive, fat-suppressed sequences)
- Moderately related to synovitis & effusion
- Weakly related to cartilage volume / thickness

Hunter et al., OA & Cartilage 2011
Correlation with Presence of Pain & Decreased Function

- "Large bone marrow lesions in the medial femoral condyle or the medial or lateral plateau were associated with substantially increased odds of reported pain"
- BML in medial compartments associated with "marked decreases in walking and stair-climbing performance (p<0.001)"
- BML’s are associated with progressive cartilage deterioration
- Resolution of BML slows this degenerative process
- BML is an important focus for the prevention of knee OA
Case Presentation

- 2005 gradual decline could no longer run.
- Dec 2012 went for a 2 mile hill walk with severe pain.
- MRI showed mild effusion with degen medial meniscal tearing with high grade full thickness medial compartmental OA with severe bone marrow edema and advanced patella/femoral OA with mild subluxation.
- Did PT with 10% improvement & presented with 7/10 sharp medial pain & failed NSAID’s.
- Failed Hyaluronic Acid Injection series x5.
Case con’t

• 5/22/13: Arthroscopic debridement of chondral surfaces, medial menisectomy & subchondroplasty (SCP)
• 7/13/13 underwent ultrasound guided synovial fluid aspiration along with BMC/PRP injection.
• 8/19/13 Follow up. Improved knee function scores, mobility & no medial tenderness. ROM improved from 0-127 vs. prior 115 deg. Able to now go up and down stairs without handrails and walk 2 blocks pain free.
• 8/21/13 Follow up MRI shows reduced Marrow Edema
• 2/14/14 >90% symptom relief with reduced BML on MR
MRI 8 wks post BMC

Pre

Post

NEAR COMPLETE RESOLUTION OF EDEMA
Chondro-Malacia Patellae

37 yo WM-3 months post 3 injections of autologous mesenchymal stem cells into the medial trochlear groove. 3.0T before and after axial PDFS sequences taken on different magnets.

Note appearance of cartilage in white dashed circle, before image shows ragged appearance with breaks on the patellar surface and the medial trochlear groove surface. The two best match axial slices on the right show improved contour of the cartilage with fill in of the defects.
37 yo WM - Before image is 5 months post first MSC transplant. After is 3 months post 2nd MSC transplant. 3D FSPGR FS SAG of medial knee compartment.
51 year old otherwise healthy white female status post traumatic talar dome chondral lesion who had failed arthroscopic debridement. Returned to full function.

3.0 Tesla MRI Coronal PDFS serial images of the same slice of the medial ankle/talar dome.
### Hip & Knee BMC vs. TJ A:1 Year Data

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Year</th>
<th>Patients</th>
<th>Mean Age</th>
<th>BMI</th>
<th>Patients</th>
<th>Mean Age</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Hip Arthroplasty (THA)</td>
<td>2007</td>
<td>94 patients</td>
<td>62</td>
<td>30</td>
<td>24 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMC Hip</td>
<td>2012</td>
<td>28 patients</td>
<td>51</td>
<td>26</td>
<td>18 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Knee Arthroplasty (TKA)</td>
<td>2013</td>
<td>111 patients</td>
<td>67</td>
<td>32</td>
<td>71 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMC Knee</td>
<td></td>
<td>37 patients</td>
<td>55</td>
<td>27</td>
<td>26 patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sheinkop M. BMC intervention versus joint arthroplasty for arthritis. Presented at the Annual Meeting of The Orthobiologic Institute (TOBI); June 2013; Los Angeles, CA. Zimmer Total Hip Arthroplasty Device Outcomes Study for VerSys FMT.
Orthopaedic Scores

<table>
<thead>
<tr>
<th>REGION</th>
<th>Clinician Completed</th>
<th>Patient Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>Harris Hip Score</td>
<td>Oxford Hip Score</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HOOS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WOMAC</td>
</tr>
<tr>
<td>Knee</td>
<td>Knee Society Score (KSS)</td>
<td>Oxford Knee Score</td>
</tr>
<tr>
<td></td>
<td>Physician Global Assessment</td>
<td>KOOS, WOMAC, IKDC</td>
</tr>
</tbody>
</table>
Mean Harris Hip Score

- **THA Preop (N=94)** 56
- **THA Post (N=24)** 94
- **Pre BMC (N=28)** 68.75
- **Post BMC (N=18)** 82.89
Average Hip ROM (Ext › Flex)

- **THA Preop 75.5°**
- **BMC Pre 87.44°**
- **THA Post op 84.5°**
- **BMC Post 95.24°**
Knee Society Assessment Score

- **TKA**
  - Pre op 48
  - Post op 80

- **BMC**
  - Pre 69.08
  - Post 82.44
Knee Society Function Score

- **TKA**
  - Pre op: 40
  - Post op: 73

- **BMC**
  - Pre: 71.15
  - Post: 90.31
Currently, 65% of patients active in sports prior to a TJA return to sport. Bradbury et al., Am J Sports Med

High activity level post TKA associated with:
- Worse long term results, patient dissatisfaction, higher revision rates, lower implant survival. Kilgus et al., CORR

Increased risk of failure:
- Age <60
- Excessive loading
- High Intensity Activity

72% of BMC Hip recipients returned to sporting activities
TJA vs Bone Marrow Concentrate - Conclusions

- After TJA, patients decrease athletic participation and intensity and also diminish types of activity.
- After BMAC, patients restore and increase athletic participation and intensity after BMAC.
- Knee patients overall, had better outcomes vs. hip patients especially compared to surgical treatment but both groups did well.
## Bone Marrow Stem Cells vs. Knee or Hip Arthroplasty

<table>
<thead>
<tr>
<th></th>
<th>Stem Cells</th>
<th>Knee/Hip Arthroplasty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain associated with procedure</td>
<td>Minimal</td>
<td>Considerable</td>
</tr>
<tr>
<td>Post Procedure Recovery Time</td>
<td>Minimal</td>
<td>Considerable</td>
</tr>
<tr>
<td>Joint Infections</td>
<td>0.0% (report of 2 patients with infections at bone marrow draw sites)</td>
<td>0.72%</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>0.0%</td>
<td>As high as 3.76% or 1.19% (with anticoagulation)</td>
</tr>
<tr>
<td>Nerve Injury</td>
<td>0.0%</td>
<td>Up to 0.03%</td>
</tr>
<tr>
<td>Limb Length Discrepancy</td>
<td>0.0%</td>
<td>Up to 62%</td>
</tr>
<tr>
<td>Cost of Procedure</td>
<td>Up to $10,000</td>
<td>Up to $35,000-$45000</td>
</tr>
<tr>
<td>Need for Revision</td>
<td>Unknown</td>
<td>1.26-1.29 revisions per 100 observed component years</td>
</tr>
</tbody>
</table>
Regenexx Data

What are our Outcomes???
Prospective Data
Knee OA

Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Regenexx-SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>999 procedures</td>
</tr>
<tr>
<td>Male</td>
<td>604 (60.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>395 (39.5%)</td>
</tr>
<tr>
<td>Age</td>
<td>55.5 (13-92)</td>
</tr>
<tr>
<td>Height</td>
<td>68.1* (49-83)</td>
</tr>
<tr>
<td>Weight</td>
<td>177 (100-315) lbs.</td>
</tr>
<tr>
<td>BMI</td>
<td>26.8 (16-55.8)</td>
</tr>
</tbody>
</table>

Caution! This is registry data, which is not the same as a controlled trial. This means it was collected as patients were treated.

What's important here? The patient results detailed on this infographic are mostly men who are middle aged and only slightly overweight (BMI<25).

This data analysis is part of the fall 2014 data download of patients who were tracked in our advanced registry. For the 2012 version (with fewer patients included), click here, for the 2013 version (click here). More information can be found at the links below:

- How about functional questionnaire data on knees?
- What decisions that can be made based on this registry data. For example does age or arthritis severity impact outcomes?

Fall 2014 Data

Regenexx-SD is a same day stem cell procedure where cells are harvested in the morning and placed back in the afternoon.

Mean Improvement of All Patients

For demographics, N for age calculations was 999, for BMI 925. Numbers of patients followed up for outcomes were the following: 461 at 1 month, 444 at 3 months, 371 at 6 months, 232 at 12 months, 154 at 18 months, 100 at 24 months and 47 at 36 months, 10 at 48 months. The expected follow-up %s were 92% at 1 month, 89% at 3 months, 89% at 6 months, 84% at 12 months, 87% at 18 months, 81% at 24 months, 67% at 36 months, 20 at 48 months. There were 67 study exits during the 4 year period, 19 due to TKA. It also should be noted that 7 of the 35 patients due to report at 4 years had reported needing a TKA. Study exits were not counted above in the expected follow-up %s at any given time point as they had refused additional follow-up.
Prospective Data
Shoulder OA

Shoulder Arthritis and Rotator Cuff Tears
N=199 Patients
Collected from 14 Clinics
2014 Registry Data

What’s important?
This graph shows pain scores, function as measured by the DASH questionnaire, and the % improvement rating as determined by the patient at various points after the procedure. All of these are reported in terms of percentage improvement to make them easier to interpret. The outcome information shows robust improvement in both pain and function as well as high marks reported by patients when asked to rate their percentage improvement from 0-100% (% Improvement Rating). The patients represented here are a mix of rotator cuff tear only patients and patients who also had shoulder arthritis.

Caution-This is registry data collected as patients are treated, which is not the same as a randomized controlled trial typically used for FDA approval. In addition, later time points in this graph have more patients who did not answer questionnaires.

Details?
Mean age is 56.9 years old. BMI is 26.5. There were 56 women and 143 men. N is 199 at pre-treatment, 73 at 1 month, 83 at 3 months, 59 at 6 months, 21 at 12 months, 22 at 18 months, 15 at 24 months.

Same Day Stem Cell Procedure
This procedure involves taking bone marrow stem cells from the back of the hip and re-injecting them under precise imaging guidance into the hip joint and associated structures like labrum.
Hip Arthritis-Improvement
N=362 Patients
Collected from 16 Clinics
2014 Registry Data

Average % Improvement

% of patients reporting more than 50% improvement

What’s important?
These graphs show percentage improvement as reported by patients after their hip procedure. The top graph shows the % improvement average reported by all patients for whom information was available. The bottom graph shows the percentage of patients who reported more than 50% improvement. To find out how these same patients fared on a validated hip function questionnaire (Oxford), click here.

Details?
Mean age is 57.2 years old. BMI is 26.5. There were 154 women and 208 men. The available outcomes for each time point were the following: 154 at 1 month, 176 at 3 months, 132 at 6 months, 78 at 12 months, 48 at 18 months, 28 at 24 months.

Same Day Stem Cell Procedure
This procedure involves taking bone marrow stem cells from the back of the hip and re-injecting them under precise imaging guidance into the hip joint and associated structures like labrum.

Caution-This is registry data collected as patients are treated, which is not the same as a randomized controlled trial typically used for FDA approval. In addition, later time points in this graph have more patients who did not answer questionnaires.
Hand and Wrist

What's important here? The patient results detailed on this infographic are slightly more skewed toward older women who are normal weight (BMI<25).

<table>
<thead>
<tr>
<th>Hand/Wrist</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>55 patients</td>
</tr>
<tr>
<td>Male</td>
<td>25 (45%)</td>
</tr>
<tr>
<td>Female</td>
<td>30 (55%)</td>
</tr>
<tr>
<td>Age</td>
<td>57.3 (21-82)</td>
</tr>
<tr>
<td>BMI</td>
<td>24.0 (19.7-28.9)</td>
</tr>
</tbody>
</table>

Caution! This is registry data, which is not the same as a drug company style controlled trial.

In a chart review, >60% of these patients had severe arthritis.

Which area was treated? (Based on data reported).

- Thumb CMC
- Wrist
- Other hand joint

What does this mean?
Above is the percentage of patients who reported >25% improvement by time point after the injection. Below are the mean percentage improvements for those same patients.

Mean Improvement

Click here for a comparison of Hand/Wrist patients treated with the Regenexx-SD same day vs. the Regenexx-C cultured procedure.

The Regenexx-SD procedure is a same day bone marrow stem cell procedure that isolates the fractions of bone marrow that have the most stem cells.

Details For Both Charts: The pie chart includes an analysis of the 21 patients for which data was available. N=14 for hand CMC, 5 for wrist, and 2 for other hand joint. The graphs above and below (>25% improvement and Mean Improvement) are for n=5 at 1 month, 12 at 3 mo, 7 at 6 mo, 8 at 12 mo. Two patients were excluded from the analysis because one had severe progressive hand OA at a young age (not common wear and tear osteoarthritis) and the second had a loose body in the CMC joint prior to the procedure that was deemed a surgical issue, but the patient opted for treatment.
Foot and Ankle

Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Regenexx-SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>93 patients</td>
</tr>
<tr>
<td>Male</td>
<td>59 (63.4%)</td>
</tr>
<tr>
<td>Female</td>
<td>34 (35.6%)</td>
</tr>
<tr>
<td>Age</td>
<td>50.8 (17-79)</td>
</tr>
<tr>
<td>BMI</td>
<td>26.2 (18.4-41.3)</td>
</tr>
</tbody>
</table>

Caution! This is registry data, which is not the same as a controlled trial. This means it was collected as patients were treated.

The average of all data points shown here was 17.2 months after the procedure.

All Patients Reporting at any Time Point 3 mo or Greater

What do these two graphs mean? The graph above represents the percentage of patients who reported >25% relief at various time points after the procedure. For example, at an average of 17.2 months post procedure, 62% of patients who responded reported more than 25% relief. For the graph below, this is the mean reported relief at all available time points. For example, patients at an average of 17.2 months post procedure may have reported anything from no relief, to 50% relief, to 90% relief, the mean of all of those reports was 45% improved.

Mean Improvement of Patients

The average of all data points shown here was 17.2 months after the procedure.

Regenexx-SD is a same day stem cell procedure where cells are harvested in the morning and placed back in the afternoon.

For demographics, n for age calculation was 93, for BMI n=77. For the graphs above and below, n was 39. Likert Improvement from -100% to +100% shown on y-axis. For the graph above, patients with either AVN or loose bodies in the joint were excluded. For both graphs, the averages shown were calculated off the Likert score of the last available time point for that patient.
Post Stem Cell Injection Recovery and Rehab

1. 3-5 days minimal weight bearing
2. 4-14 days, full weight bearing, walking up to 30 minutes per day-no high impact activities
3. 3 weeks, participate in most activities of daily living (no vigorous weight bearing exercise)
4. 6 weeks, return to complete activity and normal exercise
5. OMT – myofascial, soft tissue, lymphatic drainage
6. Postural alignment therapy
• What is actually going into the patient?
• Regenerative Cells in Marrow dependent on many factors. (health status, smoking, age, active menstrual cycle, body temperature, hormone deficiencies) *
• Understanding baseline biologic profiles may explain why some respond favorably and others do not.
• May shed light on post injection flares & “rapid responders”

*S Sampson D Aufiero, A Botto-van-Bemden. Autologous Bone Marrow Concentrate: Review and Application of a Novel Intra-Articular Orthobiologic for Cartilage Disease The Physician and Sportsmedicine, Volume 41, Issue 3, September 2013, ISSN – 0091-3847
BMC Current Questions and Challenges

- Inject target vs surrounding structures and pain generators (meniscus, collateral ligaments etc)?
- Need to repeat injection or PRP Booster?
- Adding peripheral blood derived PRP or Adjuncts? (HA)
- Rehab protocols & specific activity restrictions?
- Marrow aspiration technique? 1 site vs multiple, anesthetics?
- Most optimal role of BMC? With or without surgery?
- Ideal indications?
- Hormone regulation (Testosterone, Thyroid, Estrogen etc.)
- Role of Various progenitor cells despite low MSC #'s in marrow (quantifying BMC components to better understand why it works) A challenge!
Future Research Interests

- Hyperbaric Oxygen Therapy (HBOT)
- IV Vitamin/MSC Infusions
- Biomarkers
Questions???

You can reach me at:

drthakral@healthlinkcenter.com