2018 Update: The use of bone marrow derived stem cells in irom (interventional regenerative orthopedic medicine)

Thomas k. Bond, md, ms
President, aaom
4/20/2018
Aaom 35th annual conference Clearwater beach, florida
Goals & objectives

• **GOALS:**
  - To define and describe the various types of “stem cells” being used in IROM.
  - Describe safety data to date
  - List various Orthopedic/MSK conditions being treated.
  - Review the available evidence for BMAC in Orthopedic/MSK.

• **OBJECTIVES**
  - By the end of this session, you should be able to:
  - Discuss the various types of stem cells used in IROM.
  - Discuss how they are used in different MSK conditions.
  - Describe the available research in the field
“Stem cells” used in irom

• **Adult Stem Cells: autologous, multipotent cells**
  • “Mesenchymal Stem Cells”
    • What is “Mesenchyme”?  
  • BMAC  
  • BD-MSCs  
  • Fat Graft  
  • SVF  
  • AD-MSCs

• Embryonic Stem Cells

• Many others...
Adult STEM CELLS USED IN IROM

• MSCs “Mesenchymal Stem Cells”
  • “Mesenchyme” = a tissue meshwork within the Mesoderm of a developing human embryo which gives rise to mainly mesodermal connective tissues (fascia, muscle, tendons, ligaments, capsules, bone, and cartilage), but also to blood vessels and lymphatics.

• Two Main Types / Sources of Adult-MSCs:
  • Bone-Marrow
    • “BMAC” (Bone-Marrow Aspirate Concentrate)
    • BM-MSCs (Bone-Marrow derived MSCs)
    • Culture-expanded, BM-MSCs = grown in-vitro to “expand” the number of MSCs.

  • Fat/Adipose Tissue
    • “Fat-Graft” = unprocessed “lipo-aspirate”
    • AD-MSCs / “SVF” = lipo-aspirate which has been processed via enzymatic digestion or mechanically to release MSCs.
    • Culture-expanded, AD-MSCs = grown in-vitro to “expand” the number of MSCs.
Which Orthopedic conditions?

- **OSTEOARTHRITIS**
  - Knee
  - Hip
  - Ankle
  - Shoulder
  - Basal joint/Thumb

- AVN (AVASCULAR NECROSIS) / HIP
- DISCOGENIC DISEASE / DDD of the SPINE
- ACL / KNEE
- **ROTATOR CUFF / SHOULDNER**
- Others..
Stem cells??.....mutant zombies!!??

Are stem cells safe?
Is the use of Autologous, Adult-Mesenchymal Stem Cells in patients SAFE?

2016: Centeno et al... Bond (International Orthopedics)

“A Multi-center Analysis of adverse events amount 2,372 adult patients undergoing Adult Autologous Stem Cell therapy for Orthopedic conditions”

- Total of 3,012 in 2,372 patients over 9-years: knee, hip, foot/ankle, hand/wrist, elbow, shoulder and spine.
- Adverse events in 10% (325 patients), majority of which were post-procedure pain – self limiting.
- 7 cases of reported neoplasm – which is LOWER than the general population!
- Lowest rate of Adverse events with BMC vs highest rate of AE with BMC+Adipose+Cx-cells, which is explained by nature of treatment and longer follow-up.
- No evidence that treatment with MSCs increases risk of neoplasm....?protective?

ANSWER....YES!! THE USE OF ADULT, AUTOLOGOUS, BD-MSCs ARE SAFE.
Stem-cell ebm: safety data

- **2013: Pak et al** (BMC Musculoskeletal Disorders)
  - “Safety reporting on implantation of autologous adipose tissue-derived stem cell with platelet-rich plasma into human articular joints”
- 91 patients with Knee OA
- Injected with “Non-culture-expanded ADSCs”(SVF) + PRP
- No serious side effects or cancer at 36months out; a few “minor” episodes of “swelling and tendonitis”
- Efficacy: “65% at 3months and beyond”
- **Conclusion: ADSCs/SVF + PRP in OA-Knees safe and well-tolerated**
Stem-cell evidence: “early work”

  
  “Novel maxillary reconstruction with ectopic bone formation by GMP adipose stem cells”

• **Case report**: patient with very large maxillary osteoid keratocyst requiring hemi-maxillectomy.
  
  • Liposuction / lipo-aspirate – to GMP-level lab; grown in concert with beta-tricalcium phosphate & BMP-2 (bone morphogenetic protein-2) x 8 months.
  
  • Re-implanted into patient as a microvascular flap with developed bone structure and vascular supply.
  
  • Post-op: patient did well with filling of defect.
Evidence for stem cell use in orthopedics

- Studies have focused on...
  - *The use of MSCs as an “add-on” to surgical intervention*
    - Or
  - Using MSCs independently as the treatment intervention itself:
    - ---example: Knee OA
Stem-cell ebm: surgery add-on for the knee

- Level-I Evidence: none...pending...
- Level-II Evidence:

  **Wong et al (Arthroscopy 2013):**
  - “Injectable C-BD-MSCs in Varus Knees with cartilage defects undergoing HTO: a prospective, RCT with 2-years’ follow up”
  - HTO+MFX, HA post-inject at 3 wks---versus---HTO+MFX, HA+CBDMSCs post-inject at 3 weeks: better pain/function/MRI scores.

  **Koh et al (Arthroscopy 2016):**
  - “AD-MSCs + Microfracture vs Microfracture alone: 2-year follow-up of a Prospective Randomized Trial”
  - MFX+ADSCs >> MFX alone in terms of pain/symptom subscores (KOOS) but no different in sports or QOL subscores.

  **Gobbi et al (AJSM 2016):**
  - “One-stage Cartilage repair using a HA-based Scaffold with activated BMMSCs compared with Microfracture: 5-year follow-up.”
  - Fibrin-glue activated BM-MSCs in a HA-based scaffold >> MFX at 2-years: IKDC score “normal” - 100% vs 64%
  - At 5 years: IKDC normal scores: 100%-to-100% (BM-MSCs+HA-scaffold) vs. 64%-to-28% (MFX group)!
Bmac: knee
EBM: stem cell use in orthopedics

• Studies have focused on...
  • The use of MSCs as an “add-on” to surgical intervention
    Or
  • Using MSCs independently as the treatment intervention itself:
    • ---example: Knee OA
Stem-cell ebm: knee, oa

- **2015: Emadedin et al** (Archives Iranian Medicine)
  - “Long-Term Follow-up of Intra-articular Injection of Autologous MSCs in patients with Knee, Ankle or Hip OA”
    - 18 patients, 30-month follow-up
    - **Results:** MSCs are “safe and therapeutically beneficial” – but “further study needed” “larger trials”

- **2016: Filardo et al** (Journal Orthopedic Surgery Research)
  - “Stem Cells in Articular Cartilage Regeneration”
    - **Review Article: 60 selected studies** – 7 RCTs, 13 comparatives, 31 case series, and 9 case reports.
    - 37 studies = BD-MSCs or AD-MSCs; 16 studies = BMAC
    - **Results:**
      - Using MSCs is safe!
      - Improvements in outcome reported across the board – regardless of stem cell source or method of administration.
      - **Better outcomes with younger age, lower OA grade, lower BMI.**
**Bmac: knee oa**

**2017: AJSM: Shapiro et al:**

"A Prospective, Single-Blind, Placebo-controlled Trial of Bone Marrow Aspirate Concentrate for Knee Osteoarthritis"

- **25 patients** each with Bilateral Knee OA, randomized to receive BMAC in 1 knee and NS in the other.
- **Outcomes Measured**: OARSI, Intermittent & Constant OA Pain, VAS @ 1week, 3months, and 6months.
- **Results**: all outcomes showed dramatic improvement in both knees
- **Conclusion**: early results show BMAC is safe, reliable and viable cellular product….further study...

**2017: Journal Orthop Surg Research: Al-Najar et al:**

"Intra-articular injection of Expanded Autologous Bone Marrow Mensenchymal Cells in moderate and severe Knee Osteoarthritis is safe: a phase I/II study."

- **13 patients** with mean age 50, suffering with symptomatic Knee OA, stages 2 & 3, given 2 doses of 30Million, Cx-BM-MSCs a month apart.
- **Outcomes Measured**: KOOS, pain and Cartilage thickness via quantitative-MRI T2 at 12-months post.
- **Results**: No adverse events up to 24-months, KOOS improved significantly, mean cartilage thickness improved significantly.
- **Conclusion**: Cx-BM-MSCs given IA are safe in KOS…given the significant improvement in KOOS and cartilage...
2018: Cytotherapy: Shadmanfar et al:

“Intra-articular knee implantation of autologous bone-marrow derived mesenchymal stromal cells in Rheumatoid Arthritis patients with knee involvement: results of a randomized, triple-blind, placebo-controlled phase ½ clinical trial”

• Single center, RCT with total of 30 RA-Knee patients: 15 pts received 40M—BM-MSCs vs 15 pts received NS.

• Outcomes Measured: WOMAC, VAS, time to jelling, pain-free walking distance and MTX-Prednisolone use.

• MSCs beat NS in all categories up to and including 12 months, but no significant difference thereafter.

• Conclusion: MSCs good in RA-Knee patients, but need more study.
Knee oa

• **2018: Cartilage: Goncurs et al:**

  “Treatment of Knee Osteoarthritis with Bone Marrow-Derived Mononuclear Cell Injection: 12 Month Follow-up.”

• **34 Knees** (32 patients), 16-16 (male-female), KL grades II & III injected with 10-70M BMD-Mononuclear

• **Outcomes Measured:** KOOS, KSS, and Whole Organ MRI Score (“WORMS”)

• **Results:** At 12 months, 65% still had improvement KOOS

• **Conclusion:** Single dose of BMD-MNC partially reduces clinical signs of KOA-stage II/III and in some cases, decreased degenerative changes in the joint building tissue over a 12-month period.
Stem-cell ebm: knee oa / ra

• **2018: Centeno et al...Bond** (IOF Registry Data):

  • **4,167 patient-procedures**: Regenexx-SD procedure = “Same-Day” stem cell procedure = BM-MSCs.
  • 48 month / 4-year follow-up
  • No severe AEs or Cancer.

**Results:**

• No differences observed between outcomes for age, sex, BMI or condition treated.

• **Percent of patients with >50% improvement (avoiding TKA) at:**
  • 1-year: 72%
  • 2-years: 75%
  • 3-years: 76%
  • 4-years: 79%
Knee Functional Outcomes

The number of patients reporting at these time-points are: 4167, 2070, 3097, 2869, 2218, 1595, 1153, 607, 289.
shoulder oa
Stem cell ebm: surgery add-on, shoulder

- Majority of EBM: animal data...

- **2014: Hernigou et al** (International Orthopedics):
  - “Biologic augmentation of rotator cuff repair with mesenchymal stem cells during arthroscopy improves healing and prevents further tears: a case-controlled study”
    - 45 patients received on average 51,000 MSCs as an adjunct to single-row Rotator Cuff repair.
    - 45 matched-controls (single-row RCR but no MSCs)
    - US performed every month, MRIs at 3months and 6months
    - **Results:** 100%! (45/45) of MSC+ patient healed RCT by 6months vs. 67% (30/45) of control group!
shoulder, oa & rc

• 2015: Centeno et al ...Bond (Journal of Pain Research)

• “A Prospective, Multi-Site, Registry study of a specific protocol of Autologous, Bone Marrow Concentrate for the treatment of Shoulder Rotator Cuff Tears and Osteoarthritis”
  • 115 shoulders treated with BMAC under US-guidance; all with dx of OA, +/- RC tears.
  • Data collected: Age, sex, BMI, condition type (OA vs RC vs both)
  • Outcomes measured: DASH (Disabilities of Arm, Shoulder, Hand), VAS/NPS, and subjective improvement.

• Results:
  • Statistical improvement of DASH & VAS/NPS
  • Patient-reported subjective improvement in 48.8%
  • No differences observed between outcomes for age, sex, BMI or condition treated.
Shoulder Functional Outcomes

The number of patients reporting at these time-points are: 729, 369, 495, 481, 397, 310, 235, 141, 47.
SPINE / INTRADISCAL
Intra-discal bmac/msc

• 2011: *Transplantation*: Orozco et al:
  • “Intervertebral disc repair by autologous mesenchymal bone marrow cells: a pilot study”
  • 10 patients, chronic LBP
  • Culture-expanded, autologous, BM-MSCs
  • Confirmed feasibility and safety
  • “strong indications for efficacy...improvement of pain and disability...approached 71%”
  • MSCs may be a valid alternative....requires more study
**Intra-discal bmac/msc**

- **2017: *International Orthopedic: Pettine et al***
  - “Autologous Bone Marrow Concentrate intradiscal injection for the treatment of DDD with 3-year follow-up”
  - 26 patients with DDD, recommended for spinal fusion surgery or disc replacement surgery.
  - Intra-discal injection of avg. 121M TNC, followed 3-years.
  - ***AT 3 YEARS, 20/26 (77%!!) HAD AVOIDED THE RECOMMENDED SURGERY!....23% (6/26) HAD PROGRESSED TO HAVE SURGERY.***
  - No adverse events
Intra-discal bmac/msc

• 2017: Journal of Translational Medicine: Centeno et al

• “Treatment of Lumbar Degenerative Disc disease-associated radicular pain with Culture-expanded autologous mesenchymal stem cells: a pilot study on safety and efficacy.”

• 33 patients, CLBP + MRI+post.disc, treated Cx-BM-MSCs intra-discally – followed for 6 years.

• 0/33 patients serious side effects (death, CA, tumor, infection, etc.); 2/33 = post-procedural pain, resolved.

• Pain, Function, MRI scores all improved......*not 1 patient went on to surgery!*

• Conclusion: Intra-discal injection of Culture-expanded, Bone Marrow-derived MSCs is likely safe and efficacious but requires more study.
The number of patients reporting at these time-points are: 3192, 1515, 2078, 1821, 1335, 953, 679, 432, 238.
Thumb / basal joint osteoarthritis
Basal joint oa

- **2017: Plas Recontr Surg Glob Open: Murphy et al**
  - “ASCOT: Autologous Bone Marrow Stem Cell Use for Osteoarthritis of the Thumb-First Carpometacarpal Joint”
  - **Aim:** was to determine the potential benefit of microfx + autologous BMAC for OA in Basal joint.
  - **Patients:** 15 patients, with 2 drop outs = total of 13 patients.
  - **Outcomes measured:** VAS, VAS-A, AROM, Opposition score, Disability score, Grip strength and Grind test
  - **Results:** 13/13 improved in statistically significant ways, except strength – which improved but not significantly. Also, 13/13 had negative grind test after 12 months.
basal joint oa

- Regenexx – IOF Patient Registry Data
- 151 patients; Regenexx-SD “Same-Day”-BMAC procedure.
- Statistically significant improvement in both pain and function, out to 4 years (in some patients, 10-15%)
- See following graph...
Hand/Wrist Functional Outcomes

The number of patients reporting at these time-points are: 151, 82, 133, 127, 102, 89, 69, 34, 19.
MSCs as Stand-Alone Procedures:

- **SAFE!**
  - **Knee OA:** MSCs – from BMAC – are both safe & efficacious, whether alone or in combination with PRP and/or HA.
  - **Shoulder OA & RC:** MSCs from BM are somewhat effective in Shoulder OA / RC, more studies needed.
  - **DDD / IntraDiscal:** encouraging...but need more studies
  - **Thumb / Basal Joint:** very encouraging...but more studies needed.
Msc use in orthopedics: summary

• **General Concepts / Perspectives of MSC use in Orthopedic Medicine**

  • The use of Autologous, MSCs from Bone Marrow and/or Adipose tissue is **SAFE**.
  
  • Although *more study is needed*, the use of MSCs from BM and Adipose is **EFFICACIOUS**.
  
  • **In general**, MSCs are efficacious used alone or in combination with activated PRP and HA.
  
  • **In general**, Culture-expanded BM-MSCs with very high MSC counts, ex. 100 Million cells seem to be more efficacious and effective than non-Culture expanded MSCs (with lower counts).
  
  • Culture-expanded BM-MSCs with very high MSC counts alone have been shown to regenerate hyaline cartilage in the knee, as well as, take on NP (Nucleus Pulposus) phenotype in culture.
  
  • **In general**, the higher the MSC count the more effective at regenerating hyaline cartilage in the knee, as evident by 2nd-look arthroscopy and follow-up MRI.
  
  • Data regarding the effect of gender, age, weight and comorbid conditions on MSCs is currently conflicting.
Thank you!

- drbond@TotalCare-La.com
- www.TotalCare-La.com
AAOM Educational Opportunities

Hands-On Patient Treatment Workshops
Guadalajara, Mexico: November 8th – 12th, 2018
Knee Pain Outcomes

The number of patients reporting at these time-points are: 4780, 2094, 3119, 2899, 2228, 1605, 1154, 610, 289.
Shoulder Pain Outcomes

The number of patients reporting at these time-points are: 793, 370, 512, 488, 398, 311, 235, 141, 47.
The number of patients reporting at these time-points are: 815, 435, 645, 602, 489, 369, 241, 143, 63.
Ankle/Foot Pain Outcomes

The number of patients reporting at these time-points are: 319, 166, 237, 210, 169, 125, 114, 71, 40.

Amount of Pain

- extreme pain
- no pain

Amount of time after treatment

Time of Procedure: 1-month, 3-months, 6-months, 1 year, 1.5 years, 2 years, 3 years, 4 years.
Spine Pain Outcomes

The number of patients reporting at these time-points are: 3384, 1530, 2097, 1836, 1342, 955, 682, 435, 239.