Orthobiologics in MSK Medicine: What’s the Evidence?

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DISCLOSURES:

- NONE
OVERVIEW

- Chronic injuries and degenerative diseases of the musculoskeletal system are a growing epidemic
- Tendinopathy, chronic ligament sprains, OA, degenerative disc disease
- Advent of orthobiologics may reduce pain, promote structural & functional repair, and delay or obviate surgical intervention
ORTHOBIOLOGICS

- Products derived from human, animal tissue, or microorganisms
- Include products derived from whole blood, cells, bone marrow, adipose, gene therapy or recombinant proteins
- FDA has defined human cells, tissues, and cellular and tissue-based products (HCT/Ps):
  - articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient
- NOT discussing regulatory issues in this presentation
ORTHOBIOLOGICS

- Products:
  - PRP
  - BMA/BMAC
  - Fat-derived tissue/cells
  - Perinatal products
    - Amnion
    - Placenta
    - Cord Blood
    - Wharton’s Jelly
PRP

- Stimulates recruitment, proliferation, and differentiation of regenerative cells via release of growth factors contained in the alpha granules
- E.G.: TGF-β1, PDGF, bFGF, VEGF, EGF, IGF-1
**PRP - TENDINOPATHIES:**

- **LATERAL EPICONDYLOSIS**
  - 9 meta-analyses including 8,656 patients
  - 7 of these meta-analyses found that PRP significantly improved pain and elbow function in the intermediate-term (12-26 weeks)
  - 4 studies found that corticosteroid injections relieved pain and improved elbow function in the short-term (<12 weeks).
  - The highest quality RCT by Arirachakaran found that PRP is most effective in the intermediate-term, while corticosteroid injection improves pain and functional outcomes in the short-term.
PRP - TENDINOPATHIES:

- **PLANTAR FASCIITIS**
  - Meta-analysis: PRP is superior to steroid injections for treatment of long-term pain relief (after 24 weeks), but no differences were observed between short (4 weeks) and intermediate terms (12 weeks)

- **ROTATOR CUFF**
  - Meta-analysis: corticosteroid injection plays a role in pain reduction and functional improvement in the short-term (3-6 weeks), but not in the long-term (over 24 weeks);
  - In contrast, PRP injection yields better outcomes in pain and function in the long-term (over 24 weeks)
PRP - TENDINOPATHIES:

- **ACHILLES TENDON**
  - Meta-analysis of 5 RCTs comparing PRP versus placebo (saline or eccentric loading)
  - No differences in Victorian Institute of Sports Assessment-Achilles (VISA-A) scores. VAS pain scores did not differ at 6 weeks and 24 weeks
  - VISA-A scores were lower in the PRP group at 12 weeks.
  - Conclusion: Limited evidence supports that PRP injection is superior to placebo

- **PATELLAR TENDON**
  - Meta-analysis: Eccentric exercise had the best result at short-term (<6 months)
  - PRP superior results at long-term follow-up (>6 months)
PRP - TENDINOPATHIES:

– GLUTEUS MEDIUS/MINIMUS
  ▪ Fitzpatrick et al. Single USG LR-PRP vs CSI for chronic (>15 mos) gluteal tendinopathy
  ▪ Improvement after LR-PRP injection is sustained at 2 years
  ▪ CSI: maximal improvement @ 6 weeks, not maintained beyond 24 weeks.

– HAMSTRINGS
  ▪ Seow et al. Systematic review. 10 studies were included with 207 hamstring injuries in the PRP group, and 149 in the control group.
  ▪ Statistically nonsignificant evidence to suggest that PRP injection ± PT reduced mean time to RTP or reinjury rates compared to no treatment or PT alone for hamstring injuries in a short-term follow-up.


AOASM 2021 VIRTUAL CONFERENCE
PRP - OSTEOARTHRITIS

- OVERVIEW
  - Estimated worldwide prevalence of 10% in men and 18% in women >60 yo
  - OA constitutes the most widespread musculoskeletal disease in the world.
  - Trials suggest that PRP may offer chondroprotection, anti-inflammatory effects, cell-phenotype modulation, and joint pain attenuation.
PRP - OSTEOARTHRITIS

**KNEE**

- Currently more Level 1 research showing that PRP is better for treating knee OA than *any other* nonsurgical treatment.
- 15 RCTs comprising 1,314 patients.
- A meta-analysis reported that PRP injections reduced pain more effectively than hyaluronic acid (HA) injections at 6 months and 12 months follow-up. Better functional improvement was demonstrated in the PRP cohort at 3, 6, and 12 months.
PRP - OSTEOARTHRITIS

- HIP:
  - Review & meta-analysis (Medina-Porqueres 2021).
  - Total of 4 trials (334 participants, 340 hips) were included, all marked as “moderate risk of bias”
  - The superiority of PRP against comparative treatments was only reported in one study
  - Longer-term evaluations from 4 to 12 months showed diverse results, with only one study reporting significantly better results for PRP.
  - PRP may be beneficial and safe for patients with HOA at mid-term follow-up. However, its superiority over other procedures such as hyaluronic acid remains unclear.

PRP - OSTEOARTHRITIS

- SHOULDER (GLENOHUMERAL):
  - 3rd most commonly affected large joint affected by OA (after knee & hip)
  - Yet studies are scarce!
  - NO RCT trials exist
PRP – SUMMARY

- Good evidence for: Lateral epicondylitis, plantar fasciitis, trochanteric syndrome, knee OA
- Moderate evidence for: Patellar tendinosis and RTC, hip OA
- Weak evidence for: Achilles, hamstring, other OA
- Inconclusive evidence for spine & muscle injuries
- No consensus currently regarding optimum platelet counts or injected volumes
- Some evidence for:
  - LR-PRP better for tendinopathies
  - LP-PRP better for OA
PRP – SUMMARY, Cont.

- Most studies plagued by:
  - Poor design
  - Short follow-ups
  - PRP not characterized (e.g., LR, LP, RBC count, platelet concentration, etc.)

- No consensus currently regarding optimum platelet counts or injected volumes

- *Some* evidence for:
  - LR-PRP better for tendinopathies
  - LP-PRP better for OA
BONE MARROW DERIVED TREATMENTS

- Technically cannot call these “stem cell” treatments!
- Nomenclature: BMAC vs BMA (centrifuged vs non-centrifuged)
- Harvests typically performed via the posterior ilium (PSIS)
- Can also harvest from ASIS
- Do NOT want to harvest from long bones in older population (due to fatty degeneration of marrow)
- Most studies suggest that of the cells in bone marrow, only 0.01% to 0.001% are actually “stem/progenitor cells” (60-600 cells per ml of harvest)
BMA/C FOR OSTEOARTHRITIS

- By far the most commonly studied condition
- Very few high quality (Level I-II) studies
BMA/C FOR OSTEOARTHRITIS

- KNEE OA
  - Kim et al (2019) review & meta-analysis of Level II studies
  - 5 RCT’s (220 patients). Only 2 studies had low risk of bias
  - 4 studies used BMAC, 1 used fat-derived treatment
  - Significant difference in VAS score and Lysholm score, but not WOMAC at 12 & 24 months
  - No difference in cartilage repair via MRI

BMA/C FOR OSTEOARTHRITIS

- OSTEOCHONDRAL LESIONS
- KNEE
  - Hernigou et al (2021) RCT of intraosseous BMAC injection
  - 15-year follow up!
  - Patient was own control – bilateral OA of equal severity; only 1 knee was treated.
  - Subchondral BMC had a sufficient effect on pain to postpone or avoid the TKA in the contralateral joint
  - Bone marrow lesions were predictive factors for future knee arthroplasty in the knee with subchondral cell therapy at 10 years follow-up; persistent BML’s > 3 cm³ had incr. surgery

BMA/C FOR OSTEOARTHRITIS

- Hernigou et al, cont
BMA/C FOR OSTEOARTHRITIS

**HIP OA**
- Whitney et al (2020). 24 patients, single BMAC injection, 6-month f/u
- WOMAC, modified Harris Hip Score, SF-12, and others
- Significant improvement in subjective pain and function scores up to 6 months

**HIP & KNEE OA**
- single I-A BMAC inj.
- Mean follow-up was 13.2 ± 6.3 months
- “satisfactory results in 63.2% of patients”


BMA/C FOR OSTEOARTHRITIS

- HIP AVN
  - 24 hips, randomized either to core decompression (CD) or CD + I/O BMAC
  - Significant reduction in pain and in joint symptoms and reduced the incidence of fracture stages.
  - At 60 months, 8 of the 11 hips in the control group had deteriorated to the fracture stage vs only 3 of the 13 hips in the BMAC group.
  - Survival analysis showed a significant difference in the time to failure between the two groups at 60 months.
BMA/C FOR OSTEOARTHRITIS

- **KNEE – BMA vs PRP**
  - Anz et al (2020). RCT (Level II). 90 patients, between 18 and 80 years with symptomatic knee OA (Kellgren-Lawrence grades 1-3) were randomized into 2 study groups: PRP and BMC.
  - All IKDC and WOMAC scores for both the PRP and BMC groups significantly improved from baseline to 1 month after the injection (P < .001).
  - Improvements were sustained for 12 months after the injection, with no difference between PRP and BMC at any time point.
  - Conclusion: No difference between BMC and PRP.

BMA/C FOR OSTEOARTHRITIS

- SUMMARY
- Very limited high quality human studies
- Treatments often confounded by inclusion of other co-treatments (PRP, surgery)
- Best evidence currently seems to be for knee OA and BML’s/AVN, followed by hip OA
- Harvest can be painful, depending on technique.
MICRONIZED FAT TREATMENTS

- **Nomenclature**
  - Can be confusing
  - Micronized fat (“MFAT”) vs. processed lipoaspirate (“PLA”)
  - SVF
  - ADSC’s

- **Regulatory concerns**
  - Cannot enzymatically digest fat to extract regenerative cells
  - Bedside micronization appears to be OK

- **Cell content**
  - 5,000 - 200,000 ADSCs /ml of adipose (compare to 60 - 600 per ml bone marrow)
ADIPOSE COMPOSITION

- Adipocytes
- Progenitor Cells
- Extracellular Matrix
- Mesenchymal Stem cells
- Capillaries & Pericytes
MICRONIZED FAT for OA

- **KNEE**
  - For patients with all grades of knee osteoarthritis who were treated with intra-articular injections of MFAT, statistically significant improvements in pain, function, and quality of life were reported.
  - 12-month f/u
  - For patients with all grades of knee osteoarthritis who were treated with intra-articular injections of MFAT, statistically significant improvements in pain, function, and quality of life were reported.

MICRONIZED FAT for OA

- **KNEE**
- 30 patients, KL I-III. 1- & 3-year follow up.
- A total median improvement of 20 points in IKDC-subjective and total KOOS
- 24- and 31-point improvement, respectively, in VAS pain and Tegner Lysholm Knee
- Results observed at 1 year were maintained.
- @ 3 years 41, 55, 55 and 64% of the patients improved with respect to the 1-year follow-up in the Tegner Lysholm Knee, VAS, IKDC-subjective and total KOOS, respectively.


MICRONIZED FAT for OA

- HIP
- There are currently no level 1 RCTs investigating the use of MSCs for the treatment of hip OA.
MICRONIZED FAT TREATMENTS - SUMMARY

- Paucity of high-quality human studies
- Most studies are in animal models
- Most studies use enzymatically digested and/or culture-expanded adipose-derived MSCs – prohibited by FDA
- Many studies are done by incorporating regenerative medicine tx at time of surgery (e.g. rotator cuff).

HOWEVER:
- Appears to be safe.
- Anecdotally effective.
- Well tolerated.
PERINATAL PRODUCTS

- Amnion-, placenta, and umbilical cord blood-derived
- No human studies
- Marketing hype and clinical use has far outpaced research
- NONE of these products contain ANY live viable “stem cells!”
- Some may have beneficial growth factors.
- Concerns re FDA regulatory compliance
PERINATAL PRODUCTS – "STEM CELL" PRODUCTS?

Acridine orange
all nuclei

Liveyon
PERINATAL PRODUCTS – "STEM CELL" PRODUCTS?

Acridine orange
all nuclei

Propidium iodide
dead cells

Liveyon
PERINATAL PRODUCTS – ”STEM CELL” PRODUCTS?

Hematology Analysis

- RBC
- nRBC
- HGB
- retic
- WBC

Cell #, x10^6

Cord Blood  Early  Late  PURE Fresh  After Thaw

Liveyon
PERINATAL PRODUCTS – ”STEM CELL” PRODUCTS?
SUMMARY

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  - Good evidence for: Lateral epicondylosis, plantar fasciitis, trochanteric syndrome, knee OA
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  - Studies limited by:
    - Poor design, short follow-up, PRP not characterized
SUMMARY

- BONE MARROW
  - Best evidence is for OA and BMLs
  - Some limited evidence for disc annular tears
  - No clear advantage of BMA/C over BMA
  - Studies plagued by:
    - Limited number of high-quality studies
    - Poor study design
    - Short-term follow-up
  - No apparent downsides though
SUMMARY

- ADIPOSE
- Good anecdotal and case report data for OA
- Studies limited by:
  - Paucity of high-quality studies
  - Mostly animal studies
  - Most studies use SVF
  - Poor study design
- No apparent downsides though
SUMMARY

- PERINATAL PRODUCTS
  - NO human studies
  - No live cells
  - Marketing hype
  - FDA regulatory concerns
  - Not autologous
Thank You!

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