The Wild West – Stem Cell: From the Athlete to the Weekend Warrior

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Overview

• IOC consensus paper on the use of PRP in sports medicine
    • “Work in Progress, need more studies, indications and outcomes better understood”

• The number of STEM cell clinics has roughly doubled every year since 2010
Father of Sports Medicine

- Galen 100AD
  - “Athletes over indulge, live shorter and get arthritis”
Regenerative Medicine for Cartilage in the Athlete

• The problem
• Managing expectations
  – All regenerative medicine is not created equal
• What can we treat
• Outcomes
• Next Steps
Cartilage Injury

- ACL tears
  - Up to 50% of athletes that undergo ACL reconstruction have cartilage damage
  - 200,000 ACL injuries per year = ~100,000 cartilage lesions just from ACL injuries
Articular Cartilage Injury Mechanisms

• Acute Injury: ACL
  • Catabolic “Bone Bruise”
    • ↓ GAG Content (chronic)
    • ↓ Aggrecan Levels after 2 yrs
    • Chondrocyte Apoptosis

• Traumatic Focal OC Defect
  • Incidence 9-60%
  • Shear Injury/Compression
  • Forces > 25-35 MPa
  • Subchondral Bone Fracture
Chondroprotection and Chondrofacilitation

• **Hyaluronic Acid Injection**
• **Cytokine Modulation**
  – IL-Ira - Inhibition of Inflammatory Response
• **PRP**
• **Growth Factor Augmentation**
  – Factors: BMP-7, BMP-4, FGF-18, IGF-1
    Stimulation of: MSC-Differentiation, Proliferation, Metabolism
• **Stem Cells**
  – Adipose derived
  – BMAC
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STEM cell Expectations…Need to know basis

- What and why is effective?
- For what and when?
- Which do we use?
- How much?
  - Dose / volume of treatment?
  - Number of injections
  - Treatment Intervals
- Need Platelet activation?
- Treatment protocol
  - When to treat?
  - Adjuvants HA, ADSCs/BMAC
  - Rehab, exercise, RTS?
Hyaluronic Acid

- Safety has been documented: over 675 published studies
- Efficacy has been demonstrated: **28 RCTs/ 3 meta analyses**
- Questions still persist about associated chondroprotective effect in humans
- Short-term efficacy
What Does it Treat?

- Regenerative medicine has been used to treat a variety of injuries and conditions:
  - Tendon injuries
    - Achilles tendonitis, rotator-cuff injuries and “tennis elbow.”
  - Arthritis and cartilage injuries.
  - Plantar fasciitis
  - Muscle strains.
  - Ligament sprains.
  - Degenerative disc disease.
  - Facet joint arthritis.
Biologic Therapy Contraindications

- Acute systemic infection
- Local infection at or near site
- Malignancy (remission), with the exception of nonmetastasizing skin tumors such as squamous cell carcinoma or basal cell carcinoma
- PRP therapy is not recommended in thrombocytopenia or those who use nonsteroidal anti-inflammatories in the two weeks
- Pregnancy
Autologous Interleukin-1 receptor antagonist improvements RCT in OA

- Will I get what Kobe got?
  - Regenokine

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<th>Platelets (growth factors)</th>
<th>WBC (catabolic cytokines)</th>
<th>Stem Cells</th>
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<td>PRP</td>
<td>+++</td>
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<td>ACS / IRAP</td>
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- Theory: blood is removed weeks before and incubated with borosilicate (CrSO₄) coated glass beads with stimulates IL-1ra
- Likely not as effective as PRP.
- Cost: $1,000 to $2,000
Platelet Rich Plasma

- Growth factors released from platelet a-granules
  - Enhances release of NF-kappa-beta inhibitor, and thus reduce NF-kappa-beta signaling and dampen its downstream inflammatory cytokine activation
  - (TGF, PDGF, VEGF, BMPs, IGF-I)
    - Some is good  more is better

- Cost: $500 - $2,000
Not All PRPs are Created Equal

• Platelets, WBCs, RBC reduction, and Platelet:WBC vary widely in the different commercially available products
• Leukocyte-rich vs leukocyte poor
More Than Just Platelets
Bone Marrow Aspirate Concentrate - BMAC

- Bone Marrow contains a high concentration of "pluripotent" stem cells that can be withdrawn from the hip bone
- The theory: “undifferentiated” cell will replicate into various types of tissues that could heal injuries
- Where’s the Matrix?
- Cost: $2,000 - $5,000
Mesenchymal Stem Cell (MSC) from Bone Marrow

• Rare, undifferentiated multipotent stem cell
  – Relatively mature
  – Less capacity for differentiation
    • Must differentiate in to fat, bone, and cartilage
    • Can differentiate in to muscle, tendon, and ligament
  – MSC receive local paracrine signals
    • Leads to proliferation and differentiation to surrounding host tissue
  – Immunosuppressive
  – 0.01 to 0.001% of nucleated marrow cells
  – Declines with age
Adipose Derived Concentrate _ ADC

- Harvested from adipose tissue
- Very powerful cells
  - Many different pathways
- Need a scaffold
- Cost: $2,000 - $15,000
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Tendon Injury - PRP

• "The evidence for all primary outcomes was judged as being of very low quality."
  – Methods for preparing and quantifying PRP therapies lack standardization.
  – Evidence to support the use of PRP therapies for treating muscle and tendon injuries is lacking, both overall and for specific conditions.

• Common problems with research
  – Small number of participants
  – Blinding of participants and/or outcome assessors not performed or not described
  – Treatment preparation not standardized among trials
Tendon Injury – STEM cell

- Current evidence is limited and unconvincing
  - Low patient numbers
  - Small number of trials using expanded MSCs
  - Little to no control groups
  - High risk of bias
Muscle Injury

- Few randomized trials
  - High risk of bias
- No statistical significant difference in reinjury rates with PRP
- STEM cell treatment – limited research
Osteoarthritis

- Luekocyte poor superior to leukocyte rich
- High degree of bias in studies
  - Studies were favorable for both PRP and STEM cells
- Not many good control trials
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Patients with Early OA did better
Early OA – HA vs PRP

- Patients treated with PRP showed better results at 1-year follow-up than patients treated with hyaluronic acid; the results deteriorated over 12 to 24 months of follow-up
Anecdotally – it works

- That said, there is a high placebo effect
- Get what you pay for
- More willing to be compliant with rehab/restrictions
Next Steps

• Three Food and Drug Administration scientists in the *New England Journal of Medicine* looking at the benefits and risks of this kind of stem cell therapy, “This lack of evidence is worrisome.”
Case Western Reserve / University Hospitals
Sports Medicine Institute
FDA Approved Stem Cell Study
Collaboration: UH Sports Medicine and NCRM

- FDA IND approved
- Pilot study: Intra-articular autogenous, expanded MSC injections (50 x 10^6 MSCs) in 20 patients age 18-60 y.o. with:
  - Early knee OA
  - Focal cartilage defects.
- Stem cell expansion performed by the Cellular Therapy Integrated Services (CTIS) of the NCRM
- Followed 2 years, functional outcomes, pain scale, MRI, synovial fluid analysis.
- **Does increased concentration of stem cells improve outcome?**
Thank You

• Questions