Current Use of Regenerative Therapies in Sport Horse Injuries

Indiana Association of Equine Practitioners
November 2012

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Introduction

- Injuries that are amenable to biologic regenerative therapy
- Regenerative therapies
- Clinical use and results

Introduction

- "Hot topic" for injury repair (Prades 2007, Brehm 2008, Fortier 2009, Frisbee 2009)
- Clients are asking about and for it
- Harness the body's own reparative mechanisms
- No foreign substance
- More "functional" healing
- Formation of NAVRMA with meetings Feb 2010, Jun 2011 and Nov 2012- www.navrma.org

Sport Horse Injuries- Joints

- Acute-
  - Sprain, synovitis, cartilage damage, subchondral bone trauma, "bad step"
- Chronic-
  - Due to repetitive mature of activity on joint
  - Instability of joint- conformation, soft tissue support
  - Cartilage wear- degeneration and cellular byproducts
  - Osteoarthritis- chronic synovitis
- Developmental-
  - Osteochondral fragments or bone cysts- fetlock, hock, stifle, pastern

Sport Horse Injuries- Ligaments

- Acute desmitis-
  - Overload injury due to altered mechanical overload or lack of "conditioned" tissue for load
  - Footing, weight of animal, shoeing
  - Location- body SL, branch SL, DSL, ALDDFT
- Chronic desmopathy-
  - Repetitive stress with progressive weakening, damage, poor attempted repair, swelling, thickening, fibrosis
  - Possible lack of recognition of problem, not particularly painful or limiting in early stages, conformation
  - Many at bone/ligament attachment- PSL, sesamoids

Sport Horse Injuries- Tendon

- Acute tendinitis-
  - Trauma, overload
  - Margin vs. core vs. tears- SDFT, DDFT (low)
  - Apineurosis of muscle to tendon
- Chronic tendinopathy-
  - Recurrent injury at juncture of previously damaged region- proximal or distal

Regenerative Therapies

- Bone marrow aspirate (BMA)
- Platelet rich plasma (PRP)
- Interleukin-1 receptor antagonist protein (IRAP)
- Stem cells- mesenchymal or embryonic (SC)

Regenerative Therapy- General Aspects

- Centered on use of biologics from natural sources
- Autologous- Enhancing already present healing mechanisms
- Allogeneic- “Off the shelf” source, prepared and stored
- Embryonic source- universal aspect
- Provide growth factors- Regulate cellular metabolism
- Provide cellular matrix or scaffolding
- Provide multipotent or pluripotent cells that may differentiate

Regenerative Therapy- Growth Factors

- Protein signaling molecules that regulate cellular metabolism- either positively or negatively
- Enhance tissue healing- stimulate cell proliferation, increase extracellular matrix synthesis, promote vascularization
- Down or Up regulate catabolic cytokines- interleukins and matrix metalloproteinases
- Available as recombinant, purified protein or within a "slurry"- platelet rich plasma, bone marrow aspirate

Growth factors

- Platelet derived growth factors (PDGF)
- Bone morphogenetic protein-2 (BMP-2)
- Insulin-like growth factor-I (IGF-I)
- Transforming growth factor-B (TGF-B)
- Vascular endothelial growth factor (VEGF)
- Growth/differentiation factor (GDF)
- Basic fibroblast growth factor (BFGF)

Evidence for Growth Factor Efficacy

- In vitro and animal studies (Waselau 2008, Schnabel 2008, Sampson 2008, McCarrel 2009)
- In vivo rat model- increase breaking strength of Achilles tendon (Smith 2006)
- Tendon and ligament results suggest tissue response differs with sites (Schnabel 2007)
- Enhanced cartilage/osteochondral repair (Mishra 2009)
- Little long term, multicentered human or equine data available

Bone Marrow Aspirate

- Slurry of cells, growth factors
- Proteins from bone marrow stroma
- Hematopoietic stem cells
- Undifferentiated multipotent cells- mesenchymal stem cells
- Potential of cells to differentiate- variable/unknown
- Often combined with PRP (Herthel 2001)
- Used in tendon, ligament, bone lesions (Smith 2003/2006, Crovace 2007, Schnabel 2008)

Bone Marrow Aspirate

- Obtained from the sternum or tuber coxae
- Standing or under general anesthesia
- Sterile preparation
- Heparinized syringe
- Separated in close optic base systems
  - Magellan Technology

Bone Marrow Aspirate

Platelet Rich Plasma

- Obtained from blood- autologous, (ACS)
- Concentration of platelets and some leukocytes- centrifugation, filtration
- High growth factor concentration
- Forms scaffold within tissues upon injection
- Relatively low cost
- Use in soft tissues- intralesional, wounds (Prades 2007, Schnabel 2007/2008, Smith 2006)
- Use intraarticular (Sanchez 2008, Abellanet 2009, Saite 2009)

Platelet Rich Plasma

- Obtained from anticoagulated blood
- Desired concentration of platelets is 4-5 times circulatory levels
- Obtained by centrifugation or differential filtration
  - Remove red blood cells RBC
  - Remove platelet poor plasma PPP

Platelet Rich Plasma

PRP- Factors to Consider

- Four fold (4X) increase of platelet concentration over plasma concentration gives maximal stimulation of healing- greater numbers not better
- Leukocyte concentration affects inflammation and delays positive response
- Freezing lysis leukocytes
- Evidence that NSAIDs may diminish benefits of PRP
- Few "flares"/reactions- more during early inflammatory phase of lesion (1-10 days)
- Can use subsequent treatments (soft tissue or IA) or with BMA

Interleukin-1 Receptor Antagonist Protein (IRAP)

- First characterized 1984 to block inflammatory cascade
- Treatment for synovitis, osteoarthritis, rheumatoid arthritis in humans (Orthogen, Germany)
- Both symptom and disease modifying effects (Frisbee 2007)
- Basic science describes preferential upregulation of "good" cytokines (Meijer2003)
- Patented system in equines- Arthrex or Arthrex II
- Utilized primarily in synovial spaces- joints, sheaths, bursas

IRAP

- Preparation
- Draw blood into a syringe with etched glass beads
- Incubate for 24 hrs
- Centrifuge
  - Supernatant divided in 3-5 ml syringes
    - 100 fold increase in IL-1 Ra

IRAP- Clinical Considerations

- >30,000 human / >5000 equine kits utilized
- Usually series of intrasynovial injections (3-5) at 7-14 day intervals
- Anecdotal reports of positive results in corticosteroid "unresponsive" joints
- Utilized as scheduled "maintenance" treatment for chronic diagnosed intrasynovial concerns
- Few inflammatory flares- filtering, incubation times
- Additives of corticosteroids, HA, PSGAG may diminish efficacy (Frisbee 2009)
- Use in other tissues?

Stem Cell Therapy

- Mesenchymal vs. embryonic cells
- Literature on efficacy of stem cells is expanding rapidly (Dahlgren 2005, Clegg 2008, Brehm 2008, Oliveira 2008, Fortier 2009)
- Some difficulty defining "stem cells"
- Specific tissue derived and isolated- adipose, muscle, bone, embryonic, blood
- Culture expanded- more "pure" aliquot of cells

Stem Cell Therapy

- Potential for "regeneration" of tissue- ideal
- Affinity to bind to injured tissue (Murphy 2003, Frisbee 2006)
- Recruitment of other cells and growth factors
- Utilized in tendons, ligaments, joints (Richardson2005, Smith 2004, Frisbee 2006)
- May not accelerate regenerative process but promising results in structure and function of repair (Oliveira 2008)
- Used in regional perfusion

Stem Cell Therapy – Questions?

- Best source of cells?
- "Slurry" or "purified" cells
- Clinical issues- how many cells?, when?, how often?, how delivered?, other additives?
- Undifferentiated or pre-differentiated cells best?
- Can we select stem cell populations?

Stem Cell Therapy

- Vet Stem
- Celavet
- VetCell BioScience, LTD
- Cornell / CSU / UCD
- Numerous other tissue culture labs

Clinical Use- BMA and PRP- Soft Tissue Lesions

Soft tissue lesions	SDFT	DCL	SL	BSL	DDFT	DSL
#	5	4	5	7	5	3

- Varied severity of lesions
- Varied location (within specific tissue)
- Varied rehabilitation protocols
- Varied sport horse activity
- Multiple additional treatments

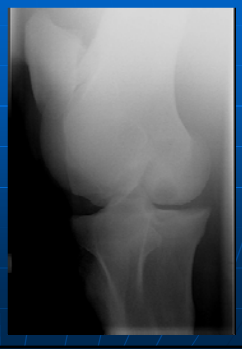
Clinical Use- BMA and PRP

BMA and PRP Results

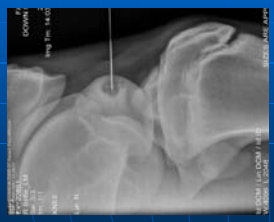
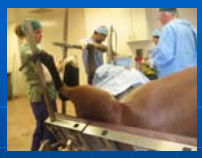
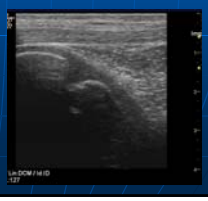
- Results- Soft tissue
  - Return to show at same level- 12/22 (55%)
  - Reduced level of activity- 7/22 (32%)
  - Not able to return to activity- 3/22 (13%)
  - Reinjured- 3/19 (16%)
  - Presently rehabbing- 7

Clinical Use-BMA/PRP- Subchondral Bone Cysts

- Five sport horses
- Acutely clinical in mature horses
  - Medial femoral condyle - (4)
  - Pastern - (1)



Clinical Use-BMA/PRP-Subchondral Bone Cysts

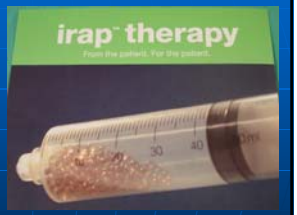




BMA/PRP- Subchondral bone cysts

- Clinical problem is cartilage disruption and cellular debris in joint
- Results- MFC
  - Back to show – (1)
  - Reduced work – (1)
  - Chronic lame – (2)
- Pastern - sound

Clinical Use IRAP

- Intraarticular – 15 cases
  - Fetlock- 8
  - DIP- 5
  - Stifle- 2
- High motion joints
- Unresponsive to previous treatment- rest, corticosteroids, HA*
- Series of 3-4 txs, 7-14 day interval
- Not used in tendon sheaths



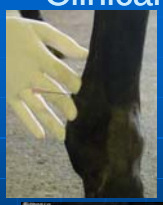
Clinical Use IRAP- Results

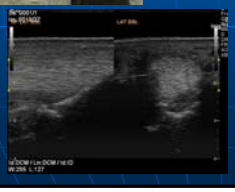
- Fetlock- 6/8 (75%) returned to previous activity
- DIP- 4/5 (80%) returned to previous activity
- Stifle- 1/2 (50%) returned to previous activity
- Total- 11/15 (73%)
- Interpretation?*

Clinical Use- Stem Cells

- Fat derived- 4 cases
  - Joint– 2 (DIP, fetlock)
  - Soft tissue- 2 (DSL, DDFT)
- Bone marrow origin- 5 cases
  - Joint- 2 (fetlock)
  - Soft tissue- 3 (SDFT, SL)
- Embryonic derived- 2 cases
  - Joint- 1 (tibial tarsal)
  - Soft tissue- 1 (SDFT)

Clinical Use- Stem Cells





Stem Cells- Results

- Fat derived-
  - DIP- reduced level
  - Fetlock- retired
  - DSL, DDFT- previous level
- Bone marrow cultured-
  - Fetlock- (1) retired, (1) in progress?
  - SDFT- previous level*
  - SL- previous level*
- Embryonic derived-
  - Hock– retired*
  - SDFT- previous level

Summary

- Number of regenerative therapy options
- Basic science concerning these therapies is needed- growth factors, gene expression, what is actually going on?
- Will continue to be a requested treatment modality by horse clients
- Does not shorten “healing” time; rehabilitation programs important
- Clinical studies are difficult to compare

Thank You - Questions?