Biologics in ACL: What’s the Data?

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I have no conflicts to disclose

Clinical Goals

- Conservative treatment of partial ACL injuries with biologic augmentation
- Primary repair of ACL injury
- Optimization of healing and remodeling of ACL autograft and allograft
- Intra-tunnel healing
- Intra-articular graft repopulation
- Tissue engineering of ligament replacements
Acute Ligament Injury

- Several studies have evaluated PRP for augmentation of healing of an ACL reconstruction graft
- Essentially no controlled studies for other ligament injuries
- "No evidence in human clinical trials of the efficacy of PRP in treating ligament injuries"

Effects of platelet concentrate and a bone plug on the healing of hamstring tendons in a bone tunnel
(Orrego et al, Arthroscopy 2008)

- Randomized controlled trial; LOE 2
- ACL reconstruction with semitendinosus graft
- 108 patients prospectively randomized into 4 groups:
  - Control (27 patients)
  - Platelet concentrate (26 patients)
  - Bone plug (28 patients)
  - Combination platelet concentrate + bone plug (27 patients)
- MRI at both 3 and 6 months post-surgery
- Maturation of the graft was evaluated at the femoral tunnel using MRI maturation criteria:
  - low-intensity graft signal
  - absence of osteoligamentous interface and no widening of the femoral tunnel
**Effects of platelet concentrate and a bone plug on the healing of hamstring tendons in a bone tunnel**

*(Orrego et al., Arthroscopy 2008)*

- Superior graft maturation in PRP group at 6 mo (p=.04)
- No statistical differences in bone-tendon interface or tunnel widening between the various groups
- The use of a bone plug effectively prevented tunnel widening
- Platelet concentrate + bone plug combination did not show a synergistic effect as compared to either individually
- No difference in clinical outcomes (IKDC and Lysholm scores)

**Has platelet-rich plasma any role in anterior cruciate ligament allograft healing?**

*(Kim et al., Arthroscopy 2009)*

- Level of evidence 3
- Studied effects of PRP on ACL reconstruction using hamstring autograft (n=40)
- Patients sequentially enrolled in four groups:
  - Control (10)
  - PRP in femoral tunnel (10)
  - PRP in femoral tunnel and intra-articular injection of PRP at 2- and 4 weeks after surgery (10)
  - PRP in femoral tunnel activated with thrombin (10)
- Outcome: MRI signal intensity of the fibrous interzone in the femoral tunnels at 3 months
- No difference among the groups when comparing the graft signal intensity on MRI

**Anatomic ACL reconstruction: Does the platelet-rich plasma accelerate tendon healing?**

*(Silva and Sampaio, Knee Surg Sports Traumatol Arthroscopy 2009)*

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Effects of a platelet gel on early graft revascularization after ACL reconstruction: a prospective, randomized, double-blind clinical trial (Vogrin et al, Eur Surg Res. 2010)

- Prospective, random, double-blind study; level of evidence 1
- 25 PRP gel, 25 controls
- MRI to quantitatively evaluate the revascularization process at the bone-ligament interface in the bone tunnels and in the intra-articular part of the graft
- MRI evidence of greater revascularization at bone-ligament interface was seen at 4-6 wks (p < 0.001) but no difference at 12 wk
- No difference was seen in the intra-articular part of the graft
- Limitations:
  - Short follow-up
  - Limited to MRI
  - No clinical correlation
  - Small sample size

PRP in ACL Reconstruction

- PRP may have an effect on early graft revascularization
- Difficult to draw conclusions because of variability in:
  - Graft types studied
  - Graft fixation techniques
  - Femoral vs tibial tunnel evaluated
- No demonstrated effect on clinical outcome
- All published studies on the use of PRP must clearly describe the techniques for preparation and the composition of the injected or implanted material

Tendon-to-bone attachment

- Potential "weak link" following surgical repair
- Rehabilitation is limited by repair site protection
- Insertion site composition and morphology are not re-established after surgical repair
- Tendon insertion following tendon-to-bone repair has inferior biomechanical properties in animal studies
- Cellular and molecular mechanisms of healing are poorly understood
- Mechanical environment plays a role in healing and tissue composition
- Understanding basic biology of healing will facilitate development of methods to augment or improve healing
Is there basic science to support the use of biologic or mechanical augmentation of ACL reconstruction?

Cell Signaling in Ligament Injury

- MCL: multiple in vivo animal studies demonstrating effect of load on modulation of matrix production and material properties
  - Injury results in increases in TGF-beta which result in upregulation of myofibroblasts in ligament
  - Cyclic load optimizes cell proliferation and matrix reorganization
- ACL: disruption of ligament (stress deprivation) results in atrophy and retraction of ligament stump
  - Increase in alpha SMA expression in ACL stump
  - Increase in SMA in early wound healing in MCL
  - Increase in MMP in absence of load promotes retraction and remodeling

How can we study ACL healing and remodeling?

- Rabbit partial ACL injury model
- Studied at 2 and 6 weeks
- Ligament cells mount a healing response
- Partial transection:
  - Intact segment demonstrates increase in col1-1 and col1-3
  - No significant change in alpha SMA expression
- Complete ligament and cut partial specimens:
  - Marked increases in MMP-1, MMP-13 which result in matrix dissolution
  - Increased alpha SMA expression which increases myofibroblast population and may be responsible for involution of the ACL stump
Future Approaches to Ligament Repair/Regeneration

- Use of MSC selected for bone or ligament producing properties
- There are no published clinical trials demonstrating the efficacy of MSC
- Use of targeted and specific growth factors such as TGF-beta to enhance healing, cell proliferation and remodeling
- BEAR = Bridge Enhanced ACL Repair (M. Murray et al)
  - Open primary repair of ACL
  - Augmented by proprietary collagen matrix + autologous blood
  - Phase 2 clinical trials ongoing

FDA Guidance Guidelines for Regenerative Medicine

- Guidance documents will define what constitutes minimal manipulation of cells with a goal to establish the threshold for regulation by the FDA
- Scott Gottlieb, Commissioner of the FDA describes novel innovations in the regenerative field as a “movement past science fiction that needs a clearer pathway for those developing new therapies”
- We remain surrounded by clinics and CME training programs that claim success in the absence of scientific evidence

Thank you