Biologic Therapy for Joint Disease
Platelet-Rich Plasma, Interleukin-1 Receptor Antagonist Protein/Autologous Condition Serum, and Bone Marrow Aspirate

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1. Introduction
Regenerative therapies are based in biologics that capture the body’s natural ability to heal. There are several types of regenerative therapies being used, including platelet-rich plasma (PRP), stem cells of several varieties (only bone marrow aspirate is discussed herein), and autologous condition serum (ACS)/interleukin-1 receptor antagonist protein (IRAP). Each of these therapies is relatively new, so there is very limited clinical data accumulated to date and none published on naturally occurring joint disease in equine patients.

2. Autologous Conditioned Serum
ACS was probably the first biologic to be tested in horses. ACS is generated through the same process as IRAP, but for primarily legal reasons, it is called ACS. It is thought to act by blocking the receptor to the inflammatory cytokine interleukin-1 (IL-1). When injected intra-articularly into horses with surgically created synovitis/early arthritis, ACS resulted in decreased synovial hyperplasia and lameness compared with placebo-treated groups. There is a newer generation of ACS termed IRAP II, which boasts increased IRAP levels and is presently being evaluated by the Comparative Orthopaedic Research Laboratory at Colorado State University.

3. Platelet-Rich Plasma
The definition of PRP is highly variable and can range from plasma with a 2-fold or more increase in platelet concentration above baseline levels or >1.1×10⁶ platelets/μl. PRP is generated primarily by centrifugation or gravity filtration. There are differences in the volume of autologous blood required, time and speed of centrifugation, addition of an activating agent, leukocyte concentration, method of delivery, and qualitative/quantitative dif-
ferences with respect to final PRP volume and final platelet and growth factor concentrations between the available systems. Overall, the final PRP platelet concentration is 2 to 8 times over baseline. It is important to recognize and understand that there are obvious differences between types of platelet concentrates that are being used; the general abbreviation PRP will be used herein.

The concept that PRP would improve joint disease is based on the physiologic role of platelets in wound healing. Through a modulation of the inflammatory response, promotion of local angiogenesis, attraction of fibroblasts and local stem cells to the site of injury, and an induction of autocrine growth factor production by uninjured adjacent cells, platelets, and their products are instrumental in normal tissue repair and regeneration. However, PRP contains white blood cells as well, and work in our laboratory suggests that there is a correlation between white blood cells in PRP and increased tissue catabolism and decreased matrix synthesis. In addition, unpublished data from our laboratory group indicate a positive correlation between white blood cells, predominantly neutrophils, and both IL-1 and tumor necrosis factor-α. Combined, these data suggest that white blood cells deliver catabolic cytokines, and they increase tissue degradation and inhibit matrix synthesis. These data suggest that the optimal PRP preparation would be one with the lowest white blood cell content to maximize the benefits of platelet-derived growth factors while minimizing the inflammatory and tissue-degrading effects of white blood cells. Presently, there is no head-to-head comparison among the various PRP products, but the practitioner should ask the manufacturer what the platelet content is in the PRP preparation and what the white blood cell content is, as well.

Once isolated, PRP can be injected into a joint with or without an activating (clotting) agent. The addition of bovine thrombin to the PRP sample just before or during injection is used in some systems to activate platelets, resulting in initiation of the clotting cascade. Clotted PRP serves as a fibrin matrix scaffold for tissue repair and a reservoir for retention and slow release of growth factors.

The application of PRP in joints is relatively new and therefore there are limited publications investigating its use. Chondrocytes and mesenchymal stem cells exposed to PRP have significantly increased cell proliferation and cartilage extracellular matrix synthesis of proteoglycans and collagen type II compared with controls. Synoviocytes from osteoarthritis patients cultured in PRP demonstrated significantly increased hyaluronic acid production and secretion, suggesting that PRP could potentially stimulate an endogenous source of chondroprotection and joint lubrication after intra-articular application. There are several human clinical studies supporting the use of PRP for arthritis, but no horse data are presently available in peer-reviewed form.

In a collaborative effort with Dr. Brian Cole and colleagues at Rush Memorial Hospital in Chicago, Illinois, we have used end-stage arthritic human cartilage and synovium collected during total knee replacement and determined that application of PRP (with low white blood cell concentrations and an average of 2- to 3-fold increase in platelets) decreases markers associated with pain including tumor necrosis factor-α, substance P, and IL-1 (preliminary data). It is unclear at this time which component of PRP (platelets, white blood cells, or another plasma component) is responsible for the anti-nociceptive effects, but it is probably the growth factors.

4. Bone Marrow Concentrate

Bone marrow concentrate (BMC) is generated through centrifugation of bone marrow aspirate. The advantage of BMC over PRP is that it contains mesenchymal stem cells, which have demonstrated utility for regeneration of cartilage and other tissues of the musculoskeletal system. Like PRP, BMC is a fully autogenous biologic that can be generated patient-side and, when clotted, form a scaffold. Also, like PRP, BMC contains platelets and therefore is a rich source of growth factors, including platelet-derived growth factor and transforming growth factor-β.

In an equine model of 15-mm-diameter, full-thickness cartilage defects, BMC resulted in significantly improved cartilage repair compared with microfracture, using short-term arthroscopic inspection and longer-term macroscopic, histologic, and quantitative magnetic resonance imaging analyses. Differences between BMC and microfracture observed arthroscopically at 12 weeks persisted at 8-month evaluation. In particular, repair tissue in BMC-treated defects was integrated much better into surrounding normal cartilage, and the tissue was thicker and had a smoother surface. Like PRP, BMC is being used as a direct primary intra-articular joint injection, but no clinical data have been reported on its use.

In summary, regenerative therapies are showing tremendous promise for the treatment of equine joint disease, but the therapies are too new to draw any firm conclusions regarding specific indications, contraindications, or prognosis after their use.

References and Footnotes