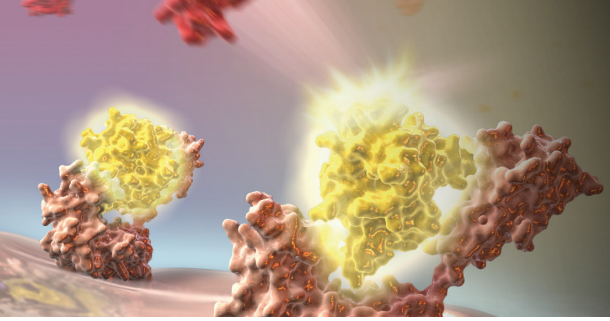

IRAP for Veterinary Applications Scientific Update

Osteoarthritis (OA) causes pain with daily movement, inhibiting function, and is associated with increased chronic inflammation within the joint, leading to cartilage degeneration. The main inflammatory protein that has been associated with this joint inflammation in OA is interleukin (IL)-1β. Our IRAP devices, sometimes described as autologous condition serum (ACS), processes whole blood with a 16- to 24-hour incubation period that stimulates the immune cell called a monocyte to release high levels of the IL-1β antagonist protein. This protein is the IL-1 receptor antagonist protein (IL-1Ra or IRAP), which blocks the IL-1 receptor on cells that IL-1β interacts with to cause a release of other inflammatory and degradative proteins. The autologous product from this device effectively blocks these receptors, which are overactivated in the OA joint environment, leading to a decrease in the pathological joint environment seen in OA.

In Vitro

Mehta S, Akhtar S, Porter RM, Önnerfjord P, Bajpayee AG

Interleukin-1 receptor antagonist (IL-1Ra) is more effective in suppressing cytokine-induced catabolism in cartilage-synovium co-culture than in cartilage monoculture. *Arthritis Res Ther.* 2019;21(1):238. doi:10.1186/s13075-019-2003-y

- This study's objective was to investigate single and multiple doses of IL-1Ra in cartilage and cartilage-synovium in vitro culture.
- A single dose of IL-1Ra was ineffective at suppressing the continuous IL-1α stimulation.
- Continuous dosing of IL-1Ra rescued chondrocyte metabolism and cell viability more effectively than a single dose.
- The presence of the synovium increased other anti-inflammatory (IL-4) proteins and decreased inflammatory chemicals (nitrite) in the cell environment more than cartilage alone.

Takeaway

The supplementation of IL-1Ra to joint tissue that is exposed to inflammatory proteins can reduce cartilage degradation, and this is further supported when the synovium is added to the model, indicating the synovium may better regulate a pathological joint environment with supplementation. This provides basic scientific support to treating pathological joints, like OA, with IRAP to decrease joint inflammation and decrease the degradation that follows.

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Pezzanite LM, Chow L, Griffenhagen GM, Bass L, Goodrich LR, Impastato R, Dow S

Distinct differences in immunological properties of equine orthobiologics revealed by functional and transcriptomic analysis using an activated macrophage readout system. *Front Vet Sci.* 2023;10:1109473. doi:10.3389/fvets.2023.1109473

- The purpose of this study was to analyze the mechanism of how ACS affects the synovial macrophages when under an inflammatory environment.
- ACS was found to reduce the production of IL-1β (inflammatory protein) by the macrophages (immune cells).
- ACS was found to significantly reduce the pro-inflammatory proteins of IL-6 and IP-10.
- ACS was found to reduce some genes related to inflammation, including interferon type 1 signaling, reactive oxygen species, and mTOR but did slightly upregulate some inflammatory processes of TNFα and IL-2.

Takeaway

ACS can reduce macrophage-produced IL-1β, along with its binding to the IL-1 receptor on cell types. ACS can also reduce other inflammatory proteins produced by the macrophages. ACS impacted the gene production of the macrophages with the up- and downregulation of genes, indicating a complex process of how ACS interacts with macrophages and what is released to the joint environment.

Clinical—Equine

Frisbie DD, Kawcak CE, Werpy NM, Park RD, McIlwraith CW

Clinical, biochemical, and histologic effects of intra-articular administration of autologous conditioned serum in horses with experimentally induced osteoarthritis. *Am J Vet Res.* 2007;68(3):290-296. doi:10.2460/ajvr.68.3.290

- The purpose of this study was to assess the clinical, biochemical, and histologic effects of intra-articular administration of autologous conditioned serum (ACS) in the treatment of experimentally induced osteoarthritis in horses.
- At day 70, there was a significant improvement in lameness among ACS-treated horses versus placebo-treated horses.
- There was a mean decrease in extracellular matrix proteins and inflammatory PGE2 in the synovial fluid in the ACS-treated OA group compared to the placebo-treated OA group, and there was a significant increase in IL-1Ra in the ACS-treated group at days 35 and 70 compared to the placebo-treated group.
- There was a significant decrease in hyperplasia in ACS-treated animals compared to placebo-treated animals.

Takeaway

ACS decreased lameness and inflammatory proteins out to 70 days compared to the OA group. There was also a decrease in cellular changes with ACS treatment. Longer-term studies are needed and may show additional benefits from ACS.

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Ortved KF, Goodale MB, Ober C, Maylin GA, Fortier LA

Plasma firocoxib concentrations after intra-articular injection of autologous conditioned serum prepared from firocoxib positive horses. *Vet J.* 2017;230:20-23. doi:10.1016/j.tvjl.2017.11.005

- This case study examined 7 horses, primarily used for sport or pleasure riding, with acute flexor tendon or ligament inflammation that limited their activity.
- These patients were treated with two injections of ACP 2 weeks apart with a follow-up of 10 to 13 months.
- Overall, there was a trend toward decreased injury zone and cross-sectional area of the injury for both tendons and ligaments.
- All 7 horses in this study returned to their previous workload or were back in full training at the end time point with no reinjury reported.

Takeaway

ACP was shown to be safe and effective in reducing tendon and ligament injury-related limitations in activity for an equine population with improvements in objective measures of injury size.

Lasarzik J, Bondzio A, Rettig M, Estrada R, Klaus C, Ehrle A, Einspanier R, Lischer CJ

Evaluation of two protocols using autologous conditioned serum for intra-articular therapy of equine osteoarthritis—a pilot study monitoring cytokines and cartilage-specific biomarkers. *J Equine Vet Sci.* 2018;35-42. doi.org/10.1016/j.jevs.2016.09.014

- The purpose of this study was to analyze the treatment intervals, , three times per week or three doses every 2 days, of intra-articular ACS injections and how it beneficially affected the synovial fluid concentrations of relevant proteins
- Following injection, concentrations of the anti-inflammatory protein (IL-1Ra) injected with ACS were significantly increased 1 and 4 hours after administration and returned to baseline 48 hours after administration
- After 42 days of treatment, levels of inflammatory proteins in the synovial fluid of animals treated every 2 days were decreased, almost to normal joint levels.

Takeaway

Injecting ACS every 2 days for a week appears to have superior outcomes, with decreases in inflammatory proteins in the joint compared to weekly injections. This significant decrease to 42 days indicates that this injection protocol may provide increased protection from degradation in cartilage.

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Clinical—Canine

Sawyere DM, Lanz OI, Dahlgren LA, Barry SL, Nichols AC, Werre SR

Factor concentrations in canine autologous conditioned serum. *Vet Surg.* 2016;45(5):582-586. doi:10.1111/vsu.12506

- The purpose of this study was to compare the cytokine and growth factor concentration in canine ACS to plasma.
- The concentration of IL-1Ra was increased by ~5× over baseline plasma.
- The ratio of IL-1Ra to IL-1β was increased by ~5.5× over baseline.
- The rest of the proteins analyzed in this study were variable and were not consistently or significantly increased over baseline plasma.

Takeaway

The study results indicate that ACS has the capability to increase IL-1Ra concentrations in the canine species. This study used the first generation of ACS devices sold by Arthrex, and the new generations have been shown to increase IL-1Ra in the equine population more over baseline. So, the ProEAS™ device may be able to increase IL-1Ra even greater than what is reported in this study.

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