Safety Study of Hilltop BioSciences™ Therapies

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Author: David M. Dutton, DVM, DACVS

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ABSTRACT

Hilltop BioSciences™ products are cryopreserved or lyophilized exosome therapies, minimally manipulated using Hilltop BioSciences™ proprietary process to maintain the functions of placental tissues containing extracellular vesicles, extracellular matrix, exosomes and bioactive cytokines. The safety study results presented in this review demonstrate that Hilltop BioSciences™ products are safe for administration related to tendon, ligament, or joint therapies

1. Introduction

Hilltop BioSciences products are a refrigerated liquid or lyophilized exosome based therapy supplying growth factors and anti-inflammatory mediators for tissue healing. Tissue healing indications include, but are not limited to, wounds, tendon/ligament injuries, joint injuries, and several other medical conditions the company is investigating. There are also several methods of administration for different medical conditions. Safety trials were instituted to document any adverse administration response as well as any signs of reactions both systemically and locally with the different modes of administration.

2. Methods

In total 37 horses, 44 sites, were treated with the products and were included in the safety trials with the horses monitored for a minimum of 5 days post administration.

Six horses were administered **intravenously.** Six horses were administered **subcutaneously.** Six horses were administered **intramuscularly.** Seven horses were administered **periligamentous.** Six horses were administered intra-articular. Six horses were administered peri-articular.

3. Results

There were no adverse events during administration and there were no adverse systemic signs of reaction in any of the 37 horses. Local signs of reaction, which mostly consisted of transient swelling, were observed in 30% of the horses (11/37). To discuss local reactions, each mode of administration will be broken down for further discussion.

Six horses were administered **intravenously** and no reactions were observed. Six horses were administered **subcutaneously** and 1 out of 6 had a mild swelling at the injection site that resolved within 36 hours. Six horses were administered **intramuscularly** and 2 out of 6 had mild swelling at the injection site that also resolved within 36 hours. Thus, with these first three modes of systemic administration we can conclude that the product is safe for systemic administration. In the next safety study we investigated its use locally for soft tissue injuries, specifically ligaments and joints. Product was injected **periligamentous** around the suspensory ligaments on both forelimbs of 7 horses, thus 14 suspensory ligaments were treated. Two out of the 7 horses showed local reactions with swelling at the site and in both horses the swelling was the same on both forelimbs. In one horse the swelling of both forelimbs was mild and resolved within 24 hours. In the other horse, the swelling was moderate on both forelimbs and resolved within 3 days. None of the horses with peri-ligamentous injections showed any lameness. With both horses showing equal swelling on both limbs, it can be hypothesized that each horse mounted a localized immune response to the products. The next phase of safety studies involved administration via **intra-articular** injections in 6 horses. All 6 horses developed mild joint effusion that completely resolved in all horses within 3 days. Four out of the 6 horses had an associated transient limb lameness that on average resolved within 24 hours of the onset of the lameness. The lameness was considered mild in the four cases and was graded 2/5 on the standardized AAEP grading scale. Many practitioners prefer not to have any localized reactions to intra-articular injections, so for those practitioners we went a step further and performed a safety trial for peri-articular joint therapy. Product was administered **peri-articular,** in the subcutaneous tissue around the joint, in 6 horses. No signs or reactions were observed in all 6 horses in the peri-articular study group.

4. Discussion

The review and study indicate that Hilltop BioSciences™ product is mounting a localized response with intra-articular placement as evidenced with transient effusion and lameness. It appeared this localized response did not have any deleterious consequences and from a clinical standpoint does not have a negative effect on healing. In fact, some contend the response is an expected response for initiating healing within the joint. It should be noted no systemic anti-inflammatories were administered at the time of the intra-articular injections as well. Thus peri-articular injections eliminate any localized signs to offer an alternative approach for joint therapy. It is beyond the scope of this paper, but concurrent studies are documenting peri-articular treatment as effective and, in some cases, more effective than intra-articular administration.

5. Conclusion

In this review, evidence is demonstrated that the regenerative therapeutic, exosome based product is safe for local and intravenous administration related to tendon, ligament, and joint therapies.