SABER™ FORMULATION FOR INTRA-ARTICULAR DELIVERY OF rhGH

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Abstract

Purpose: To assess the capability of SABER™ formulations of recombinant human growth hormone (hGH) to deliver joint local exposure following intra-articular injection for treatment of osteoarthritis.

Methods: SABER formulations of hGH were prepared as dispersions of spray-dried protein in vehicles composed of hydrosoluble excipients (SAIB), salol/urea, and/or biodegradable polymer(s). Six formulations were fabricated with different combinations of SAIBs and polymer(s). The formulations were evaluated for pharmacokinetics (PK) and biocompatibility in canine studies. The production of hGH is stimulated in the synovial fluid following intra-articular injection. To achieve local efficacy and avoid undesirable systemic effects, the initial release rates of the biomarker IGF-1 were stimulated 2-3 fold over baseline levels for a period of 2 weeks.

Results: rhGH was chemically and physically compatible with a range of common vehicles. Among the formulations studied, two demonstrated particularly favorable PK characteristics for joint therapy. Specifically, SABER formulations (± Zn) at a concentration of 5 mg/mL hGH provided a sustained delivery profile in the blank joint over time. The PK parameters achieved were comparable to those observed in previous studies. The synovial and serum PK parameters obtained with the SABER formulations were favorable for early PK characterization.

Conclusions: SABER formulations are promising candidates for continuous delivery of hGH in the intra-articular space of the canine joint.

Intra-Articular Growth Factors & Cartilage Repair

- Growth Hormone Actions:
  - Stimulates general proliferation and differentiation of progenitor cells
  - Stimulates IGF-1 production in differentiating and mature articular chondrocytes
  - Promotes chondrocyte proliferation and matrix synthesis

- Cartilage Repair:
  - Animal Models and Clinics:
    - Sustained local delivery of hGH in a cartilage defect induced repair
    - Repair of partial thickness defects in articular cartilage, cartilage can be autologous or from the synovial membrane (Hudnut et al. J. Bone Joint Surg. 71: 241-250)
    - Bone dose of hGH to stabilize chondrocyte differentiation

- Study Design:
  - Groups: 1. SABER-hGH + Zn IA 2. SABER-hGH - Zn IA 3. IA - SC extended PK/PD 4. IA of aq. bolus of hGH 5. IA of aq. bolus of hGH + Zn 6. IA SABER formulation 1

- Pharmacokinetics:
  - Serum concentrations of IGF-1 exceeded levels in synovial fluid at all time points after injection of hGH in the joint.
  - Increased levels of IGF-1 in the synovial fluid may not be due solely to stimulated synthesis in the joint, but may be due to the injection of hGH in the synovial fluid.

Conclusions & Next Steps:

- We have explored SABER depot formulations of hGH and studied their delivery characteristics following intra-articular (IA) injection into the canine hind knee.
- Synovial hGH levels following an IA aq. bolus of hGH were much lower than those observed following IA injection of SABER formulations. This implies that the effect of hGH may not be due solely to IGF-1 stimulation in the joint.
- IGF-1 is a protein-bound and cannot diffuse freely between the serum and synovial fluid. Terminal elimination rates of serum and synovial levels were comparable. Thus, the joint acted as an extended release depot for systemic delivery.

- Synovial IGF-1 concentrations after IA injection of hGH were 2-3 Logs lower than levels in synovial fluid. Terminal elimination rates of serum and synovial levels were comparable. Thus, the joint acted as an extended release depot for systemic delivery.

- Mean hGH concentrations in synovial fluid and serum after IA injection and in serum after IA injection of 1.5 mg protein/mL as aqueous bolus.
- Synovial fluid levels exceeded those in serum and declined more slowly, suggesting that the IA space behaved as a separate PK compartment.
- Serum levels after the aqueous IA bolus required 2 hours to reach their peak and were 2-3 Logs lower than those in synovial fluid. Terminal elimination rates of serum and synovial levels were comparable. Thus, the joint acted as an extended release depot for systemic delivery.