Purpose

Viscosupplementation is a common treatment administered to patients with symptomatic osteoarthritis of the knee. Human synovial fluid aspirates taken from small knee effusions in six patients that arose one week following viscosupplementation injections were analyzed and demonstrated elevated white blood cell (WBC) counts and the presence of mononuclear cells clustered on the surface of globular gel-like structures. These globular structures are the gel component of the viscosupplementation agent (Synvisc). The WBC’s aggregated on the large globules have not previously been described in the literature. It was the objective of this study to further delineate this WBC response and to determine the joint residence time of the soluble and gel components of a Synvisc-like preparation in an animal model.

Methods

Synvisc is composed of two chemically modified hyaluronans known as hylan A and hylan B in an 8:2 ratio. Hylan A is a soluble derivative of hyaluronan with a molecular weight (MW) of 4-6 million and hylan B is a crosslinked gel form of hylan A. The Test Material consisted of a green fluorophore covalently bound to hylan A (viscous fluid fraction) and a second red fluorophore covalently bound to hylan B. In this IACUC approved study, 36 mature Spanish female goats were anesthetized and the right knee received 0.5ml and left knee 1.5ml of Test Material or unbound fluorophores mixed with the Hylans. Gross and histological evaluations were performed at 0, 3, 6, 24hrs, 7, 28, and 56days. Statistical analysis of the WBC counts was done using log transformed data and non-parametric ANOVA with Dunn’s post hoc test. A p values less than 0.05 was considered significant.

Results

Post injection analysis of the covalently linked labels demonstrated the green fluorophore hylan A persisted to 28 days in superficial synovial layers, articular cartilage, fat pad and synovial fluid. The red fluorophore linked hylan B was seen only as globule structures in the synovial fluid Fig 1A & B. Mononuclear cells remained attached to these globules for 28 days and showed phagocytosis of the globules as well as the green fluorophore hylan A Fig 1 C & D. Synovial fluid WBC count peaked at 24hr (0.5ml, mean 10,130 cells/mm 3 ± 1782 SEM) and declined by 7 days (mean 431 cells/mm 3 ± 43 SEM) Table 1. Synovial fluid WBC’s from untreated animal knees (control) and contralateral knees were relatively low. No linked fluorophores were detected in the joint tissues at 56 days after injection. Unbound fluorophores were not detected at 24 hrs after injection. No effusions were noted in the animals.

Discussion and Conclusions

The presence of cells associated with the modified hyaluronans was characterized in an animal model to help understand the mode of action. Monocytes/macrophages on the surface of the globules suggests they are activated and phagocytizing them. The observations in the large animal model paralleled what we had seen in six human synovial fluid aspirates. The animal data suggest that the elevated synovial fluid WBC is transient and peaks at 24 hours. The large MW globules attracted and were phagocytized by surface clusters of macrophages. The majority of the lower MW components and covalently labeled dye was cleared within 24 hours and seen in vascular channels. Some residual remained in the surface cells and tissues (cartilage, synovium and fat pad) for up to 28 days.

The results of this animal study suggests that following viscosupplementation using Hylan Test Material there is a transient elevation of white blood cell’s peaking at 24 hours and subsiding within one week. The globular (larger cross-linked molecular weight component) is phagocytized by surface cells arising in the synovial fluid. The joint residence time for the more soluble component is significantly shorter and removed primarily by a non-cellular process in a much more rapid manner than the gel form that resides in the joint for up to 56 days.

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