Inflammatory and immunological responses to bolus vs. three injections of Synvisc in a murine biocompatibility model

Syed Sami, MD, Nancy M. Jackson, PhD, Amanda Esquivel PhD, Jeffrey C. Flynn PhD, Weiping Ren MD, PhD, and David Markel, MD
Department of Orthopaedic Surgery

Objectives: Multiple therapeutic injections of various hyaluronan preparations are commonly used to relieve pain secondary to various arthritides. Although local reactivity to the different preparations has been studied, no study has been done which compares the reactivity of hyaluronan in multiple vs. bolus injections using both systemic and local parameters. The murine biocompatibility model allows the study of the inflammatory response to various preparations of Synvisc, a hyaluronan commonly used for osteoarthritis of the knee.

Study Design: Institutional approval was obtained. Air pouches were established subcutaneously in the dorsum of 50 BALB/c mice. Ten mice were randomly placed into each group, phosphate-buffered saline (PBS, negative control); 5 mg ultra-high molecular weight polyethylene particles (to simulate synthetic joint wear debris, positive control); 0.5 ml Synvisc (one injection/week for three weeks, harvest 14 days after last injection); and 1.5 ml Synvisc bolus (harvest either 14 or 28 days after last injection). At the time of sacrifice, sera and air pouch tissues were collected. Antibody titers to Synvisc were determined by enzyme-linked immunosorbent assay. Inflammatory gene expression of air pouch tissue was quantified by polymerase chain reaction. Inflammation was also evaluated by histological analysis of wall thickness and cellularity in several locations on the H&E-stained pouch.

Results: Inflammation was observed with all Synvisc treatments, as pouch wall thickness and cellular density were increased, relative to PBS ($P<0.01$). However, three injections of Synvisc resulted in significantly ($P<0.05$) greater tumor necrosis factor-alpha gene expression compared to both PBS and bolus Synvisc harvested after 14 or 28 days. While all Synvisc treatments resulted in serum antibody titers to Synvisc ($P<0.01$), mice that received three injections of Synvisc had higher titers than mice receiving a single injection ($P<0.02$).

Conclusion: A single injection of Synvisc led to less inflammation when compared to multiple injections. This result justifies the current change in treatment from multiple to single injection of Synvisc. Additional clinical and mechanistic studies could further elucidate this response.