Results: Body weights, blood chemistry and histology of the major organs showed that the viscosupplement without the TA, and the low and high dose TA-containing viscosupplement did not result in any systemic toxicity. The gross analysis of the joint and the synovial fluid showed that the viscosupplement, with and without the TA, did not result in any local adverse reaction as determined by gross joint scores, synovial fluid analysis and cell counts. The differential counts of cells within the synovial fluid showed that the viscosupplement, with and without the TA, was non-inflammatory. Histological analysis showed that the popliteal lymph nodes were non-reactive and that the product was well tolerated within the synovium.

The Safranin O stain depletion score of the Mankin scores (Figure 1) showed that incorporation of the TA into the hydrogel component of the viscosupplement resulted in a greater preservation of the proteoglycans in the joint cartilage as compared to an equivalent bolus dose of the TA. These differences were statistically significant for Hydros-TA(10) compared to TA(10) at both 28 days and 84 days ($p=0.002$ and $p=0.03$ respectively) and for the Hydros-TA(40) compared to TA(40) at 84 days ($p=0.02$).

Conclusions: Hydros-TA is biocompatible at 28 days and 84 days following intra-articular injection into the knee joint of a goat model. Hydros-TA formulations demonstrated reduced adverse effects on the articular cartilage as compared to a similar dose of a bolus injection of a TA suspension. This study demonstrated that the Hydros-TA was safe for initiating human clinical studies and that incorporation of the corticosteroid within the hydrogel component could potentially provide protection of the cartilage.

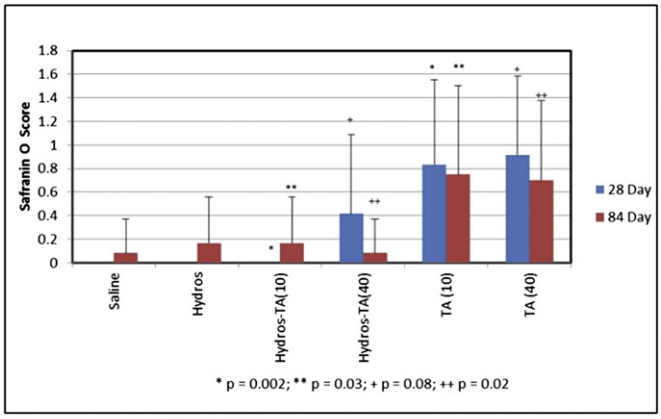

Figure 1. Safranin O scores for cartilage sections
(0 = normal staining; 4 = complete depletion of staining)

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VISCOELASTIC PROPERTIES AND ELASTIC RECOVERY OF HYADD®4 HYDROGEL COMPARED TO CROSSLINKED HA-BASED COMMERCIAL VISCOSUPPLEMENTS

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Purpose: Viscosupplementation with hyaluronan (HA)-based hydrogels is used in clinical practice to reduce pain and improve joint function in osteoarthritis (OA) patients. Rheological properties of intra-articular viscosupplements are fundamental for the quality and duration of mechanical performance. Most of the highly viscoelastic HA-based products are obtained through crosslinking techniques, causing a strong increase of the biopolymer molecular weight but raising new issues of biocompatibility and safety in the clinical environment. HYADD®4 (HA partial hexadecylamide, contained in Hymovis®) is a novel partially hydrophobic linear (i.e. not chemically crosslinked) HA derivative with low modification degree, forming a viscoelastic hydrogel with enhanced intra-articular residence time and whose clinical safety and effectiveness as viscosupplement has already been proved. The aim of this study is to compare the rheological properties of the HYADD®4 hydrogel and of some commercially available crosslinked-HA based viscosupplements, focusing on the rheological response following mechanical stresses.

Methods: A stress-controlled rheometer was used to study the mechanical response of the samples in oscillatory shear and in steady shear experiments at 25°C. The dynamic viscosity (η) at 1 sec^{-1} shear rate was determined, while viscoelasticity was measured in the frequency (ω) range of 10^{-3} to 10 Hz. The recovery of the mechanical properties after a shock was investigated as a function of time in a single or repeated cycle by oscillatory measurements at the constant frequency of 1 Hz after destruction of the gel network. Resistance of the hydrogels to stress was also assessed by measuring the viscoelastic moduli as a function of increasing stress at constant frequency.

Results: The dynamic viscosity of the HYADD®4 hydrogel is comparable to that of Synvisc® although the former is a linear HA derivative and the latter is a crosslinked one. Durolane® shows the highest viscosity in the same conditions. Similarly, the viscoelastic moduli G' and G" of HYADD®4 and of Synvisc® are comparable, whereas Durolane® is characterized by a higher viscoelasticity. For all of the three products the elastic modulus G' is higher than the viscous modulus G" in almost the whole range of frequency observed, thus confirming the "gel" character of the samples. When viscoelasticity is measured after a strong mechanical shock, the elastic modulus G' is completely recovered in less than 2 minutes only in HYADD®4. Synvisc® and Durolane® lose about 30% of their initial elastic properties, most probably due to the partial cleavage of the chemical crosslinks of the network. This tendency is confirmed by the analogous measurement after repeated mechanical stresses, where HYADD®4 shows a constant recovery of elasticity whilst the performance of Synvisc® and Durolane® is progressively impaired. Furthermore, HYADD®4 shows a stronger resistance to stress than the two crosslinked HAs, proved by the constancy of viscoelastic moduli in response to higher forces, probably due to its less rigid structure.

Conclusions: Although Durolane®, due to its more solid-like behavior, is characterized by a higher viscosity and viscoelasticity than Synvisc® and the HYADD®4 hydrogel, HYADD®4 shows more favorable features than both crosslinked HA-based hydrogels in stress-related tests. In fact in the new hydrogel a strong resistance to stress and a self-healing mechanism after disruption of the gel structure, given by mechanical shocks, have been observed. This is very probably due to the chemical structure differences between rigid crosslinked HAs (Synvisc® and Durolane®) and the linear modification of HA in HYADD®4, that allows for formation of reversible interactions yielding a gel-like structure. The unique rheological features of HYADD®4 could be potentially useful for the preservation of viscosupplementation therapy effectiveness in time for active OA patients.

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EFFICACY AND SAFETY OF CONTINUOUS INTRA-ARTICULAR HYALURONIC ACID INJECTION (HYALGAN®) IN TREATMENT OF KNEE OSTEOARTHRITIS PATIENTS WHO UNDERWENT HIGH TIBIAL OSTEOTOMY, CLINICAL AND MRI EVALUATION

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Purpose: Knee osteoarthritis is a disease of progression, causes by deterioration of both mechanical and biochemical factors. High tibial osteotomy is one of standard surgical procedure to correct abnormal mechanical load on the knee joint, whereas, intra-articular hyaluronic acid have mechanism to restore viscoelastic property of synovial fluid and balance abnormal biochemical process. Theoretically, combination of these modalities can create synergistic effect for treatment in knee osteoarthritis. This study aimed to evaluate the efficacy and safety of continuous intra-articular hyaluronic acid injection for treatment in osteoarthritis knee patients who underwent high tibial osteotomy.

Methods: This study was designed as a randomized, controlled, observer blinded study method. Forty patients with medial compartmental osteoarthritis knee were randomly assigned into control and study groups. The study group (n=20) received 2 cycles of 5 intra-articular injection with sodium hyaluronate (Hyalgan®) after high tibial osteotomy operation. The control group (n=20) did not receive any intra-articular injection. Treatment efficacies were evaluated by Western Ontario and McMaster Universities (WOMAC) osteoarthritis index (at 6, 12, 24, 48 weeks after