VISCO-SUPPLEMENT COMBINING HIGH MOLECULAR WEIGHT HYALURONIC ACID AND SORBITOL DEMONSTRATES HIGH ANTALGIC ACTIVITY IN OSTEOARTHRITIS PATIENTS

Franck RADENNE **Anteis SA – Geneva - Switzerland**

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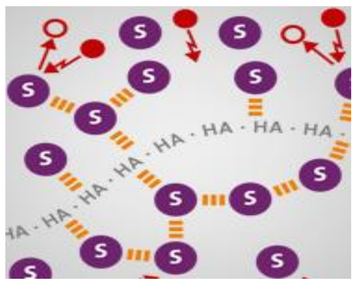
Background

OsteoArthritis (OA) is a very common joint disorder with increasing prevalence. It is projected that by the year 2030, almost 67 million US adults will have been diagnosed with arthritis [1].
ViscoSupplementation (VS) has been used for more than 20 years and is recommended in the treatment of OA. There are currently more than 20 commercial VS products available worldwide. These products differ in Hyaluronic Acid (HA) origin, concentration, molecular weight, HA chemical modification, rheological properties, dosing regimens, claims for safety and efficacy, and residence time into the joint.

Objective

Synolis® (Anteis SA) is a novel patented Visco-Antalgic composed of high molecular weight (> 2 MDa in the final sterilized gel), highly concentrated, non-crosslinked HA (2%) from biofermentation origin combined with a high concentration of sorbitol (4%).
Sorbitol is an endogenous molecule that functions as a strong Oxygen Free Radical (OFR) scavenger. We hypothesize that anti-oxidant effect of sorbitol may play an active role in rapid and strong pain reduction in patients with OA.



Method

1147 OA patients, with a majority suffering from knee OA (92.9%), were enrolled in a Non-Interventional Study conducted in 398 centres in Germany.
Studied population had an average age of 63.3 years, included 499 males, 614 females and 34 patients without reported gender.
Patients were distributed into the following grades according to Kellgren-Lawrence (K-L) scale: 6.7% with Grade I, 31.4% with Grade II, 48.0% with Grade III and 13.9% with Grade IV.
Patients pain level was assessed using 5 points Likert scale (from “No Pain” scoring 0 to “Very Severe Pain” scoring 4) and was distributed into 1.9% patients with missing information, 0.9% with “No Pain”, 5.9% with “Mild Pain”, 35.1% with “Moderate Pain”, 45.3% with “Severe Pain”, 10.9% with “Very Severe Pain”.
Statistical analysis was conducted on a subpopulation of 997 patients with knee OA who have received either 1 or 3 IntraArticular (IA) injections of 2ml of Synolis®.

Primary study criterion was the variation of pain score (Likert scale) between baseline and following time points: week1, week 2, week 3, week 12 and week 24.

Secondary study criteria comprised the evaluation of the initial pain level in relation to the reported Kellgren-Lawrence Grade and observation of Adverse Events (AEs) reported during the study.

This post-marketing surveillance was conducted in accordance to “Empfehlungen zur Planung, Durchführung und Auswertung von Anwendungsbeobachtungen” of the BfArM (Federal Institute for Drugs and Medical Devices) and the Paul-Ehrlich-Institute, dated 7 July 2010.

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Results

Figure 1

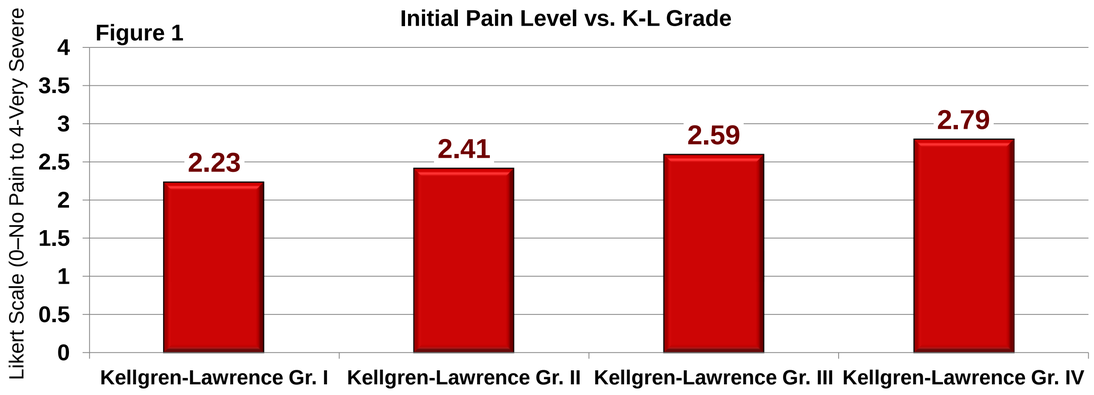


Figure 1 - On the population with Knee OA with both K-L Grade and Initial Pain Level reported (n=509), mean pain level is steadily increasing as a function of Kellgren-Lawrence Grade (K-L Gr.) severity with a mean of 2.23 for K-L Gr. I (n=35), 2.41 for K-L Gr. II (n=160), 2.59 for K-L Gr. III (n=243) and 2.79 for K-L Gr. IV (n=71).

Figure 2

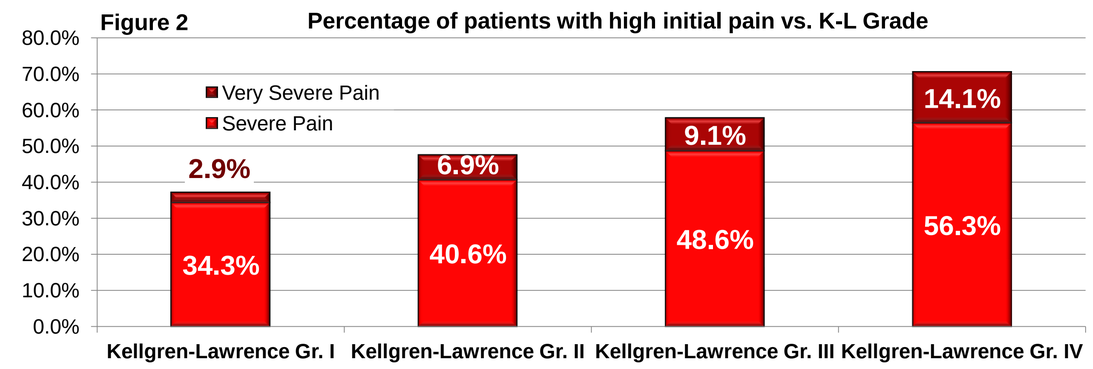
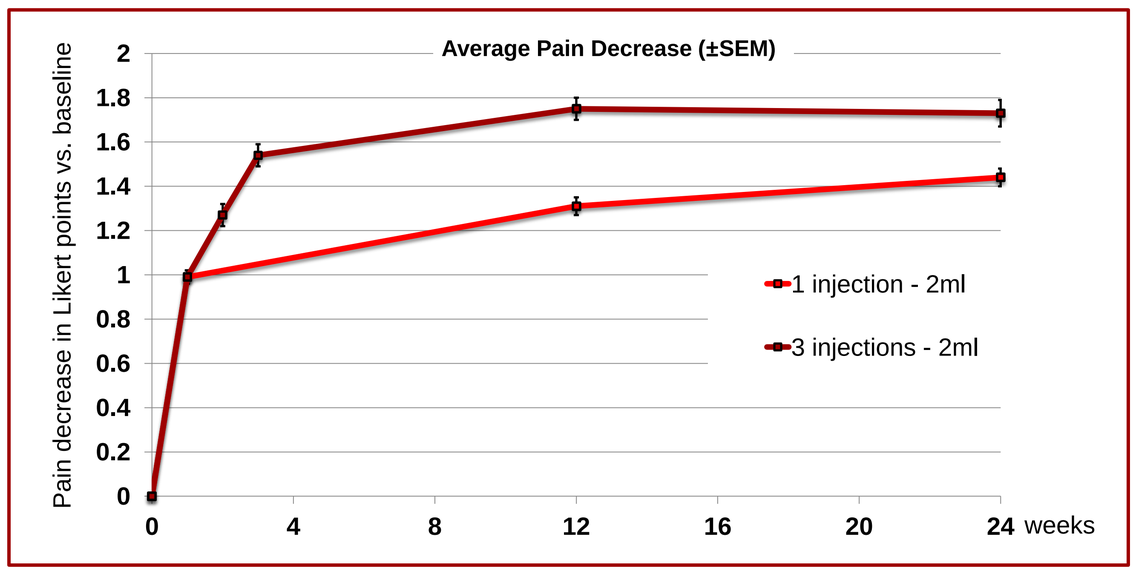


Figure 2 - The percentage of patients with Severe Pain (Likert score 3) and Very Severe Pain (Likert score 4) was correlated to K-L Gr., with 37% of patients with pain level scoring at 3 & 4 in K-L Gr. I, 47% in K-L Gr. II, 56% in K-L Gr. III and 70% in K-L Gr. IV.

Figure 3



With a treatment regimen of a single injection of 2ml of Synolis®, the average observed pain level (pooled data) was 2.6 at baseline, 1.61 at week 1, 1.29 at week 12 and 1.16 at week 24 (Standard Error of the Mean SEM ≤ 0.04 & n=662). The reported evolution of pain level suggests a prolonged pain relief activity increasing until week 24, and potentially even further.

With a treatment regimen of 3 injections one week apart, the observed average pain level (pooled data) dropped from 2.6 at baseline to 1.61 at week 1, 1.33 at week 2, 1.06 at week 3, 0.85 at week 12 and 0.87 at week 24 (SEM ≤ 0.06 & n=335). The average pain evolution would support the assumption of cumulative effect of the additional injections. Pain relief seems sustained at least until week 24 – Figure 3.

Table 1 - Out of 1147 patients only 24 Adverse Events (AEs) were reported for 22 patients (1.9%), the most common Adverse Event being “Injection site joint pain”

Table 1

System Organ Class	Preferred term	n
Musculoskeletal and connective tissue disorders	Injection site joint pain	15
	Joint swelling	4
	Joint warmth	2
	Joint effusion	2
	Joint instability	1
Number of AEs		24

Discussion

Link between Pain Level and Radiographic Severity
Despite several publications questioning the relation between radiographic-determined severity and pain level [2-3], this study conducted on a large scale population demonstrates the existence of a trend linking Kellgren-Lawrence Grades and average pain level (based on Likert scale). The percentage of patients with high pain level (Severe and Very Severe) is increasing in relation to the K-L Grade to reach 70% for K-L Gr. IV.

1 injection regimen vs. 3 injections
One week after the first injection, the observed average pain decrease reached 38% (virtually 1 point drop on the Likert scale). It is hypothesized that unique HA/sorbitol combination of Synolis® confers its high capacity to scavenge free radicals (= antioxidant effect), neutralizing of those key factors of the HA resorption in the joint [4-8] and of inflammation signaling [8].
Following a single injection, evaluated average pain continues to decrease until week 24 (55% pain decrease), suggesting a prolonged, direct or indirect, effect of Synolis® on pain.
Whereas, second and third injections seems to bring additional cumulative effect of pain reduction sustained until week 24 (66% pain decrease).

Safety
With 1.9% of low severity AEs reported by investigators, Synolis® injections seem to be very safe to perform; especially taking into account that about 30% of injections might miss the intra-articular space [9] potentially generating pain or flare reaction not directly associated with the used viscosupplement.

Conclusion

This study suggests that a strong pain relief occurs immediately after the first injection of Synolis®. Pain relief effect was reinforced by additional injections, reaching a maximum pain decrease of 67% at week 12 after 3 injections, pain decrease was sustained at least until week 24. However, patients who received only a single injection of 2ml of Synolis® also demonstrated a strong and continuous pain decrease, reaching 55% of pain relief at week 24. These results demonstrate efficacy of both 1 and 3 injections regimens of Synolis®.
In addition, despite existing literature reporting absence of direct relation between severity of Kellgren-Lawrence Grade and pain level, this study shows existence of a trend linking both criteria. Finally, Synolis® proves to be a safe treatment.

References:
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