Can we adapt the regimen of viscosupplementation to the severity of knee osteoarthritis? Result of a cohort study of 412 patients.

Translation

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Rational and objective

Viscosupplementation is a symptomatic treatment of osteoarthritis widely used.

The most common protocol is 1 weekly intra-articular injection, 3 consecutive weeks, a solution of hyaluronic acid (HA) at a concentration of 0.8 to 2 mg / ml.

This protocol does not take into account the clinical or anatomical severity of knee osteoarthritis.

The aim of this work was to study the possibility of proposing an alternative regimen by adapting the dose of HA to the patient's condition.

Patients and methods

Observational subgroup analysis of a cohort of 1147 patients treated with 1 to 3 injections of a visco-antalgic composed of HA (20 mg / ml, PM = 2MDa) and sorbitol (40 mg / ml) *[J and Heisel al. Drug Res 2013; 445-49]*

- 412 patients received 1 (N = 253) or 3 (N = 159) SYNOLIS-VA injections (Aptissen, Switzerland)
- Having all radiographs at D1 (day of injection No. 1) for assessment of Kellgren-Lawrence score and clinical assessment at D1 and S26 (week 26, end of follow-up) with self-assessment of pain on a Likert scale 5 points (0 = none, 4 = very severe)

Classification of patients:

- Depending on the radiological Kellgren-Lawrence grade (I / II versus III / IV)
- Depending on the clinical severity of pain (SC 1 = mild to moderate; SC 2 severe or very severe)

Statistics:

-Inter-group comparison based regimen (1 versus 3 injections)

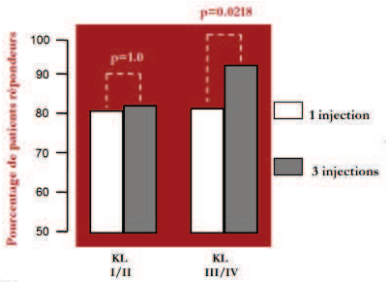
Results

At the least painful SC-1 patients (n = 187), there was no significant difference in effectiveness between protocols 1 and 3 injections (p = 0.51).

In contrast to the very painful subjects SC-2 (n = 225) 3 injections was significantly greater than 1 alone (p = 0.006).

Sévérité clinique (n)	Nombre d' injections	Score de douleur moyen: 0-4 (deviation standard) J1	S 24 semaine 24	Variation J1-S24	Différence intergroupe (IC 95%)	p-value
Faible (143)	1	1.78 (0.84)	0.84 (0.68)	-0.94 (0.77)	0.086 (-0.168, 0.340)	0.507
Faible (44)	3	1.89 (0.32)	0.86 (0.63)	-1.02 (0.66)		
Elevée (130)	1	3.14 (0.33)	1.44 (0.92)	-1.70 (0.90)	0.353 (0.103, 0.602)	0.006
Elevée (95)	3	3.17 (0.38)	1.012 (0.97)	-2.05 (0.98)		

Comparison of the effect of 1 or 3 injections on the percentage of responders (reduction of 1 point of the pain scale) based on the radiological stage Kellgren-Lawrence.



Patients classified KL I-II (n = 159) as in subjects KL III-IV (n = 253) Protocol 3 injections was significantly higher, but this superiority was less marked for KL I-II (p = 0.02) than for KL III-IV (p = 0.0004).

Stade radiologique de Kellgren-Lawrence KL (n)	Nombre d' injections	Score de douleur moyen: 0-4 (deviation standard) J1	S 24 semaine 24	Variation J1-S24	Différence intergroupe (IC 95%)	p
KL I/II (107)	1	2.29 (0.79)	0.99 (0.83)	-1.30 (0.91)	0.393 (0.063, 0.723)	0.020
KL I/II (52)	3	2.65 (0.79)	0.96 (0.91)	-1.69 (1.13)		
KL III/IV (166)	1	2.51 (0.77)	1.21 (0.86)	-1.30 (0.92)	0.456 (0.203, 0.688)	<0.001
KL III/IV (87)	3	2.83 (0.63)	1.08 (0.87)	-1.75 (0.94)		

Stade Radiologique / Nombre d'injections		Variation du score de douleur entre J1 et S24 KL I/II 1 injection (n=107)	KL I/II 3 injections (n=52)	KL III/IV 1 injection (n=166)	KL III/IV 3 injections (n=87)
Amélioration de 4 classes	%	-	5.6%	0.6%	3.4%
Amélioration de 3 classes	%	6.5%	16.7%	7.2%	17.2%
Amélioration de 2 classes	%	38.0%	33.3%	34.1%	36.8%
Amélioration d' 1 classe	%	36.1%	24.1%	39.5%	35.6%
Pas de changement de classe	%	15.7%	20.4%	16.2%	6.9%
Aggravation	%	3.7%	-	2.4%	-

This superiority of 3 injections disappeared in patients [KLIII-IV / SC 1] while it persisted for subjects [KLIII-IV / SC 2).

Conclusion 1

An adapted regimen is possible in patients with knee osteoarthritis slightly evolved anatomically and slightly or moderately painful. For these patients as a single injection appears effective as 3 injections.

	Douleur légère ou modérée	Douleur sévère ou très sévère
K-L I/II	1 injection	1 injection minimum
K-L III/IV	1 à 3 injections maximum	3 injections

Proposed dosage regimen tailored to the clinical and radiographic severity of knee osteoarthritis

Conclusion 2

The results of this study need to be confirmed by a controlled study can not be extrapolated to other viscosupplements.

Indeed the presence of a high concentration of sorbitol, antioxidant protecting HA degradation by free radicals, make Synolis-VA a particular visco-antalgic.

PAIN DECREASE MAY BE A MORE SENSITIVE ILLUSTRATION OF VISCOSUPPLEMENTATION EFFICACY THAN FUNCTIONAL IMPROVEMENT WHEN INJECTING COMBINED SODIUM HYALURONATE & SORBITOL (ANTI-OX-VS) - CLINICAL OBSERVATION OF 1147 PATIENTS

F. RADENNE – Aptissen - Switzerland

Introduction

Creamer P. et al.[1] demonstrated that loss of function in knee OsteoArthritis (OA) is determined more by pain and obesity than by structural change. The hypothesis is that inversely, reduction of knee pain would proportionally impact knee function improvement.

Background

To compare pain and functional impairment reduction performance in a population of 1147 patients receiving between 1 & 3 injections of 2ml viscosupplement combining Hyaluronic Acid (HA) and sorbitol: ANTI-OX-VS

Objective

This treatment 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 an 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. And that this fast and strong effect would translate into knee function improvement.

Method

A total of 1147 patients (male: n=499, female: n=614, unknown: n=34) with OA enrolled in 398 centres have been treated with 1, 2 or 3 injections of 2ml of sodium hyaluronate (20mg/ml) combined with sorbitol (40mg/ml) one week apart, depending on the decision of clinicians or patients[2].

Both Pain and Functional Impairment levels were assessed using a Likert-type scale (none = 0; mild = 1; moderate = 2; severe = 3; very severe = 4). Assessment was performed at 1st injection (week 0: baseline) and during 5 follow up visits for a treatment period up to 24 weeks.

All Kellgren-Lawrence Grades were represented with 48% of patients with Grade III, 31.4% with Grade II, 13.9% with Grade IV and 6.7% with Grade I. Moreover patients with treated knee joint represented 92.9% of monitored patients. The remaining of patients were treated for hips, shoulders and other joints with OA.

Only patients with reported information were analyzed for average pain and/or function impairment decrease vs. baseline, in both absolute score value and percentage. In order to establish the existence of a correlation between pain decrease and function improvement, the ratio Pain (%) / Function Impairment (%) was calculated at each time point, independently.

Results

For more than half of patients enrolled in the study, pain (table 1) and functional impairment (table 2) data were not reported at week 2 and week 3, mainly because this majority of patients received only a single injection of ANTI-OX-VS (57.7% of patients) compared to those who received 3 injections (29.7% of patients). Still, most of patients with reported pain level also reported functional impairment level, which allowed accurate comparison between both evaluation items.

Table 1: *Number of patients reported by pain level at each follow-up time point*

Pain

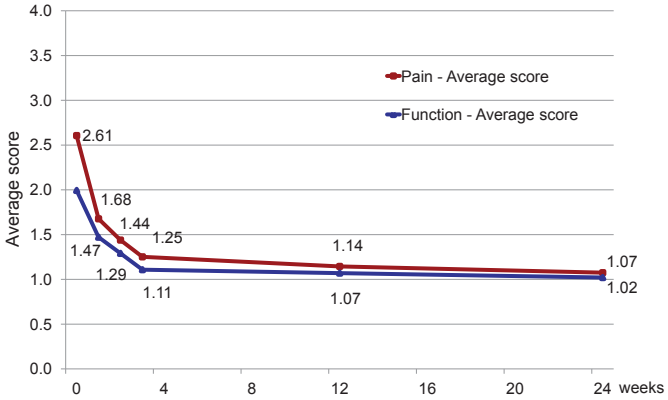
	Score	W0	W1	W2	W3	W12	W24
Missing		22	315	712	738	62	117
None	0	10	61	43	72	242	259
Mild	1	68	282	194	193	524	511
Moderate	2	402	366	166	116	248	192
Severe	3	520	111	28	25	62	60
Very Severe	4	125	12	4	3	9	8
Total		1147	1147	1147	1147	1147	1147

Table 2: *Number of patients reported by functional impairment level at each time point*

Functional impairment

	Score	W0	W1	W2	W3	W12	W24
Missing		44	328	717	741	73	116
None	0	74	101	80	97	281	299
Mild	1	257	325	172	180	481	463
Moderate	2	438	301	151	117	271	224
Severe	3	270	90	27	12	38	39
Very Severe	4	64	2	0	0	3	6
Total		1147	1147	1147	1147	1147	1147

Figure 1: *Average score (Likert scale) for patients with reported pain and function data*



Average pain (figure 1) scored at 2.61 at baseline; 1.68 (-35.7% vs. baseline) at week 1; 1.44 (-44.8%) at week 2; 1.25 (-52.0%) at week 3; 1.14 (-56.1%) at week 12 and 1.07 (-58.8%) at week 24 for patients who shared data.

Similarly, average functional impairment (figure 1) scored at 1.99 at baseline; 1.47 (-26.2% vs. baseline) at week 1; 1.29 (-35.3%) at week 2; 1.11 (-44.4%) at week 3; 1.07 (-46.3%) at week 12 and 1.02 (-48.8%) at week 24.

Table 3: *Ratio between pain decrease (%) and functional improvement (%) at each time point*

Week	W1	W2	W3	W12	W24
Av. pain decrease	35.7%	44.8%	52.0%	56.1%	58.8%
Av. functional improvement	26.2%	35.3%	44.4%	46.3%	48.8%
Ratio pain / function	1.4	1.3	1.2	1.2	1.2

The ratio of pain over functional impairment decrease (table 3) was calculated at 1.4 at week 1; 1.3 at week 2; 1.2 at week 3; 1.2 at week 12 and 1.2 at week 24.

At week 24, 84.35% of patients reported a meaningful pain decrease (≥ 1 point), whereas 64.63% reported a significant functional impairment decrease (ratio of 1.3).

Discussion

More than 60% of patients didn't report pain and functional impairment at week 2 and week 3 because they received only one single injection and didn't return to their clinician for follow-up. But most of patients who reported data, did it for both pain and functional impairment levels.

For those patients, the ratio between pain decrease and functional improvement was rather constant from 1.4 at week 1 to 1.2 at week 24; suggesting a clear link between both criteria. The upper value at week 1 and week 2 might be explained by the non-linearity of the Likert scale.

Data also showed that average pain level was more sensitive to treatment than functional impairment, presumably because of the higher number of responders. Therefore, patients with significant pain decrease might not necessarily obtain significant functional improvement.

Conclusion

The injection(s) of ANTI-OX-VS demonstrated a comparable effect on Average Pain and Functional Impairment with a fast decrease within the first few weeks and stabilization up to 24 weeks. The pain / functional impairment ratios comprised between 1.4 and 1.2 at each time point strongly suggest a correlation between those two parameters. However, the fact that less patients report meaningful decrease for functional impairment than for average pain could indicate that despite pain being a major influencing factor of function, other factors might impact function.

References:

1 - P. Creamer et al. – Factors asssociated with functional impairment in symptomatic knee osteoarthritis – Rheumatology 2000;39:490-496

2 - J. Heisel, et al. - Safety and Effi cacy Findings from a Non-interventional Study of a New Hyaluronic Acid/Sorbitol Formulation (GO-ON ® Matrix) for Intra-articular Injection to Relieve Pain and Disability in Osteoarthritis Patients – 2013 Drug Res

Pain Relief, Functional Recovery and Associated Medical Treatments Reduction in Large-Scale Population with Osteoarthritis Receiving Injections of ViscoSupplement Incorporating High Concentration of Sorbitol

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Poster # 729

Introduction

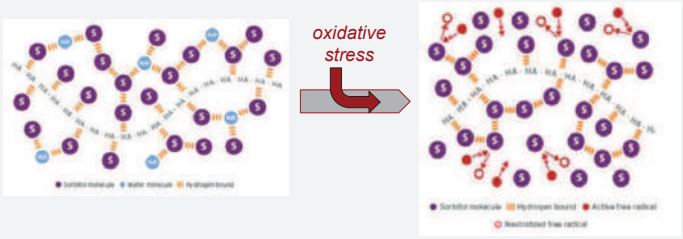
Creamer P. et al.[1] demonstrated that loss of function in knee OsteoArthritis (OA) is determined more by pain and obesity than by structural change. Tallon D. et al.[2] showed that the most commonly prescribed and used treatment for knee OA was oral drugs (analgesics or anti-inflammatories), but they also observed that many patients are suspicious of tablets. The hypothesis is that reducing knee pain and improving functional recovery would result in a reduction of medical treatment (especially oral drugs), therefore answering some of the patients' concerns.

Background

To compare pain and functional impairment reduction performance in a population of 1147 patients receiving between 1 & 3 injections of 2ml viscosupplement combining Hyaluronic Acid (HA) and sorbitol: ANTI-OX-VS (Synolis V-A).

Objective

ANTI-OX-VS is a visco-antalgic composed of highly concentrated non-crosslinked hyaluronic acid (2%) from biofermentation origin combined with a high concentration of Sorbitol (4%). Sorbitol is an endogenous molecule which functions as an oxygen free radical (OFR) scavenger. We assume that anti-oxidant effect of sorbitol may play an active role in rapid and strong pain reduction in patients with ostheoarthrits by counteracting oxidative stress effects, and therefore influence function recovery and medication intake reduction.



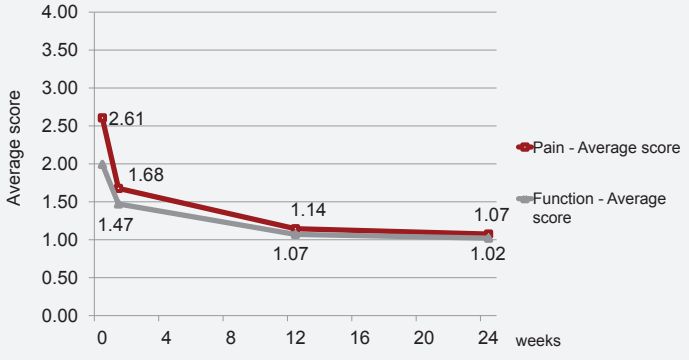
Material and Methods

1147 patients, with a majority suffering from knee Osteoarthritis (92.9%), were enrolled in a Non-Interventional Study conducted in 398 centres in Germany[3].
Studied population had an average age of 63.3 years, including 499 males and 614 females, and was distributed into the following grades according to Kellgren-Lawrence scale: Grade I - 6.7%, Grade II - 31.4%, Grade III - 48.0% and Grade IV - 13.9%. Patients were assessed for pain level and functional impairment using 5 points Likert scale (scoring from 0=None to 4=Very Severe).
Patients received between 1 and 3 intra-articular (IA) injections of 2ml of ANTI-OX-VS (Synolis V-A).
Selected primary criteria were variations of pain and function impairment scores, between baseline and the following time points: week 1, week 12 and week 24.
Selected secondary criterion was the evaluation of the use of adjunctive medical treatments (topical, NSAIDs, corticosteroids and analgesics) prior to treatment initiation and at week 24.

Results

Average pain level (pooled data) scored at 2.61 (n=1125) at baseline, 1.68 (n=832) at week 1, 1.14 (n=1085) at week 12 and 1.07 (n=1030) at week 24.
Average functional impairment level (pooled data) scored at 1.99 (n=1103) at baseline, 1.47 (n=819) at week 1, 1.07 (n=1074) at week 12 and 1.02 (n=1031) at week 24 *(figure 1)*.

Figure 1: *Average score (Likert scale) for patients with reported pain and function impairment data*



Average number of medical treatments, comprising topical, NSAIDs, corticosteroids, analgesics and surgery decreased from 1.3 given prior viscosupplement treatment initiation to 0.37 over the period of the 24 weeks following the injection(s) of ANTI-OX-VS *(table 1)*.

Patients with no reported medical treatment increased by from 354 patients prior viscosupplement treatment initiation to 780 over the period of the 24 weeks following the injection(s) of ANTI-OX-VS *(table 2)*.

The number of patients taking NSAIDs and analgesics, and who answered the survey, could be reduced by 72.7% with the initiation of viscosupplementation *(table 3)*.

Table 1: *Number of patients (%) who received medical treatment(s) prior to the initiation of viscosupplementation - multiple citations possible*

Previous treatment	n (%)
Topical	443 (38.6)
NSAIDs	735 (64.1)
Corticosteroids	385 (33.6)
Analgesics	421 (36.7)
Surgery	228 (19.9)

Table 2: *Number of medical treatments (excluding surgery) experienced by patients before and during treatment with ANTI-OX-VS*

Number of medical treatments	Number of patients with previous treatment	Number of patients with additional treatment
0	354	780
1	319	313
2	294	51
3	137	3
4	41	0
5	2	0

Specification of previous medical treatment including topical, NSAIDs, corticosteroids and analgesics was given in 793 (69.1%) of all patients

Table 3: *Number of patients (%) for who NSAIDs / Analgesics could be reduced*

NSAIDs / Analgesics could be reduced ?	n	%
Unknown	151	13.2%
Yes	518	45.2%
No	195	17.0%
N/A	283	24.7%

Discussion

This study suggests that a strong pain relief occurs immediately after the first injection of Synolis V-A, with a relief that amplifies until week 24.
Functional improvement has been observed to follow a similar pattern than pain relief. With a baseline score slightly lower, the amplitude of the observed improvement was also slightly inferior to that of pain relief. Never-the-less, both average scores ended up around 1 (Mild) at week 24. The patterns similarities between pain relief and functional improvement suggest a direct link between both factors; link that can be explained by the impact of pain on loss of function.

In parallel to the reduction of pain and functional impairment induced by ANTI-OX-VS, the number of patients using additional pain relief treatment and the number of those treatments have been strongly reduced. This reduction logically results from the decreasing need of addressing pain, but also reinforces the fact that pain reduction observed in the study is mainly the result of the ANTI-OX-VS treatment, and not of adjunctive medical treatments.
It can be fairly implied that the reduction of oral medications such as pain killers or anti-inflammatory drugs should help reducing their side effects such as nausea, vomiting and other stomach disturbances. In addition, it should positively impact overall medical costs.

Conclusion

On a large population, viscosupplementation using ANTI-OX-VS clearly leads to a fast and strong pain relief for at least 6 months, as well as a proportional functional recovery.

This pain relief has been observed to result in an important reduction of adjunctive oral medical treatments, like NSAIDs and analgesics, which would most probably lightening the occurrence of side effects.

References:
1 - P. Creamer et al. – Factors asssociated with functional impairment in symptomatic knee osteoarthritis – Rheumatology 2000;39:490-496
2 - Tallon D et al.; Exploring the Priorities of Patients with Osteoarthritis of the Knee; Arthritis Care and Research: vol. 13, No. 5, October 2000
3 - J. Heisel, et al. - Safety and Efficacy Findings from a Non-interventional Study of a New Hyaluronic Acid/Sorbitol Formulation (GO-ON ® Matrix) for Intra-articular Injection to Relieve Pain and Disability in Osteoarthritis Patients – 2013 Drug Res

AN INNOVATIVE HYALURONIC ACID PRODUCT FOR VISCOSUPPLEMENTATION IN PATIENTS WITH OSTEOARTHRITIS

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Background

Osteoarthritis (OA) is a very common joint disorder and its prevalence is increasing. It is projected that by the year 2030, almost 67 million US adults will have been diagnosed with arthritis [1].
Viscosupplementation (VS) is 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, HA concentration, HA molecular weight, HA chemical modification, rheological properties, dosing regimens, claims of safety and efficacy and residence time into the joint.
Synolis® V-A (Anteis SA) is an innovative VS launched on the market in 2010. The patented [HA+sorbitol] formulation of this VS is based on a high molecular weight of HA (> 2 MDa in the final sterilized gel) from non animal origin, with a high HA concentration (20 mg/ml), combined with a high concentration of a free radical scavenger, the sorbitol (40 mg/ml).

Purpose

The aims of this study are to evaluate the rheological properties and the resistance to free radicals degradation of Synolis® V-A

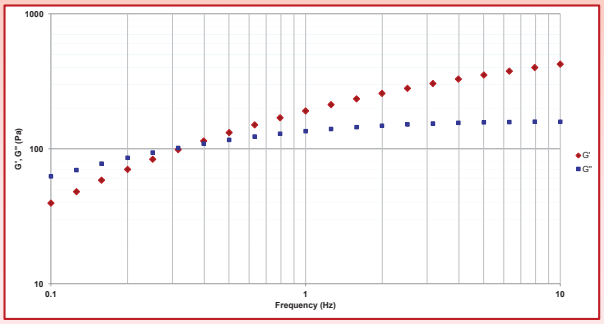
Method

The rheological properties (elastic and viscous moduli : G' and G'') of Synolis® V-A are measured by frequency sweep experiments at 25°C thanks to an AR2000 rheometer (TA Instruments), using a plate and plate geometry with 1 mm gap.

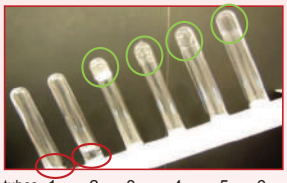
The resistance to free radical degradation of Synolis® V-A is measured with 2 different tests and the results are compared with other VS of the market:
- Test 1 (visual observation): addition of an oxidant agent (H_2O_2) on the tested VS (weight of H_2O_2 = 1/15 x Weight of VS) followed by the heating of the mixture at 60°C in order to accelerate the oxidative reaction. A visual observation of the flow is performed over time.
-Test 2 (rheological test): addition of an oxidant agent (H_2O_2) on the tested VS (weight of H_2O_2 = 1/15 x Weight of VS) and measurement of the rheological properties by time sweep experiments at 37°C thanks to an AR2000 rheometer (TA Instruments), using a plate and plate geometry with 1 mm gap.

Results

Rheological properties of Synolis® V-A



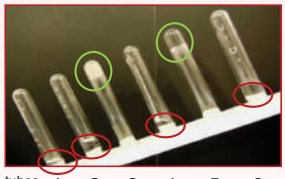
Resistance to free radical degradation of Synolis® V-A and other products of the market



Test 1:
Visual observation of the flow for each VS during free radical degradation - after having turned the test tube over:

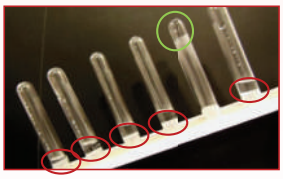
Before Heating

tubes 1 2 3 4 5 6



After 1h at 60°C

tubes 1 2 3 4 5 6

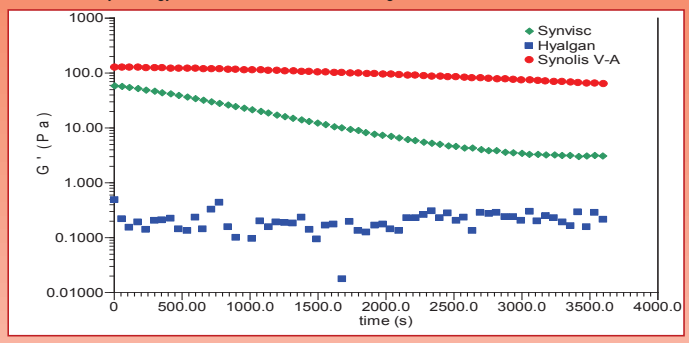


After 3h at 60°C

tubes 1 2 3 4 5 6

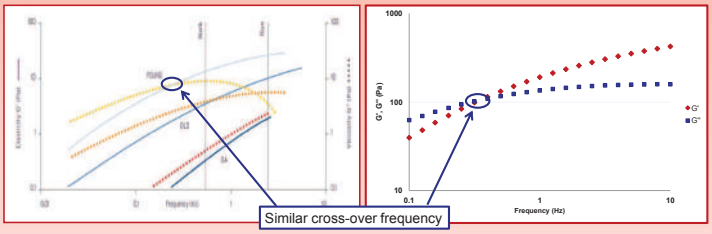
Tubes:
1 – Sinovial®
2 – Hyalgan®
3 – Durolane®
4 – Ostenil® Plus
5 – Synolis® V-A
6 - Synvisc®

Test 2:
Measurement by rheology of the resistance to free radical degradation



Discussion

Rheological properties of Synolis® V-A
The rheological analysis of Synolis® V-A shows that this VS is characterized by a visco-elastic behavior close to the synovial fluid (viscous and elastic moduli crossing at about 0.4 Hz, as with the healthy synovial fluid) [2-3].



Thanks to this specific frequency crossover, Synolis® V-A mimics the rheological properties of the healthy synovial fluid:

- for a high frequency (f > 0.4 Hz / strong stress exerted in the joint : running, jumping), the elastic modulus of the VS is higher than the viscous modulus: there is a strong protection of the joint by absorption of the produced energy.

Synolis V-A response to strong mechanical stress (same as synovial fluid)

High elasticity of the VS : Shock absorption in the joint

- on the contrary, for a low frequency (f < 0.4 Hz / weak stress exerted in the joint: resting), the viscous modulus of the VS is higher than the elastic modulus: there is a good lubrication of the joint.

Synolis V-A response to weak mechanical stress (same as synovial fluid)

High viscosity of the VS : Lubrification of the joint

Moreover, due to the high affinity between HA and sorbitol, the structure of Synolis® V-A is stabilized through a very dense network of hydrogen bonds. This complex structure of gel presents remarkably high visco-elastic properties, even higher than animal or crosslinked products. It allows Synolis® V-A to have a very high capacity to lubricate and absorb the shock in the joint.

Resistance to free radical degradation of Synolis® V-A and other products of the market

According to the literature [4-8], the free radical degradation is a key factor of the HA resorption in the joint and is an important factor of the OA.
Synolis® V-A was designed to have a high capacity to scavenge and neutralize free radicals (= antioxidant effect) thanks to its unique [HA / sorbitol] combination (high ability of the sorbitol to scavenge the free radicals).
As demonstrated by 2 different in vitro tests, Synolis® V-A presents a high capacity to resist to free radicals, better than all the other studied VS. This advantage is key to maintain the Synolis® V-A formulation and its specific rheological properties longer in the joint.

Conclusion

Synolis® V-A is an innovative viscosupplement made of a combination of HA and sorbitol.
Due to its patented formulation and manufacturing process, Synolis® V-A has outstanding rheological properties and a high resistance against *in vivo* degradation in the joint.

As demonstrated by several experiments described in this study, Synolis® V-A is characterized by:
▪ a visco-elastic behaviour close to the human synovial fluid and a very high elasticity and viscosity to have a VS with a high capacity to lubricate the joint and to absorb shocks, as with a healthy synovial fluid
• a high capacity to scavenge and neutralize free radicals, which allows to maintain the VS longer in the joint, for better clinical outcomes.

References:
1 – Altman RD, Pain, osteoarthritis, and intra-articular HA…Today and beyond, OA pain management update, Special report, 2007; 2 – Mazzucco D, McKinley G, Scott RD, Spector M, Rheology of joint fluid in total knee arthroplasty patients, J Orthop Res, 2002 Nov;20(6):1157-63.; 3 – Fam H, Bryant JT, Kontopoulou M, Rheological properties of synovial fluids, Biorheology, 2007;44(2):59-74; 4 – Henrotin Y, Kurz B, Antioxidant to treat osteoarthritis: dream or reality?, Curr Drug Targets, 2007 Feb;8(2):347-57; 5 – Fermor B, Christensen SE, Youn I, Cernanec JM, Davies CM, Weinberg JB, Oxygen, nitric oxide and articular cartilage, Eur Cell Mater, 2007;13:56-65.; 6 – Saari H, Oxygen derived free radicals and synovial fluid hyaluronate, Ann Rheum Dis, 1991 Jun;50(6):389-92.; 7 – Lunec J, Halloran SP, White AG, Dormandy TL, Free-radical oxidation (peroxidation) products in serum and synovial fluid in rheumatoid arthritis, J Rheumatol, 1981 Mar;8(2):233-45.; 8 – Zoskoven C, Jäger M, Zilkens C, Bloch W, Brixius K, Krauspe R, Oxidative stress in secondary osteoarthritos: from cartliage destruction to clinical presentation?, Orthopaedic Reviews, 2010, volume 2:e23

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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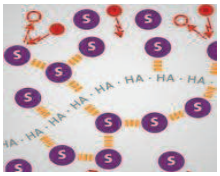
Background

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.

.

Results

Figure 1

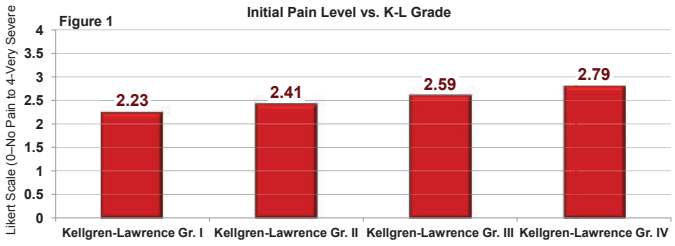


Figure 1 - On the population with Knee OA with both K-L Grade and Initial Pain Level reported (n=509), mean pain level is steadily increasing as a function of Kellgren-Lawrence Grade (K-L Gr.) severity with a mean of 2.23 for K-L Gr. I (n=35), 2.41 for K-L Gr. II (n=160), 2.59 for K-L Gr. III (n=243)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

Figure 2

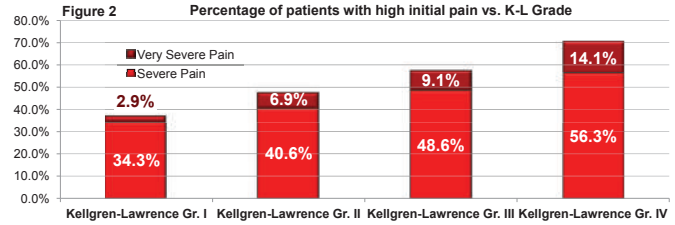
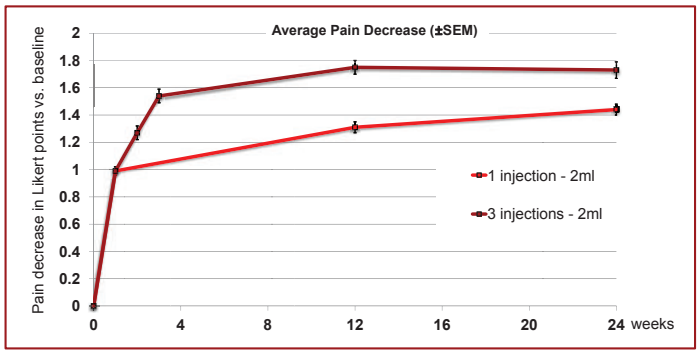


Figure 2 - The percentage of patients with Severe Pain (Likert score 3) and Very Severe Pain (Likert score 4) was correlated to K-L Gr., with 37% of patients with pain level scoring at 3 & 4 in K-L Gr. I, 47% in K-L Gr. II, 56% in K-L Gr. III and 70% in K-L Gr. IV.

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:
1 – Altman RD, Pain, osteoarthritis, and intra-articular HA…Today and beyond, OA pain management update, Special report, 2007; 2 - John Bedson, Peter R Croft, The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature, BMC Musculoskeletal Disorders 2008, 9:116; 3 – Hannan MT, Felson DT, Pincus T, Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee,J Rheumatol. 2000 Jun;27(6).1513-7. 4 – Henrotin Y, Kurz B, Antioxidant to treat osteoarthritis: dream or reality?, Curr Drug Targets, 2007 Feb;8(2):347-57; 5 – Fermor B, Christensen SE, Youn I, Cernanec JM, Davies CM, Weinberg JB. Oxygen, nitric oxide and articular cartilage, Eur Cell Mater, 2007;13:56-65.; 6 – Saari H, Oxygen derived free radicals and synovial fluid hyaluronate, Ann Rheum Dis, 1991 Jun;50(6):389-92.; 7 – Lunec J, Halloran SP, White AG, Dormandy TL, Free-radical oxidation (peroxidation) products in serum and synovial fluid in rheumatoid arthritis, J Rheumatol, 1981 Mar;8(2):233-45.; 8 – Ziskoven C, Jäger M, Zilkens C, Bloch W, Brixius K, Krauspe R, Oxidative stress in secondary osteoarthritos: from cartliage destruction to clinical presentation?, Orthopaedic Reviews, 2010, volume 2:e23; 9 – J. Tehranzadeh J, Booya F, Root J, Cartilage metabolism in Osteoarthritis and the influence of viscosupplementation and steroid: a review, Acta Radiol 2005 (3)

Knee OsteoArthritis Radiographic Severity and Initial Pain Level Influencing Short and Mid-Term Response Rate After Viscosupplementation Treatment by Combined Hyaluronic Acid and Sorbitol

Dr. T. CONROZIER– Belfort Hospital - France
Dr. C. KIPSHOVEN – Rottapharm / Madaus – Germany
F. RADENNE – Anteis - Switzerland

Background

Synolis V-A is a visco-antalgic formulation indicated for viscosupplementation in OsteoArthristis. Synolis V-A is composed of highly concentrated non-crosslinked hyaluronic acid (2%) from biofermentation origin combined with a high concentration of sorbitol (4%). Sorbitol is an endogenous molecule which functions as an oxygen free radical (OFR) scavenger. Rapid and strong pain reduction in patients with knee OsteoArthritis (OA) has been observed in several previous studies using Synolis V-A.

Objective

We hypothesize that one of the dimensions of average pain reduction is a variable response rate to treatment. In addition, we hypothesize that this variable response rate could be associated to radiographic severity, initial pain level and intra-articular injection regimen.

Patients and Methods

Among 1147 patients with a majority suffering from knee Osteoarthritis (92.9%) enrolled in a Non-Interventional Study conducted by Rottapharm Madaus in 398 centres in Germany following recommendations from the BfArM (Federal Institute for Drugs and Medical Devices) and the Paul-Ehrlich-Institute, 455 patients met the inclusion criteria (reported Kellgren-Lawrence grade and initial pain level at baseline, at week1 and/or at week 24) and received either 1 or 3 injections of Synolis V-A 2ml (GO-ON matrix in Germany) one week apart.

This population was then grouped according to two severity evaluation factors:

- Two groups were created according to Kellgren-Lawrence (K-L) based severity (K-L.) I/II (39.3%) & K-L. III/IV (60.7%) – *figure 1*.
- Two groups were created according to Walking Pain (WP) at baseline (5 points Likert scale): None (1.1%), Mild (8.6%), Moderate (35.8%), Severe (45.1%), Very Severe (7.5%) and Not Reported (2.0%) – *figure 2*. The Low Pain group combined patients with Mild/Moderate pain and the High Pain group combined patients with Severe/Very Severe Pain.

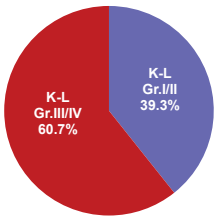


Figure 1: Patients repartition based on their Kellgren-Lawrence Grade

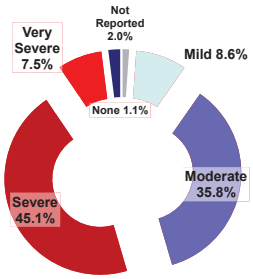


Figure 2: Patients repartition based on their Initial Pain level

Two analyses were conducted comparing at week 1 and week 24 vs. the rate of responders for both 1 and 3 injections regimen vs. baseline, for Low K-L. (I/II) and High K-L. (III/IV) on one hand, and for Low Pain (Mild to Moderate) and High Pain (Severe to Very Severe) on the other hand.

Patients defined as responders were patients with pain decrease of at least 1 point on the Likert scale vs. baseline.

Results

For both Low and High K-L patients groups, the percentage of responders was similar at week 1 with respectively 68.6% and 66.1%.

At week 24 all sub-groups of patients (Low and High K-L groups receiving either 1 or 3 injections) obtained an average response rate above 80%. However, when patients from the Low K-L group receiving 1 or 3 injections and patients from the High K-L goup receiving 1 injection had comparable average response rate, comprised between 81.3% and 82.7% of responders; patients from the High K-L group who received 3 injections obtained a much higher responders rate of 93.1% - *figure 3*.

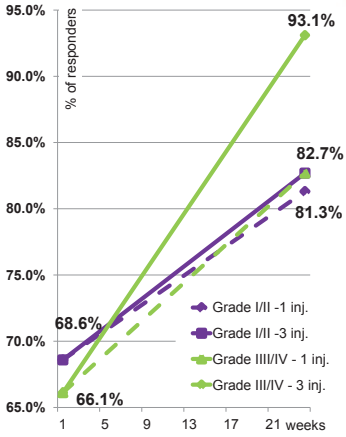


figure 3: rate of responders according to K-L and inj. regimen

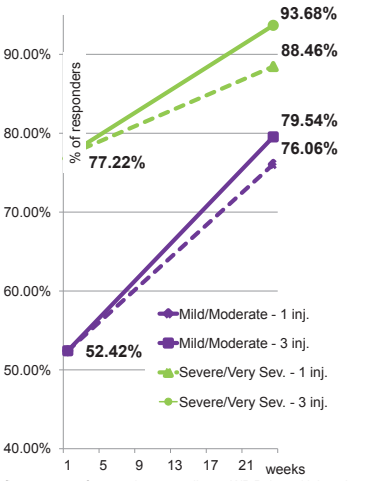


figure 4: rate of responders according to WP Pain and inj. regimen

On the other hand, the percentage of responders between Low Pain and the High Pain groups was different right from week 1 with respectively 52.4% and 77.2%.

At week 24 all sub-groups of patients (Low and High Pain groups receiving either 1 or 3 injections) obtained response rate above 75%. Three injections regimen always provided better response rate vs. 1 injection regimen with respectively 79.5% vs. 76.1% for the Low Pain group and 93.7% vs. 88.5% for the High Pain group – *figure 4*.

Conclusion

This study suggests that the fast average pain relief commonly observed after the first injection of Synolis V-A could partly be explained by the high number of responders reported at week 1 (67.1%).

On the short-term, the initial pain level seemed to be a better predictor of response rate, with a response rate 47.3% higher for High vs. the Low Pain group; which could be explained by the non-linear pain scoring system used.

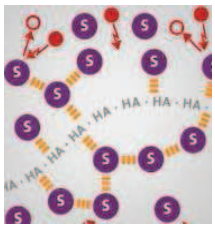
At week 24, the radiographic severity seemed to be an efficient indicator for adapting the injection regimen, suggesting the use of 3 injections for K-L Gr. III & IV patients since the observed response rate was 12.6% higher than for the single regimen.

Efficacy of Knee OsteoArthritis Viscosupplementation Treatment by Combined Hyaluronic Acid and Sorbitol According to Radiographic Severity or Initial Pain Level

Dr. T. CONROZIER– Belfort Hospital - France
Dr. C. KIPSHOVEN – Rottapharm / Madaus – Germany
F. RADENNE – Anteis - Switzerland

Background

Synolis V-A is a visco-antalgic formulation indicated for viscosupplementation in OsteoArthristis. Synolis V-A is composed of highly concentrated non-crosslinked hyaluronic acid (2%) from biofermentation origin combined with a high concentration of sorbitol (4%). Sorbitol is an endogenous molecule which functions as an oxygen free radical (OFR) scavenger. Rapid and strong pain reduction in patients with knee OsteoArthritis (OA) has been observed in several previous studies using Synolis V-A.



Objective

To compare the effectiveness of two dosing regimen (single injection vs. 3 injections one week apart) according to the radiographic and clinical severity.

Patients and Methods

Among 1147 patients with a majority suffering from knee Osteoarthritis (92.9%) enrolled in a Non-Interventional Study conducted by Rottapharm Madaus in 398 centres in Germany following recommendations from the BfArM (Federal Institute for Drugs and Medical Devices) and the Paul-Ehrlich-Institute, 455 patients met the inclusion criteria (reported Kellgren-Lawrence grade and initial pain level at week 0, week1 and/or week 24) and received either 1 or 3 injections of Synolis V-A 2ml (GO-ON matrix in Germany) one week apart – *figure 1*.

The studied population was grouped according to radiographic severity using Kellgren-Lawrence (K-L.) grading system. Two groups were defined: K-L I/II & K-L. III/IV – *figure 2*.

Four sub-groups according to the K-L. Grading and the number of injection of Synolis V-A 2ml were then analyzed: Low K-L. (Gr. I/II)-1 injection; Low K-L.-3 injections; High K-L. (III/IV)-1 injection and High K-L.-3 injections .

This same population was evaluated for Walking Pain (WP) at baseline, using 5-point Likert scale. Level of pain observed was None (1.1%), Mild (8.6%), Moderate (35.8%), Severe (45.1%), Very Severe (7.5%) and Not Reported (2.0%) – *figure 3*.

Four sub-groups according to the Likert score before treatment initiation and the number of injections of Synolis V-A 2ml were then analyzed: Low Pain (mild to moderate)-1 injection; Low Pain-3 injections; High Pain (severe to very severe)-1 injection and High Pain-3 injections

The analysis compared the average response (pain decrease vs. baseline) between sub-groups on the short-term (week 1) and on the mid-term (week 24) following treatment initiation.

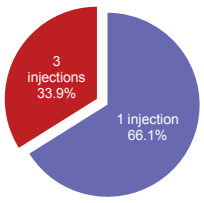


figure 1: Patients repartition by number of injections

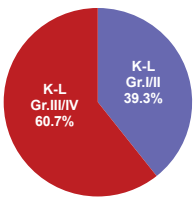


figure 2: Patients repartition based on their Kellgren-Lawrence Grade

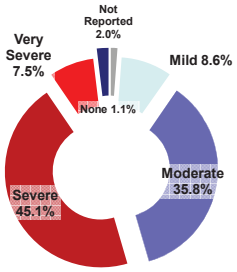


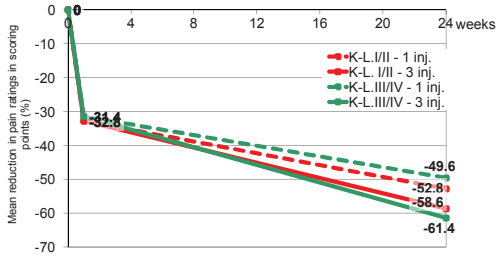
figure 3: Patients repartition based on their Initial Pain level

Results

At week 1, pain decrease in both Kellgren-Lawrence groups (K-L. I/II & III/IV) was similar, with an average pain decrease of 32.6% and 31.4% respectively (p=0.7354) but significant vs. baseline (p<0.001).

At week 24, 3 injections provided greater pain relief than single injection whatever the patients' sub-groups. Never the less, for the K-L. I/II group, the 3-injection regimen brought 11% additional average pain decrease vs. the 1-injection (p=0.0363), whereas for the K -L. III/IV group, the 3-injection regimen brought 24% additional pain decrease vs. the 1-injection (p=0.0003) – *figure 4* .

figure 4: pain decrease in scoring points (%)

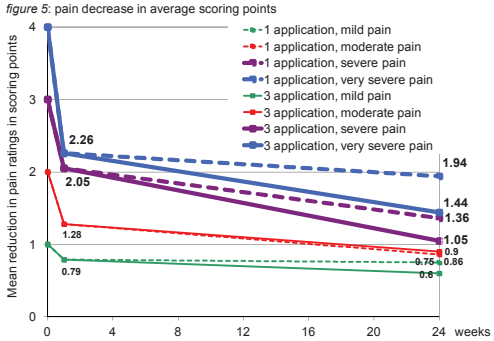


In WP based groups (Likert scores 1, 2, 3 & 4) at week 1, pain decrease correlated to the pain score observed at baseline: Patients with very severe pain scored an average of 1.74 points below; Patients with severe pain scored 0.95 points below; Patients with moderate pain scored 0.72 points below and patients with mild pain scored 0.21 points below.

At week 24, average pain (for patients with Mild to Very Severe pain receiving 1 or 3 injections) dropped by 56.5% from an average baseline score at 2.52.

More precisely, pain scores reported at week 24 after 3 injections were significantly lower than after 1 injection for Very Severe and Severe initial pain, with respectively 26% and 23% better average score. This difference was not observed for Moderate to Mild initial pain – *figure 5*

figure 5: pain decrease in average scoring points



Conclusion

At week 24, average pain decrease vs. baseline was correlated to both the number of injections and the radiographic severity, with a higher benefit of the 3-injection regimen for K-L Gr. III/IV, despite the absence of observed correlation at week 1.

A fast pain relief proportional to the initial pain level has been observed soon after the first injection of Synolis V-A (week 1). Despite the pain decrease trend preserved until week 24 even with one single injection, patients with Very Severe to Severe pain at baseline particularly benefited from the 3-injection regimen.

PAIN REDUCTION ASSESSMENT IN 1147 PATIENTS USING COMBINED SODIUM HYALURONATE AND SORBITOL VISCOSUPPLEMENTATION

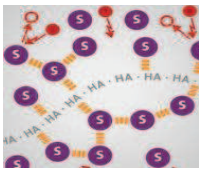
Dr. C. KIPSHOVEN – Rottapharm / Madaus – Germany
F. RADENNE – Anteis - Switzerland

Background

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. The aim of this study was to evaluate the pain reduction performance and to confirm the safety of single or triple injections of 2ml viscosupplement combining sodium hyaluronate and sorbitol.

Objective

This treatment 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

A total of 1147 patients with OsteoArthritis (OA) enrolled in an Non-Interventional Study conducted 398 centres in Germany were mainly been treated with a single 2ml IntraArticular (IA) injection (approximately 55% of patients) or a triple injection (approximately 33% of patients) of sodium hyaluronate (20mg/ml) combined with sorbitol (40mg/ml).
Studied population had an average age of 63.3 years, included 499 males, 614 females and 34 patients without reported gender. The majority of patients were treated for knee OA (92.9%) whereas the rest of patients were injected in the shoulder (2.8%), the hip (4.4%) and in other joints (1.6%). No data were reported for 2.1% of patients and 40 patients were treated for multiple joints.
- 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) at 1st injection (Visit 1: baseline) and during 5 follow up visits for a treatment period of 24 weeks.

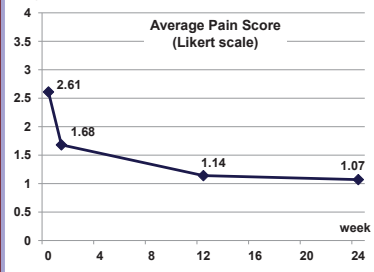
Primary study criteria was the variation of pain score (Likert scale) between baseline and following time points: week1, week 12 and week 24 as well as the variation of the functional impairment score (Likert scale) at baseline, week 12 and week 24.

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.

Results

Figure 1



At baseline, 1125 (98.1%) patients reported pain score. Patients were 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". The average pain score was 2.61 (figure 1).

At week 1, the 830 patients with data also reported at baseline (average score: 2.65) had their average pain scoring at 1.68 (-36.6%).

At week 12, the 1069 patients with data also reported at baseline (average score: 2.61) had their average pain scoring at 1.14 (-56.3%).

At week 24, the 1016 patients with data also reported at baseline (average score: 2.61) had their average pain scoring at 1.07 (-59%).

At week 1, after a single injection, 70.6% (586/830) of patients responded to the treatment, with pain score decreasing by at least 1 point on the Likert scale.

At week 12, 83.8% (896/1069) of patients were responding to treatment. Finally, at week 24, 84.4% (857/1016) of patients were classified as responders.

A total of 1103 patients reported functional impairment score at baseline, 1074 patients at week 12 and 1031 patients at week 24.

-Patients with "No Impairment" evolved from 6.7% at baseline to 26.2% at week 12 and 29% at week 24.

-Patients with "Severe" or "Very Severe impairment" evolved from 30.3% at baseline to 3.8% at week12 and 4.4% at week 24 (figure 2).

Figure 2

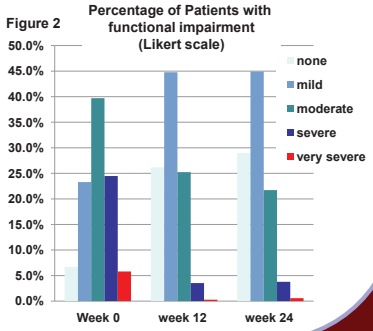


Figure 3

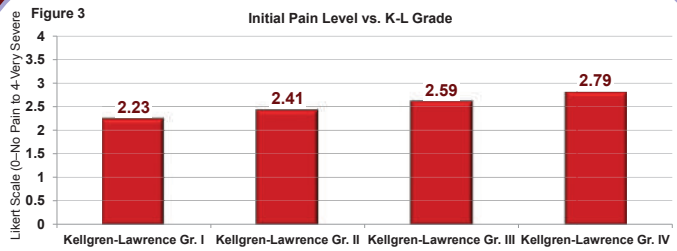


Figure 3 - On the population with Knee OA with both K-L Grade and Initial Pain Level reported (n=509), mean pain level is steadily increasing as a function of Kellgren-Lawrence Grade (K-L Gr.) severity with a mean of 2.23 for K-L Gr. I (n=35), 2.41 for K-L Gr. II (n=160), 2.59 for K-L Gr. III (n=243) and 2.79 for K-L Gr. IV (n=71).

Figure 4

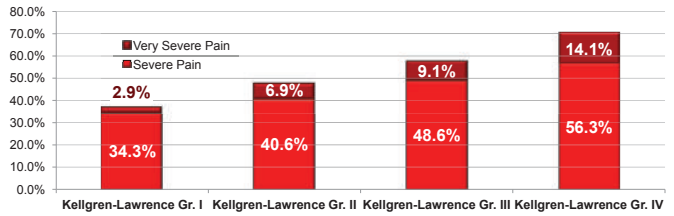


Figure 4 - The percentage of patients with Severe Pain (Likert score 3) and Very Severe Pain (Likert score 4) was correlated to K-L Gr., with 37% of patients with pain level scoring at 3 & 4 in K-L Gr. I, 47% in K-L Gr. II, 56% in K-L Gr. III and 70% in K-L Gr. IV.

Table 1

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"

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

Efficacy of the treatment
On a large cohort of patients, despite a relatively large number of patients with Kellgren-Lawrence grade IV (13.9%) and despite the majority (about 55%) of patients receiving only a single IA injection of 2ml, the level of pain decrease observed from week 1 to week 24 is extremely high; close to 60% at week 24. It could be hypothesized that this performance is strongly supported by the very high rate of responders (84.4%) observed. The decrease of functional impairment is of the same scale, with a baseline average score of 1.99 decreasing to 1.02 (-48.8%) at week 24.

Link between Pain Level and Radiographic Severity
Despite several publications questioning the relation between radiographic-determined severity and pain level [1-2], 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.

Safety
With 1.9% of low severity AEs reported by investigators, this treatment seems to be very safe to perform; especially taking into account that about 30% of injections might miss the intra-articular space [3] potentially generating pain or flare reaction not directly associated with the used viscosupplement.

Conclusion

Viscosupplementation using the combination of sodium hyaluronate and sorbitol has been observed to significantly and safely reduce both joints pain and functional impairments for patients with osteoarthritis at all Kellgren-Lawrence grades, on a period of 24 weeks, at least.

References:
1 - John Bedson, Peter R Croft, The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature, BMC Musculoskeletal Disorders 2008, 9:116;
2 – Hannan MT, Felson DT, Pincus T, Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee,J Rheumatol. 2000 Jun;27(6).1513-7.
3 – J. Tehranzadeh J, Booya F, Root J, Cartilage metabolism in Osteoarthritis and the influence of viscosupplementation and steroid: a review, Acta Radiol 2005 (3)

IMPROVED PREDICTABILITY, EARLY EFFICACY AND SAFETY OF A NOVEL VISCO-ANTALGIC COMBINING HYALURONIC ACID AND SORBITOL (SYNOLIS V-A) IN PATIENTS WITH SYMPTOMATIC KNEE OA

Dr. Mauro Bausani
Piazza Matteotti, Sienna, Italy

Viscosupplementation by intra-articular injections of hyaluronic acid (NaHA) reduces pain and improves function in patients with knee OsteoArthritis (OA) but the improvement is delayed and occurs usually 6 to 8 weeks after the first injection.

RATIONALE

Synolis V-A is an innovative viscosupplement made of a high concentration (20 mg/ml) of a 2mDa Hyaluronic Acid (HA) from non animal origin, combined with a high concentration of a free radical scavenger, the sorbitol (40 mg/ml).

The high affinity between HA and sorbitol, stabilizes the complex through a very dense network of hydrogen bonds (figure 1).

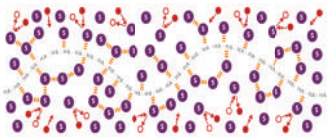


Figure 1

Furthermore the high ability of sorbitol to scavenge and neutralize Oxygen Free Radicals (OFR) has been demonstrated to delay the degradation of the gel compared to linear and cross-linked HA viscosupplements (VS); conserving viscosity properties for a longer period (figure 2).

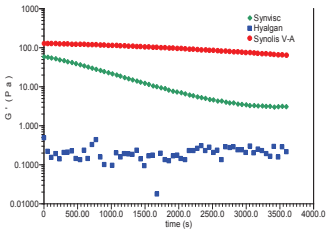


Figure 2

OBJECTIVES

To show evidences of quick pain relief and mobility recovery in the days following the 1st injection, whatever the disease Kellgren-Lawrence (K-L) grade (ranging from II to IV); and of long-term efficacy (up to 6months)

METHODS

Study design

Prospective, open-label 26 weeks study including 29 patients fulfilling the American College of Rheumatology clinical criteria for the diagnosis knee OA.

Inclusion criteria

-Patients suffering from symptomatic knee OA and considered by the physician as requiring viscosupplementation
-30 ≤ Age ≤ 85 years
-K-L grade II to IV on standing AP view, Lyon-schuss view, profile, skyline view of the patella.

Main exclusion criteria

-Flare or significant effusion at any joint.
-Viscosupplementation of any knee within 6 months prior to the initiation of treatment.
-Intra-articular steroid injection of any knee within 3 months prior to the initiation of treatment.
-Know hypersensitivity to NaHA and/or sorbitol

Treatment procedure

Three 2ml intra-articular injections of Synolis-VA were performed 1 week apart by an experienced rheumatologist.

Authorized treatments

-Paracetamol ≤ 4 g/jour
-NSAIDs if taken before inclusion
-SYSADOAs (*chondroïtin sulfate, diacerhein, avocado / soja unsaponifiables, glucosamin , diacerhein*) if taken at stable doses at least 3 months before inclusion and during the whole follow-up period.

Evaluation

At baseline, week (W)1, W2, W13 and W26: WOMAC A (pain) with score from 0 to 20 (figure 3), WOMAC stiffness with score from 0 to 8 (figure 5), Patient Global Assessment (PGA) in % (figure 6) using single or multi-criteria Likert 5 points scale.

All end-points for Walking Pain (WP) with score 0 to 4, WOMAC A, WOMAC stiffness, PGA and adverse events were collected by the physician during patient's visits.

At W1, W2, W13 and W26:
Percentage of improvement vs. baseline were obtained (figure 6)

Study criteria

-Primary criteria was the variation of mean WP between baseline and W26

-Secondary end points were variations of WP, WOMAC A, WOMAC stiffness and PGA between baseline and W1, W2, W3, W13, W26; percentage of improvement vs. baseline for all those criteria, and safety and tolerance quantitative assessment (number of side effects / number of treatments)

RESULTS

Mean age 68 ± 9
K-L (grade/N): II/12; III/16; IV/1

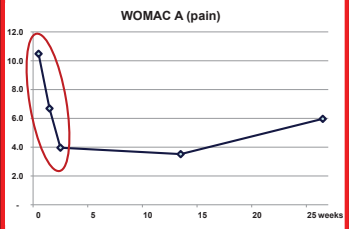


Figure 3

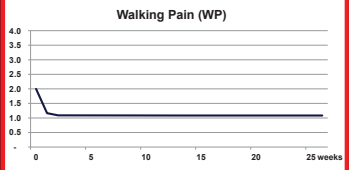


Figure 4a – K-L grade II

Figure 4b – K-L grades III & IV

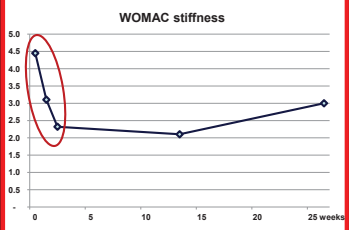


Figure 5

At W26, 100 % of the patients considered Synolis-VA moderately to extremely effective (figure 6).

No device-related adverse event was reported.

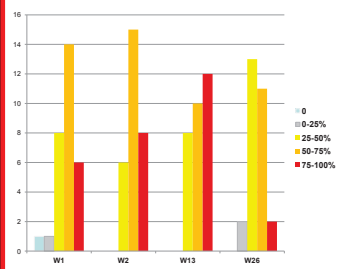


Figure 6 – Level of improvement

RESULTS

At baseline:
- Mean WOMAC A = 10.5
- Mean WOMAC stiffness = 4.4

At week 1:
- Mean WOMAC A = 6.7 (p<0.0001)
- Mean WOMAC stiffness = 3.1 (p<0.005)

At week 2:
- Mean WOMAC A = 4.0 (p<0.0001)
- Mean WOMAC stiffness = 2.3 (p<0.0001)

At week 13:
- Mean WOMAC A = 3.5 (p<0.0001)
- Mean WOMAC stiffness = 2.1 (p<0.0001)

At week 26:
- Mean WOMAC A = 6.0 (p<0.0001)
- Mean WOMAC stiffness = 3.0 (p<0.0001)

- Variation of WOMAC A between baseline and W1, W2, W13 and W26 was respectively -3.8, -6.5, -7-0 (-66%) and -5.5 (-43%) (figure 3).

- WP has been evaluated in 12 patients with KL Grade II & 17 patients with K-L Grades III & IV (III/16 & IV/1). Mean WP at baseline was 2.9. At W1, WP was already reduced to 2.1 (p<0.0002), ending up at 1.9 (p<0.0002) at W26.

- For KL Grade II patients, average WP at baseline was 2.0, down to 1.2 (-40%) with 10 responders at W1 and remaining flat to 1.1 at W26 (-55%) with 11 responders (92% of responders) (figure 4a).

- For Grades III & IV, average WP at baseline was high at 3.5, down to 2,6 -(-28%) with 13 responders at W1, with a minimum of 1.8 (-49%) at W13, and rising to 2.4 (-31%) at W26 with 16 responders (94% of responders) (figure 4b)

CONCLUSION

This exploratory study demonstrates a quick and strong pain relief occurring immediately after the first injection of Synolis V-A, followed by a continuous improvement until week 13 and a sustainable effect up to week 26.

The high concentration of sorbitol combined with a high concentration of Hyaluronic acid is believed to both stabilize the structure of the gel for prolonged mechanical benefits but more importantly to neutralize the oxidative stress responsible for the appearance of OA symptoms

These data support the need for a large-scale, prospective clinical trial comparing the safety and long term efficacy of Synolis-VA to regular viscosupplement.

INTRAARTICULAR INJECTIONS IN TREATMENT OF KNEE OSTEOARTHRITIS: CLINICAL RESULTS WITH COMBINED ANTIOXIDANT AND VISCOSUPLEMENT PRODUCT.

Authors: Valdis Gončars[1], Rihards Piņķis[2]

[1] Hospital of Traumatology and Orthopedics, Riga , Latvian University

[2] Riga Stradina University

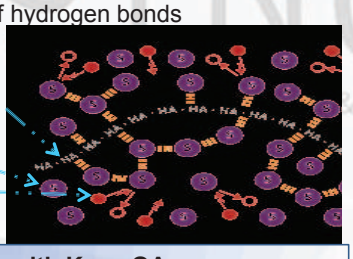
Introduction

SYNOLIS-VA is an innovative viscosupplement made of a high concentration (20 mg/ml) of a 2MDa hyaluronic acid from non animal origin, combined with a high concentration of a free radical scavenger, the sorbitol (40 mg/ml). The high affinity between NaHA and sorbitol, stabilizes the complex through a very dense network of hydrogen bonds

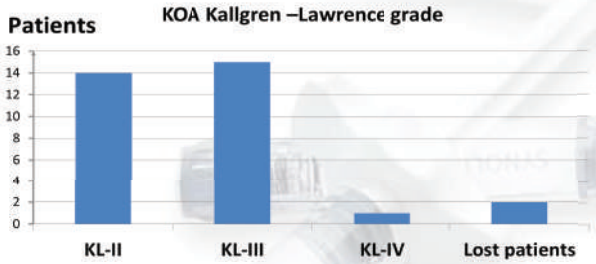
Hyaluronic acid

Sorbitol

Free radicals



Material : 30 patients with Knee OA

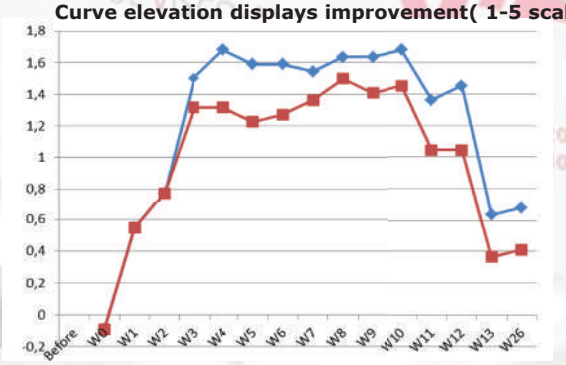


Mean age 61 +/- 3.9

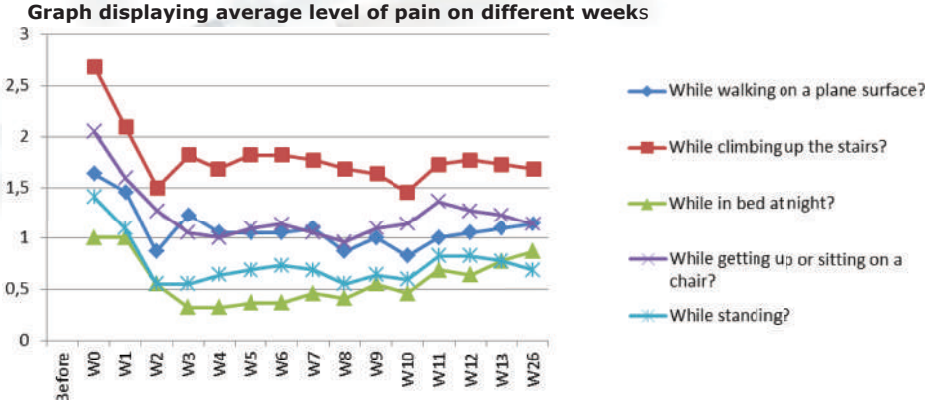
Methods

Treatment regimen consisted of 3 IA injections of 2 ml of Synolis® V-A weekly apart. Pain and function (WOMAC scale, walking pain, physician global assessment, WOMAC A and WOMAC stiffness) were obtained at W0, W1, W2, W13 and W26. Treatment satisfaction and amount of responding patients was also evaluated at the end of the follow up period.

Curve elevation displays improvement(1-5 scale)



Graph displaying average level of pain on different weeks

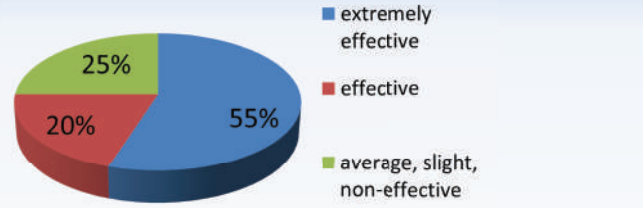


Results

At W26, Walking pain improved for 0.9 points average (5 point scale), WOMAC A (10 point scale) improved for 3.9 points average. Womac stiffness (5 point scale) improved for 1.6 points average. At W26, 75% of the patients considered the treatment as effective to extremely effective and 55% considered it extremely effective.3 patients had no positive effect after the treatment. On two of them the meniscus injury was proved with MR. On the one patient with grade 4 osteoarthritis the knee arthroplasty was performed in W18.

Conclusion(s)

- The treatment course of 3 Synolis® V-A injections in most cases leads to fast and significant pain reducing.
- The effect of Synolis® V-A maintains for at least 26 weeks.
- No major said effects were observed.
- The clinical benefits for the use of this treatment for the patients with high grade osteoarthritis or meniscus lesion were not being found.



EARLY EFFICACY OF A NOVEL VISCOSUPPLEMENT COMBINING HYALURONIC ACID AND SORBITOL, ANTI-OX-VS (SYNOLIS) IN PATIENTS WITH KNEE OSTEOARTHRITIS

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[1]Rheumatology, Lyon-Sud University Hospital, Pierre-Bénite, France; [2]Anteis SA, Genève, Switzerland; [3] Lyon-Presqu'île Rheumatology Centre, Lyon, France

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CHANGE STARTS HERE

ABSTRACT

Title: EARLY EFFICACY AND SAFETY OD A NOVEL VISCOSUPPLEMENT COMBINING SODIUM HYALURONATE AND SORBITOL (ANTI-OX-VS) IN PATIENTS WITH SYMPTOMATIC KNEE OSTEOARTHRITIS.

Objective(s): ANTI-OX- VS is an innovative viscosupplement (VS) made of a high concentration (20 mg/ml) of a > 2MDa Sodium Hyaluronate (NaHA) from non animal origin, combined with a high concentration of an oxygen free radical (OFR) scavenger, the Sorbitol (40mg/ml). The high ability of Sorbitol to scavenge and neutralize OFR has already been proven to delay the degradation of the gel. We hypothesis the antioxidant effect of a Sorbitol may also play a role to reduce the time to onset of analgesia.

Materiel and Methods: 26 patients with symptomatic KOA were included in a 13 weeks prospective open pilot study. Treatment regimen consisted of 3 IA injections of 2 ml of ANTI-OX-VS on week apart. Pain and function (WOMAC scale, walking pain (WP), patient and physician global assessment (GA) using a 5 points Likert scale were obtained at W1, W2 and W13. Between W2 andW14 patients were asked to complete a weekly self evaluation questionnaire (WP, WOMAC A between W0 and W1, w2, W8, W13. The treatment efficiency was also evaluated at W13.

Results: Mean age was 71+10, BMI 27.9???3.9. KL grades 1,2,3,4 in 0, 6, 8, 12 cases respectively. At W0 mean WP was 2.1 and WOMAC A 8.3. At W3 mean WP to 1.5(p<0.0003). As early as W1 WP was already reduced to 1.6 (p<0.0003) and decrease again 1.0 (p<0.0001) at W13. Variation of mean MP between W0 and W1, W2, W3, W8, W13 was resp. -0.5; -0.4; -0.5 and -1.1. Variation of mean WOMAC A between W0 and W1, W2, W8, W13 was resp. -2.1, -2.0, -2.0, -3.9. At W13, 82% of the patients considered ANTI –OX-VS treatment is moderately to extremely effective. There was no advice related adverse event reported.

Conclusion(s): This study suggests a quick and strong pain relief occurring immediately after the first injection on ANTI-OX-VS followed by continuous improvement until W13. Pain decreases much faster than what obtained with other VS probably because of the presence of a high concentration of Sorbitol through its antioxidant activity.

Viscosupplementation by intraarticular injections of hyaluronic acid (HA) reduces pain and improves function in patients with knee osteoarthritis (KOA) but the improvement is delayed and occurs usually 6 to 8 weeks after the injections.

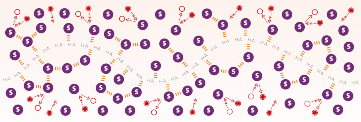


Figure 1

Rationale

ANTI-OX-VS (Synolis™) is a new innovative viscosupplement made of a high concentration (20 mg/ml) of a 2mDa hyaluronic acid (HA) from non animal origin, combined with a highconcentration of a free radical-scavenger, the sorbitol (40 mg/ml).

Figure 2

The high affinity between HA and sorbitol, stabilizes the complex through a very dense network of hydrogen bonds (figure 1).

Furthermore the high ability of sorbitol to scavenge and neutralize oxygen free radicals (OFR) has been demonstrated to delay the degradation of the gel, compared to linear and cross-linked HA viscosupplements (Figure 2).

OBJECTIVES

To evaluate the short term pain-relief effect of ANTI-OX-VS in patients suffering from knee osteoarthritis.

Study design

Prospective, open-label 13 week study 26 outpatients fulfilling the American College of Rheumatology clinical criteria for the diagnosis knee OA.

Inclusion criteria

- Patients suffering from symptomatic knee OA and considered by the physician as requiring viscosupplementation
- 30 ≥ Age < 85 years
- Kellgren-Lawrence grade (KL) II to IV on standing AP view, Lyon schuss view, profile, skyline view of the patella.

Main exclusion criteria

- Flare at any joint.
- VS of any knee within 6 months prior to the initiation of treatment.
- Intra-articular steroid injection of any knee within 3 months prior to the initiation of treatment.

Treatment procedure

Three 2mL intra-articular injections of ANTI-OX-VS (Synolis™) were performed 1 week apart by an experienced rheumatologist.

Authorized treatments

- Paracetamol < 4 g/jour
- NSAIDs if taken before inclusion
- SYSADOAs *(chondroïtin sulfate, diacerhein, avocado/soja unsaponifiables, glucosamin , diacerhein)* if taken at stable doses at least 3 months before inclusion and during the whole follow-up period.

Evaluation

At baseline, W1, W2 and W13 : WOMAC A, WOMAC aggregate, walking pain (WP), patient and physician global assessment (PGA) using a Likert 5 points scale.

Between the third injection and end-point patients were asked to complete once a week **a self evaluation questionnaire** for WP, WOMAC A, patient GA and adverse events.

At W1, W2 and W13 : Percentage of improvement since the first injection were obtained (figure 4).

Treatment satisfaction was also evaluated at the end of the follow up period (Likert 4 points scale).

Primary criteria : Variation of WP between first injection and W3.

Secondary criteria : Variation of WP, WOMAC A, PGA between baseline and W1, W2, W3, W8, W13. Variation of WOMAC between baseline and W13. Percentage of improvement between baseline and W1,W2,W13.

RESULTS

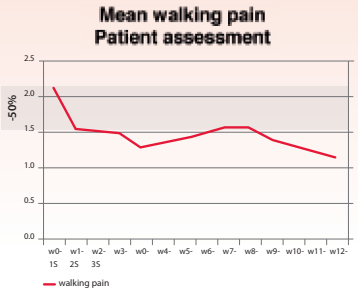


Figure 3

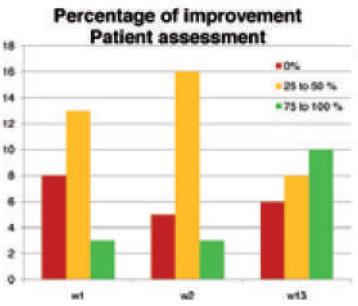


Figure 4

Mean age 71 ± 10
Mean BMI 27.9 ± 3.9
KL (grade /N): II/6; III/8; IV/12

At baseline:
- Mean WP = 2.1
- Mean WOMAC A = 8.3

At week 1:
- Mean WP 1.6 (p<0.0003)
- Mean WOMAC A = 6.2 (p<0.0000)

At week 3:
- Mean WP 1.5 (p<0.0003)
- Mean WOMAC A = 7.5 (p<0.05)

At week 13:
- Mean WP 1.0 (p<0.0001)
- Mean WOMAC A = 4.9 (p<0.0000)
- Variation of WP between baseline and W1, W2, W8 and W13 was respectively -0.5, -0.4, -0.5 and -1.1 (figure 3)

- Variation of WOMAC A between baseline and W1, W2, W8 and W13 was respectively -2.1, -2, -2 and -3.9. At W13, 82 % of the patients considered ANTI-OX-VS moderately to extremely effective.

No device-related adverse event was reported.

CONCLUSION

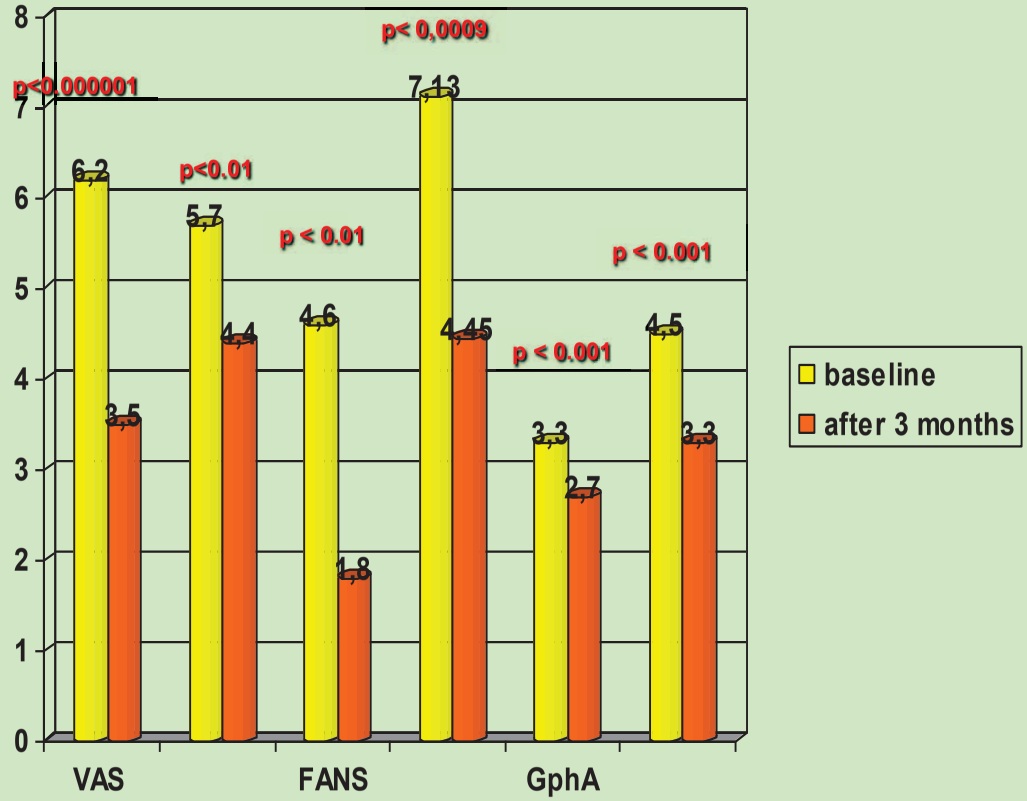
This exploratory study demonstrates a quick and strong pain relief occurring immediately after the first injection of ANTI-OX-VS, followed by a continuous improvement until the end of follow-up (W13) .

Improvement was achieved much faster than that usually obtained with other commercial viscosupplements probably because of the presence of a high concentration of sorbitol acting through its antioxidant activity.

These data support the need for a large scale, prospective clinical trial comparing the safety and long term efficacy of Synolis™ to regular viscosupplement.

Long term efficacy profile of Synolis V-A in patients affected by symptomatic hip osteoarthritis: The "SYCA" study. Preliminary data

U.Massafra*; E.Bizzi*; F Vacca*; F Giovannangeli*; S.Tormentaº; A.Migliore*
*Rheumatology Unit Saint Peter Hospital Fbf Rome italy
º Radiology dipartement Saint Peter Hospital Fbf Rome italy



Objective: Osteoarthritis (OA) is one of the more frequent pathology in clinical practice; hip OA is less frequent than knee or hand OA but it is more frequently symptomatic than other localizations. Although this relevant impact in clinical practice, still not conclusive data about safety and efficacy of hip viscosupplementation are reported in litterature. This study investigated on the safety and efficacy profiles of ultrasound-guided intra-articular injections of Synolis V-A (2% sodium hyaluronate 4% sorbitol, 2 ml, Anteis) in hip osteoarthritis affected patients.
Synolis V-A is a new product for intra-articular treatment of osteoarthritis; it mixed sorbitol and sodium hyaluronate to improve analgesic effect of hyaluronate and to maintain its effect until 12 months after one injection

Design: This is an open, spontaneous, prospective, monocentric, postmarketing study.
Material and methods: We enrolled adult outpatients affected by symptomatic hip OA; all patients has to show a radiographic grade 2, 3 or 4 according to Kellgren & Lawrence criteria; all patients underwent to one intra-articular (IA) injection of 4 ml (2 vials) of Synolis V-A under ultrasound guidance. Patients characteristics, such as gender, age, weight, height and BMI, smoking habit, unilateral or bilateral hip osteoarthrits involvement, radiological grade and duration of disease were evaluated. Patients were assessed at baseline and at every three months, during control visit; parameters evaluated were: Lequesne algo-functional index, Visuo Analogic Scale (VAS) for pain and NSAID consumption (calculated on the number of days patients assumed NSAID in the last month), Global patient assessment (GPA) and Global physician assessment (GPhA) and Health assessment questionnaire (HAQ). Drop out were recorded; distribution and causes of drop out were noted.

Results: We enrolled 50 patients in the study. All of them received one IA US-guided injection of Synolis V-A in the hip joint. We report preliminary data about three monts of follow-up A total of 2 drop outs were registered. A total of 50 injections was performed. Five patients were affected by bilateral hip OA (see tab 1)
No local or systemic infectious side effects were reported during the follow-up period.

Conclusions: Our preliminary data evidenced a good efficacy and safety profile of Synolis V-A for the treatment of symptomatic hip osteoarthritis after 3 months follow-up

Addition of sorbitol to hyaluronic acid may reduce the onset of action of viscosupplementation in patients with symptomatic knee osteoarthritis

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Résumé

Purpose

Viscosupplementation by intraarticular injections of hyaluronic acid (HA) reduces pain and improves function in patients with knee osteoarthritis (KOA) but the improvement is delayed and occurs usually 6 to 8 weeks after the injections.

ANTI-OX-VS is an innovative viscosupplement made of a high concentration (20 mg/ml) of a 2mDa hyaluronic acid (HA) from non animal origin, combined with a high concentration of a free radical scavenger, the sorbitol (40 mg/ml). The high affinity between HA and sorbitol, stabilizes the complex through a very dense network of hydrogen bonds. The high ability of sorbitol to scavenge and neutralize reactive oxygen specie (ROS) has been demonstrated to delay the degradation of the gel due to ROS. We hypothesise that the antioxidant effect of sorbitol may also play a role to reduce the time to onset of analgesia.

Objectives

To evaluate the short term pain-relief effect of ANTI-OX-VS in patients suffering from KOA.

Patients and methods

Thirteen-week (W) prospective open pilot study. 30 patients suffering from symptomatic KOA (tibiofemoral and/or patellofemoral, grade 2 to 4) were treated by intra-articular injections of ANTI-OX-VS. Each patient received 3 intra-articular injections of 2 mL one week apart. Pain and function using the WOMAC scale, walking pain (WP), patient and physician global assessment (GA) using a 5 point Likert scale, and percentage of improvement since the first injection were obtained at baseline, W1, W2 and end point (W13). Between the third injection and W13 patients were asked to complete once a week a self evaluation questionnaire including WP, WOMAC A, patient GA and adverse events (AEs).

Primary criteria was the variation of WP between first injection and W3. Secondary criteria: were: Variation of WP, WOMAC A, PGA between baseline and W1, W2, W3, W8, W13. Variation of WOMAC between baseline and W13. Percentage of improvement between baseline and W1,W2,W13.

Results

At baseline mean WP was 2.1 and WOMAC A 8.3. WP dramatically decreased 1 week after the first injection (1.6, p<0.0003). At W3 mean WP was 1.5 (p<0.0003) and decreased again to 1.0 at W13 (p<0.0001). The mean decrease of WOMAC A at W1, W2, W8 and W13 was -2.1, -2, -2 and -3.9 respectively.

Conclusions

This exploratory study suggests a quick and strong pain relief occurring immediately after the first injection of ANTI-OX-VS, followed by a continuous improvement until the end of follow-up. Improvement was achieved much faster than that obtained with other viscosupplements probably because of the presence of high concentrations of sorbitol through its antioxidant activity. These data support the need for a large-scale, prospective clinical trial comparing the safety and long term efficacy of ANTI-OX-VS to regular viscosupplement.

Rationale

Viscosupplementation by intraarticular injections of hyaluronic acid (HA) reduces pain and improves function in patients with knee osteoarthritis (KOA) but the improvement is delayed and occurs usually 6 to 8 weeks after the injections.

ANTI-OX-VS (Synolis™) is a new innovative viscosupplement made of a high concentration (20 mg/ml) of a 2mDa hyaluronic acid (HA) from non animal origin, combined with a high concentration of a free radical scavenger, the sorbitol (40 mg/ml)

The high affinity between HA and sorbitol, stabilizes the complex through a very dense network of hydrogen bonds (figure 1).

Figure 1

Furthermore the high ability of sorbitol to scavenge and neutralize oxygen free radicals (OFR) has been demonstrated to delay the degradation of the gel, compared to linear and cross-linked HA viscosupplements (Figure 2).

Figure 2

Objectives

To evaluate the short term pain-relief effect of ANTI-OX-VS (SYNOLIS®) in patients suffering from knee osteoarthritis.

Methods

Study design
Prospective, open-label 13 weeks study
30 outpatients fulfilling the American College of Rheumatology clinical criteria for the diagnosis knee OA

Inclusion criteria
-Patients suffering from symptomatic knee OA and considered by the physician as requiring viscosupplementation
-30 ≥ Age ≤ 85 years
-Kellgren-Lawrence grade (KL) II to IV on standing AP view, Lyon-schuss view, profile, skyline view of the patella

Main exclusion criteria
-Flare at any joint.
-VS of any knee within 6 months prior to the initiation of treatment.
-Intra-articular steroid injection of any knee within 3 months prior to the initiation of treatment.

Treatment procedure
Three 2mL intra-articular injections of ANTI-OX-VS (SYNOLIS™) were performed 1 week apart by an experienced rheumatologist.

Authorized treatments
-Paracetamol ≤ 4 g/jour
-NSAIDs if taken before inclusion
-SYSADOAs (*chondroïtin sulfate, diacerhein, avocado/soja unsaponifiables, glucosamin , diacerhein*) if taken at stable doses at least 3 months before inclusion and during the whole follow-up period.

Evaluation
At baseline, W1, W2 and W13: WOMAC A, WOMAC aggregate, walking pain (WP), patient and physician global assessment (GA) using a Likert 5 point scale

Between the third injection and end-point patients were asked to complete once a week a **self evaluation questionnaire** for WP, WOMAC A, patient GA and adverse events.

At W1, W2 and W13:
Percentage of improvement since the first injection were obtained.

Treatment satisfaction was also evaluated at the end of the follow up period (Likert 4 points)

Primary criteria : Variation of WP between first injection and W4.

Secondary criteria: Variation of WP, WOMAC A, PGA between baseline and W1, W2, W3, W8, W14. Variation of WOMAC between baseline and W14. Percentage of improvement between baseline and W1,W2,W13.

Results

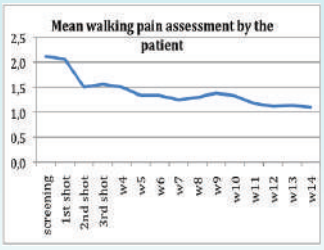

Figure 3

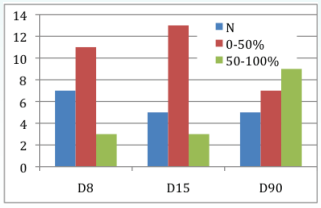

Figure 4

Results

Mean age 71 ± 10
Mean BMI 27.9 ± 3.9
KL (grade /N): II/6; III/8; IV/12

At baseline:
-Mean WP = 2.1

At week 1:
-Mean WP 1.6 (p<0.0003)

At week 3:
-Mean WP 1.5 (p<0.0003)

At week 13:
-Mean WP 1.0 (p<0.0001)

-Variation of WP between baseline and W1, W2, W8 and W13 was respectively -0.5, -0.4, -0.5 and -1.1 (figure 3)

-At baseline Mean WOMAC A = 8.3
-Variation of WOMAC A between baseline and W1, W2, W8 and W13 was respectively -2.1, -2, -2 and -3.9.

At W13, % of the patients considered ANTI-OX-VS moderately to extremely effective (figure 5)

No device-related adverse event was reported.

Conclusion

This exploratory study demonstrates a quick and strong pain relief occurring immediately after the first injection of SYNOLIS®, followed by a continuous improvement until the end of follow-up (W14) .

Improvement was achieved much faster than that usually obtained with other commercial viscosupplements probably because of the presence of high concentrations of sorbitol acting through its antioxidant activity.

These data support the need for a large-scale, prospective clinical trial comparing the safety and long term efficacy of Synolis® to regular viscosupplement.