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LETTER TO THE EDITOR

SAFETY AND TOLERABILITY OF INTRA-ARTICULAR HYALURONIC ACID (SINOVIAL®/GELSYN-3™) INJECTIONS IN THE TREATMENT OF KNEE OSTEOARTHRITIS

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Osteoarthritis (OA) is a progressively degenerative joint disease, with a very high prevalence rate that is expected to increase worldwide with the ageing of the population. Considering that OA requires long-term treatment, therapies with minimal side effects and which can be repeated as needed are warranted. Hyaluronic acid (HA), a natural glycosaminoglycan with viscoelastic properties, is a major component of synovial fluid and the extracellular matrix of the joint cartilage, and plays key roles in maintaining synovial fluid viscosity and the bio-mechanical integrity of healthy cartilage. Intra-articular administration of exogenous HA has therefore been used to successfully improve the viscoelastic properties of the joint to improve lubrication, modulate inflammation and modify the catabolic micro-environment. Sinovial®/GELSYN-3™ is a sterile, non-pyrogenic formulation of highly purified, chemically unmodified HA of bio-fermentative origin, which has been introduced in several different concentrations in clinical use within the European market. This expert opinion reports on the published data regarding the efficacy and tolerability of first and multiple injection series of Sinovial®-based product formulations. The data regarding the tolerability of Sinovial® in patients with knee osteoarthritis were analyzed, showing that this formulation, beside favourable therapeutic effects, has a very good tolerability profile, with only mild, transient, and easily managed, local injection-site reactions and absence of systemic reactions. In particular, repetitive cycles of HA have been shown to yield positive results in terms of both efficacy and safety and therefore should be offered to patients who had undergone a successful first course of therapy when their symptoms reoccur.

To the Editor,

Osteoarthritis (OA) is a progressively degenerative joint disease. The prevailing paradigm suggests that OA results from an impaired regenerative ability of the damaged cartilage due to bio-mechanical and bio-chemical changes. The clinical signs associated with these changes include pain, stiffness, and decreased functionality, which may compromise overall health and quality of life, leading to disability (1).

The prevalence of OA is very high, expected to affect more than 50 million subjects in the US by 2020, and will increase with the ageing of the population. According to the American College of Rheumatology, nearly 70% of people aged over 70 years have X-ray evidence of OA, although only half ever develop symptoms (2).

While several pharmaceutical approaches to managing the symptoms of OA exist (i.e. analgesic treatment with non-steroidal anti-inflammatory drugs, COX-2 inhibitors and steroids), many of

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these agents carry known systemic risks, with the incidence of adverse reactions increasing with age (3). Furthermore, intra-articular steroids must be used sparingly, with dosing every 3-4 months due to the potential for soft tissue damage (4).

Considering the limits of these treatments, therapies with minimal side effects and the possibility to be repeated as needed are therefore warranted. One such therapy is viscosupplementation, wherein exogenous hyaluronic acid (HA) is injected into the affected joint. During the progression of OA, synthetic levels and concentrations of HA in synovial fluid are reduced. Administration of exogenous HA has therefore been used to restore the viscoelastic properties of the joint, which aids in improving lubrication, modulating inflammation and modifying the catabolic micro-environment (5). Moreover, HA is recommended in patients with intolerance or contraindications to other pharmacological treatments and in patients who are unable to elect surgery.

Recent data have suggested that repeated use of HAs may help to delay the need for total knee replacement (TKR) for up to 3.6 years (6). Several authors found that the time to TKR is proportionate to the number of HA injection series, with ensuing economic benefits and improvement in the quality of life (7).

This review reports on published data regarding the safety and tolerability of first and repeated intra-articular injections with HA in knee OA, focusing on Sinovial®-based product formulations (IBSA, Institut Biochimique SA, Lugano, Switzerland). Sinovial®, branded GELSYN-3™ (Bioventus LLC, Durham, North Carolina, USA) for the US market, is FDA approved based on a single course of therapy.

The pathogenesis of OA and the mechanisms of action of HA, which are widely addressed in the literature (5), are beyond the scope of the present paper.

MATERIALS AND METHODS

Data sources, search strategy and inclusion criteria

We performed a systematic electronic literature search in PubMed, Web of Knowledge and EMBASE using the terms Sinovial or hyaluronic acid or hyaluronan, combined with intra-articular or osteoarthritis or knee. Trials, selected manually and supplemented by searches of the bibliographies of articles, were deemed relevant if they contained original research providing relevant knowledge related to this topic. All searches were limited to human studies; all randomized controlled trials and observational

Table I. *Sinovial product family dosing regimen.*

					Concentration/volume		
Product	**Initial (n of injections)**	**Repeat interval**	**Repeat Product**	**Repeat Course (n of injections)**	**First course**	**Repeat course**	**Total**
Sinovial®	Once weekly (3 injections)	6 months	Sinovial®	Once weekly (3 injections)	48 mg/6 mL	48 mg/6 mL	96 mg/12 mL
Sinovial®	Once weekly (3 injections)	6 months	Sinovial® Forte	Once weekly (3 injections)	48 mg/6 mL	96 mg/6 mL	144 mg/12 mL
Sinovial® Forte	Once weekly (3 injections)	6 months	Sinovial® Forte	Once weekly (3 injections)	96 mg/6 mL	96 mg/6 mL	192 mg/12 mL
Sinovial® Forte	Once weekly (3 injections)	4 months	Sinovial® One	Once every 4 months (3 injections)	96 mg/6 mL	150 mg/7.5 mL	246 mg/13.5 mL
Sinovial® One	1 injection	4 months	Sinovial® One	Once every 4 months (1 injection)	50 mg/2.5 mL	50 mg/2.5 mL	100 mg/5 mL
Sinovial® HL	Once weekly (3 injections)	6 months	Sinovial® HL	Once weekly (3 injections)	192 mg/6 mL	192 mg/6 mL	384 mg/12 mL

studies which reported the efficacy and tolerability for intra-articular injection of Sinovial® in knee OA patients were included.

Data extraction and outcome measures

From each publication, relevant study details (design, inclusion and exclusion criteria, number of injections, treatment duration, follow-up times), patient characteristics (number, demographic and clinical data), and efficacy outcomes were extracted. The overall incidence of adverse events (AEs) (reported separately by type and severity), after the first and multiple courses of Sinovial® injections, were examined and collated.

Product overview

Sinovial® is a sterile, non-pyrogenic, sodium chloride (phosphate buffered) solution of highly purified, chemically un-modified HA of bio-fermentative origin (*Streptococci* of Lancefield groups A and C). It is a linear polymer composed of the disaccharide units N-acetyl-D-glucosamine and sodium-D-glucuronate, linked by glycosidic bonds, with a mean molecular weight (MW) of 800-1200 kDa. Sinovial® is available in pre-filled, ready to use syringes for injection into large or small joints.

There are several different concentrations of the product in clinical use within the European market, including Sinovial® Mini (8 mg/1 mL), Sinovial® (16 mg/2 mL; branded GELSYN-3™ for US market), Sinovial® Forte (32 mg/2 mL), Sinovial® One (50 mg/2.5 mL). Moreover, a new formulation, Sinovial® HL (64 mg/2 mL), composed of both low molecular weight (80-100 kDa) and high molecular weight (1100-1400 kDa) HA, has recently (2015) become available on the market.

Sinovial® Mini is a specific formulation mostly indicated in the treatment of OA of small joints (wrist, hand, foot, temporo-mandibular joint, etc.) and synovial sheaths (e.g. trigger finger), while the others are mainly used in the treatments of OA of large joints (hip, knee, ankle, shoulder, etc.).

The clinical dosing regimen may vary from a single dose (Sinovial® One), to two/three (Sinovial® Mini, Sinovial® HL, Sinovial® Forte), and three/five (Sinovial®/ GELSYN-3™) (once weekly) for each cycle of treatment. The interval between cycles is usually 4-6 months, but it can be modified by the treating physician on the basis of the specific clinical situation and individual experience (Table I).

RESULTS

Six clinical trials (two retrospective (8, 9), two open double-blind (10, 11) and two open observational (12, 13) studies) were performed on the efficacy and safety of Sinovial® product family in the management of knee OA. The design of the studies is reported in Table II.

These trials demonstrated that first and repetitive cycles of Sinovial® product family have been shown to yield positive results in terms of clinically relevant pain relief (reduced pain scores at VAS and WOMAC scales), improved joint mobility (Lequesne Index, WOMAC sub-scores and KOOS scale) and reduced use of rescue medication in patients affected by mild to moderate knee OA (Table III).

Table II. *Sinovial treatment in knee OA (design of the studies).*

Author (year) [ref]	Study type	N. of patients	K-L	HA	N. of injections	Total HA concentration and volume injected/patient	Study Duration
Castellacci (2004) **[8]**	Retrospective	40 28 M;12 F	Primary and secondary OA I-IV	Sinovial®	5 once weekly	80 mg/10 mL	7 weeks
Depont (2006) **[9]**	Retrospective observational open label	408 146 M; 262 F	Primary and secondary OA	Sinovial®	1	16 mg/2 mL	4-12 months
Pavelka (2011) **[10]**	Multicenter, phase III, double blind, controlled, randomized, parallel-group, non-inferiority study	192* 188**	Primary OA II-III	Sinovial® Synvisc®	3 once weekly	48 mg/6 mL 48 mg/6 mL	26 weeks
Polacco (2013) **[11]**	Open label, double blind, single center study	21 8 M; 13 F	II-IV 16 II; 6 III; 2 IV	Sinovial® One (mepivacaine 2%)	1	50 mg/2.5 mL	4 months
Theiler (2005) **[12]**	Longitudinal, prospective, single group, open label observational	63 26 M; 37 F	Primary and secondary OA II-IV	Sinovial®	5 once weekly	80 mg/10 mL	24 weeks
Abate (2015) **[13]**	Open design, observational trial	15 6 M; 9 F	II-III	Sinovial® Forte + Sinovial® One	3 once weekly + 3 (one every 4 months)	246 mg/13.5 mL	14 months

** Patients treated with Sinovial® (53 M; 139F) ** Patients treated with Synvisc® (50 M; 138 F)*

Table III. *Sinovial treatment in knee OA (efficacy and safety).*

Author (year) [ref]	VAS scores	WOMAC	WOMAC sub-scores	KOOS	Lequesne Index	Adverse events (AEs)
Castellacci (2004) **[8]**					From 7.9 to 3.2	40% mild
Depont (2006) **[9]**	64.5% patients reported subjectively an improved knee function, less pain and less need for pain medication. Successful injections were associated with recent OA onset (<5 years) and lower BMI.					4% mild
Pavelka (2011) **[10]**	From 64.5 to 26.9	From 55.7 to 22.7			From 11.5 to 7.6	0.5% mild 0.5% severe 0.5% serious
Polacco (2013) **[11]**	Reduced pain at rest and during activities	From 14.7 to 7.9 in 77.6% of the 24 treated knees				No
Theiler (2005) **[12]**		From 4 ± 1.9 to 2.4 ± 1.8	Reduced pain Improved stiffness and physical function			5.8%
Abate (2015) **[13]**	Reduced pain at rest and during activities			From 51.9 to 70.2	From 10 to 5.4	13% mild

In Pavelka's study [10] positive results were observed also in patients treated with Synvisc® (VAS: from 66.7 to 30.5; WOMAC: from 55.5 to 23.1; Lequesne: from 11.6 to 8). Mild, severe and serious AEs were observed in 2.1%, 3.2% and 2.1%, respectively (The authors did not declare in the paper the characteristics of these AEs, however stated that they were not treatment-related).
In Abate's study [13], NSAIDs consumption was reduced, and 73.3% (11/15) of patients reported a rating of "extremely/very satisfied" associated with their treatment.

Moreover, intra-articular injections of Sinovial® have demonstrated a remarkable tolerability profile, with a low incidence of AEs (Table III). Indeed, in all the trials performed, after the first and repeated course of injection, early mild AEs (pain, burning sensation, irritation or erythema at the injection site) were observed in a very low percentage of patients, which, when reported, ranged from 0.5% to 40% of cases. These AEs are common and known reactions to any intra-articular injections. Furthermore, those reported in these studies were short lasting and resolved spontaneously in a few hours post administration or in the following 2-3 days without any concomitant therapy (only RICE treatment). The overall tolerability was judged as "good" or "very good" by nearly all the patients (95%) and investigators (97.5%). None of the patients treated with Sinovial® injections discontinued the treatment due to an AE. All authors considered Sinovial® as safe and well tolerated with a low incidence of AEs and that treatment did not interfere with the product's clinical performance.

Anectodal Italian and European researchers' experiences

In our daily clinical practice, we have been using different formulations of Sinovial® for about six years in the management of hip, knee and ankle degenerative/overuse pathologies, performing roughly 150-200 injections of Sinovial®-based formulations per year. The type of Sinovial® used varies according to the subject's characteristics (age, BMI, activity) and severity of OA. Sinovial® or Sinovial® Forte is usually preferred in young patients with low OA degree (K-L I-II) and BMI <25. Sinovial® One or Sinovial® HL are mostly used in elderly and/or obese patients with K-L III-IV score or in subjects who are submitted to higher joint demands (heavy work, professional athletes) in order to exploit the shock absorption activity of HA.

The treatment regimen varies according to the joint to be injected. Specific to the knee, the first course of therapy for Sinovial®, Sinovial® Forte, and Sinovial® HL is typically 3 injections spaced once a week; Sinovial® One is delivered as a single injection.

After 3 and 6 months, clinical (pain evaluation, swelling, use of painkillers, patients' satisfaction, etc.) and functional (ROM, muscular strength, function, etc.) parameters are evaluated and, on this basis, we judge whether the patient should be re-treated. Typically, in case of positive clinical results re-treatment is carried out approximately six months following the initial course of therapy. The interval between courses can be variable according to the patient's need (on demand).

Among the Sinovial® product family, Sinovial® Forte (at twice the HA concentration as compared to Sinovial) is mainly used (70% of patients) by our group, while Sinovial® One and Sinovial® HL are injected in a limited number of cases (25% and 5%, respectively).

Similar to other authors, we have observed mild AEs (pain, burning sensation, irritation or erythema at the injection site) after the first course of injections, but only in very few patients (2-3%). These events were short lasting and resolved spontaneously in a few days without any concomitant therapy. It must be underlined that the percentage of AEs was reduced (below 1%) after repeated courses.

During these years many patients have been treated with multiple repeated courses of the product, with up to 20 total injections of Sinovial®-based products with positive results in absence of AEs which may compromise the continuation of the treatment.

These anecdotal data (not supported by statistical analysis) are in line with those reported by several other European clinicians (Table IV) (collated based upon medical records review). In total, 2,475 patients (25-84 years) suffering from moderate-severe knee OA or chondropathy were treated with different products (Sinovial®, Sinovial® One, Sinovial® Forte,

Table IV. *Sinovial® treatment in knee OA (Italian and European experiences).*

Name (Facility)	N. of patients	Initial Treatment Course		Subsequent Treatment Course				
		HA	n. of injections	HA	n. of injections	Total HA concentration and volume injected/patient	Observational period	AEs *
AP (Italy)	60 (25-80 ys)	Sinovial®	5 (one weekly)	Sinovial®	5 (one weekly) after 6 months	160 mg / 20 mL	9 months	No
ADV (Italy)	500 (> 60 ys)	Sinovial® Forte	3 (one weekly)	Sinovial® One	2 injections 2 weeks apart after 15 days from 3rd injection of Sinovial® Forte	196 mg / 11 mL	12 months	4% *
ADV (Italy)	50 (< 50 ys)	Sinovial® HL	2 (2 weeks apart)	Sinovial® HL	2 (2 weeks apart) after 4-6 months	256 mg / 8 mL	12 months	4% *
FM (Italy)	70 (40-80 ys)	Sinovial®	5 (one weekly)	Sinovial®	5 (one weekly) after 6 months	160 mg / 20 mL	10 months	No
LF (Italy)	734	Sinovial®	5 (one weekly)	Sinovial®	3 (spaced 1 month apart) after 5th injection of first course	128 mg/ 16 mL	From January 2015 to May 2016	No
LT (Italy)	81	Sinovial® Forte	3 (one weekly)	Sinovial® Forte	3 (one weekly) after 6 months	192 mg / 12 mL	From April 2014 to April 2016	No
LT (Italy)	45	Sinovial® Forte	3 (one weekly)	Sinovial® Forte	3 (one weekly) after 6 months	192 mg / 12 mL	From April 2014 to April 2016	No
AP (Italy)	62 (44-84 ys)	Sinovial®	3 (one weekly)	Sinovial®	One injection/month for 12 months	240 mg / 30 mL	12 months	No
AR (Italy)	195	Sinovial® Forte	3 (one weekly)	Sinovial® One	One injection after 4 months from 3rd injection of Sinovial® Forte	146 mg / 8.5 mL	From June 2015 to June 2016	No
KP (Czech Rep)	208	Sinovial® or Sinovial® One	3 (one weekly) or 1	Sinovial® or Sinovial® One	3 (one weekly) or 1	96 mg / 12 ml or 100 mg / 5 mL	From January 2014 to December 2015	10-20% §
ES (Czech Rep)	314	Sinovial® or Sinovial® One	3 (one weekly) / 1	Sinovial® / Sinovial® One	3 (one weekly) / 1	96 mg / 12 ml or 100 mg / 5 mL	From May 2013 to April 2015	0.6% *

** Local pain in the area of the injection*

§ slight pain or hematoma in the injection site

Sinovial® HL) and dose regimens (1 injection, 2-5 injections; single, one every 1 or 2 weeks). In all the reports available, subsequent injections were administered, ranging from one month up to thirteen months after the initial course of therapy. Total HA exposure per patient ranged from 96 mg (Table IV: PK and ES) to up to 256 mg (Table IV: ADV).

No AEs were observed after the first cycle of treatment or subsequent cycles, except for some mild post-injection pain for 3-4 days [which disappeared spontaneously in a few hours or in the following 2-3 days without any concomitant therapies (only RICE treatment)]. These AEs were experienced in subjects treated with Sinovial® One and Sinovial® HL, both of which are at higher total concentration of HA as compared to Sinovial/GELSYN-3™.

Post-marketing surveillance information on Sinovial® product family

The Sinovial® (GELSYN-3™ for US market) formulation was initially introduced onto the European market in November 2002. A recent analysis of post-marketing surveillance data (through December 2015) shows that there have been a total of 64 AEs (8 serious and 56 non-serious) reported to the manufacturer (14). Of the serious cases, only five were considered possibly related to the Sinovial® product; three events were associated with injection site reactions (swelling, inflammation or pain) and the other two involved myositis and septic arthritis (confirmed with a positive bacterial culture). Of the 56 non-serious events, approximately 50% (i.e., 29) were associated with injection site reactions and occurred either immediately or within 24 hours of the injection; in most cases, RICE therapy without a need for drugs or surgical intervention was required. The remaining reactions were mainly considered to be associated with the underlying disorder (e.g., arthritis) or an anticipated reaction due to the injection procedure (e.g., tachycardia triggered by anxiety arising from the injection).

Considering that approximately 5 million syringes of the Sinovial®16mg concentration has been sold to date (15), the incidence of adverse reactions to the product is remarkably low (0.001%). Although within this data the proportion of patients receiving repeated courses of therapy is not known, it is not unreasonable to assume that it is common practice across Europe to do so as outlined in the preceding sections. Thus, these data spanning 13 years supports a long-standing, safe clinical history of repeated use of Sinovial®/GELSYN-3™.

DISCUSSION

According to published clinical trial data, Sinovial® product family is considered safe and has a remarkable tolerability profile with a low incidence of mild local AEs at the injection site. Such events are not clinically relevant, and are more likely associated with the procedure of any intra-articular injection itself rather than the product, with most AEs observed during the first course of treatment. Indeed, a similar incidence of this type of AEs has been observed in most studies with intra-articular injections, including the placebo groups (5).

Repeat treatment with a course of Sinovial®/GEL-SYN-3™ would equate to 96 mg of sodium hyaluronate. As summarized in this report, repeated exposure up to 4-times this amount (i.e., 384 mg) of sodium hyaluronate has not given rise to any safety signals for Sinovial®-based formulations. Moreover, repeated administration of Sinovial®-based products is currently standard clinical use within Europe. It must be underlined that two clinical consortiums consisting of several experts in OA and viscosupplementation from Europe and US [European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and European Viscosupplementation Consensus (EUROVISC) group] recommend, in a systemic literature review, that repeated treatments of HAs should be offered to patients who had undergone a successful first course of therapy when their symptoms reoccur.

Adverse events to Sinovial® are very low in patients who received both a single or subsequent courses of injections. The risk associated with a high frequency of Sinovial® use is not increased and therefore there is sufficiently valid scientific evidence to offer reasonable assurance of the safety of this product.

Declaration of conflict of interest

The preparation of this manuscript was conducted independently from the influence of the funding source. Both authors were involved in the preparation of this manuscript from its inception and approved the final version for submission. MA has received consulting fees or honorarium and support for travel to meetings from IBSA; VS has received consulting fees or honorarium and support for travel to meetings from IBSA.

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