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EDITORIAL

SAFETY AND TOLERABILITY OF INTRA-ARTICULAR HYALURONIC ACID INJECTION (SINOVIAL®) IN EXPERIMENTAL AND CLINICAL PRACTICE

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Osteoarthritis (OA) requires long-term treatment, therefore, tolerability is a key factor in treatment choice. Hyaluronic acid (HA), a glycosaminoglycan with viscoelastic properties, a major component of synovial fluid and the extracellular matrix of the joint cartilage, plays key roles in synovial fluid viscosity and maintaining normal cartilage. Viscosupplementation is an intra-articular (IA) injection of exogenous HA in an effort to delay joint mobility loss. Commercially available viscosupplementation includes HA of different average molecular weight (MW), concentration and origins, with varying tolerability. This review describes the tolerability and safety profile of Sinovial® in knee and hip OA. A literature search of PubMed using the search queries [Sinovial® OR hyaluronic acid OR hyaluronan] and [intra-articular OR osteoarthritis] was performed using terms as medical subject headings and free text searches. Studies were selected manually for inclusion in this review. Sinovial® is a low-medium MW HA of non-avian origin, produced by biofermentation to ensure the product is pure and free of allergenic animal proteins. We analyzed data regarding the tolerability of Sinovial® in OA patients. This formulation has a favorable tolerability profile; no systemic reactions have been reported and most adverse events (AEs) are mild, transient and easily managed local injection site reactions. Reactions – pain and burning at the injection site – are typical of IA injections. AEs with Sinovial® used in the hip are similar to knee OA.

Osteoarthritis (OA) is the most common form of joint disease, affecting almost one in 10 men and one in five women over 60 years of age (1), with approximately one in four OA patients over 55 years of age being severely disabled (2). This public health problem will soon become even greater, because of an aging population and the obesity pandemic. OA is characterized by local pain and progressive loss of joint function, stability and mobility and is predicted to become the fourth leading cause of disability by the year 2020 (3).

OA is a disease of the whole joint that targets the cartilage but also involves the synovial membrane, the subchondral bone, muscles, ligaments and the meniscus. Eventually, loss of shock absorption by cartilage and synovial fluid, hypertrophy of bone and thickening of the joint capsule leads ultimately to biomechanical joint failure

OA is a lifelong progressive condition requiring long-term treatment, and thus tolerability becomes an important consideration in the choice of treatment. The aims of treatment are pain relief and the improvement of joint function, which help delay debilitating and costly immobility (3). Initial and conservative

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recommendations include weight loss, physical and/or occupational therapy, exercise, physiotherapy, patient education, simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) (4, 5).

Viscosupplementation is a treatment strategy for OA that supplements synovial fluid with a solution of exogenous hyaluronic acid (HA, hyaluronan) to improve the shock absorption capability of the joint and therefore reduce pain and improve joint mobility (6, 7). This review describes the tolerability and safety profile of viscosupplementation with IA HA in knee and hip OA, focusing on Sinovial®[1] (IBSA Institut Biochimique SA, Switzerland) a sodium hyaluronate formulation (either as HA 0.8%, 1.6% or 2%) as it is widely used in clinical practice.

A literature search of PubMed using the search queries [Sinovial OR hyaluronic acid OR hyaluronan] AND [intra-articular OR osteoarthritis] was performed using terms as medical subject headings and free text searches. Studies were selected manually for inclusion in this review, supplemented by searches of the bibliographies of review articles and by the authors' own experience in the field. Six studies were selected. First a brief overview of IA HA is provided.

OVERVIEW OF INTRA-ARTICULAR HYALURONIC ACID INJECTION

Intra-articular hyaluronic acid injection

HA is a glycosaminoglycan, which is a complex polysaccharide molecule, with viscoelastic properties (8). HA is an important constituent of synovial fluid, acting as a lubricant for slow joint movement and as a shock absorbent during fast joint movement and is also a key component of the extracellular matrix of the cartilage, responsible for its elasticity, affording it resistance to shear and compression (8). The concentration and molecular weight (MW) of the endogenous hyaluronan in synovial fluid in a joint affected by OA is lower than that of a healthy joint, and consequently the viscosity/elasticity is lower, leading to loss of shock absorbing and lubricant properties. Thus, synovial fluid from an OA joint may not protect the cartilage superficial layer correctly and, consequently, may contribute to cartilage deterioration (7, 8). Restoring the rheological properties of synovial fluid for a healthy and functional joint environment and re-establishing normal HA metabolism is the rationale for viscosupplementation (6, 8).

[1]Other brand names: Intragel® - Yaral®

Intra-articular hyaluronic acid mechanism of action

The exact mode of action of IA HA in improving joint pain and mobility is still unclear. Beside rheological improvements for the biomechanical function of the joint, chondroprotective, analgesic, anti-inflammatory and anti-oxidant activity has also been demonstrated *in vitro* on chondrocytes (6, 8, 9). There is also some evidence that HAs with MW >500 kDa stimulate paracrine HA biosynthesis and that this restoration of natural HA synthesis is due to a CD-44-mediated metabolic modulation termed "viscoinduction" (10, 11). This effect on joint homeostasis might explain why the duration of efficacy of IA HA is in the order of months, and far exceeds the apparent half-life of the HA molecule/solution in the joint (a few days) (11). Studies on animal models of OA have shown that HAs with MWs around 1,000 kDa were generally more effective in reducing indices of synovial inflammation and restoring the properties of synovial fluid (11), although well-conducted clinical trials are still required to confirm any actual differences in clinical efficacy between formulations of different average MW.

Efficacy of intra-articular hyaluronic acid in osteoarthritis

The efficacy of IA HA in knee OA has been well documented in several literature reviews and meta-analyses (12-14), though it is still a matter of debate since a recent negative meta-analysis concluded that clinical benefit is minimal (15). However, in the case of meta-analyses, particular attention must be paid to the types of studies that have been included, the type of comparator, the length of follow-up, and the clinical endpoints used in the trials and therefore in the meta-analyses, which may explain such surprising differences between meta-analysis on HA. Thus, in the recent negative meta analysis from Rutjes, several comparators not restricted to placebo were included and the length of follow-up was only 16 weeks (15). Given that the methodologies of meta-analyses of IA HA for knee OA are varied and that meta-analysis cannot reverse study design flaws of the original studies, results from medical device registries and cohort studies must also be taken into

account since they may better reflect the use and effectiveness of IA HA in real clinical practice.

European League Against Rheumatism (EULAR) (5) clinical practice guidelines still support the use of IA HA for knee OA, although the American College of Rheumatology is more controversial on the use of HA (16). Indeed, evidence from studies indicates that the improvement in pain relief and joint function with IA HA in knee OA is greater than that seen with IA placebo and similar to the efficacy seen with oral NSAIDs (12-14). When compared to IA corticosteroids, the effect with HA is longer lasting (14). One important point that should be underlined is the long carry-over effect of IA HA, which may last for up to 12 months (17).

Intra-articular hyaluronic acid formulation differences

Different IA HA formulations are available, varying by their average MW (300 to 6000 kDa), source of HA (biofermentation *vs* rooster combs), and dosage and administration (e.g. number of injections per course of treatment). These differences may have clinical implications, e.g. some rare immuno-allergic reactions have been reported with HA formulations containing avian proteins (18). Efficacy differences between formulations of different average MW have not yet been fully clarified, as there are few quality head-to-head comparisons.

Efficacy of Sinovial®

Sinovial® is of non-avian origin and low-medium MW (800–1200 kDa), for IA injection. It is presented in pre-filled, ready-to-use syringes for injection into large or small joints. A total of six efficacy studies with Sinovial® in knee and hip have been identified (Table I) (19-24).

Sinovial® has demonstrated clinically relevant pain relief, improved joint mobility and reduced use of rescue medication in knee OA (19, 20, 22, 23). This formulation has also shown promising clinical efficacy in reducing pain and improving function in other joints, such as the hip (21, 24).

TOLERABILITY OF INTRA-ARTICULAR HYALURONIC ACID

Adverse events

Intra-articular HA as a treatment class is considered to have a remarkable tolerability profile, with a low incidence of adverse events, and is registered worldwide. The most frequently reported events are local side effects (8, 9, 25), such as site reactions of mild to moderate pain and swelling at the injection site, similar to the events observed with any IA injection. They are generally not clinically relevant, and resolve spontaneously or with conservative treatment (8, 9, 25). Furthermore, they do not preclude a clinical response to HA injection.

Being a locally administered treatment, there is a minimal chance of systemic effects, and drug interactions and attendant difficulties are avoided, which makes it a safer treatment option than NSAIDs and IA corticosteroids for a substantial proportion of patients (8, 9, 25). The resultant pain relief and joint function improvement tends to lead to reduced consumption of rescue medication (analgesics and/or NSAIDs), further reducing the incidence of systemic effects (8, 9, 25).

A meta-analysis of trials of IA HA for knee osteoarthritis shows that adverse events occur slightly more frequently in patients receiving the study injection than in those receiving placebo [relative risk (RR) 1.08; 95% CI 1.01, 1.15] (26). The events were mostly pain at the injection site, but were of minor clinical significance and always transient. Recommendations for the management of injection site reactions include rest, application of cold packs, analgesics and sometimes NSAIDs. In case of significant synovial fluid effusion, arthrocentesis is always required to eliminate any sepsis, and subsequently NSAIDs or local corticosteroid injection could be contemplated (26).

It has been suggested that some local reactions may be due to misplacement of the needle, so that the injection is not strictly IA and might, therefore, induce local tissue injury. Correct placement of injection and aspiration of the synovial fluid (at least a few drops) is essential for minimizing adverse events (25). These local reactions do not necessarily recur on repeat injections. This point is still controversial in the literature (6, 27). The pain relief and mobility benefits are still evident when the local reaction subsides (6, 27).

The potential for joint infection has been a concern, but the literature does not bear out that concern. Bacterial infection is extremely rare, and no cases of viral infection have ever been reported

with IA HA (25, 28-30).

Low-medium vs high molecular weight hyaluronic acid

Hyaluronan formulations of different MWs or of different origins (avian or non-avian) or extraction processes might induce differences in tolerability (6). It has been postulated that high MW hyaluronans are associated with a greater risk of adverse events, with more frequent adverse events and acute painful local reactions (31). Comparing high MW hylan to other hyaluronans, a meta-analysis revealed a two-fold increased risk of adverse events with the higher MW; adverse events (RR 1.91; 85%CI 1.04, 3.49) and flares (RR 2.04; 95%CI 1.18, 3.53) (31). However, conclusions of this meta-analysis should be cautiously interpreted, depending on how the side effects have been classified. Furthermore, these local adverse events, regardless of the HA used, do not preclude a clinical response.

Animal vs non-animal origin

Hyaluronic acid in the Sinovial® formulation comes from a non-avian source, is derived using biofermentation and is highly purified, which may reduce the risk of immunogenic reactions compared to protein derived formulations of HA (5, 32, 33). In a large trial in which patients received courses of three weekly injections of IA HA of avian (n = 1,726) or non-avian (n = 1,971) origin at self-determined intervals, weight-bearing pain was significantly better in the non-avian HA group than in the avian HA group ($p < 0.01$); this became apparent after the seventh course of injections (34).

TOLERABILITY OF SINOVIAL® IN CLINICAL TRIALS

Knee osteoarthritis

There were no systemic effects or serious treatment-related adverse events in patients with knee OA treated with Sinovial® in prospective comparative and single group studies (22, 23) and retrospective studies (19, 20). Adverse events were local, mild and related to the injection site (Table I).

The overwhelming majority of patients (93–97%) in the comparative study of Sinovial® versus hylan G-F 20, reported local tolerability as 'good' or 'very good', and the patient- and investigator-assessed global tolerability at 4-, 12- and 26-week follow-up points were rated similarly (22). The pain-on-injection score averaged the same in both groups, as did pain on the second and third injection. Of the six

Table I. *Characteristics and adverse events of published studies on Sinovial®.*

Author	Year	N/n treated with Sinovial®	Study	Target joint	No. of injections	Time of follow up	AEs in Sinovial® treated patients
Pavelka (22)	2011	381/192	Double-blind, RCT, prospective	Knee	3	6 months	1[a]
Theiler (23)	2005	63	Open, prospective	Knee	5	24 weeks	22[b]
Castellacci (19)	2004	40	Retrospective	Knee	5	7 weeks	16[c]
Depont (20)	2006	408	Retrospective	Knee	1[d]	10 months	16[e]
Migliore (21)	2012	114	Open, prospective	Hip	2	6 months	7[e]
Abate (24)	2013	20	Open, prospective	Hip	2	12 months	2[f]

[a] *Injection site pain*
[b] *18 out of these 22 AEs were pain and/or a burning sensation at the injection site*
[c] *slight to moderate burning sensation at the injection site*
[d] *patients receiving at least 1 injection*
[e] *mild pain and burning sensation, erythema, irritation at the injection site*
[f] *pain, heat, redness*
AEs: adverse events; RCT: randomised controlled trial

treatment-related adverse events, five in four patients receiving hylan G-F 20 consisted of injection-site hematoma, injection-site pain, arthralgia, joint swelling (two instances) and one in the Sinovial® consisted of injection-site pain (22)

The most frequent adverse event was pain/ burning at the injection site on or immediately after injection (in 5.8% of injections) in a prospective, single-group, open-label study of 63 patients with OA of the knee who received 5 weekly injections and were followed for 24 weeks (23). The reactions resolved in 1–2 days and were considered no different to events following any IA injection, including placebo. The 1.3% incidence of other treatment-related events included skin hematoma at injection site, tension in the knee, fever, diarrhea and one case of mild vasovagal collapse lasting a few minutes. Tolerability recorded in retrospective studies support that observed in prospective trials (19, 20). Only local events, including mild burning sensation, erythema and irritation at the injection site, at an overall rate of 4%, were reported in a large retrospective study of Sinovial® in 408 patients with knee OA; there were no systemic effects at all (20). Tolerability was rated by patients and investigators as good or excellent in 95% of patients at week 5 and in 97.5% at week 7 in a retrospective study of 40 outpatients with knee OA (19). Slight to moderate burning at the injection site was recorded in 40% of patients, more frequently following the first injection. The sensation lasted a few minutes, no systemic affects were reported, and all patients completed treatment (19). No laboratory test abnormalities have been observed with sodium hyaluronate (23).

To summarize, there are no major safety concerns with IA injection of Sinovial® in patients with knee OA.

Other joints

The adverse events and tolerability profile of Sinovial® in hip is similar to that observed when used for knee OA. Tolerability was considered to be excellent in 114 patients who received one 4 mL injection of Sinovial® 1.6% for hip OA. Mild local reactions were the only events reported (7 patients) (21). They consisted of transient mild pain, and were all managed without medication. None of the patients in this series had more than one localized reaction. No systemic, severe or moderate reactions were reported (21).

Side effects after injection (pain, heat, redness) were observed in 2 patients treated for femoroacetabular impingement (a condition that may predispose to hip OA); these effects lasted less than 3 hours and did not require the use of any medication (24).

Post-marketing surveillance

The widespread use of Sinovial® has confirmed this formulation to be very well tolerated and safe for IA injection. Sinovial® has been available since 2002, and more than 5,100,000 syringes have been used during these 11 years of commercialization, with only 27 not serious adverse events reported (IBSA, data on file).

Even if the surveillance of adverse events of medical devices is not totally comparable with that of drugs and is often underestimated, it can provide further evidence of the good tolerability of the product and can be considered in line with the current safety information reported in the product leaflets. Underestimation of reported adverse events (AEs) in medical device registries is generally related to omission of minor and mild events rather than major or serious AEs. The post-marketing safety data confirm the good tolerability of Sinovial® and are in accordance with the positive benefit/risk profile of the product as shown in the clinical trials (19-24).

DISCUSSION AND CONCLUSION

The tolerability of treatment in OA is an important consideration when assessing treatment options for OA, it being a lifelong progressive disease requiring long-term therapy. To date, investigations into the treatment of OA of the knee suggest that the IA use of HA may be a relevant option in the management of patients with persistent pain (35) as viscosupplementation by IA injection of HA is an effective and very well tolerated treatment for mild to moderate OA of the knee. For hip OA, findings from open studies are promising, but randomized controlled trials are necessary to confirm this preliminary impression (21). Based on these studies, HA is explicitly recommended in patients presenting with intolerance or contraindications to other

pharmacologic treatments and in patients who are unable to afford surgery. When IA HA injections are used early in the disease process, one may expect that they relieve pain, improve joint function, and may retard the progression of structural damage, though this needs to be validated. Finally, IA HA is an interesting treatment option in terms of sparing consumption of rescue medications which have potential adverse events.

The question of whether different formulations of HA may offer a superior clinical benefit is still open, but to date there is no proven evidence of superiority of any HA over any other HA (31, 36). However, the benefit/risk profile of these formulations should always be considered. According to the recent Rutjes meta-analysis, viscosupplementation is associated with a small and clinically irrelevant benefit and an increased risk for serious adverse events (15). However, despite this recent publication, both clinical practice and the bulk of scientific evidence published so far (including the EULAR guidelines for knee OA) (5) indicate that the use of IA HA is a well-tolerated and effective approach in the management of knee OA. Furthermore, IA HA as a class has a remarkably benign tolerability profile and a low incidence of adverse events, the most frequent being local reactions of mild/moderate pain and swelling at the injection site (6). These reactions are generally not clinically relevant and resolve spontaneously. However, there are very rare reports in the published literature claiming a potential risk of moderate adverse events, including pseudogout, pseudosepsis and anaphylactoid reactions (32-34). No systemic adverse events have been reported with the use of Sinovial® and the local injection site reactions of pain, swelling, and warmth/burning are generally mild and transient, defining a benign tolerability profile. We could even highlight that the lack of systemic/serious adverse events (and no deaths) in patients treated with Sinovial® is a differentiating factor versus other treatments (e.g. NSAIDs). There was a surprisingly low rate of AEs reported in the IBSA post marketing surveillance.

As for Sinovial®, even without sufficient data from randomized controlled trials demonstrating no risk of immunologic hazard, the biofermentation process and the technology used in the production of HA (both of which assure that the final product is highly purified and free from potentially allergenic animal proteins and pathogenic agents) leads us to believe that a lack of immunologic hazard can be assumed (37).

The efficacy of viscosupplementation with Sinovial® in relieving joint pain and improving joint function in patients with OA is complemented by the very favorable and manageable tolerability profile of this product in all its formulations, as supported by its high level of use in clinical practice.

Among the different available IA products, our specific experience with Sinovial® suggests that this device is effective in the management of OA. The positive benefit/risk profile of Sinovial® has been proved in clinical trials and confirmed in post-marketing surveillance. Tolerability is an important issue for patient compliance with treatment, for the success of the treatment itself and for cyclic repetition of an effective treatment in a chronic disease.

In the future, considering the increasing use of IA HA, together with the aging population, it will be important to determine the efficacy and the tolerability of IA products in other joints, on which, at the moment, only preliminary evidence is available.

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