Review article

Viscosupplementation: Techniques, indications, results

V. Legré-Boyer a, b, c, *

a Institut de l’Appareil Locomoteur Nollet, 23, rue Brochant, 75017 Paris, France
b Service de Rhumatologie, Hôpital Universitaire Pitié-Salpêtrière, 75013 Paris, France
c Hôpital américain de Paris, 92200 Neuilly-sur-Seine, France

ARTICLE INFO

Article history:
Accepted 10 July 2014

Keywords:
Viscosupplementation
Hyaluronic acid
Osteoarthritis
Chondroathy
Hylan
Sodium hyaluronate

ABSTRACT

Viscosupplementation by hyaluronic acid (HA) injections is frequently used for local treatment of osteoarthritis (OA), due to ease of use and good tolerance. A profusion of linear or reticulated HA derivatives are marketed, with varied characters and levels of evidence. Viscosupplementation has demonstrated moderate but significant efficacy (20%) versus placebo in terms of pain and function, with a high rate of responders (60–70%) in knee osteoarthritis. It allows reduced administration of opioid analgesics and NSAIDs, with improved risk/benefit ratio, and may delay joint replacement. Cartilage protection remains to be proven. Clinical efficacy shows 1–4 weeks’ later onset than corticosteroids, but is maintained for 6 or even 12 months. Systematic association of corticosteroid and HA injection is not justified, and an interval has to be left before undertaking arthroplasty. Intra-articular injection of HA requires a skilled specialist, and may be difficult in a non-swollen joint; some tips and tricks may be helpful. In other joints than the knee, radiologic or ultrasound guidance is recommended. The efficacy of viscosupplementation is a matter of ongoing debate, after discordant findings in some meta-analyses. Some poor results may be due to inappropriate use of HA injections, poorly adapted to the patient’s OA phenotype. Viscosupplementation is a treatment for chronic moderate symptomatic OA, and not for flares with joint swelling. Application in sport-related chondroathy has yet to be properly assessed. The optimal response profile remains to be determined. The ideal indication in the knee seems to be moderate femorotibial OA without swelling. Results have been generally disappointing in hip osteoarthritis but promising in OA of the ankle and shoulder (with and without rotator cuff tear). Further studies are needed to determine response profile and optimal treatment schedule, according to the joint.

© 2014 Elsevier Masson SAS. All rights reserved.

1. Introduction

Viscosupplementation, consisting in intra-articular injection of hyaluronic acid (HA) derivatives, is the main local treatment in osteoarthritis (OA) along with corticosteroid injection. It has been used in humans for more than 30 years, mainly in OA of the knee but increasingly in other joints.

A very large number of clinical trials have been performed; in knee OA, several meta-analyses gave discordant results, sparking controversy around the efficacy of the technique.

The present update aims to determine good practice and indications for viscosupplementation as local treatment for symptomatic OA, so as to optimize efficacy.

1.1. Action of intra-articular HA injection [1]

HA, the main constituent of cartilage and synovial fluid, is a long polysaccharide (glycosaminoglycan) chain, with a hydrophilicity that gives it the viscoelastic properties underlying the mechanical properties of cartilage (shock absorption) and synovial fluid (joint lubrication, cartilage protection).

OA involves qualitative and quantitative HA deficiency: mean molecular weight (MW), corresponding to chain length, is 4–5 mM in the healthy joint and 2–4 mM in OA, with concentration halved.

Injecting exogenous HA into the joint is intended not only to restore the mechanical properties of the cartilage and synovial fluid, but also to achieve certain biological effects. The HA is taken up by specific joint receptors, providing numerous beneficial effects: moderate anti-inflammatory action, reduced cytokine-induced enzyme production, anti-oxidant action, anabolizing effect on cartilage, and direct analgesia by masking the joint nociceptors.

Its visco-inductive properties (synoviocyte-mediated stimulation of endogenous HA production) could account for the prolonged

* Correspondence. Institut de l’Appareil Locomoteur Nollet, 23, rue Brochant, 75017 Paris, France. Tel.: +33 6 13 60 09 36; fax: +33 1 47 27 08 76.
E-mail address: virginlegr@aol.fr

http://dx.doi.org/10.1016/j.otsr.2014.07.027
1877-0568/© 2014 Elsevier Masson SAS. All rights reserved.

Please cite this article in press as: Legré-Boyer V. Viscosupplementation: Techniques, indications, results. Orthop Traumatol Surg Res (2015), http://dx.doi.org/10.1016/j.otsr.2014.07.027
Table 1
Hyaluronic acid forms available in France in 2014.

<table>
<thead>
<tr>
<th>Hyaluronic acid</th>
<th>Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear HA</td>
<td>Sodium hyaluronate: (MW 0.5–3 mD) Multi-injection: Adam®, Arthrum®, Euflexxa®, Go-on®, Hyaloglan®, Orthovisc®, Ostenil®, Synovial®. Structovial®, Synocrom® Single-injection: Arthrum monodose®, Coaxanth®. Synochrom forte®</td>
</tr>
<tr>
<td>Reticulated HA</td>
<td>Hylan CF-20: Synvise®, Synvisc one® Sodium hyaluronate: Monovisc®, Synocrom forte one® happycross NASHA: Durolane®</td>
</tr>
<tr>
<td>Combined HA</td>
<td>Single-injection Mannitol: Ostenil plus® Happysc®, Happycross® Chondroitin sulfate: Arthrum HCS®, Synovium surgical®</td>
</tr>
</tbody>
</table>

NASHA: non-animal stabilized hyaluronic acid.

efficacy of injected exogenous HA despite its short joint residence time, as it is rapidly degraded after injection.

1.2. What forms of HA are available in France?

In France, more than 12 HA derivatives are on the market, classified as “devices”, except in the case of Hyalgan®, which counts as a drug with market authorization in knee OA.

Two groups can be distinguished (Table 1): low-MW linear HA; and reticulated HA (3-dimensional structure of linked HA chains), with higher MW and probably slower degradation and longer joint residence, often administered as a single-injection.

Low-dose (1 ml) preparations are available for small joints.

Preparations with associated adjuvants (mannitols, sorbitol, chondroitin sulfate), reticulated or not, have come onto the market more recently, with the aim of prolonging joint residence, although this has not been demonstrated.

HA derivatives differ not only in reticulation and MW (chain length) but also in origin: avian; cockshorn; synthetic; bacterial fermentation; sterilization process (heat or ultra-filtration); conditioning (2–6 ml syringes) and validation on high-quality therapeutic trials.

The reference forms, which have been the focus of most studies, are Hyalgan® for linear HA and Synvisc® for reticulated HA. The clinical impact of the various characteristics of HA remains unclear, and no product can be clearly recommended over another.

2. Technique

Injection technique is of prime importance for both efficacy and tolerance. Injection must be strictly intra-articular, which is not easy to ensure in non-swollen joints, which are the main indication for visscosupplementation.

In the knee, 10–30% of injections performed by senior physicians are known to be defective [2]. A lateral patellar approach has been shown to be clearly preferable; anterior approaches show high rates of failure and poor tolerance. Local reaction rates of up to 30% have been found for anteromedial injection [3].

In the hip, shoulder and thumb joints, success is even less sure, and radiologic guidance is recommended.

2.1. General rules for injection

The classic technique for HA knee injection is presented in Fig. 1. The general procedure is as follows:

- relevant personalized prior information to patient;
- asepsis as in joint corticosteroid infiltration. Certain HA derivatives, like ready-to-use corticosteroid syringes, do not have sterile exterior conditioning (outer surface of syringe) and this is to be borne in mind;
- choice of appropriate approach according to joint;
- appropriate needle caliber (21-gauge for reticulated derivatives);
- aspiration of any synovial fluid;
- injection without resistance or pain;
- joint mobilization after injection;
- record of HA batch number;
- 24 hours’ relative rest (no sports, no effort with the limb).

2.2. Tricks and tips

Some tricks and tips may be useful in difficult cases: obesity, postoperative fibrosis, severe femoropatellar OA, etc.:

- the back-flow technique (Fig. 2), which we developed and validated for the knee, provides very precise injection, with the needle positioned intra-articularly in 100% of cases when backflow is clearly obtained [4]. The method can be applied in other joints, notably the ankle, although not yet validated;
- the “squishing sound” confirms that injection has been successful. It can be heard in passive flexion-extension of the knee after injection of an HA derivative with air-bubble once the needle has been withdrawn. This frequently employed test has been validated [5], but is just a retrospective check, as it requires the substance to have been actually injected;
- in some less easily accessible joints (hip, shoulder, thumb), radioscopic guidance with a small injection of contrast medium (Fig. 3) or ultrasound guidance is recommended. Ultrasound has advantages: with no radiation and no risk of allergic reaction, it detects deep effusion; however, it requires a trained operator and special asepsis.
If a local intra-articular anesthetic is to be used, lidocaine should be low-dose and low-concentration (0.5%) because of its bacteriostatic and possible chondrotoxic effects.

2.3. Administration schedules

Viscosupplementation comprises 1 to 5 injections at 1–4 week intervals.

Dose depends on the form of HA (linear or reticulated) and the joint, as joint capacity varies.

In knee OA, a series of 3 injections are performed at 1-week intervals; alternatively, a single-injection may be made.

In joints other than the knee, the procedure is not well codified. We suggest a schedule based on the data of the literature (Table 2).

Single-injection schedules are attracting growing interest. These often involve reticulated HA derivatives which should have longer joint residence. Reducing the number of injections reduces the risk of infection and, in patients under anticoagulants, the risk of hemorrhage.

2.4. Attitude in case of joint effusion

Synovitis should be treated in priority before HA injection: rest, joint ice treatment, NSAIDs and, if necessary, puncture and corticosteroid infiltration. HA injection will then be postponed for 1–4 weeks.

2.5. Can corticosteroids be associated to HA in the same injection?

The association, in the first of the 3 injections or in a single-injection, may be considered, especially in case of severe pain or persistent effusion. Systematic association, on the other hand, is not justifiable, especially in non-swollen knee, as clinical benefit lasts no more than a week [6], and the risks associated with corticosteroid injection are non-negligible.

In patients awaiting arthroplasty, an interval of more than 6 weeks (12–24 weeks in our practice, depending on the form of corticosteroid) should be left between the last injection and the arthroplasty surgery, to limit the risk of implant infection [7]. Concerning HA, no study has yet been done, but we consider that a 4 weeks interval before arthroplasty is safe, regarding to the absence of local immunosuppressive effect of HA.

3. Indications

3.1. General indications

Viscosupplementation is classically implemented in OA, on condition that the OA is symptomatic, that medical treatment (non-pharmacologic, analgesics, NSAIDs) has failed or induced intolerance, and that there is no acute inflammation (i.e., no severe effusion).

National health insurance cover in France currently applies only to knee OA, and not other locations, and includes most HA derivatives, at a rate of 1 treatment per year per knee, on condition that the OA is painful and resistant to medical treatment and that the HA is prescribed and administered by a specialist (rheumatologist, physical and rehabilitation physician or orthopedic surgeon).

HA used to have an integral role in international guidelines for knee, hip and thumb OA, including the European League Against Rheumatism (EULAR) guidelines, in which HA injection was recognized as having real if moderate impact on symptoms [8].

The role of viscosupplementation was, however, questioned recently by most international scientific societies in updates to their guidelines for knee OA treatment [9–12] (Table 3):

- according to the Osteoarthritis Research Society International (OARSI), the recommendation of HA is “uncertain” in isolated knee OA and “not appropriate” in polyarthritis [9]. Despite the lack of any real analysis of adverse effects in the literature, the OARSI experts considered (as “expert opinion”) that risk is greater with HA injection than corticosteroid infiltration or NSAIDs; this opinion is highly questionable;
- the American College of Rheumatology (ACR) revised its guidelines in 2012 [10]: the experts laid down no general guidelines for HA in knee OA, but did recommend its use in case of medical failure, especially in over 75 year olds. Their position was the same regarding hip OA;

Viscosupplementation is not indicated for preventive purposes, no chondroprotective effect having been demonstrated in human
clinical studies. It is reserved to symptomatic OA. Yearly renewal is indicated only if symptoms recur.

According to the scientific societies, who found OA therapy on a combination of pharmacologic and non-pharmacologic treatments [8], viscosupplementation should be utilized in conjunction with:

- non-pharmacologic modalities (counseling on weight reduction, physical activity and joint sparing and stabilization, and orthoses)
- possibly other drugs.

3.2. Indications according to OA phenotype

OA characteristics vary from patient to patient and may affect the efficacy of viscosupplementation. It is difficult to predict the type of responder, as studies do not often take account of phenotype in interpreting results. Certain trends, however, seem to emerge:

3.2.1. Severity of radiologic joint space narrowing

Moderate OA is the indication of choice for viscosupplementation, efficacy being better in moderate joint space narrowing (Kellgren and Lawrence grades II and III), whichever the joint. Some studies, however, have reported efficacy in highly advanced knee OA (grade IV), in which HA injection can provide interim relief awaiting arthroplasty [3,13]. Advanced hip OA, on the other hand, does not respond to viscosupplementation, and treatment is arthroplasty.

3.2.2. Compartmental location

In the knee, the ideal indication is femorotibial OA. In less severe femoropatellar OA, viscosupplementation appeared less effective in an open British study, with a response rate of around 50% [14], as observed in clinical practice.

3.2.3. Inflammatory flare of OA

In acute inflammation, with severe effusion, viscosupplementation is not indicated. Synovitis has been shown to be associated with accelerated joint cartilage degradation [2]. Moreover, it impairs the efficacy of HA, less by dilution in the effusion fluid than due to enzymes and oxidants (hyaluronidases, free radicals) degrading the HA chains. The acute episode should be treated in priority (NSAIDs, corticosteroids) and HA treatment postponed.

3.2.4. OA with subchondral bone lesions

Acute intense mechanical pain with extensive bone edema, bone fissure or stress necrosis on MRI does not respond to HA and should be managed by non-weight-bearing [2], viscosupplementation being postponed.

3.2.5. OA associated with other lesions

Certain lesions (unstable meniscal tear, ligament laxity, limb malalignment, etc.) need to be taken into account and treated in parallel to viscosupplementation, as they are aggravation factors of OA. In case of conservative surgery (osteotomy, ligamentoplasty, arthroscopic treatment of meniscal lesions, femoroacetabular impingement, osteochondral lesions of the talus (OLT), etc.), HA injection may be performed secondarily, some weeks after surgery, if pain persists. Systematic HA injection at end of surgery cannot be recommended, being poorly assessed and showing only very short-term benefit in the few published studies.

3.2.6. Radiologic chondrocalcinosis

Chondrocalcinosis is extremely frequent in elderly patients, but is not a contraindication for HA injection, on condition that there is no gout-like acute inflammation of the knee [15]. According to some reports, it is actually a factor of good response to HA [16]. The injection technique should be non-traumatic with regard to the cartilage, to avoid crystal release inducing a micro-crystalline flare. Preventive NSAID treatment during the days following injection is optional.

3.3. Indications in athletes

HA is recognized to be non-doping, making it an interesting adjuvant option for athletes.

Table 2

<table>
<thead>
<tr>
<th>Approach</th>
<th>Guidance</th>
<th>Quantity per injection</th>
<th>Schedule (poorly codified)</th>
<th>Knee</th>
<th>Hip</th>
<th>Shoulder</th>
<th>Ankle</th>
<th>Metacarpophalangial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral lateropatellar</td>
<td>No Except difficult cases</td>
<td>2–6 ml (single-injection)</td>
<td>3 injections (1 per week or single-injection)</td>
<td>Anterior (radioscopy) or posterior (US)</td>
<td>Radioscopy or US</td>
<td>NO Or radioscopy &gt;US</td>
<td>2–3 ml</td>
<td>0.5–1 ml</td>
</tr>
<tr>
<td>Lateral anterolateral</td>
<td>Radioscopy or US</td>
<td>2–4 ml</td>
<td>2–3 injections (1 per month) or single-injection</td>
<td>Anteromedial or anterior</td>
<td></td>
<td></td>
<td>1–3 injections (1 per week or per month)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Scientific society</th>
<th>HA guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>EULAR (2003)</td>
<td>Recognized efficacy as slow-action treatment in symptomatic OA</td>
</tr>
<tr>
<td>ACR (2014)</td>
<td>No general recommendation</td>
</tr>
<tr>
<td>NICE (2014)</td>
<td>Not recommended</td>
</tr>
<tr>
<td>OARSI (2014)</td>
<td>Uncertain recommendation in isolated knee OA</td>
</tr>
<tr>
<td></td>
<td>Not appropriate in polyarthritis OA</td>
</tr>
</tbody>
</table>

Table 4
Indications for viscosupplementation according to symptomatic joint.

<table>
<thead>
<tr>
<th>Joint</th>
<th>Ideal indication</th>
<th>Possible indications</th>
<th>No indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td>Moderate femorotibial OA without effusion</td>
<td>Chondropathy</td>
<td>Advanced hip OA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Femoropatellar OA</td>
<td>Rapidly destructive hip OA</td>
</tr>
<tr>
<td>Hip</td>
<td>Moderate hip OA without effusion, not hip replacement candidate</td>
<td>Dysplasia (femoroacetabular impingement etc.)</td>
<td>Isolated cuff tear Capsulitis</td>
</tr>
<tr>
<td>Shoulder</td>
<td>Moderate shoulder OA with or without cuff tear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle</td>
<td>Moderate talocrural OA without effusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>Moderate thumb OA resistant to corticosteroids</td>
<td>Osteochondral lesions of the talus</td>
<td>Trigger finger</td>
</tr>
</tbody>
</table>

In knee OA with radiologic signs in athletes, indications follow general guidelines, with viscosupplementation scheduled if possible out of season and adapting the patient’s sports activity.

In infra-radiologic chondropathy (often focal cartilage lesions detected on MRI, CT arthroscopy or conventional arthroscopy), which generally affects younger subjects, rules are poorly defined for lack of high-quality studies. The efficacy of viscosupplementation is probable, but has not been properly assessed.

Usual precautions should be taken (post-injection rest, complete therapeutic schedule, no preventive injection in asymptomatic knee, etc.) despite the pressure brought to bear on both athlete and physician.

3.4. Summary of indications according to joint

Ideal indications with maximal chance of efficacy are basically moderate OA without effusion or associated lesions (ligamentous, meniscal, malalignment etc.).

Various specificities emerge from clinical studies according to joint (Table 4):

- in hip OA, results have generally been disappointing. There would seem to be no role for HA in advanced or rapidly destructive hip OA, which require total hip replacement. There are beginning to be reports of benefit with viscosupplementation in femoroacetabular impingement [17];
- shoulder OA with or without rotator cuff tear appears to be a good indication, but not isolated cuff tear or capsulitis;
- in the ankle (talocrural joint), a subtalar component in symptomatic arthritis has been ruled out, possibly by local anesthetic test. HA injection may be useful after arthroscopic treatment of osteochondral lesions of the talus;
- abarticular pathology is beginning to be assessed (trigger finger, epicondylalgia, ankle sprain, etc.), but there have been no validation studies.

4. Results

4.1. Clinical efficacy of viscosupplementation

Many studies have been published, especially on knee OA, reporting overall positive results on pain and function, while genuine clinical trials have found negative results; this has given rise to ongoing controversy.

4.1.1. Knee OA

More than 100 controlled clinical trials have been published on knee OA, comparing various HA derivatives versus placebo, NSAIDs, corticosteroid infiltration or a reference HA. Most found moderate efficacy of around 20% versus placebo.

More interesting for clinical practice:

- 60–70% of patients are responders, on the OMERACT-OARSI, PASS and MCI criteria [13];
- efficacy is delayed but long-lasting. Six-month effect kinetics was assessed in a meta-analysis of HA versus placebo, measuring effect size on pain in various time intervals: efficacy became significant at 4 weeks, peaked at 8 weeks and persisted for 6 months [20].

4.1.1.1. HA versus placebo: the controversy. Most studies have been versus placebo, with sometimes contradictory results. Ten meta-analyses have been made, mostly positive but three negative, including Rutges’, which was notably virulent but questionable [18], raising controversy as to the efficacy of viscosupplementation and thus of its legitimacy in terms of cost/benefit.

This is why there is a threatened withdrawal of national health insurance cover in France. Rutges’ meta-analysis was mainly founded on a negative risk/benefit ratio, which is open to serious doubt inasmuch as HA shows efficacy that is greater than for analgesics, and equivalent to that of NSAIDs with much better tolerance.

The discordance in findings between the meta-analyses may partly be due to their great heterogeneity [13]: they were based on studies of heterogeneous OA series that took no account of phenotype (acute inflammatory or osseous episode, associated lesions, etc.). Assessment criteria and statistical methodology varied greatly, affecting interpretation. HA schedules differed: 1, 2, 3 or 5 injections per cycle for 1 to 3 cycles per year. The HA derivatives differed: linear or reticulated, varying MW and concentration. And finally, injection techniques were not specified and quality was uncertain.

Analysis of these meta-analyses suggests a beneficial, although slight, effect of HA on pain and function in knee OA [13,19]. In some studies, efficacy appeared better in certain phenotypes, and notably moderate OA without effusion.

4.1.1.2. Efficacy of viscosupplementation versus other treatments. The pain effect size versus placebo is slight (−0.37), but better than that of paracetamol (−0.20) and comparable to that of NSAIDs (−0.32) with a better risk/benefit ratio [13].

4.1.1.2.1. Analgesics. Analgesics have first-line indication in OA according to international guidelines [8]. Paracetamol is usually well tolerated (although digestive toxicity has recently been highlighted), but efficacy is slight. Opioids show greater analgesic efficacy (effect size −0.79), but with poor tolerance, especially in the elderly (risk of falls).

4.1.1.2.2. NSAIDs. Prolonged use of NSAIDs is not recommended, due to digestive, cardiovascular and renal toxicity. Bannuru’s meta-analysis [21] showed HA to be as effective as NSAIDs, but with better tolerance, tipping the risk/benefit ratio in favor of viscosupplementation. There is no advantage in systematically associating NSAIDs to HA, as this does not improve efficacy.

Thus viscosupplementation seems to be a good alternative to opioid analgesics and NSAIDs, with a better risk/benefit ratio than...
the latter. It is thus clearly of interest in elderly patients or in case of multiple pathology and multi-medication.

4.1.1.2.3. Corticosteroid infiltration. Although far from being a recent therapy, corticosteroids have been the focus of only 7 randomized controlled trials in knee OA, showing slight benefit for pain over placebo (pain effect size −0.39), comparable to that of HA.

Efficacy kinetics differs: the effect of corticosteroids is fast but short (about 1 to 3 weeks), whereas that of HA is delayed but lasts several months [20]. This was detailed in a meta-analysis of HA versus corticosteroid infiltration in knee OA, analyzing pain effect size over time in randomized trials against placebo [22]. Corticosteroid efficacy was greater at 2 weeks, equivalent at 4 weeks and then poorer than that of HA at 8, 12 and 26 weeks.

However, it was not specified whether the patients in these studies had joint effusion, which is unfortunate as it could influence the efficacy of one or the other treatment.

It may be wondered whether there is benefit in associating HA to a local corticosteroid: theoretically, this could accelerate onset of efficacy, but this failed to be confirmed by the one randomized study on the subject: systematic association of a corticosteroid (triamcinolone hexacetonide: Hexatron®) to single-injection HA (hylan: Synvisc-One®) in the same injection was compared to hylan alone, in a prospective randomized study of knee OA with or without effusion [6]. Results for the association were slightly better only during the first week, the two groups being comparable at 1, 3 and 6 months. Thus associating a corticosteroid to HA transiently improves efficacy but without synergy over time, and does not seem justifiable as a systematic attitude. Analysis of the subgroup with effusion would have been interesting, but data were not shown.

4.1.1.3. Studies versus a reference HA. In France, HA manufacturers were recently asked for randomized double-blind trials of non-inferiority versus a reference substance (Hyalgan® or Synvisc®) by the Health Authority as a condition for continued coverage. Results in terms of pain and function, within the limits of this kind of study with only 6 months’ follow-up, indicated non-inferiority for Arthrum® versus Hyalgan®, Structovial® versus Synvisc®, Go-On® versus Hylan®, Sinovial® versus Synvisc® and Ostenil® versus Synvisc® [13].

4.1.1.4. Response factors. Predictive factors for treatment response are poorly identified.

4.1.1.4.1. Type of HA derivative. The type of HA derivative, and especially its molecular weight, does not appear to be a response factor according to the clinical studies. Results comparing high- and low-MW HA are very discordant, preventing choice between the HA derivatives available. For single-injection forms:

- efficacy at 6 months seems comparable to the 3-injection schedule, at least for hylan GF-20 [23], but long-term (1 year) efficacy has not been assessed in randomized comparative trials;
- injection technique quality certainly plays an important role.

4.1.1.4.2. OA phenotype. OA phenotype plays a role, as we have seen, despite the paucity of studies taking account of patient characteristics: absence of joint effusion, moderate degree of radiologic joint space narrowing and femorotibial location emerge as predictive factors for good results.

4.1.1.4.3. Other OA locations

Outside of knee OA, initial hope raised by positive results for HA in the first open studies was dashed by disappointing results from recent randomized studies, especially in hip OA. In shoulder and ankle OA, results have been encouraging. Here we will not go into the detail of results in small joints, which were moderate in the thumb and inconclusive for single-injection in hallux rigidus.

4.1.2. Hip. HA efficacy is particularly controversial in hip OA. A 2006 meta-analysis [24] of 8 open studies and the first 2 controlled studies found 40–50% efficacy in early forms, and viscosupplementation was therefore included in international guidelines for the treatment of hip OA [8].

Three recent controlled studies [25–27], however, sowed doubt about the efficacy of HA hip injections by finding no superiority to placebo. Some poor results may have been due to poor indication: one negative trial included advanced hip OA scheduled for hip replacement, and a majority of hips showed synovitis on ultrasound [26]. In another study, with ultrasound-guided injection, subgroup analysis found superiority of HA versus placebo and corticosteroids in early hip OA with no effusion [25]. A smaller number of injections in the hip, due to poorer access (just one injection of linear HA in one trial) may also explain poorer efficacy [27]. Less restrictive schedules (1 injection every 3–6 months) are being published [28]. Retrospective analysis of hip replacement rates in a large series of hip OA with HA injection found that iterative injection enabled arthroplasty to be postponed [29]. However, HA does not seem effective in severe hip OA.

In all, HA seems to have some interest in moderate hip OA without effusion, given a sufficient number of injections.

4.1.2.2. Shoulder. HA injection appears effective in shoulder OA. Two open prospective studies, including one recent one with hylan GF-20 (Synvisc®), were very encouraging in pure shoulder OA [30].

An American large-scale controlled study of more than 600 patients with chronic shoulder pain showed 3 or 5 sodium hyaluronate injections to be effective versus placebo, at 2, 3 and 6 months, only in the shoulder OA subgroup, with or without rotator cuff tear [31]. In contrast, articular injection in isolated rotator cuff tear showed no efficacy. Tolerance was excellent.

A recent Japanese meta-analysis found HA to be more effective against chronic shoulder pain than NSAIDs, rehabilitation or corticosteroids with 0.39 (0.26–0.53) pain effect size [32].

4.1.2.3. Ankle. Open studies of 3-injection schedules in moderate-severe talocrural OA were encouraging [33], but the few controlled studies showed contradictory results.

A recent meta-analysis reported efficacy in ankle OA if a sufficient number of HA injections were made with dose adapted to joint capacity [34]. A randomized study suggested efficacy for 3 HA injections 3 weeks after arthroscopic treatment of osteochondral lesions of the talus [35].

4.2. Results for chondroprotection

Several in vitro studies (cartilage cell culture) suggested HA has a chondroprotective effect, as did animal trials (OA models by meniscectomy or anterior cruciate ligament section). Most reported slower disease progression on the treated side, with certain variations according to model and animal [36].

There have been few human studies; all concerned knee OA, with discordant results:

- two old studies with linear HA (Hyalgan®) versus placebo (3 injections every 3 months for 1 year) led to contradictory results [36];
• a French controlled study showed improvement in arthroscopy score but not in radiologic impingement in the HA group at 1 year’s follow-up;
• a recent randomized series of 78 patients, with 4 cycles of 3 weekly hylan GF-20 (Synvisc®) injections every 6 months for 2 years versus usual treatment, found a significant chondroprotective effect (cartilage volume on MRI) with reduced annual condylar cartilage loss at 2 years in the Synvisc® group as compared to controls [37].

A structural impact of HA in frequent-injection schedules is thus suggested, but requires confirmation; at the present time, preventive visscosupplementation for chondroprotection cannot be formally recommended.

4.3. Tolerance

General tolerance for HA injection is excellent and local tolerance satisfactory despite usually minor reactions that can be limited by good injection technique [38].

Caution remains mandatory, and any apparently inflammatory post-injection effusion requires joint aspiration and systematic screening for infection.

In reply to the worrying but questionable doubts concerning the safety of HA raised in Rutges’ meta-analysis [18], a recent literature review reiterated the harmless of visscosupplementation [39].

4.3.1. General tolerance

Rare cases of allergy to avian derivatives (Hyalgan®, Synvisc®) and some cases of transient asthenia have been reported.

4.3.2. Local tolerance

Post-injection injection is exceptional with HA, with only a few reported cases although this is probably an underestimation; but this severe complication is not to be overlooked and mandates prevention in the form of perfect asepsis and patient information on signs of infection.

The main adverse effect is painful or inflammatory local reaction. Frequency is low, at 2–6% in the knee, a little more in other joints, and treatment efficacy does not seem to be impaired. Pain is mainly at the injection site and inflammation is early, moderate and transient; the patient should be alerted to such risk.

More rarely, spectacular acute inflammatory reactions with a pseudoseptic aspect may occur (1–2%). These are unforeseeable and mainly associated with hylan GF-20, although linear HA may also be implicated. Early onset, 1–24 hours post-injection, is a reassuring sign of aseptic reaction; in case of the slightest doubt, however, fine-needle aspiration and bacteriological analysis should be performed.

There have been a few reports of genuine acute chondrocalcinosis following HA injection. An open prospective study of HA injection in knee OA with radiologic chondrocalcinosis found good injection tolerance with no acute episodes [15]; the patients, however, were not in the acute inflammatory phase of chondrocalcinosis.

Exceptional cases of granulomatous reaction have been described, exclusively implicating hylan [38].

5. Conclusion

Viscosupplementation remains an attitude of choice as a disease-modifying treatment for symptomatic OA, especially when moderate and free of effusion.

It is simple and well tolerated, on condition that the injection technique is adapted.

Efficacy is admittedly only moderate, but the rate of responders is high. It thus enables economy of opioid analgesics and NSAIDs, with a better risk/benefit ratio, and may allow knee replacement to be postponed.

There is probably a chondroprotective effect, but this needs confirming before preventive visscosupplementation can be formally recommended.

The field of HA derivatives is evolving, with the development of single-injection and combined forms. It is hard to choose between the plethora of products on the market, with their differing characteristics and poorly codified schedules, especially in joints other than the knee.

Some points remain unclear, such as predictive factors for treatment response or the role of HA is sports chondropathy.

Disclosure of interest

The author declares ties to Rottapharm (seminar speaker, therapeutic trial co-investigator), Sanofi Genzyme (symposium and seminar speaker), Expanscience (congress participation), Genevrier, Pierre Fabre (occasional scientific advisor, congress participation), Labhra (therapeutic trial co-investigator), Smith Nephew (therapeutic trial principal investigator), Chemedica (congress participation).

References


