Best Practice & Research Clinical Rheumatology
Vol. 15, No. 4, pp. 609–626, 2001
doi:10.1053/berh.2001.0177, available online at http://www.idealibrary.com on IDEAL®

BEST PRACTICE & RESEARCH

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Injections in the treatment of osteoarthritis

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Injections, especially of corticosteroids but also of hyaluronan, are widely used in the treatment of osteoarthritis. The various joints – knee, hip, hand – affected by OA are accessible to these local treatments. This chapter concentrates on the evidence for efficacy of these treatments and attempts to delimit their respective indications and optimal doses. The side-effects of corticosteroid injections are reviewed, and the potential interest in post-injection rest is discussed. Finally, the potential structure-modifying effect of hyaluronan is investigated.

Key words: osteoarthritis; corticosteroids injections; hyaluronan injections.

The use of intra-articular (IA) injections to treat osteoarthritis dates back to the 1930s. Faced with a local articular problem, physicians logically proposed various intra-articular treatments, directly injected close to the cartilage lesions and synovial membrane in order to improve symptoms and eventually to delay or stop disease progression. This chapter focuses on IA corticosteroid and hyaluronic acid (HA) injections.

CORTICOSTEROIDS

Corticosteroid injections are widely used for symptomatic treatment of osteoarthritis of peripheral joints, especially the knee joint. Injections are mostly intra-articular, sometimes peri-articular.

Efficacy

Intra-articular injections

Evidence for efficacy of IA steroids in OA is mostly confined to the knee joint.[1] Eight randomized controlled trials versus placebo have been published[2–9] and are summarized in Table 1. Except for the two earliest studies, patients received a single corticosteroid injection. The steroids studied were hydrocortisone, prednisolone, triamcinolone hexacetonide, methylprednisolone and cortivazol. Placebo was either normal saline or the suspending vehicle. The clinical parameter of efficacy was pain. The three earliest studies found no difference between hydrocortisone (25 or 50 mg) or prednisolone 25 mg and placebo injections.[2–4] The five most recent studies demonstrated a significant short-term benefit of steroids over placebo of 1 or 2 weeks

1521–6942/01/040609+18 $35.00/00

Table I. Randomized controlled trials of intra-articular corticosteroids versus placebo in knee OA.[a]

Author	Corticosteroid	Control	Patients	Design	Injections	Duration (weeks)	Results
Miller et al (1958)[2]	HC 50 mg	• Placebo • Novocaine • Lactic acid • Feigned injection	202	Parallel, single blind	5	24	Equal at W6 and W24 (pain)
Wright et al (1960)[3]	HC 25 mg	• Placebo • HC.TBA	25	Cross-over Double-blind	4	4	W2: HC = P HC. TBA > P W4: HC (± TBA) = P (pain, function, tenderness, motion)
Cederlof and Jonson (1966)[4]	Prednisolone 25 mg	• Placebo	44	Parallel, double-blind	1	8	Equal at W1, W3, W8 (pain, global assessment)
Friedman and Moore (1980)[5]	TH 20 mg	• Placebo	34	Parallel, double-blind	1	8	TH > P at 1 week only (pain)
Dieppe et al (1980)[6]	TH 20 mg	• Placebo	12 and 16	Parallel/cross-over Single blind	1	6 and 2	TH > P at 2 weeks only (pain)
Gaffney et al (1995)[7]	TH 20 mg	• Placebo	84	Parallel, double-blind	1	6	TH > P at 1 week only (pain)
Jones and Doherty (1996)[8]	MP 40 mg	• Placebo	59	Cross-over Double-blind	1	8	MP > P at 3 weeks only (pain)
Ravaud et al (1999)[9]	Cortivazol 3.75 mg	• Placebo • Cortivazol • Lavage • Lavage + cortivazol	98	Parallel, 2 × 2 factorial Double-blind	1	24	Cortivazol > P at W4 only (pain) Lavage (± cortivazol) > P at W24 for pain

HC = hydrocortisone; HC.TBA = hydrocortisone tertiary butylacetate; TH = triamcinolone hexacetonide; MP = methylprednisolone; P = placebo; W = week.
[a]Modified from Ayral (1999, *La Presse Médicale* **28**: 1195–1200) with permission.

for triamcinolone hexacetonide 20 mg[5–7], of 3 weeks for methylprednisolone[8] and 4 weeks for cortivazol.[9]

IA steroids are used at the hip joint, but very few controlled data are available. In 1956, Leveaux and Quin, in a randomized cross-over study, compared the effects of 50 mg hydrocortisone plus 5 ml procaine 2% versus procaine alone.[10] They concluded that hydrocortisone injections had greater efficacy, with an average benefit of 2.5 weeks versus 0.06 weeks with procaine alone.

Despite the common use of corticosteroid injection within the thumb-base[11] and fingers in OA, controlled data are lacking.

In summary, there is evidence that IA steroids are effective but their benefit over placebo may be relatively short-lived, lasting from 1 to 4 weeks.[11–14] This evidence of efficacy has been graded as 1B (best evidence being 1A, worst 4) by a task force for the EULAR Standing Committee for Clinical Trials.[14]

However, Creamer pointed out that there is some discordance between the short-lived effect of steroids seen in controlled studies and the clinical experience of rheumatologists that some patients achieve a significant and sustained response.[13] It could be argued that most of these randomized trials were dealing with small populations of patients, using only one injection of steroids even though, in clinical practice, injections may be repeated one or two times in case of a partial result, and that the steroid dose was usually lower than those usually injected and recommended in the ACR guidelines (40 mg of triamcinolone hexacetonide recommended for the knee joint instead of the 20 mg evaluated in clinical trials).[12] A confounding factor may be the strong beneficial response to intra-articular placebo injection, ranging from 36%[3], 55%[7], 65%[5] to 86%[2] For Creamer, the inability to detect an effect of IA steroids beyond 3 weeks may reflect insensitivity to pain as an outcome measure, rather than a lack of corticosteroid effect.[13]

Peri-articular injections

Pain in osteoarthritis may arise not only from intra-articular structures but also from peri-articular structures such as the capsulomeniscal junction or ligament. Lequesne et al have pointed out the interest of juxtameniscal cortisone injection in patients with knee OA, suffering from the medial juxtameniscal area, with a localized tender point reproduced by pressure.[15] This localized pain seems related to an inflammatory reaction at the peripheral edge of the meniscus, found in operated cases. The proposed treatment was juxtameniscal infiltration with 1 ml of steroid on a semiflexed knee into the most tender point.[15] In 30 patients, more than 80% of good results were obtained with one to three injections. Radiographical study with a contrast substance showed no intra-articular penetration. Moreover, many of these patients had received several intra-articular injections without relief.

One randomized, parallel group, double-blind study in 38 patients with painful OA demonstrated that peripatellar injection of 80 mg methylprednisolone was as efficacious as the same intra-articular injection at 1 to 3 months follow-up.[16]

Side-effects

Various side-effects may occur after corticosteroid injections.[11,13,17,18]

Sepsis

A major fear in the use of IA injection is the risk of introducing infection, which may result in severe morbidity and significant mortality. In 1969, Hollander noted 18 infections in about 250 000 injected joints – about one infection per 14 000 injections.[19] In 1983, Gray and Gottlieb estimated that they had witnessed two infections after 100 000 injections, or one in 50 000 injections.[18] A recent French retrospective study[20], conducted among 69 rheumatologists in private practice in and around Paris, found a mean frequency of sepsis after IA steroids of 1/77 300 during the last 21 years, a decrease since the 1970s. The rate of sepsis for the older rheumatologists was lower than that of their younger colleagues (1/112 000 versus 1/35 000, respectively). The incidence of sepsis was clearly lower with the use of corticosteroid packaged in a sterile syringe (1/162 000 versus 1/21 000 without sterile package).

Post-injection flares

Post-injection flares begin 6 to 12 hours after injection and resolve spontaneously in 1 to 3 days.[18] The incidence of such reactions is unclear, as is their specificity for steroid injections. Incidence ranges from 2–4%[17] to 12–24% in other studies.[11] Inflammatory arthritis similar to that of gout or pseudogout has been sugggested based on the crystalline structure, low solubility and size of the long-acting corticosteroids and their phagocytosis by mononuclear and polymorphonuclear leucocytes.[18] In a direct comparison of two corticosteroids, four of 21 patients receiving triamcinolone hexacetonide experienced flares, compared to one to 21 receiving betamethasone.[21] However, post-injection flares following saline are reported in a number of studies.[5,7] Gaffney et al[7] reported four of 42 (10%) flares after saline injection, and some in the triamcinolone group, suggesting that other factors, perhaps the injection technique, may be responsible for such reactions.

Skin

Atrophy of the skin and subcutaneous tissues and dermal pigmentation changes may occur following approximately 1% of injections.[17] These peri-articular adverse events are more common with the longest-acting corticosteroids, such as triamcinolone hexacetonide, especially when the steroid is mis-injected within the soft tissue or when it is injected into superficial joints such as fingers or wrist with excess pressure resulting in outflow from the joint to soft tissues.

The injection of triamcinolone hexacetonide in 'difficult' joints should be performed under fluoroscopic guidance to avoid this unfortunate event, with the steroids prepared in a 1 ml syringe for the small joints in order to control the pressure and volume of injection, and by ending the injection with rapid compression of the site after removal of the needle. These precautions would also minimize the incidence of peri-articular calcifications, most of which are harmless.[17,18]

Systemic effects

Diabetes and arterial hypertension might be temporarily disturbed after corticosteroid injection due to systemic absorption of steroids.[11] Facial flushing, presumably due to altered vascular tone, is relatively frequent. In a prospective study, it occurred in 40% of patients, although it was severe in only 12%[22]; changing to a different

corticosteroid may reduce the risk of subsequent flushing. Patients should be warned that flushing may occur but is not an allergic event. By contrast, anaphylaxis is extremely rare.[11]

Osteonecrosis

There are very few reports of vascular necrosis appearing in joints several months after steroid injection. Close review of the case reports failed to produce convincing evidence of causal relationships between osteonecrosis and the injection.[17]

Cartilage

The earliest studies reported the possibility of marked destructive cartilage changes[18] resulting from excessive intra-articular use of steroids. However, the necessity for repeated injections reflects active disease and/or a short-lived benefit of steroids. Thus, Charcot-like accelerated joint destruction after steroid injections may reflect severity of the disease itself (acute chrondrolysis) rather than a deleterious effect of IA steroids.[13]

In more recent studies, repeated corticosteroid injections in various joints[23–25] affected by chronic arthritis[23–25] or by knee osteoarthritis[25], showed mild progressive radiological changes compatible with the underlying disease. These studies do not support the contention that repeated intra-articular injections of corticosteroids will inevitably lead to rapid joint destruction. For Roberts et al, a strategy of frequent intra-articular steroid injections in rheumatoid arthritis does not increase the rate of total joint arthroplasty and may offer some chondroprotection when the alternative is continuous disease activity with a potential deleterious effect for the articular cartilage.[24] Preliminary results of a randomized study comparing intra-articular injections of 40 mg triamcinolone hexacetonide with a vehicle in knee OA, at 3-month intervals, for a prospective period of 2 years, showed the stability of joint space width in both groups (68 patients).[26] Clinicians should thus be reassured by the lack of evidence of deleterious effects of intra-articular steroids in most patients.[13]

Post-injection rest

In 1985, Neustadt pointed out the usefulness of a post-injection rest regimen to improve steroid efficacy in inflammatory knee arthritis.[27] His protocol involved bed rest for a minimum of 3 days, with the exception of time for bathroom and meals, then crutches for 3 weeks to protect the injected knee. The duration of response of prednisolone tebutate without ($n = 58$) or with ($n = 56$) a rest regimen was 5.5 and 9.5 weeks, respectively. With triamcinolone hexacetonide injection, the mean duration of response increased from 21 weeks ($n = 44$) to 35 weeks ($n = 50$) after the rest regimen.

In 1994, Chakravarty et al[28] reported a randomized trial in which patients with knee arthritis were randomized to receive either 24-hour strict, non-weight-bearing bed rest in hospital following intra-articular steroid injection (40 mg triamcinolone hexacetonide plus 2 ml lignocaine 2%) or were treated as outpatients. By 12 weeks, the degree of improvement in the pain score, stiffness score, function score, knee circumference and CRP was significantly better in the group that experienced 24-hour bed rest and this difference persisted up to 24 weeks.

Theoretical reasons for rest are based on evaluation of radiosynoviorthesis in knee arthritis showing the rapid uptake of intra-articular yttrium 90 by the circulation associated with mobilization of weight-bearing joints.[29] Benefit of strict bed rest with either a simple bandage[30] or a semi-rigid bandage[29] is equivalent to the extra-articular spread of the isotope. An alternative to strict bed rest would be walking with a rigid splint.[29] Increase in intra-articular pressure associated with quadriceps muscle activity combined with flexion of the knee may be the important factors affecting extra-articular spread of the isotope.

The interest of rest after IA steroids has never been studied in OA but seems logical. Injections in outpatients should be performed before the weekend to allow rest for at least 24 hours, with bed rest for lower limb injection and rigid bandage or splint for fingers or thumb-base injection.

Which patients should be treated?

Possible predictors of response to IA steroids

Type of corticosteroid. In a parallel group, observer-blind comparison of 20 mg triamcinolone hexacetonide versus 6 mg betamethasone in the knee joint, triamcinolone hexacetonide was more effective in reducing pain.[21]

Clinical parameters. In a recent study, Jones and Doherty failed to pick up any clinical predictors of response among the following: range of movement, effusion, local heat, synovial thickening, tenderness, functional, anxiety or depression scores and quadriceps strength, although tenderness was a predictor in an unadjusted analysis.[8] However, a real effect may have been missed by the small sample size of the study ($n = 59$). For Friedman and Moore, the efficacy of corticosteroids was also not related to the presence or absence of knee effusion.[5] By contrast, Gaffney et al reported that improvement in a triamcinolone group was greater among patients with clinical evidence of joint effusion and those who had synovial fluid (SF) successfully aspirated at the time of injection, the magnitude of the response being greater in the latter group.[7] At variance, aspiration of SF was not associated with greater reduction in pain in the placebo group.

Different hypotheses might explain the importance of SF aspiration. Aspiration before IA steroid diminishes the dilution factor of the steroid suspension, which might subsequently be more efficient. But the greater pain relief after successful aspiration of SF may relate to the accuracy of the intra-articular injection. Jones et al reported in a contrast radiography study that one-third of knee injections were extra-articular or uncertain and that aspiration of SF was associated with improved accuracy.[31] Another explanation may be that the presence of knee effusion seems correlated with the presence of synovitis in OA[32] and that IA steroids may be particularly indicated and efficient in this inflammatory flare of the disease.[13]

Other factors such as duration of symptoms, baseline intensity of pain, radiographic score, SF volume[7], SF leukocyte count[6,7] or the presence of crystals[6] did not influence the clinical response of IA steroids in the knee joint.

At the hip, in an open study on 45 patients with hip arthritis (27 of whom had OA), it was suggested that patients with a purely atrophic radiological pattern respond less well to steroid injections than those with a hypertrophic or mixed bone response.[33] Response was not influenced by radiographic severity or by the direction of migration of the femoral head.

Indications

Corticosteroid is a fast-acting symptomatic drug in OA. Several studies failed to demonstrate any clear-cut predictors of response, apart possibly, from the presence of effusion.[7] It should be noted that in a prospective study of 360 knee OA patients, Dougados et al found that structural deterioration was correlated with intermittent exacerbation of pain and with the number of synovial fluid aspirations during the 1-year follow-up.[34] These findings suggest that chondrolysis may not be a continuous phenomenon but might occur during OA flares[13], defined by episodes of exacerbation of pain with synovial effusion. Moreover, in a 6-month follow-up arthroscopic study of 46 patients with patello-femoral chondropathy, knee effusion at baseline and progression of chondropathy correlated with the presence of synovitis at baseline.[32] Thus, effusion might be a surrogate clinical marker of an inflammatory burst of the OA process with the potential risk of accelerated degradation of cartilage. Due to the short-lived effect of IA steroids in both knee and hip joints, the frequent need for repeated injections limits the usefulness of this agent in long-term management of OA. Thus, their use should be logically focused on short-term treatment of disease flares, i.e. exacerbation of pain accompanied by effusion.[12,14] Joint effusion is easily clinically detected at the knee and finger joints and suspected at the hip joint by the presence of nocturnal pain.[35] The aim of IA steroid injection is to obtain the disappearance of joint effusion. It should be added that this invasive treatment is indicated when effusion persists despite simpler treatment combining limitation of joint activity and intake of NSAIDs. At variance, peri-articular injections should be used in local perimeniscal pain without effusion.[15]

How often?

In 1995, ACR guidelines, although not well supported by published data, recommended that injection of corticosteroid in a given knee joint not be performed more than three or four times in a given year because of concern about the possible development of progressive cartilage damage through repeated injection in the weight-bearing joints.[12] However, based on recent studies[23–26], this risk of cartilage degradation seems minimal. At variance, the risk of degradation in the presence of chronic effusion seems real.[34] If knee effusion persists after one or two steroid injections 8–10 days apart, joint lavage combined with steroid injection could be recommended[12] because this association has proved to have a longer symptomatic effect.[9] In individuals requiring more than three or four IA injections per year to control symptoms, hyaluronan injections or appropriate surgical intervention could be proposed.[1,12]

HYALURONIC ACID/HYALURONANS

Hyaluronic acid (HA), a high-molecular-weight polysaccharide, is a major component of synovial fluid (SF) and cartilage. In osteoarthritis, the molecular weight and concentration is diminished. The concept of viscosupplementation suggests that intra-articular injection of HA could help restore the viscoelasticity of the SF, but HA has also been demonstrated to have a multiplicity of biological actions.[36] Several HA preparations are currently available (Table 2), in two categories: low-molecular-weight HA (0.5–2 MDa) and high-molecular weight hylan (cross-linked HA, 6–7 MDa). Two

Table 2. Hyaluronan preparations currently used in human osteoarthritis.

Trade name	Molecular weight (MDa)	Unit dose	Number of injections (one per week)
Artz® (or Supartz®)	0.6–1.2	2 ml	5
Orthovisc®	1.0–1.2	2 ml	3
Hyalgan®	0.5–0.75	2 ml	3 to 5
Synvisc®	6–7 + gel	2 ml	3

non-cross-linked HA preparations (Hyalgan® and Supartz®) and one hylan (Synvisc®, hylan G-F 20) have been approved by the US Food and Drug Administration (FDA).

Efficacy

Recent papers have reviewed the clinical trials published during the past 25 years conducted with different HA preparations.[1,36–38]

Hyaluronan versus placebo

Nine controlled, randomized, double-blind (seven of nine) studies compared Hyalgan® to placebo in knee osteoarthritis, with three to five injections (one per week) and 2- to 12-month follow-up periods[39–47] (Table 3). The double-blind design is of importance because hyaluronic acid is viscous, and blinding of the injector is difficult to achieve.[36] However, seven of nine studies were double-blind. Eight studies found Hyalgan® to be more effective than placebo for pain but also for function in three studies and for reduction in the number of IA steroid injections in a 1-year study.[42] The symptomatic effect was obtained from week 3 and week 5 and could persist until 6 to 12 months. Henderson found no difference between HA and placebo, but at the 5 month evaluation, 35 patients (38%) were lost to follow-up.[43]

Three controlled studies found Synvisc® (three injections, one per week) to be superior to placebo from week 2 and week 4 until 3 to 6 months after the beginning of treatment[48–50] (Table 3).

Three controlled studies compared Artz® (five injections, one per week) to placebo.[51–53] The first found Artz® more effective after week 3 and 10 for function and pain, respectively, lasting up to 3 months.[51] In the second study, Artz® and placebo obtained equal results.[52] In the third, no difference was found at 20 weeks between unstratified groups treated with placebo or Artz®, but a significant difference in favour of Artz® was found for a subgroup of patients older than 60 years, with a baseline algofunctional Lequesne's index greater than 10.[53]

Hyaluronan versus corticosteroids injections

Five controlled studies compared Hyalgan® to various steroids[54–58] (Table 4). Despite their controlled and randomized design, three of the five were open and should be considered with caution. Two open studies found a similar benefit of HA and steroids at 1 month followed by a superiority of Hyalgan® until 2 months. The single-blind study failed to demonstrate differences between the two treatments after 1 year. The double-blind study of Jones et al corroborated the results of open studies, with a

Table 3. Randomized trials of hyaluronan versus placebo in knee OA.[a]

Author	HA	Patients	Design	Injections	Duration (months)	Results
Bragantini et al (1987)[39]	Hyalgan	55	Parallel, double-blind	5 HA 20mg 5 HA 40mg 5 P	2	HA > P from W3 to M2 (pain–patient's assessment) HA 20 mg = HA 40 mg
Grecomoro et al (1987)[40]	Hyalgan	34	Parallel, single-blind	3	2	HA > P from W3 to M2 (pain-patient's assessment)
Dixon et al (1988)[41]	Hyalgan	63	Parallel, double blind	11 (in 23 weeks)	11	HA > P from W5 to M11 (pain on movement)
Dougados et al (1993)[42]	Hyalgan	110	Parallel, single blind	4	12	HA > P at W7 (effusion-pain-Lequesne's index) HA > P at M12 (Lequesne-number of IA steroid injections)
Henderson et al (1994)[43]	Hyalgan	91	Parallel, double blind	5	5	HA = P at W5 and M5 (pain) HA > P on time to NSAID intake in moderate OA
Carabba et al (1995)[44]	Hyalgan	20/group	Parallel, double blind	5 HA, 3 HA, 1 HA 5 arthrocentesis, 5P	2	3 and 5 HA > 1 HA, P, arthrocentesis from W4 to M2 (pain-Lequesne's index)
Formiguera et al (1995)[45]	Hyalgan	20/group	Parallel, double-blind	5	3	HA > P from D35 to M3 (pain-patient's assessment)
Altman et al (1998)[46]	Hyalgan	225	Parallel, double blind	5	6	HA > P from W5 to M6 (pain)
Huskisson et al (1999)[47]	Hyalgan	100	Parallel, double-blind	5	6	HA > P from W5 to M6 (pain-Lequesne's index)
Adams (1993)[48]	Synvisc	118	Parallel, double-blind	3	3	HA > P from W2 to M3 (pain-patient's assessment)
Scale et al (1994)[49]	Synvisc	50 and 30	Parallel, double-blind	2 vs 3	3	2 and 3 HA > P from W4 to M3 (pain-handicap) 3 HA > 2 HA at M3
Wobig et al (1998)[50]	Synvisc	110	Parallel, double-blind	3	6	HA > P from W3 to M6 (pain-function)
Puhl et al (1993)[51]	Artz	209	Parallel, double-blind	5	3	HA > P from W3 to M3 (function) HA > P from W10 to M3 (pain)
Dahlberg et al (1994)[52]	Artz	52	Parallel, double-blind	5	12	HA = P
Lohmander et al (1996)[53]	Artz	240	Parallel, double-blind	5	5	HA = P (total population) HA > P from W5 to M5 (patients > 60 years + Lequesne > 10)

HA = hyaluronic acid; P = Placebo; D = Day W = Week; M = month.
[a]Modified from Ayral (1999, *La Presse Médicale* **28**: 1195–1200) with permission.

Table 4. Randomized trials of hyaluronan versus intra-articular corticosteroid injections in knee OA.[a]

Author	HA	Control	Patients	Design	Injections	Duration (months)	Results
Leardini et al (1987)[54]	Hyalgan	MP 40 mg	36	Parallel Single blind	3	12	HA = MP (pain-mobility)
Leardini et al (1991)[55]	Hyalgan	MP 40 mg	40	Parallel Open	3	2	HA = MP until D28 (pain) HA > MP from D28 to M2 (pain) HA = MP (analgesic intake, patient's assessment)
Pietrogrande et al (1991)[56]	Hyalgan	MP 40 mg	90	Parallel Open	5 HA 3 MP	2	HA = MP until D35 (pain) HA > MP at M2 (pain)
Grecomoro et al (1992)[57]	Hyalgan	Dexa 0.4 mg	40	Parallel Open	5 HA 5HA+Dexa at 1st inj.	2	HA + Dexa > HA at M2 (pain)
Jones et al (1995)[58]	Hyalgan	TH 20 mg	63	Parallel Double-blind	5 HA 1 TH + 4 P	6	HA = TH until W5 (pain) HA > TH from W5 to M6 (pain)

HA = hyaluronic acid; P = placebo; MP = methylprednisolone; TH = triamcinolone hexacetonide; Dexa = dexamethasone; D = day; W = week; M = month.
[a]Modified from Ayral (1999, *La Presse Médicale* **28**: 1195–1200) with permission.

similar efficacy of HA and steroids until week 5, followed by a superior efficacy of HA on pain from week 5 to the end of the 6-month follow-up period.[58]

Thus, hyaluronan acts as a slow-acting symptomatic drug and its delayed effect should be explained to patients used to the rapid effect of steroid injections. However, steroids and hyaluronan should not be opposed but considered as complementary therapies. According to the preliminary open study of Grecomoro et al[57], the addition of dexamethasone to the first of five Hyalgan® injections led to better results on pain after 2 months.

Hyaluronan versus NSAIDs

Two randomized studies compared hyaluronan with NSAID. Altman found that five weekly injections of Hyalgan® obtained a similar benefit as naproxen 1000 mg daily for 26 weeks, with fewer gastrointestinal side-effects.[59] Adams found Synvisc® and NSAID to be equivalent at month 3.[60] The association of Synvisc® + NSAID was superior to NSAID alone, showing the interest of combining local and general treatments. Hyaluronan injections appear to be at least as good as continuous NSAID therapy and could be used as an alternative or complementary treatment.

A task force for the EULAR Standing Committee for Clinical Trials[14]concluded that there is evidence to support the efficacy of hyaluronic acid in the management of knee OA for both pain reduction (category of evidence:1B) and functional improvement (evidence: 1B).

Other joints

Two open studies using Hyalgan® in painful shoulder[61] and hip OA (three or four injections)[62], found a symptomatic benefit on pain and mobility with a sustained effect at 6 months in hip OA. A large retrospective Japanese study using Artz® in 1619 cases of periarthritis of the shoulder found a highly effective effect in 76% of the patients; therefore, this HA preparation is also indicated in this pathology.[63] Open studies evaluating Synvisc® in hip OA are ongoing.

Which patients are suitable for treatment?

Possible predictors of response

Predictive factors of hyaluronan efficacy have not been specifically evaluated in prospective clinical trials. A post hoc analysis favoured HA (Artz®) in patients older than 60 years, with important functional impairment (Lequesne's index >10).[53] However, in a subgroup analysis of one Hyalgan® study, Altman et al did not disclose significant differences in pain responses of patients over or under age 65, or with moderate or severe pain.[59]

A Canadian retrospective study of 336 patients suffering from knee OA (458 knees), treated over a period of 2–5 years with hylan G-F 20, found that response to hylan treatment was statistically influenced by structural severity of OA and the presence or absence of synovial effusion.[64] Early and intermediate radiographic grade patients (medial, lateral or patellofemoral OA) obtained better results than those with endstage disease (better or much better:72 to 91% versus 44 to 58%, respectively). The efficacy of hylan was found to be somewhat reduced in patients presenting with effusion before the first hylan injection, in that 71% of patients were categorized as better or much

better, but 7.3% were categorized as much worse, compared with 70 and 1.1%, respectively, in patients without effusion ($P = 0.05$). Subsequently, the product literature for hylan cautioned that it should not be injected in patients with a large intra-articular effusion.

In the hip joint, one open study also found that patients with mild-to-moderate disease experienced the best symptomatic improvement.[62]

The use of hyaluronan as first-line treatment in the presence of a large effusion does not seem particularly indicated. In this acute situation with the potential risk of accelerated degradation of cartilage[34], more rapid-acting drugs, such as IA corticosteroid injections, should be recommended. Slow-acting treatment by hyaluronan could be started in association with the IA steroid, as suggested by the study of Grecomoro et al[57], or started 1 week later on a 'dry' knee, in order to potentialize HA action and to obtain a longer symptomatic effect.

Indications

At this time, in the absence of clearly defined predictors of response, the best indications of hyaluronan could be the following[1]:

1. painful knee osteoarthritis despite other pharmacological and non-pharmacological therapies, radiologically moderate, with no or mild effusion, in the absence of mechanical symptoms (sudden and brief pains, locking) which could indicate arthroscopic treatment[12];
2. second-line treatment after a period of acute radiologic chondrolysis, when knee 'dryness' has been obtained.

Other indications could be the following:

1. painful endstage osteoarthritis when knee prosthesis is contra-indicated or refused by the patient.
2. alternative to NSAIDs treatment when it is contra-indicated, not tolerated or not effective.

Dose schedule, duration of effect and eventual utility of repeated treatment cycles

Most of the studies carried out with hyaluronan showed the same trends concerning the clinical kinetic profile of action: after a delayed onset of efficacy of 2 to 5 weeks, the symptomatic improvement could be long-lived, lasting 6 months or up to 1 year. Carrabba et al[44] looked for an eventual dose–effect relationship on clinical benefit. He found that 3- and 5-weekly injections of Hyalgan® were significantly superior to one injection, placebo or arthrocentesis in knee OA with joint effusion. No statistical difference was noted between three and five injections, although there was a trend in favour of five. These results suggest that the optimum number of injections seems to be between three and five for Hyalgan.® Scale et al found that three weekly injections of Synvisc® were more effective than two injections.[49]

Given the 6 months to 1-year lasting effect of the treatment course, another point is to establish whether a new course of injections has to be performed and when. Few data are available to date. Lussier et al[64] in their retrospective study found that the mean time elapsing between the first and second course of 3-weekly injections of Synvisc® was 8.2 ± 0.5 months and noted that there was no significant difference in

the duration of benefit comparing the first and second courses of treatment. In a recent multicentre open-label study of 108 patients, Kotz and Kolarz[65] observed that relief of symptoms of knee OA occurred 4 weeks after the end of treatment in 68% of the patients, and that relief was maintained through the 12-month follow-up for 55% of the patients. Some 50% of the patients who required a second treatment cycle after 4 to 8 months had improvement of their symptoms for an additional period of time. This could mean that a new treatment cycle may be usefully repeated when symptoms re-appear. However, long-term prospective studies should be conducted in order to evaluate whether a new course of treatment has to be administered systematically 6 months or 1 year later, or when symptoms re-appear. At this time, due to its invasivity and to logistical and cost issues, a new course of HA is usually proposed when pain re-appears.

Are there any structural modifying effects?

Animal model studies evaluating a potential structure-modifying effect of hyaluronan have been reviewed by Brandt et al.[38] They produce conflicting results. Studies in beagles and rabbits subjected to anterior cruciate ligament transection or meniscectomy suggested that HA injections reduced both gross cartilage damage and abnormalities in articular cartilage biochemistry. In contrast, injection of HA into sheep that had undergone meniscectomy resulted in significantly more extensive osteophytosis and cartilage fibrillation and in reduction in the net rate of proteoglycan synthesis. In one canine model with anterior cruciate ligament transection, it was found that HA treatment had no effect on morphological changes in the OA joint but that levels of proteoglycans were reduced.[38] At variance, in a similar canine model, Marshall et al found that the knees treated with three hylan injections at a time consistent with mild OA (curative treatment group) demonstrated long-term (6 months) gross and histopathological amelioration of disease activity compared with the controlateral control knees.[66]

In human OA, the capacity of HA to reduce the need for IA steroid injections during a 1-year follow-up period[42], suggests a possible structure-modifying effect by reducing the number of disease flares. Two studies have been performed to determine this possible disease-modifying effect. Frizziero et al[67] studied the structural effect of five weekly injections of hyaluronan by microarthroscopic assessment and morphological analysis of biopsy samples taken at baseline and at 6 months. The samples were histologically studied under blind conditions. At month 6, according to microarthroscopic evaluation, 60% of patients were unchanged while 32.5% showed improvement in the grading and/or extension of the cartilage lesions and 7.5% had worsened. Biopsies analysis confirmed these results.

A pilot study of 1 year duration has been conducted by Listrat et al[68] according to a prospective, controlled, randomized design, in 36 knee medial OA patients. Patients were allocated to receive either nine injections of Hyalgan® (three courses of 3-weekly HA injections) or no injections, after having an arthroscopic lavage. Arthroscopy was repeated after 1 year. Baseline and final arthroscopic evaluations were recorded on separate videotapes, then paired videotapes were analysed by a single observer blinded to treatment and to chronology of videotapes. Less deterioration was found in the structural parameters (scoring systems of chondropathy) in the Hyalgan® group than in the control group. The Hyalgan® group also scored higher for quality of life and reduced NSAID use during the study period.

These preliminary studies require further larger prospective placebo-controlled, double-blind trials to confirm the hypothesis that hyaluronan could be a structure-modifying agent.

SUMMARY

There is evidence to support the symptomatic efficacy of corticosteroid and hyaluronan injections in knee osteoarthritis for both pain (steroids and HA) and functional improvement (HA). These two intra-articular treatments should not be opposed but considered as complementary therapies because their kinetics of action seem different: rapid but short-lived for steroids, delayed but prolonged for HA.

Despite the lack of large prospective studies evaluating predictors of response, IA steroid injections seem to be particularly indicated for rapid treatment of the flares of the disease, i.e. exacerbation of pain accompanied by joint effusion. Steroid injection should be preceeded by synovial fluid aspiration and followed by a 24-hour joint rest, the usefulness of which remains to be proven in OA.

Hyaluronan should be indicated as an alternative long-term treatment in patients with no effusion who continue to suffer despite pharmacological and non-pharmacological treatments, especially in the case of non-endstage disease, where response to HA seems more favourable. The optimal time for a second course of HA remains to be evaluated, but such a course is usually proposed when pain re-appears. Hyaluronan is also logically indicated as second-line treatment in acute chondrolysis, after achieving dryness of the joint by steroids, in order to prolong the symptomatic effect of steroids and, perhaps, to slow cartilage degradation.

Practice points

- intra-articular steroid injection acts as a symptomatic fast-acting drug with a short-lived beneficial effect on pain of 1 to 4 weeks
- side-effects of steroid injections are infrequent; the incidence of sepsis is clearly less with the use of corticosteroid packaged in a sterile syringe
- based on clinical studies in arthritis, a 24-hour post-injection rest seems logical in osteoarthritis after steroid injection
- intra-articular steroids are particularly indicated in patients with exacerbation of pain accompanied by joint effusion
- hyaluronan acts as a symptomatic slow acting drug with a delayed onset of efficacy of 2 to 5 weeks and a long-lived benefit on pain and function which may persist until 6 to 12 months
- depending on hyaluronan preparations, a course of 3 to 5 injections, one per week, is recommended and a new course of treatment is usually proposed when symptoms re-appear
- hyaluronan treatment seems particularly indicated in a painful knee OA despite other pharmacological and non-pharmacological therapies, radiologically moderate, with no or mild effusion, in the absence of mechanical symptoms

Research agenda

- efficacy of intra-articular steroid injections in hip OA and finger OA remains to be evaluated
- predictors of response to steroid injections need to be further delimited with large prospective studies
- interest of post-injection rest should be clarified in osteoarthritis after steroid injection
- effect of steroid injections on human osteoarthritic cartilage requires further studies
- predictors of response to hyaluronan treatment, optimal regimen and interval between two courses need to be further delimited in controlled, large, long-term follow-up studies
- symptomatic effect of hyaluronan treatment in other OA joints should be evaluated in placebo-controlled studies
- possible synergetic effect of combined IA steroids and hyaluronan injections should be further investigated
- pharmacoeconomic aspects of hyaluronan treatment need to be well established
- possible structure-modifying effect of hyaluronan treatment

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