



TITLE: Hyaluronic Acid for Treatment of Osteoarthritis of the Knee:
Repeated Injections and Progression to Knee Replacement

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INTRODUCTION

The California Technology Assessment Forum (CTAF) is requested to review the scientific evidence for the use of hyaluronic acid (HA) for the treatment of osteoarthritis. Several prior reviews and meta-analyses including two done by The Blue Cross Blue Shield Technology Evaluation Center have concluded that despite study flaws, there is a positive effect of hyaluronic acid on the symptoms of knee osteoarthritis.^{1,2} Although there is evidence that injections of hyaluronic acid can improve symptoms of knee osteoarthritis, other questions remain. In this review, CTAF will specifically focus on the efficacy of repeat injections of HA and whether or not repeated injections of intra-articular HA can slow the progression of OA or reduce the need for joint replacement. This is the first time that CTAF has addressed this topic.

BACKGROUND

Osteoarthritis (OA) is characterized by degeneration of cartilage and its underlying bone within a joint as well as bony overgrowth, which ultimately lead to pain and joint stiffness. Most commonly affected joints are the knees, hips, and joints in the hands and spine. OA of the weight bearing joints (eg knee and hip) typically have the most clinical significance. The causes of OA are presumed to be related to mechanical and molecular events in the joint.

(<http://www.cdc.gov/arthritis/basics/osteoarthritis.htm>).



OA usually begins after the age of 40. OA affects 13.9% of adults aged 25 and older and 33.6% of those aged 65 and over (<http://www.cdc.gov/arthritis/basics/osteoarthritis.htm>). Among those affected, approximately one quarter of them are severely disabled.³ Osteoarthritis is the leading cause of mobility disabilities such as difficulty walking or climbing up stairs. OA of the knee is one of five leading causes of disability among non-institutionalized adults.⁴

Knee OA is the most prevalent, followed by hip OA. Both knee and hip OA result in joint pain and stiffness which can ultimately interfere with function and restrict activities of daily living.⁵

There is no cure for OA. In addition, there are currently no known therapies that can prevent progression of OA. Treatment of OA typically focuses on minimizing pain and swelling, reducing disability and improving quality of life.

Treatment typically starts with nonpharmacologic therapy approaches including exercise programs, weight loss, patient education and shoe insoles.⁶ Nonpharmacologic approaches are typically tried before medications are started.

Pharmacologic treatment is typically the next step and focuses on relief of pain. Pharmacologic therapy typically includes acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase (COX-2) inhibitors and opiates. Each of these medications can be beneficial in some patients and each is associated with characteristic side effects. Given that the patient



population is typically an older one, often with other comorbid conditions, the side effects associated with long term use of some of the OA medications can be particularly problematic.

Intra-articular glucocorticoid injections are another potential component of OA treatment. These can be useful for patients who still have one or a few painful joints despite NSAID use and in patients with one or a few involved joints in whom NSAIDs are contraindicated. In a meta-analysis, glucocorticoid injections have been shown to lead to short term improvements in knee pain and function.⁷

The idea of viscosupplementation was first proposed by Balazs in 1993.⁸ HA is a naturally occurring macromolecule that is an essential part of synovial fluid and is thought to contribute to its viscoelastic properties. The theory is that injection of the HA into joints with OA could restore some of the properties of the synovial fluid, and could promote endogenous synthesis of a more functional (and higher molecular weight) HA, therefore increasing mobility, decreasing pain and restoring function.

The effects of HA injections have primarily been evaluated in the knee and HA injections are only FDA approved for use in the knee. Multiple trials focusing on the knee have compared intra-articular HA to either placebo, NSAIDs or intra-articular glucocorticoids. A meta-analysis included results from 22 trials comparing intra-articular hyaluron with intra-articular placebo and found that intra-articular HA was better than placebo, but the effect was generally small.⁹ A subsequent meta-



analysis assessed HA and placebo groups at different time periods and found a small improvement in rest pain at 2 and 6 weeks, although the clinical significance of the difference was questioned.¹⁰

Studies comparing intra-articular HA to NSAIDs have led to conflicting results and have not clearly shown intra-articular HA to be superior.^{11,12} Intra-articular HA has also been compared to intra-articular glucocorticoids. It seems that the benefits from each injection are somewhat similar; there were greater benefits of HA at some time points, although these benefits did not appear to be sustained long term.¹³⁻¹⁵

A recent Cochrane review that included a meta-analysis of 40 placebo controlled trials with five different HA products found statistically significant improvements in pain and weight bearing when results were pooled.¹⁶ Overall, the conclusion of the Cochrane review was that viscosupplementation for knee osteoarthritis was an effective treatment for osteoarthritis of the knee with demonstrated beneficial effects on pain, function and patient global assessment. Maximum benefits appear to be achieved between five and 13 weeks, and that the effects seemed to be more prolonged than the effects of corticosteroids.

Intra-articular HA is relatively well established as a treatment option for knee OA in some patients and is recommended as a treatment option by many organizations, including the American College of Rheumatology and the Osteoarthritis Research Society International.^{17,18} The American College of Rheumatology recommends intra-articular HA as a treatment option for patients with knee OA who are at increased risk for GI tract adverse events as an alternative for oral agents.¹⁷ The



Osteoarthritis Research Society International (OARSI) developed a set of evidence based, expert consensus guidelines and graded the strength of evidence for each. They recommend the consideration of intra-articular HA stating that it may be useful, and state that onset of action may be delayed but there is a prolonged duration of symptomatic benefit.¹⁸

Although the efficacy of intra-articular HA for pain relief and functional improvement in knee osteoarthritis has been shown, important questions about the use of intra-articular HA remain. What is the efficacy of repeated injections of HA into an affected joint? Can viscosupplementation reduce the need for joint replacement and or slow the progression of OA? Although intra-articular HA is being evaluated for use in many other joints, including hip, shoulder and ankle, it is not currently FDA approved for use in joints other than the knee, and thus its use in other joints will not be addressed here.

TA Criterion #1: The technology must have final approval from the appropriate government regulatory bodies.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

The FDA classifies HA for intra-articular use as Class 3 devices. There are six HA products that have FDA PMA approval for osteoarthritis of the knee. Intra-articular HA is not currently FDA approved for use in other joints. The recommended course of a single treatment varies from one injection only to one injection per week up to five weeks.



Product Name	Manufacturer	Formulation	Typical recommended course of treatment
Eufflexa	Ferring Pharmaceuticals	1% Sodium Hyaluronate	One injection per week for three weeks
Nufflexxa	Savient Pharmaceuticals	1% Sodium Hyaluronate	One injection per week for three weeks
Synvisc	Genzyme Biosurgery/Sanofi	Hylan GF-20 (high molecular weight fluid containing derivatives of hyaluronan or sodium hyaluronate)	Synvisc: One injection per week for three weeks Synvisc-One: Single injection
Orthovisc	Registered trademark of Anika Therapeutics, Inc. Distributed by DePuy Mitek, Inc	High Molecular Weight Hyaluronan (Sodium Hyaluronate)	One injection per week for three or four weeks
Hyalgan	Fidia Farmaceutical	Sodium Hyaluronate	One injection per week for five weeks
Supartz	Smith & Nephew Seigakaku Corp.	Sodium Hyaluronate	One injection per week for five weeks

TA Criterion #1 is met

TA Criterion #2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and Database of Abstracts of Reviews of Effects (DARE) were searched using the search terms osteoarthritis, hyaluronic acid, and hyaluron. The search was performed for the period from 1966 to November, 2011. The bibliographies of systematic reviews and key articles were manually searched for additional references and references were requested from the device manufacturer.



The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

Inclusion criteria:

- Study had to evaluate intra-articular hyaluronic acid in patients with osteoarthritis of the knee
- Comparative studies had to intra-articular hyaluronic acid to another treatment
- Study had to measure clinical outcomes
- Included only humans
- Published in English as a peer reviewed article

Studies were excluded if they only focused on non-clinical outcomes.

A total of 424 potentially relevant articles were identified. All 424 titles were reviewed. Three hundred ninety articles were excluded for not addressing the research question. A total of 34 abstracts were evaluated. Twenty three abstracts were excluded. Reasons for exclusion included not evaluating multiple courses of HA, not focusing on the knee, or not reporting clinical or structural outcomes. Of these, three published prospective studies, three published retrospective studies and five clinical trials are included in this evaluation.

Ten studies addressed the question of whether or not there is efficacy of repeated injections of HA into an affected joint. Two studies addressed the question of whether repeated injections of intra-articular HA can reduce the progression of OA or reduce the need for joint replacement

Details of the studies assessing the impact of HA on clinical outcomes are described in Tables 1 and 2. Details of studies assessing the impact of HA on progression of osteoarthritis are described in Tables 3 and 4.



Although the outcomes varied among the studies, typical outcomes included visual analog pain scales, patient activity level, Osteoarthritis Research Society International (OARSI) 2004 responder criteria and the Western Ontario and McMaster University Osteoarthritis indices (WOMAC).

Two standardized outcome variables have been developed for measuring the impact of osteoarthritis on an individual's life. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale is a commonly used pain scale for assessing the impact of arthritis. The WOMAC is a self-administered disease specific quality of life instrument that asks the patients questions about the study knee. There are three subscales - pain, stiffness and aggregate functioning - as well as an aggregate total score.¹⁹

The second outcome variable is the OARSI 2004 responder criteria. The OARSI developed two sets of responder criteria to be used as a uniform set of outcome measures for osteoarthritis trials. The goal was to develop a set of criteria based on multiple domains that could be used as a single variable in clinical trials. The included symptomatic variables were pain, functional impairment and patient's global assessment. These criteria have been proposed to be used across clinical trials that evaluate the impact of osteoarthritis treatments.²⁰

Level of Evidence: 1,3

TA Criterion # 2 is met

Table 1: Descriptions of studies of the efficacy of repeated intra-articular injections of HA in knee osteoarthritis

Study, Author	Study type	N	Country	Inclusion Criteria	Intervention	Intervention Outcomes
Lussier, 1996 ²¹	Retrospective	336	Canada	OA of the knee	<ul style="list-style-type: none"> All patients with knee OA treated with hylan by five Canadian clinicians 	<ul style="list-style-type: none"> Patients overall response to treatment and changes in patient activity level (both measured on a 5 point scale on a survey)
Waddell, 2007 ²²	Retrospective	863	USA	Received hylan G-F 20 intra-articular injection and were TKR candidates	<ul style="list-style-type: none"> Intra-articular hylan G-F 20 injection: one or more courses 	<ul style="list-style-type: none"> Time to TKR
Puttick, 1995 ²³	Retrospective	22	Canada	Patients who received hylan G-F 20 injections to one or both knees from three rheumatologists	<ul style="list-style-type: none"> Intra-articular hylan G-F 20: one or more courses 	<ul style="list-style-type: none"> Safety Reactions after injections
Neustadt, 2003 ²⁴	Prospective cohort	76	USA		<ul style="list-style-type: none"> Five weekly injections of intra-articular HA Optional repeat course 	<ul style="list-style-type: none"> VAS for pain
Scaili, 1995 ²⁵	Prospective Open Label, uncontrolled	75			<ul style="list-style-type: none"> Intra-articular Hyalgan: 5 courses at 6 month intervals 	<ul style="list-style-type: none"> “Clinical benefit”
Kolarz, 1999 ²⁶	Prospective open label, uncontrolled	108	Austria	Knee OA	<ul style="list-style-type: none"> Intra-articular hyalgan- 5 injections at one week intervals. Second injection could be requested at 4 months 	VAS pain scale

Listrat, 1997 ²⁷	Prospective controlled study	39	France	Painful knee arthritis	<ul style="list-style-type: none"> Conventional therapy or three cycles (every three months) of three intra-articular injections of Hyalgan 	<ul style="list-style-type: none"> Visual pain analog score Functional impairment Lequesne's index Arthritis impact measurement scale (AIMS2)
Pham, 2004 ²⁸	Multicenter randomized double blind RCT	301	France	Symptomatic knee osteoarthritis JSW > 2 mm	<ul style="list-style-type: none"> Three courses of three HA injections Diacerein 100 mg a day Placebo 	<ul style="list-style-type: none"> Changes in pain VAS
Raynauld, 2005 ²⁹	Prospective randomized open label trial	255	Canada, Australia, US	Symptomatic knee osteoarthritis and prior treatment with NSAIDS or acetaminophen	<ul style="list-style-type: none"> Appropriate care without hylan G-F 20 Appropriate care with hylan G-F 20. Those who got hylan G-F 20 were partitioned into two subgroups- those who got a single course of hylan G-F 20 and those who received two or more courses 	<ul style="list-style-type: none"> Change in Western Ontario and McMaster universities osteoarthritis index (WOMAC)
Navarro-Saraboa, 2011 AMELIA ³⁰	RCT	306	Spain	American College of Rheumatology criteria for knee OA.;	<ul style="list-style-type: none"> Four cycles of five Intra-articular injections of HA vs placebo 	<ul style="list-style-type: none"> OARSI 2004 responder criteria Use of rescue medications Adverse events

AIMS: Arthritis Impact Measurement Scale

HA: Hyaluronic Acid

JSW: Joint Space Width

OA: Osteoarthritis

OARSI: Osteoarthritis Research Society International

TKR: Total Knee Replacement

VAS: Visual Analog Scale

WOMAC: Western Ontario and McMaster Universities Arthritis Index

Table 2: Outcomes of studies of the efficacy of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis

Study, Author	N	Length of follow-up	Main outcomes	Comments
Lussier, 1996 ²¹	336	2 years	<ul style="list-style-type: none"> 77% of knees better or much better after one course of treatment 87% of knees were better or much better after two courses Activity level: 76% better after one course and 84% better after two courses 	Retrospective and no comparison group
Maddell, 2007 ²²	863		<ul style="list-style-type: none"> 19% had TKR 75% of knees did not have TKR by 3.8 years 	No comparison group
Puttick, 1995 ²³	22	Not stated	<ul style="list-style-type: none"> 88 injections to 28 knees 10/88 injections associated with reaction 6 out of 22 patients had an adverse reaction 	Small retrospective study focusing on safety
Neustadt, 2003 ²⁴	78	1 year	<ul style="list-style-type: none"> VAS pain score was 3.2 vs 5.9 at baseline 15/19 who were considering knee replacement did not get knee replaced 	Not randomized for 1 vs 2 injections No comparison group
Scali, 1995 ²⁵	75	30 months	<ul style="list-style-type: none"> 60% with good to excellent results after first round of injections (six months) 88% had good to excellent results after five rounds of injections (30 months) VAS level of pain improved from 6 up to 30 months 	No comparison group
Kolarz, 2003 ³¹	1081	1 year	<ul style="list-style-type: none"> 14 received a second cycle of hylan and nine of these were lost to follow up 	Hylan single or multiple injections were efficacious but few received multiple injections
Listrat, 1997 ²⁷	39	1 year	<ul style="list-style-type: none"> AIMS 2 better in hyalgan group Less deterioration in structural parameters in hyalgan group (overall assessment of chondropathy) 	Small study

Study, Author	N	Length of follow-up	Main outcomes	Comments
Pham, 2004 ²⁸	301	1 year	<ul style="list-style-type: none"> Pain VAS score improved in all 3 groups; no difference between groups 	
Raynauld, 2005 ²⁹	255 n=128 usual care n=78 single course n=48 repeated course		<ul style="list-style-type: none"> Change in WOMAC pain score from baseline 41% in single, 35% in repeat course groups vs 14% in usual care group (p<0.05 for either course vs usual care; NS for difference between single and repeat course) 	<ul style="list-style-type: none"> Post hoc analysis The subgroups among those who received hyaluron were not randomized
Navarro-Saraboa. 2011 AMELLA ³⁰	306	40 months	<ul style="list-style-type: none"> At 40 months more patients responded to HA than to placebo Number of responders to HA increased during the study 	<ul style="list-style-type: none"> Improvement noted during treatment and carry over for at least a year

AIMS: Arthritis Impact Measurement Scale
 AMELLA: Osteoarthritis Modifying Effects of Long-Term Intra-articular Adant
 HA: Hyaluronic Acid
 VAS: Visual Analog Scale
 TKR: Total Knee Replacement

Table 3: Description of studies of the efficacy of repeated courses of hyaluronic acid on progression of osteoarthritis

Study, Author	Study type	N	Country	Inclusion Criteria	Intervention	Intervention Outcomes
Listrat, 1997 ²⁷	Prospective controlled study	39	France	Painful knee arthritis	<ul style="list-style-type: none"> Conventional therapy or 3 cycles (every 3 months) of three intra-articular injections of Hyalgan 	<ul style="list-style-type: none"> JSN SFA for measuring chondropathy Overall assessment of chondropathy using VAS
Pham, 2004 ²⁸	RCT double blind	301	France	Symptomatic knee OA	<ul style="list-style-type: none"> Three courses of three HA injections Diacerein 100 mg a day Placebo 	<ul style="list-style-type: none"> JSW JSN Percentage of progressors (JSN >0.5 mm over course of study)

Diacerein: is a NSAID disease modifying agent that affects interleukin 2 instead of cyclo-oxygenase
 JSN: Joint space narrowing
 JSW: Joint space width

SFA: Système Française D'Arthroscopie - Grading system for chondropathy measures severity of chondropathy as assessed during arthroscopy on a validated scale

Table 4: Outcome of studies of the efficacy of repeated courses of hyaluronic acid on progression of osteoarthritis

Study, Author	N	Length of follow-up	Main outcomes	Comments
Listrat, 1997 ²⁷	39	1 year	<ul style="list-style-type: none"> • Less deterioration in structural parameters in the HA group • Overall assessment of chondropathy: <ul style="list-style-type: none"> • 5.1 vs 16.7 (p=0.016) improvement in SFA scoring for HA 3.7 vs 7.3 (p=0.05) 	<ul style="list-style-type: none"> • Small study that suggests that repeated intra-articular injections of HA might delay the structural progression of the disease
Pham, 2004 ²⁸	301	1 year	<ul style="list-style-type: none"> • JSW deteriorated but with no difference between groups • Percentage of progressors similar between groups (17.7%, 18.9%, 20.3%: NS) 	<ul style="list-style-type: none"> • No structural benefits of either HA or diacerein

HA: Hyaluronic Acid

JSW: Joint Space Width

DRAMA



TA Criterion #3: The technology must improve the net health outcomes.

Intra-articular HA is a well established treatment option for OA. However, fewer studies have assessed the impact of repeated courses of intra-articular HA on treatment efficacy, and on disease progression, including the need for total knee replacement.

Potential Benefits

Ten studies have assessed the impact of repeated intra-articular injections of HA on treatment efficacy. Three were retrospective, three were prospective and uncontrolled and four were trials. Study size ranged from 22 to 863. Outcomes included visual analog pain scales, changes in the WOMAC and OARSI standardized scales. Two studies assessed the impact of a single course of HA with several courses of HA.^{21,25} Both studies found that there was more clinical improvement after two or more courses of HA than after one course of HA, although neither had a comparison group that did not receive HA. In other prospective studies, patients could receive an additional treatment course after a defined period (often four months), but the impact of repeated courses vs a single course were not always analyzed separately.^{24,31} In the trials that evaluated the impact of repeated courses of HA, all showed improvements in outcomes, including pain VAS scores, change in WOMAC pain scores, and OARSI responder criteria.^{20,27,29,30}

Two studies have assessed the impact of repeated courses of intra-articular HA for knee OA on disease progression, measured either radiographically or arthroscopically.^{20,27} In the first, a small prospective study of 39 patients, those who received repeated courses of HA had improvement in



arthroscopically measured chondropathy.²⁷ In the second, a larger RCT, outcomes were measured radiographically and there was no clear impact on radiographic disease progression.²⁰

Potential Harms

The main potential harms of intra-articular HA are local reactions (pain or bleeding at the injection site), allergic reactions (including rash and swelling) and arthralgias. Post-injection flare is characterized by increased pain, swelling and the presence of an inflammatory joint effusion and has been estimated to occur in 1.5-5% of injected knees. Post-injection flare may be more common in injections given via the medial approach than by the lateral approach.^{21,32}

Few studies have assessed the potential adverse effects of repeated courses of HA on safety outcomes. However, in the one large randomized controlled trial that compared repetitive intra-articular HA injections with placebo, safety outcomes were also assessed.³⁰ The number of adverse events were similar in the treatment and the control groups (9.8% in the HA group vs 9.1% in the placebo group). All side effects were mild to moderate. Common side effects included allergic reaction (rash and swelling), pain or bleeding at the injection site or arthralgias. There were no serious side effects in either group.

In summary, overall repeated injections of HA for knee OA has shown efficacy in symptomatic relief of OA. The side effects have generally been relatively minor in contrast to the potential



benefits. Thus repeated injections of intra-articular HA are associated with a net benefit in health outcomes.

TA Criterion #3 is met

TA Criterion #4: The technology must be as beneficial as any established alternatives.

An important question is how repeated injections of intra-articular HA compare with the established alternatives for the treatment of osteoarthritis. Established treatments would include non-pharmacologic measures such as physical therapy, weight loss, education and counseling, devices as well as medications including nonsteroidals and acetaminophen, and surgical treatments such as arthroscopy or total knee replacement.

Impact of HA on Clinical Outcomes

Three studies have compared the impact of repeated injections of intra-articular HA with another treatment on clinical outcomes. The first was a multi-center open label study conducted in multiple sites in Canada. Patients with knee osteoarthritis, who had received prior treatment with acetaminophen or NSAIDS were randomized to receive “appropriate care with hylan G-F 20 or



“appropriate care without hylan G-F 20.” Appropriate care was defined as the preferred management strategy of the referring physician, who was encouraged to follow the guidelines of the American College of Rheumatology. A course of intra-articular hylan G-F 20 was a series of three injections at one week intervals. Individuals could receive subsequent injections to the knee during the study. The main goal of the study was to compare intra-articular hylan G-F 20 plus appropriate care to appropriate care alone. The main outcome was a change in the WOMAC pain score in the study knee from baseline to the end of the study. The main study results showed that adding hylan G-F 20 to appropriate care led to significant improvement in the main outcome - reduction in the WOMAC pain scale.³³

A secondary publication from this study evaluated the safety and efficacy of repeated courses of hylan G-F 20 plus appropriate care on the same primary outcome (reduction in the WOMAC pain score).²⁹ For this analysis, the investigators divided the hylan G-F 20 group into two subgroups - 1) those who received one injection of hylan G-F 20 and 2) those who received more than one injection of hylan G-F-20. Importantly, participants were not randomized to receive one or more than one dose. For the main outcome - improvement in the WOMAC pain scale, the single course group improved by 41% and the repeat course group improved by 35%, compared with an improvement of 14% in the appropriate care subgroup. Both groups improved more than the appropriate care subgroup ($p < 0.050$), and were not statistically different from each other. The repeat course group did not have more adverse events than the other groups, nor was there a difference in arthrocentesis rates between the first and repeated courses of treatment. This post-



hoc analysis suggests that multiple courses of hylan G-F 20 may be efficacious and safe, but the study was not designed to specifically answer this question.²⁹

A French study randomized patients to receive one of three treatments: 1) three courses (3 injections each) of intra-articular HA, 2) diacerein 100 mg a day (an anti-inflammatory drug that affects the interleukin pathway) or 3) placebo. Participants and investigators were blinded to the treatments. Participants were followed for a year. The main outcome was pain score as rated by a visual analog scale. The VAS pain score improved in all three groups, but there was no significant difference between groups.

The AMELIA project (OsteoArthritis Modifying Effects of Long-term Intra-articular Adant) was designed to assess the efficacy and the carry-over effect of repeated intra-articular injections of HA in knee osteoarthritis. This was a randomized controlled multicenter trial conducted over 40 months.³⁰ Patients with knee osteoarthritis (as defined by ACR criteria with Grade II got III radiographic stage OA) were randomized to receive intra-articular Adant (1% HA) or placebo. There were four treatment cycles - each treatment cycle consisted of 5 weekly injections. Study participants could receive periodic courses of acetaminophen or nonsteroidals, but were not allowed to receive intra-articular corticosteroids over the course of the study. Follow up was for six months after the first and second cycles and one year after the third and fourth cycles. The repeated injection cycles were administered regardless of whether or not the patient had symptoms. The main outcome was the percentage of individuals with a clinical response as defined by the Osteoarthritis Research Society International (OARSI) 2004 criteria. Patients were



classified as responders if the pain or physical function score decreased at least 50% and at least 20 mm on the VAS, or if two of the following three findings were present:

1. a decrease in pain of at least 20% and at least 10 mm on the VAS,
2. a decrease in physical function of at least 20% and at least 10 mm on the VAS, or
3. an increase in the score of the patient's global assessment by at least 20% and at least 10 mm on the VAS.

Safety and tolerability were evaluated based on the incidence and type of adverse events.

A total of 306 patients were included in the study. At study termination (40 months; one year after the final series of injections), significantly more patients responded to HA than to placebo (OARSI 2004 criteria; $p=0.004$). The number of responders to HA increased throughout the study (from 71.1% to 80.5%), whereas the number of placebo responders did not change (67.8% to 65.8%). Rescue medications were taken by 71.1% of the HA patients and 71.7% of the placebo patients over the course of the study. A total of 22 patients (11 in each group) had an adverse reaction. Since all were receiving injections, the majority of the adverse reactions were related to the study intervention, such as bleeding, pain at the site or allergic reaction. There were no serious adverse events.

The results of this well done trial show that among patients with knee OA, receipt of four courses of injections over a 36 month period had evidence of lasting benefit. In addition, the benefit appeared to last at least one year after the final series of injection. Questions that remain unanswered include whether different treatment schedules will achieve the same effect, and the extent to which



the may persist after one year. In addition, a group that only received one series of injections was not included and so the incremental benefit (four series of injections vs one series of injections) cannot be determined.

In summary, although several studies have evaluated whether or not repeat injections of HA can be beneficial with respect to clinical outcomes, only one study has randomized patients to receive a series of repeated injections vs placebo. No randomized study has compared a single injection of HA with multiple injections of HA. Among patients who received four courses of HA treatment over a two and a half year period, significantly more responded to treatment than did those who received placebo and the effect appeared to last for at least a year.

Impact of HA on Progression of RA or on Need for Knee Replacement

No studies have evaluated whether or not repeated course of treatment of knee osteoarthritis with HA can delay the need for knee replacement, but several studies have assessed the impact of repeated treatments of HA on intermediate outcomes related to the progression of arthritis. These outcomes include joint space width (JSW), joint space narrowing (JSN) and the Systeme Francaise D'Arthroscopie (SFA) grading system for chondropathy as measured during arthroscopy on a validated scale.

Two studies have assessed the impact of repeated courses of HA on the progression of OA. The first was a small prospective study of 39 patients. Participants received conventional therapy or



three cycles (every four months) of intra-articular injections of Hyalgan. All participants underwent arthroscopy where chondropathy was assessed by the SFA. Chondropathy was also assessed using a VAS. At one year follow-up, there was less deterioration in the overall assessment of chondropathy in the HA group (5.1 vs 16.7: $p=0.016$). There was also an improvement in the SFA chondropathy scoring for the HA group (3.7 vs 7.3: $p=0.05$). This was a small study of one year duration. The results suggest that repeated courses of intra-articular HA may delay the structural progression of OA.

A second study was a double blind placebo controlled trial conducted in France. A total of 301 participants with symptomatic knee OA were randomized to three courses (3 injections each) of intra-articular HA, 2) diacerein 100 mg a day (an anti-inflammatory drug that affects the interleukin pathway) of 3) placebo. Participants and investigators were blinded to the treatments. Participants were followed for a year. The main structural outcomes were joint space width (JSW), joint space narrowing (JSN) between baseline and final visits, and percentage of progressors (defined as JSN >0.5 mm during the study) . They found that JSW deteriorated by an average of 0.09 mm over the course of the study, but there was no difference between groups. The percentage of progressors (those who had JSN of >5 mm over the course of the study) was 17.7% in the HA group, 18,9% in the diacerein group and 20.3% in the placebo group with no difference between groups. Thus the results of this study showed no significant effect of either repeated courses of HA or diacerein on outcomes related to OA progression.



In summary, no studies have assessed the impact of HA on need for knee replacement. Only two studies have assessed the impact of repeated injections of HA on disease progression as measured radiographically or arthroscopically, and these studies have reached different conclusions about efficacy. The larger double blind placebo controlled study did not show an impact of HA on disease progression. Additional studies will be needed to answer this question but at this time, there is no evidence that intra-articular HA slows disease progression when compared with other treatments.

TA Criterion 4 is met for whether repeated injections of HA can improve symptoms of knee arthritis

TA Criterion 4 is not met for whether repeated injections of HA can slow disease progression.

TA criterion #5: The improvement must be attainable outside the investigational settings.

A well done clinical trial showed that patients who received four courses of intra-articular HA over a two and a half year period had an improvement in OA related symptoms. However, this study did



not compare multiple courses of HA with a single course of HA. In addition, the impact of other treatment schedules on clinical outcomes has not been evaluated. One study evaluated long term outcomes of repeated injections of hyaluronic acid for the treatment of knee OA. In this study, among 897 patients referred to a large center for OA management. Among them, 537 met criteria and received a series of HA injections for knee OA. Patients were told that they could return for consideration of repeat injection series depending on their perception of symptom severity. Among the 537 patients, only 21 did not return for a second injection series. Outcomes included change in rest and walking pain visual analog scores. Participants were followed for 6.7 years. Participants experienced a significant reduction in VAS pain score after both the first and second injection series. Patient satisfaction was also improved after each injection series and there were few adverse events.³⁴ The results of this observational study of repeated injections performed in routine clinical practice suggest that repeated injections can lead to improved symptom relief in a real world setting.

For the impact of HA on knee replacement or disease progression, since the improvement has not yet been shown in the investigational setting, it cannot be shown to be attainable outside the investigational setting.

TA Criterion 5 is met for repeated injections of HA improving symptoms of knee arthritis

TA Criterion 5 is not met for whether repeated injections of HA can slow disease progression.



SUMMARY

Intra-articular HA is in widespread use for knee osteoarthritis. A single course of treatment is a well established treatment option for knee OA, but the impact of repeated injections of intra-articular HA on clinical symptoms, progression to knee replacement and progression of disease has been less clear. Although one very well done randomized trial showed that patients who received four courses of intra-articular HA over a two and a half year period had an improvement in clinical symptoms, other important questions such as how this would compare with a single course of HA or the impact of other treatment schedules remains unknown.

DRAFT RECOMMENDATION

It is recommended that treatment of knee OA with repeated injections of intra-articular HA meets CTAF criteria 1-5 for safety, efficacy and improvement in health outcomes for osteoarthritis treatment when compared with usual care.

It is recommended that treatment of knee OA with repeated injections of intra-articular HA does not meet CTAF criteria 4 or 5 for safety, efficacy and improvement in health outcomes for progression to knee replacement or progression of disease.



RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA) Technology Evaluation Center (TEC)

BCBSA TEC published a special report in 2005 titled: Intra-Articular Hyaluronan for Osteoarthritis of the Knee which was an update from its first assessment on this topic in 1998. The special report concludes that hyaluronan "...evidence shows a statistically significant effect (positive) in almost all studies, although the magnitude and clinical significance of the effect may be small." In addition, TEC found no rigorous controlled evidence showing effectiveness of repeated treatments and attributes symptom improvement after repeated treatments attributable to either placebo effects or selection bias.

National Institute for Health and Clinical Excellence (NICE)

In February 2008, NICE issued Guidance Guideline (ID:CG59): Osteoarthritis – the care and management of osteoarthritis in adults. Though the NICE recommendation was that "Intra-articular hyaluronan injections are not recommended for the treatment of osteoarthritis," this recommendation was based on a cost sensitivity analysis that showed that the efficacy/cost effectiveness of intra-articular hyaluronan injections "... would have to be three to five times higher than the estimates from the trials before reaching the standard threshold for cost effectiveness to the NHS."

From an evidence standpoint, p. 271 of the full guideline states that viscosupplementation "...evidence seems to suggest a benefit for reducing pain up to three months after a series of three to five injections, although the effect size is generally small."

Canadian Agency for Drugs and Technologies in Health (CADTH)

In November 2006, CADTH published Issues in Emerging Health Technologies - Intra-Articular Hyaluronic Acid (Viscosupplementation) for Knee Osteoarthritis which states that there is evidence for "modest short-term reductions in pain and improvements in function, and no superiority among



HA products.” In addition, the document notes that despite lack of evidence, treatments are often repeated though repeat treatments are considered safe.

Centers for Medicare and Medicaid Services (CMS)

There is not a National Coverage Determination specific to the use of this technology; reimbursement coverage is left to the discretion of local Medicare carriers.

American Academy of Orthopedic Surgeons (AAOS)

AAOS’s latest guideline from 2008 – Management of Osteoarthritis in the Knee –can be found at the National Guidelines Clearinghouse website at <http://www.guideline.gov/syntheses/synthesis.aspx?id=16434>. AAOS did not recommend for or against viscosupplementation or the use of intra-articular HA.

AAOS has been invited to provide an opinion on this technology and to send a representative to participate at the meeting.

California Orthopedic Association (COA)

COA has been invited to provide an opinion on this technology and to send a representative to participate at the meeting.

American College of Rheumatology (ACR)

ACR has been invited to provide an opinion on this technology and to send a representative to participate at the meeting.

Arthritis Foundation, Northern CA

The Arthritis Foundation has been invited to provide an opinion on this technology and to send a representative to participate at the meeting.



Attachments:

1. Special report: intra-articular hyaluronan for osteoarthritis of the knee. Technol Eval Cent Asses Program Exec Summ. Feb 2005;19(17):1-16.
2. Navarro-Sarabia F, Coronel P, Collantes E, et al. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Annals of the Rheumatic Diseases. 2011;70(11):1957-1962.

DRAFT



Abbreviations:

ACR: The American College of Rheumatology

AIMS: Arthritis Impact Management Scale

AMELIA: OsteoArthritis Modifying Effects of Long-term Intra-articular Adant

HA: Hyaluronic Acid

JSN: Joint Space Narrowing

JSW: Joint Space Width

NSAIDs: Nonsteroidal Anti-Inflammatory Drugs

OA: Osteoarthritis

OARSI: Osteoarthritis Research Society International

SFA: Système Française D'Arthroscopie grading system

TKR: Total Knee Replacement

VAS: Visual Analog Scale

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index



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