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Injectable Hyaluronan for the Treatment of Carpometacarpal Osteoarthritis: An Open Label Pilot Trial

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Abstract

Objective—Carpometacarpal osteoarthritis (CMC OA) is highly prevalent in older adults, and is often unresponsive to medical treatment. Intraarticular Hylan G-F 20 has been shown to improve pain and function in patients with knee OA; however, its effectiveness in CMC OA is less clear.

Methods—32 patients with CMC OA were injected with Hylan G-F 20, once weekly for three consecutive weeks. Patients were assessed 4, 12, 20 and 26 weeks after the first injection. A – last value carried forward analysis was performed.

Results—Average age was 64 years, (range 46–79), 69% were female and 97% Caucasian. 53% had at least one previous corticosteroid injection in the affected CMC joint. At 26 weeks, mean visual analogue scale (VAS) for pain had improved significantly (15.2mm; p-value=0.006). Disabilities of the arm, shoulder and hand questionnaire (DASH) scores also improved significantly (12.6; p-value <0.001). A DASH change of 10–14 is considered clinically meaningful. Neither key strength nor opposition grip strength improved. VAS scores for pain at 26 weeks showed good correlation with patient satisfaction (Spearman $r=0.52$, p-value < 0.01). Adverse events potentially related to the injections included three episodes of post-injection pain and swelling, and one case of crystal proven pseudogout.

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Conclusion—Intra-articular Hylan G-F 20 injections reduced pain and improved function in patients with CMC OA at 26 weeks in this small open label study. Limitations of this study include its small, open label design. Larger randomized controlled trials are needed to confirm these results, and to determine predictors of response to treatment.

This study was approved by the Institutional Review Board at the Hospital for Special Surgery, New York, NY, and registered at www.clinicaltrials.gov # NCT00198029.

Keywords

Osteoarthritis; Carpometacarpal Joint; Hyaluronan

Introduction

Carpometacarpal osteoarthritis (CMC OA) is a common condition, affecting at least 30% of women over age 65¹. Mild disease is usually treated with rest, splinting, non-steroidal medications and intra-articular corticosteroids. However, CMC OA can progress to severe pain and disability, and is the most frequent reason patients with upper extremity osteoarthritis choose to have surgery.² A randomized controlled trial (RCT) of hyaluronan, (HA) in the CMC joint would provide important evidence as to whether HA is an effective therapeutic option for these patients. However, to ensure an RCT would be optimally designed and powered, it is vital to have reliable and accurate preliminary data. This is especially true as most existing HA data is from knee OA patients, and a small, non-weight bearing joint such as the CMC may respond differently. This prospective open-label study investigates whether a non-operative treatment, consisting of repeated injections of hyaluronan, would relieve pain and improve function in patients with CMC OA.

Patients and Methods

Patients with painful CMC OA and radiographic changes of Kellgren and Lawrence (K+L) Grade 2–4 were recruited from rheumatology and hand surgery practices. Thirty-two patients were injected over ten months. Average age was 64 years (range 46–79) and 69% were female (See Table 1). Exclusion criteria included: age less than 45, systemic rheumatic disease, self-reported comorbid hand conditions (such as carpal tunnel syndrome or De Quervain's tenosynovitis), history of gout or pseudogout, bleeding diatheses, previous surgery to the involved thumb, and no evidence of CMC joint space narrowing on radiograph. All patients must have failed some form of conservative therapy, such as non-steroidal anti-inflammatories, acetaminophen or splinting. Patients were asked not to take NSAIDs/COX-2s for pain relief during the study, and to report if they did. At the weeks 2, 3, 4 (1 week after each injection) and at the 26 week visit patients were specifically asked to record what pain medications they had taken for thumb pain since their last visit. There was no minimal duration of pain required for enrollment. All hands were examined by one of the investigators (LM) prior to treatment. Patients were injected with Hylan G-F 20 (Synvisc) [Genzyme Inc., Cambridge, MA, USA] once weekly for three consecutive weeks. Injections were all performed by a hand surgeon (RH), with over twenty years' experience. Injections were performed "blind", using anatomic landmarks to guide needle placement. The joint was entered antero-medially with a 25 gauge needle, and a small amount of lidocaine was injected. If compressing the syringe met with resistance, the injector assumed the needle was not in the joint space and repositioned the needle until the lidocaine could be injected freely. Once the needle was believed to be intra-articular, the syringe was removed using sterile technique and a pre-filled syringe of Hylan G-F 20 attached. The injection protocol and its accuracy is reported elsewhere.³ One milliliter of Hylan G-F 20 was injected, the choice of volume based on previous thumb arthritis studies. One milliliter of Hylan G-F 20 was injected, the choice of volume based on previous thumb arthritis

studies⁴. The first of each series of three injections was checked for accurate medication placement using ultrasound, and injections were determined to be intra-articular in all patients. No patients were injected bilaterally; if a patient had pain in both CMC joints, the more painful side was injected. Patients were called the day after their injections and any adverse events documented.

Patients' baseline information was recorded prior to injection, including visual analogue scale (VAS) for pain, disabilities of the arm, shoulder and hand questionnaire (DASH), and key and opposition grip strength, (measured with a Digital Hydraulic Pinch Gauge, Pro-Med Products, Inc.) Satisfaction with the results of the injections was measured at each post-injection visit on a 5-point Likert scale. Patients returned for hand exams at 4 week, 12 weeks and 26 weeks, and filled out mailed-in questionnaires at 12 and 20 weeks. The primary end-point was change in DASH scores at 26 weeks. Secondary endpoints included VAS for pain, and hand strength at 26 weeks. Exploratory analyses were performed to see if improvement in pain and function differed by gender, severity of radiographic CMC OA or previous steroid injections. This study was approved by the Institutional Review Board at the Hospital for Special Surgery, New York, NY, and registered at www.clinicaltrials.gov # NCT00198029.

All analyses were performed using SAS for Windows 9.0 (Cary, NC). Improvement in pain was calculated as the final VAS minus the initial VAS; DASH scores were calculated similarly. Continuous variables were compared using T-tests and ANOVA, and dichotomous variables were compared using Chi-Square analyses. All analyses were intention to treat, with a last value carried forward for missing data.

Results

The average baseline visual analogue scale (VAS) for pain was 62 (range 38–100), and the average baseline DASH was 29.7 (range 1–68). Fifty-three percent had at least one previous corticosteroid injection. All patients had moderate or severe radiographic OA of the CMC joint: 59% were K+L Grade 4, 25% K+L Grade 3 and 16% K+L Grade 2. No patients had clinical evidence of carpal tunnel syndrome or DeQuervain's tenosynovitis. Patients had tried many previous therapies without adequate relief. (See Table 2)

Both the DASH and VAS for pain were significantly improved over baseline at 26 weeks, using T-tests to compare 26 week values with baseline, and also using ANOVA to adjust for multiple comparisons, (See Table 3, and Figure 1 and Figure 2). At 26 weeks the mean change in DASH was 12.6, (SD 17.2) and the mean change in VAS for pain was 15.2mm, (SD 29.5). Neither key nor opposition grip showed any significant improvement at any time point. VAS scores for pain at 26 weeks were moderately correlated with patient satisfaction (Spearman $r=0.52$, $p\text{-value} < 0.01$), but were not correlated with hand strength, as measured by opposition and key grip, (See Table 4). Although DASH scores at 26 weeks were significantly correlated with hand strength at 26 weeks, DASH scores showed no correlation with patient satisfaction. Improvement in pain and function at 26 weeks did not differ by severity of radiographic arthritis, gender, or among those with or without a previous steroid injection. (See Table 5). There were no obvious patterns in response to therapy when VAS results for individual patients were stratified by Kellgren and Lawrence grade, (Figure 3a-c) The data suggest DASH results may improve most for those with Kellgren and Lawrence Grade 2 disease, (Figure 4a-c), but small numbers preclude any definitive conclusions.

Four patients withdrew from the study. Two patients elected to have surgery on their CMC joint. One patient had an acute attack of crystal proven pseudogout in the ipsilateral wrist 33 days after the last CMC HA injection. The patient had no previous history of inflammatory arthritis and had been well in the interim. A 74 year old patient withdrew after a gastrointestinal

bleed that occurred 69 days after the last HA injection. The only other serious adverse event occurred when a patient slipped on the way to the hospital for the third HA injection and suffered a broken scapula; this patient completed the study. Out of the 96 total injections, 3 resulted in post-injection pain and swelling requiring treatment. Two of these were after the second injection, and one was after the third injection. None influenced DASH or VAS assessment as all hand testing was done prior to injections. All symptoms rapidly resolved with ice, NSAIDs or COX-2 inhibitor. Eighteen of the thirty-two patients reported using NSAIDs, Cox-2 inhibitors, acetaminophen or acetaminophen with codeine at some time during the study. All 28 patients completing the 26 week study were examined at study exit and were not found to have any signs of depigmentation, fat atrophy or radial neuritis in the area of the injected thumb.

Discussion

HA was effective in improving pain and function at 26 weeks in this small open label study. Mean improvement of the VAS for pain was 15.2mm (SD 29.5) at 26 weeks. This is a clinically important improvement, as studies of OA in other joints have suggested the minimal clinically important difference in VAS for pain is 9–12 mm⁵. In addition, VAS pain scores were moderately and inversely correlated with patient satisfaction (i.e. less pain was correlated with more satisfaction, Spearman $r=0.52$, p -value < 0.01). Function, as measured by the DASH, also significantly improved at 26 weeks. Unlike pain, function was not correlated with satisfaction, suggesting pain relief is what is most important to these patients. Larger studies need to confirm this important point.

There is widespread belief among physicians that intra-articular steroids are effective for patients with CMC OA not responding to NSAIDs or splinting. However, this belief is not supported by the literature. An open label trial found no benefit of steroids on CMC pain at 26 weeks⁶. A randomized controlled trial evaluating steroids vs. placebo injection showed no benefit of steroids in moderate to severe CMC OA at 24 weeks⁷.

There are some studies of HA as treatment for CMC OA. A small open label trial found HA to reduce pain and improve grip strength⁸. Another randomized controlled trial of 56 patients found neither HA nor steroids improved CMC OA pain at 6 months⁹. Another randomized controlled trial of 56 patients stated “non-inferiority” of HA compared with steroids for pain relief at 26 weeks¹⁰. A more recent study comparing HA with corticosteroids and placebo injections in 60 patients with CMC OA also found no significant difference in pain or function between groups¹¹. However, it is unlikely that any of these randomized trials were adequately powered to show a difference between treatments.

Surgery is an effective treatment for CMC OA¹². However, as a temporizing treatment prior to surgery, or in patients who do not wish to have an operation, an effective local treatment for CMC OA would be very appealing. One study of patients undergoing surgery for CMC OA showed that six to twelve months post-operatively patients’ DASH scores improved to a mean of 22¹³. In this study of less severely affected patients, mean DASH scores six months after HA injection were 17. This suggests HA confers comparable functional benefit to patients with CMC OA, at least in the short term.

There were few adverse events in this study. There was one case of histologically-proven pseudogout which occurred in the ipsilateral wrist 33 days after the last HA injection. Although pseudogout is a known potential adverse effect of HA injection, it usually occurs 24–48 hours following treatment¹⁴. The authors know of no reported cases of “sympathetic” pseudogout occurring in an adjacent joint weeks after an HA injection. There are also known associations

between HA injections and GI bleeds. Limitations of this study include a relatively small sample size and its open label design.

Whether HA provides any therapeutic benefit in patients with knee OA, -the indication for which it is approved-, remains contentious. Well designed studies report positive findings based on analyses of patients subsets or “completer’s analyses”, rather than intention to treat analyses of all randomized patients^{16,17}. These choices have lead to skepticism among many physicians, and many groups do not recommend the use of HA^{18,19}. However, the pain associated with OA is often cyclic, making it challenging to demonstrate superiority of an intervention over a placebo, and many negative studies– including studies in joints besides the knee-are clearly underpowered²⁰. Recently, the Cochrane Collaboration conducted an inclusive systematic review of all available data on HA in knee OA, and concluded that HA does have a beneficial effect on pain and function in knee OA²¹.

There is a great clinical need for a safe effective medical therapy for CMC OA. However, given the lack of truly definitive trials of HA in knee osteoarthritis, it would not be prudent to embark on a large randomized controlled trial of HA in the CMC joint without some preliminary data to both demonstrate efficacy, and allow estimation of a realistic sample size. This study adds to the existing group of small pilot trials that suggest further investigation of HA in CMC OA is warranted.

There is a need for alternate medical treatments for this condition. CMC OA affects at least 1 in 3 women over 65 and a quarter of men over 75¹. While surgery is effective in relieving pain, many older patients are not surgical candidates, or are unwilling to consider surgery¹². In fact, women-who are disproportionately affected by CMC OA-are much more likely than men to refuse elective surgical procedures¹⁵. This leaves many patients with no proven therapeutic options. These data provide further evidence that HA injections may be an effective low-risk treatment for CMC OA that is unresponsive to standard medical therapy. These findings should be evaluated in an adequately powered randomized controlled trial.

Conclusion

This open-label study suggests that HA may be a safe and effective injectable treatment for CMC OA in patients who have failed other medical therapies, including intra-articular steroids.

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References

1. Haara MM, Heliovaara M, Kroger H, et al. Osteoarthritis in the carpometacarpal joint of the thumb. Prevalence and associations with disability and mortality. *J Bone Joint Surg Am* 2004;86-A:1452–7. [PubMed: 15252092]
2. Pellegrini VD Jr. The ABJS 2005 Nicolas Andry Award: osteoarthritis and injury at the base of the human thumb: survival of the fittest? *Clin Orthop Relat Res* 2005;438:266–76. [PubMed: 16131901]
3. Mandl LA, Hotchkiss RN, Adler RS, et al. Can the carpometacarpal joint be injected accurately in the office setting? Implications for therapy. *J Rheumatol* 2006;33:1137–9. [PubMed: 16755661]

4. Reeves KD, Hassanein K. Randomized, prospective, placebo-controlled double-blind study of dextrose prolotherapy for osteoarthritic thumb and finger (DIP, PIP, and trapeziometacarpal) joints: evidence of clinical efficacy. *J Altern Complement Med* 2000;6:311–20. [PubMed: 10976977]
5. Ehrich EW, Davies GM, Watson DJ, et al. Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities osteoarthritis index questionnaire and global assessments in patients with osteoarthritis. *J Rheumatol* 2000;27:2635–41. [PubMed: 11093446]
6. Joshi R. Intraarticular corticosteroid injection for first carpometacarpal osteoarthritis. *J Rheumatol* 2005;32:1305–6. [PubMed: 15996069]
7. Meenagh GK, Patton J, Kynes C, et al. A randomised controlled trial of intra-articular corticosteroid injection of the carpometacarpal joint of the thumb in osteoarthritis. *Ann Rheum Dis* 2004;63:1260–3. [PubMed: 15361383]
8. Coaccioli S, Pinoca F, Puxeddu A. Short term efficacy of intra-articular injection of hyaluronic acid in osteoarthritis of the first carpometacarpal joint in a preliminary open pilot study. *Clin Ter* 2006;157:321–5. [PubMed: 17051968]
9. Stahl S, Karsh-Safiri I, Ratzon N, et al. Comparison of Intra-articular Injection of Depot Corticosteroids and Hyaluronic Acid for Treatment of Degenerative Trapeziometacarpal Joints. *Journal of Clinical Rheumatology* 2005;11:299–302. [PubMed: 16371798]
10. Fuchs S, Monikes R, Wohlmeiner A, et al. Intra-articular hyaluronic acid compared with corticoid injections for the treatment of rhizarthrosis. *Osteoarthritis Cartilage* 2006;14:82–8. [PubMed: 16242353]
11. Heyworth BE, Lee JH, Kim PD, et al. Hylan versus corticosteroid versus placebo for treatment of basal joint arthritis: a prospective, randomized, double-blinded clinical trial. *J Hand Surg [Am]* 2008;33:40–8.
12. Hartigan BJ, Stern PJ, Kiefhaber TR. Thumb carpometacarpal osteoarthritis: arthrodesis compared with ligament reconstruction and tendon interposition. *J Bone Joint Surg Am* 2001;83-A:1470–8. [PubMed: 11679595]
13. De Smet L. Responsiveness of the DASH score in surgically treated basal joint arthritis of the thumb: preliminary results. *Clin Rheumatol* 2004;23:223–4. [PubMed: 15168149]
14. Disla E, Infante R, Fahmy A, et al. Recurrent acute calcium pyrophosphate dihydrate arthritis following intraarticular hyaluronate injection. *Arthritis Rheum* 1999;42:1302–3. [PubMed: 10366130]
15. Karlson EW, Daltroy LH, Liang MH, et al. Gender differences in patient preferences may underlie differential utilization of elective surgery. *Am J Med* 1997;102:524–30. [PubMed: 9217666]
16. Brandt KD, Block JA, Michalski JP, et al. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. *Clin Orthop Relat Res* 2001;130–43. [PubMed: 11302304]
17. Lohmander LS, Dalen N, Englund G, et al. Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: a randomised, double blind, placebo controlled multicentre trial. Hyaluronan Multicentre Trial Group *Ann Rheum Dis* 1996;55:424–31.
18. Felson DT, Anderson JJ. Hyaluronate sodium injections for osteoarthritis: hope, hype, and hard truths. *Arch Intern Med* 2002;162:245–7. [PubMed: 11822915]
19. Conaghan PG, Dickson J, Grant RL. Care and management of osteoarthritis in adults: summary of NICE guidance. *BMJ* 2008;336:502–3. [PubMed: 18310005]
20. Richette P, Ravaud P, Conrozier T, et al. Effect of hyaluronic acid in symptomatic hip osteoarthritis: a multicenter, randomized, placebo-controlled trial. *Arthritis Rheum* 2009;60:824–30. [PubMed: 19248105]
21. Bellamy N, Campbell J, Robinson V, et al. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2006;CD005321. [PubMed: 16625635]

Figure 1.
Visual Analogue Scale for Pain

Figure 2.
Disabilities of the Arm, Shoulder, and Hand Scores

Figure 3a.

Figure 3b.

Figure 3c. **Figure 3.**

Figure 3a. Visual Analogue Scale for Pain, stratified by Kellgren and Lawrence Radiographic Grade 2

Figure 3b. Visual Analogue Scale for Pain, stratified by Kellgren and Lawrence Radiographic Grade 3

Figure 3c. Visual Analogue Scale for Pain, stratified by Kellgren and Lawrence Radiographic Grade 4

Figure 4a.

Figure 4b.

Figure 4c.

Figure 4.

Figure 4a. Disabilities of the Arm, Shoulder, and Hand Scores, stratified by Kellgren and Lawrence Radiographic Grade 2

Figure 4b. Disabilities of the Arm, Shoulder, and Hand Scores, stratified by Kellgren and Lawrence Radiographic Grade 3

Figure 4c. Disabilities of the Arm, Shoulder, and Hand Scores, stratified by Kellgren and Lawrence Radiographic Grade 4

Table 1

Study Population

Number of Participants	32
Mean age	64 (range 46–79)
Ethnicity	99% Caucasian
Female	22 (69%)
Kellgren and Lawrence Grade 2	5 (16%)
Kellgren and Lawrence Grade 3	8 (25%)
Kellgren and Lawrence Grade 4	19 (59%)

Table 2

Percentage of Patients Who Had Tried Previous Therapies for Carpometacarpal Osteoarthritis (CMC OA) Pain_____

Non-steroidal anti-inflammatory drugs (NSAIDs)/Cox-2s	72%
Splinting	66%
Glucosamine Chondroitin Sulfate	50%
Acetaminophen	50%
Topical Therapies	24%
Acupuncture	20%
Physical Therapy	16%
Herbal Therapies	8%
Narcotics	6%

Table 3
Changes in Thumb Strength, Pain and Function (DASH) at 26 Weeks

	Baseline Mean (SD)	26 weeks Mean (SD)	Mean Change (SD)	P-value (T-test)
Maximum Key Grip (lbs)	12.1(5.6)	13.1 (5.9)	1.0 (4.1)	0.19
Maximum Opposition Grip (lbs)	8.9 (5.3)	10.1(5.7)	1.2 (3.6)	0.07
VAS for pain (mm) (0=best 100=worst)	61.6(17.9)	46.3 (28.0)	15.2 (29.5)	0.006 *
DASH (0=best 100=worst)	29.7(15.6)	17.1 (14.9)	12.6 (17.2)	<0.001 *

Bold= statistically significant

DASH = Disabilities of the arm, shoulder and hand

VAS = Visual Analog Scale

* ANOVA p-value <0.01

Table 4

Spearman Correlations Between Overall Satisfaction and Pain and Function at 26 Weeks

	DASH at 26 Weeks	PAIN VAS at 26 Weeks
Overall Satisfaction: 26 Weeks	0.27	0.52 **
Opposition Grip:26 Weeks	0.52 *	0.29
Key Grip:26 Weeks	0.47 *	0.30

Bold= statistically significant

DASH = Disabilities of the arm, shoulder, and arm

VAS = Visual Analog Scale

*
p-value <0.05

**
p-value <0.01

Table 5

Previous Steroid Injection, Severity of Radiographic Arthritis, and Gender Have No Effect on Pain or Function at 26 Weeks

	Change in DASH	Change in VAS for Pain
Previous Corticosteroid Injection		
Yes	-12.8±20.9	-14.1±38.0
No	-12.3±12.9	-16.5±16.6
<i>p-value</i>	0.93 (NS)	0.82 (NS)
Radiographic Scores		
Kellgren & Lawrence Grade 4	-15.4±16.0	-19.0±28.5
Kellgren & Lawrence Grade 2&3	-10.6±18.4	-12.6±30.7
<i>p-value</i>	0.46 (NS)	0.56 (NS)
Gender		
Male	-10.6±12.9	-11.0±18.5
Female	-13.5±19.3	-17.2±33.6
<i>p-value</i>	0.67 (NS)	0.59 (NS)

NS= not significant

DASH = Disabilities of the arm, shoulder, and hand

VAS = Visual Analog Scale