

The evaluation of efficacy and tolerability of Hylan G-F 20 in bilateral thumb base osteoarthritis: 6 months follow-up

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Abstract The aims of this randomized controlled trial were to evaluate the efficacy of intra-articular Hylan G-F 20 on the pain, pinch strength, and functional status in patients with thumb base osteoarthritis (OA). Sixty-six hands of 33 female patients (mean age, 62.6 ± 6.4 years) with bilateral clinical and radiological thumb base OA were included into this study. Hands of the same patient were divided to Hylan G-F 20 and saline-injection groups. VAS pain 100 mm, pinch strength (key, tripod and pulp to pulp pinch) and functionality (Dreiser functional index) were assessed at baseline, at sixth and 24th weeks. Statistically significant improvements were detected in function ($p=0.001$), VAS pain ($p=0.002$), and pinch strength ($p=0.004$) at the 24th week in the Hylan G-F 20 group. However, only VAS pain scores decreased temporarily in control hands at the 6th week ($p=0.02$). Although short-term placebo analgesic effect could not be ignored, intra-articular hylan was effective on pain, pinch strength, and function at the 24th week.

Keywords First carpometacarpal joint · Hand · Hyaluronan · Intra-articular · Osteoarthritis · Thumb base

Introduction

Hand osteoarthritis (OA) is a common condition in people aged 55 years and over, especially in postmenopausal females. Optimal management of hand OA requires a combination of non-pharmacological and pharmacological treatment modalities individualized to the patient's requirements [1–3].

Hyaluronan, formerly termed as hyaluronic acid, is present throughout the animal kingdom from bacteria to man, permeating all connective tissues, joints, body cavities, synovial spaces, and tissue surfaces [4]. In synovial joints, hyaluronan is primarily produced by the type A synoviocytes and is entirely responsible for the elastoviscosity of synovial fluid. During movement, hyaluronan flows into the lymphatics of the joint capsule. It subsequently moves into the general systemic circulation and is ultimately taken up into the liver, where the molecule degrades into water and carbon dioxide [5]. An essential role of hyaluronan is to protect the collagen fibrils and cells of articular surfaces, synovial tissue, capsule, and ligaments from mechanical damage [6]. The hyaluronan mechanical network forms a continuum throughout the matrices of these tissues, acting as both a shock absorber and structural stabilizer through its elastoviscous properties.

Viscosupplementation, exogenous hyaluronan injection into synovial joints, can temporarily restore the normal rheologic environment to connective tissues and cells so that normal repair, regeneration and function might occur [7]. In order to increase the elastoviscosity of hyaluronan and prolong its tissue residence time, a family of cross-linked derivatives (Hylan A and Hylan B) was developed during the 1980s. Hylan G-F 20 has a significantly longer intra-articular residence time than hyaluronan, and its rheologic properties were specifically formulated to be

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similar to those of synovial fluid from healthy young adult [8]. It consists of 0.8% hylan polymer, hydrated in a phosphate-buffered saline solution.

Intra-articular hyaluronan may be useful in treating trapeziometacarpal (first carpometacarpal or 1st CMC) osteoarthritis with level IIb evidence [1]. However, there are limited numbers of study to investigate the efficacy of intra-articular hyaluronan in thumb base OA with different point of views [9–11].

We are unaware of any other published studies that have prospectively followed patients who were administered hyaluronan and saline to the different 1st CMC joints of the same patients. We thought that it may be important for the assessment of equal-perception of pain for treatment response at follow-up. The aim of this randomized controlled study was to evaluate the efficacy of Hylan on pain, function, and pinch strength for 6 months follow-up period in patients with bilateral thumb base OA.

Materials and methods

Subjects

Sixty-six hands of 33 female patients (mean age, 62.6 ± 6.4 years) with bilateral hand OA according to the ACR (American College of Rheumatology) hand OA classification criteria were included into this study on the Rheumatology and Hand Rehabilitation settings [12]. The dominant hand was right in all patients. Patients were selected for this study with visual analogue scale (VAS) score >40 mm and with thumb base OA having Eaton radiographic criteria between 1 and 4 on the anteroposterior hand radiographs. Hands of the same patient were divided to Hylan G-F 20 injection and saline-injection (control) groups, randomly. Selection of right and left hand were equal in both groups. The randomization method of the hands was according to the computer-generated identification numbers for their admission to the rheumatology clinic.

All patients had failed to prior treatment with non-steroidal anti-inflammatory medicines, physical therapy, corticosteroid injection, and splinting. Patients were free of any joint injection in the last 6 months and free of any pain medication in the last 2 weeks. Patients with major trauma history to the hand, wrist, and elbow were also excluded. Other exclusion criteria included pregnancy, prior surgery on the thumb or wrist, history of infection in the affected joint, history of inflammatory arthritis, coagulation disorders and skin disease or eruption at the joint injection site. Patients with a known allergy to eggs, feathers, avian proteins, of hyaluronic acid derivative products were also excluded, as hylan G-F is derived from rooster combs.

Radiographic criteria

All patients had pretreatment anteroposterior hand radiographs demonstrating osteoarthritis of the 1st CMC joint. Degenerative arthritis of the basal thumb joint is usually classified by the Eaton criteria [13]. Briefly, the Eaton criteria are as follows:

1. Stage 1, joint space widening; subluxation equal or less than 1/3
2. Stage 2, capsular calcification less than 2 mm, subluxation greater than 1/3
3. Stage 3, capsular calcification greater than 2 mm, joint space narrowing
4. Stage 4, cysts, sclerosis, lipping, osteophytes. Scaphotrapezial and scaphotrapezoidal changes are present.

Using the Eaton classification, there were 19 patients with stage 1 disease, eight patients had stage 2 disease, one patient had stage 3 disease, and five patients had stage 4 disease, symmetrically bilateral.

Local injection to the 1st CMC joint

All patients prepared by the standard technique for the local injection after the signed approval of the consent to be a participant. The patient was placed in a supine position with the arm fully adducted at the patient's side with the hand in neutral position with the palmar aspect resting on a folded towel [14, 15]. After sterile preparation of skin overlying the CMC joint, the space between the carpal and metacarpal was identified. The joint could be easily identified by gliding the joint back and forth. Using strict aseptic technique, a needle was inserted in the dorsal aspect of the radial side of the joint by holding the thumb in slight flexion and traction through the skin, subcutaneous tissues, and joint capsule into the joint. If bone was encountered, the needle was withdrawn into the subcutaneous tissues, and redirected medially. To avoid the radial artery, the needle was placed toward the dorsal side of extensor pollicis brevis tendon. After entering the joint space, a total of 1 mL of Hylan G-F20 (Synvisc™; Wyeth Pharmaceuticals) was gently injected to one trapezio metacarpal joint and saline injection was made to contra-lateral joint. If significant resistance was encountered, the needle was probably in a tendon and was advanced slightly into the joint space. The needle was then removed and a sterile pressure dressing and ice pack were placed at the injection site.

Outcome measures and follow-up data collection

Prior the initial injection, descriptive statistics and baseline outcome measures were collected for all subjects. Hands of the same patient were divided to interventional (1 mL intra-

articular hylan) and control (1 mL intra-articular saline) groups. Patients thought that both hands were treated by two different drugs. All patients were scheduled for follow-up visits at two time points after the initial injection: time=6 weeks, and time=6 months, the last the primary end point of the study. In these evaluations, the VAS and Dreiser's surveys were repeated and three mode of pinch-grip strength testing were also repeated in identical fashion to the initial assessment.

Pain

Patients were asked to score a VAS for pain. VAS scoring was measured by asking patients to make a vertical mark on a 10-cm horizontal line with 0 representing no pain and 10 representing the worst pain of their life; scores were quantified by the measuring the distance from the 0 point. Thumb base pain with resting, movement and pressure were evaluated using 100 mm VAS. The mean of three recorded pain measurement were calculated.

Dreiser's functional index for the osteoarthritis of the hand

Patients were asked to complete this specific index for disability level of their osteoarthritic hands [16]. Dreiser index for the hand are devoted entirely to the assessment of function with four difficulty levels (0=possible without difficulty, 1=possible with slight difficulty, 2=possible with important difficulty, 3=impossible). This index includes ten "can you" questions about activities of daily living ((1) turn a key in a lock, (2) cut meat with a knife, (3) cut cloth or paper with a scissors, (4) lift a full bottle with hand, (5) clench your fist, (6) tie a knot, (7) sewing, (8) fasten buttons, (9) write for a long period of time, (10) accept a handshake), scoring between 0 to 30.

Pinch strength

Pinch Gauge 0–60 lb, NC 70161 (B&L Engineering, Santa Fe Springs, CA 90670 model no.PG-60 S/N B6F968) was used for pinch strength measurements in our hand rehabilitation office. The pinch strengths were measured by the pulp to pulp pinch, tripod pinch, and pulp to side pinch tests. The pulp to pulp pinch test was performed when the pulp of the thumb and the index finger were opposed with the distal interphalangeal joint is extended. In the tripod pinch test, the pulp of the thumb was brought together with the pulp of the index and middle fingers. In the pulp to side or key or lateral pinch test, the pulp of the thumb was opposed with the radial side of the index finger. The highest values of each three measurements at the same morning session were recorded at the beginning and the follow-up of this study.

This study protocol was approved by the Institutional Review Board and Local Ethical Committee of the Ankara Education and Research Hospital. Informed consent was obtained from all of these patients. Throughout the course of the study, complications or adverse events, such as fever, severe pain in response to the injections, increase in pain, increase in joint stiffness, or inflammatory changes in the skin or soft tissue surrounding the joint were assessed and recorded. All injections were provided free of charge while neither participants nor the study was subsidized by any manufacturer.

Statistical analysis

For measures recorded separately for each hand of same patient (pulp to pulp pinch, tripod pinch and key pinch strength, VAS pain scores, Dreiser's functional index), the value recorded for the hands at each time was entered as a time-dependent covariate. The main effect of treatment and the interaction of treatment by time were analyzed. Statistical significance indicated by a *p* value of less than 0.05, estimates of the differences between treatment groups within a time are reported with means, standard deviation, minimum–maximum, 95% confidence intervals, and *p* values. SPSS 11.0 NPar Wilcoxon signed ranks test, MANOVA (multi-variate analysis of variance) and NPar Spearman correlation test were used for all of these statistical analysis.

Results

There were a total of 33 female patients included into the study analysis; the average age was 62.6 years (range, 51–73 years). Four hands of the two patients with grade IV osteoarthritis were dropped out follow-up of this study because of their appointments for elective knee surgery. There were no significant differences in baseline characteristics between hands of the same patients for pulp to pulp pinch, tripod pinch, and key pinch strength tests, Dreiser's score, and VAS score (Table 1). Selection of right and left hand were equal in both groups. There were no adverse events reported.

Pulp to pulp, tripod, and key pinch strength

In the hylan group, there was a significant increase in pulp to pulp pinch ($p=0.000$), key pinch ($p=0.002$), and tripod pinch strength values ($p=0.01$) between baseline and 6th weeks. A similar trend were observed only in key pinch strength ($p=0.002$) between the sixth week and the 24th week. Both pulp to pulp pinch ($p=0.004$) and key pinch strength ($p=0.04$) values were increased at 24th weeks compared to baseline.

Table 1 Baseline characteristics of the bilateral osteoarthritic hands of the same patients ($p<0.05$)

	Hylan group Mean±SD	($n=29$) (min–max)	Control group Mean±SD	($n=29$) (min–max)
Age (years)	62.6±6.4	(51–73)	62.6±6.4	(51–73)
Symptom duration (years)	6±4.7	(3–16)	6±4.7	(3–16)
VAS pain (cm)	4.7±3.3	(0–10)	4.5±3.5	(0–10)
Dreiser's score (0–30)	10.1±8.4	(0–27)	10.8±7.3	(0–28)
Pulp to pulp pinch (poundsforce)	9.8±3.6	(5–17)	10±4.2	(6–19)
Tripod pinch (poundsforce)	10±4.2	(4–18)	9.7±4	(4–17)
Key pinch (poundsforce)	10.8±3.9	(5–19)	10.2±3.5	(4–18)

Results of pinch meter assessment were shown in Fig. 1. No statistically significant improvement of pinch strength has been detected in control group ($p=0.4$).

Dreiser scores and VAS pain scores

There were significant differences in VAS pain scores between baseline and 6th weeks in hylan group ($p=0.000$) and in control group ($p=0.02$). However, the pain relief continued only in the hylan group ($p=0.01$), but not in the control group ($p=0.2$) at the 24th week. The hylan group has significant pain reduction between baseline and the 24th week ($p=0.002$). VAS pain changes were shown in Fig. 2. Complete and partial pain resolution has been reported by 48.3% ($n=14$) and 31% ($n=9$) of the hylan group, respectively. Six patients (20.7%) reported no change on pain in this group.

Improvement in Dreiser scores of function was slower than those of VAS pain. There were statistically significant improvement between the 6th and 24th week ($p=0.02$) as

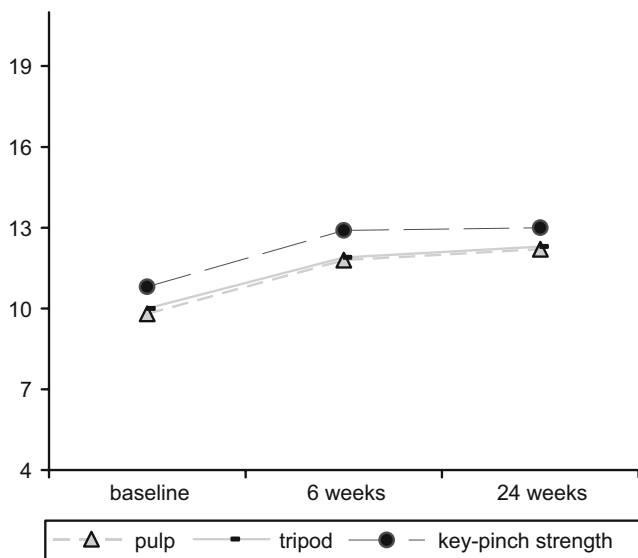


Fig. 1 Pinch strength values (poundsforce). Mean pinch strength is plotted over time. Hylan was effective on both key and pulp to pulp pinch strength ($*p<0.05$ compared with baseline) but not effective on tripod strength statistically at the 24th week

baseline and 26th week ($p=0.001$) in hylan group. Functional improvement has been detected in 89.7% of hands ($n=26$) in this group. Functional changes seen in groups were shown in Fig. 3. There were no statistically significant functional changes in any period of control group ($p=0.5$).

Changing scores of function were moderately correlated with changing scores of pain ($\rho=0.5$, $p=0.02$) controlling for X-ray grade. Pain relief and functional improvement were not correlated with X-ray grade ($p=0.5$).

Discussion

Although injectable corticosteroid remains one of the staples of conservative treatment of thumb base OA, because of concerns over deleterious effects on cartilage, it is generally not recommended that a joint be injected more than four times per year [17]. It also has the risk of infection, crystalline synovitis, and paradoxical increase in symptoms due to overuse. There were a couple of studies reported no clinical benefit was gained from intra-articular steroid injection to the osteoarthritic CMC joint compared with placebo injection [9, 18]. Therefore, we suggested that

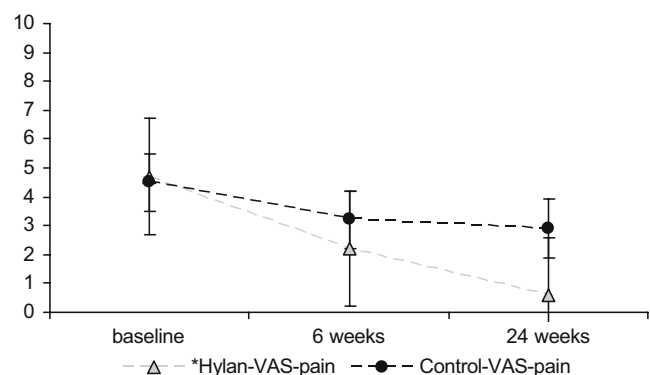


Fig. 2 Scores of VAS pain. Mean scores were decreased immediately over time with pain relief in both group at 6th weeks. Hylan was effective on the joint pain at the 24th week ($*p<0.05$ compared with baseline)

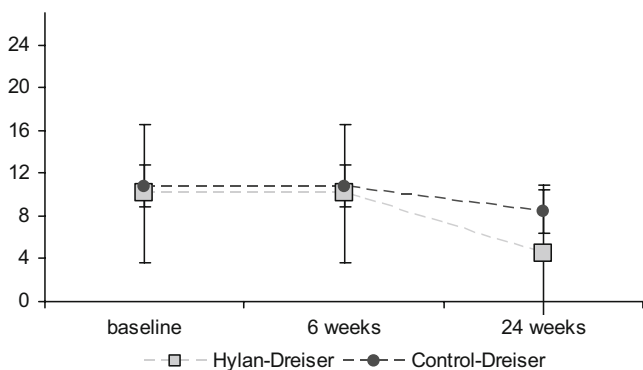


Fig. 3 Scores of Dreiser's functional index. Mean scores are decreased slowly over time with functional improvement only in the Hylan group. Hylan was also effective on hand functions ($*p < 0.05$ compared with baseline)

hyaluronan may be alternative to corticosteroids in thumb base OA with results of this study.

Hyaluronan is a symptomatic slow-acting drug for osteoarthritis (SYSADOA). And evidence for SYSADOAs (for example, glucosamine, chondroitin sulfate, avocado soybean unsaponifiables, diacerein) predominantly derives from randomized controlled trials (RCTs) in the knee, and data for OA at other sites are sparse.

SYSADOAs may give symptomatic benefit with low toxicity, but effects sizes are small, suitable patients are not defined and clinically relevant structure modification and pharmacoeconomic benefits have not been established [1–3]. As a matter of fact, ESCISIT (EULAR standing committee for international clinical studies including therapeutics) recommended intra-articular hyaluronan for the thumb base OA with level Iib evidence [1]. However, intra-articular hyaluronan is a Food-and-Drug-Administration-approved treatment only for the knee osteoarthritis, with conflicting results [19].

There were mixed results in literature about the efficacy of different molecular weights of hyaluronic acid derivatives [7–9, 17, 19, 20]. The implications of molecular weight in visco-supplementation therapy has been discussed in both in vitro and in vivo models, have clearly supported the contention that higher molecular weight derivatives may lead to enhanced rheologic properties, more effective inflammatory inhibition, and potentially better symptomatic improvement than their lower molecular weight counterparts [8, 9, 19].

Hyaluronan's primary structure is quite simple, consisting of repeated units of *N*-acetylglucosamine and sodium glucuronate and has a molecular weight of about 4 to 6 million Da in normal human tissues. For visco-supplementation, there are currently three intra-articular forms of hyaluronic acid: sodium hyaluronate (0.5–1 million Da), hylan G-F 20 (6 million Da), and bioengineering product of hyaluronan (900 Da), molecular weights from 0.5 to over 6 million Da

[17]. Sodium hyaluronate and bioengineering product of hyaluronan have a lower molecular weight derivative than hylan [8, 9]. Interestingly, it has been reported that dual molecular weight hyaluronan (DMW; 580–780 kDa+1.2 to 2.0 million Da) had better results than low molecular weight (LMW; 500–730 kDa); high molecular weight (HMW; 6 million Da); or saline placebo in patients with knee OA [20].

Because of a limited half-life in the joint, intra-articular hyaluronan exerts a short-term lubricant and biomechanical effect. Long-term effect of hyaluronan may be due to anti-inflammatory effect, reduced neuroreceptor activity, altered cartilage metabolism, and/or altered synoviocyte behavior [17]. Hylan G-F 20 has a significantly longer intra-articular residence time than hyaluronan, and its rheologic properties were specifically formulated to be similar to those of synovial fluid from healthy young adult [8]. Our results suggested that intra-articular hylan G-F 20 is effective on both pain and function in patients with bilateral thumb base osteoarthritis at 6 months follow-up. We are not aware of other prospective, randomized controlled trial to date that has investigated the efficacy of visco-supplementation therapy for bilateral thumb base OA comparing both hands of the same patients. The similar changes in pain perception and function scores at follow-up may be important.

Radiologically eligible patients for hylan therapy are grade I or II OA on the Kellgren–Lawrence scale, with <50% joint space narrowing. We have agreed with these criteria except in four patients. Most of our patients had stage I or II on the Eaton criteria (87.1%). Because of that, the pain relief and functional improvement were not correlated with X-ray grade. We had not enough patients with 1st CMC OA for severe radiological involvement.

There were some major limitations in our study. First of all, we could not confirm precise injection into the small joint cavity of 1st CMC. However, Pollard et al. suggested that 1st CMC injections can be performed accurately similar to larger joints without the need for radiologic guidance [21]. Rates of intra-articular accuracy and soft-tissue extra-vascularisation for successful intra-articular injections were 100% and 25% for the fluoroscopy-guided group and 81.8% and 25% for the "blind" group in this study. Currently, there is a wide agreement in the medical community to perform local injections using the ultrasound (US) guidance. It would be better that we could use US guidance for this injection. Mandl et al. reported that 91% accuracy rate with US guidance for the 1st CMC injection in the office setting [22].

The second limitation was the possibility of different involvement could be present in the two 1st CMC joints in the same patient. Therefore, results of Hylan G-F20 may depend on this aspect and not on the different response to treatment. On the other side, the symptom duration, pain, function and pinch strength were similar in both groups. It

could be more important than the possibility of different joint involvement stage.

In fact, the major problems in nearly all of published hyaluronan studies were accuracy of injection into the joint, a scarce number of studies, small sample size, short-term results and confounding placebo factor. We used saline injection to the contra-lateral hand to eliminate the placebo effect of hylan.

Despite its disabling and painful properties of thumb base OA, there were limited numbers of randomized controlled trials to investigate the hyaluronic acid derivatives on this type of osteoarthritis [9–11]. Recently, Heyworth et al. reported that two-time intra-articular hylan injections provided pain relief, and grip strength improvement at 26 weeks compared with corticosteroid and placebo in sixty patients with basal joint OA [9]. They found no significant differences in disability of arm, shoulder, and hand (DASH) scores. Actually, DASH questionnaire were designed for painful upper extremity disorders and it is not specific for thumb base osteoarthritis. Therefore, functional assessment was not correctly evaluated in this study.

Similarly, Stahl et al. found that single-course intra-articular sodium hyaluronate was more effective than methylprednisolone acetate in the improvement of Purdue pegboard test (PPT), grip and pinch strength in 52 patients with grade 2 trapeziometacarpal osteoarthritis at 6 months follow-up [10]. Indeed, PPT is a frequently used dexterity assessment tool and is not a functional index.

Fuchs et al. compared three injections of sodium hyaluronate and triamcinolone acetonide in 56 patients with rhizarthrosis [11]. They found that sodium hyaluronate had better results in lateral pinch power than triamcinolone acetonide at 26 weeks. However, three times intra-articular injections would lead to a greater ratio of injection material to joints space when compared with the FDA-approved protocol used in the knee. Functional assessment was also deficient in this study.

We had to decide single hylan injection for 1st CMC because of its low synovial space volume and cost-issues. Roux et al. reported that no significant differences were found between one, two, or three injections of intra-articular hyaluronic acid in 42 osteoarthritic hands at 3 months follow-up [23]. We also suggested that single-injection of hyaluronan is enough for the osteoarthritic 1st CMC joint on both the pain relief and functional improvement.

Our patients also have failed to conservative treatments including education concerning joint protection together with an exercise regimen, local heat applications before exercise, splints for thumb base OA, topical NSAIDs, oral analgesics including paracetamol and NSAIDs, and intra-articular injection of long-acting corticosteroid. Before referral to surgery for marked pain and/or disability, and/or inefficacy of intra-articular corticosteroids, intra-articular

hyaluronan should be considered in patients with thumb base osteoarthritis. Future trials containing large number of patients with different radiologic grade are needed to determine the indications of intra-articular hyaluronan injections and to analyze cost–benefit issues in thumb base osteoarthritis. With the appropriate precertification and billing protocol, reimbursement could have been provided by health insurance systems.

Disclosures None

References

- Zhang W, Doherty M, Leeb BF et al (2007) EULAR evidence based recommendations for the management of hand osteoarthritis: report of a task force of the EULAR standing committee for international clinical studies including therapeutics (ESCISIT). *Ann Rheum Dis* 66:377–388
- Mejjad O, Maheu E (2000) Therapeutic trials in hand osteoarthritis: a critical review. *Osteoarthritis Cartilage* 8(suppl A):S57–S63
- Towheed TE (2005) Systematic review of therapies for osteoarthritis of the hand. *Osteoarthritis Cartilage* 13:455–462
- Laurent TC, Frasher JRE (1992) Hyaluronan. *FASEB* 6:2397
- Smedsrod B (1991) Cellular events in the uptake and degradation of hyaluronan. *Adv Drug Deliv Rev* 7:265
- Balazs EA, Denlinger JL (1985) Sodium hyaluronate and joint function. *J Equine Vet Sci* 5:217
- Rydell N, Balazs EA (1971) Effect of intra-articular injection of hyaluronic acid on the clinical symptoms of osteoarthritis and on granulation tissue formation. *Clin Orthop* 80:25
- Weiss C, Band P (1995) Musculoskeletal applications of hyaluronan and hylan. *Clin Podiatr Med Surg* 12:497–517
- Heyworth BE, Lee JH, Kim PD et al (2008) Hylan versus corticosteroid versus placebo for treatment of basal joint arthritis: a prospective, randomized, double-blinded clinical trial. *J Hand Surg* 33A:40–48
- Stahl S, Karsh-Zafir I, Ratzon N et al (2005) Comparison of intraarticular injection of depot corticosteroid and hyaluronic acid for treatment of degenerative trapeziometacarpal joints. *J Clin Rheumatol* 11:299–302
- Fuchs S, Mönikes R, Wohlmeiner A et al (2006) Intra-articular hyaluronic acid compared with corticoid injections for the treatment of rhizarthrosis. *Osteoarthritis Cartilage* 14:82–88
- Altman R, Alarcon G, Appelrough D et al (1990) The American College of Rheumatology Criteria for classification and reporting osteoarthritis of the hand. *Arthritis Rheum* 33:1601–1610
- Eaton RG, Glickel SZ (1987) Trapeziometacarpal osteoarthritis. Staging as a rationale for treatment. *Hand Clin* 3:455–471
- Waldman SD (2000) Atlas of pain management injection technique. Saunders, China
- Obermiller JP, Lox DM (2000) Peripheral joint injections. In: Lennard TA (ed) Pain procedures in clinical practice. 2nd edn. Hanley & Belfus, Philadelphia, pp 124–138
- Dreiser RL, Maheu E, Guillou GB et al (1995) Validation d'un indice fonctionnel dans l'arthrose de la main. *Rev Rhum* 62 (6bis):129S–139S
- Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH (2003) Rheumatology. Mosby, Spain
- Meenagh GK, Patton J, Kynes C et al (2004) A randomized controlled trial of intra-articular corticosteroid injection of the

- carpometacarpal joint of the thumb in osteoarthritis. *Ann Rheum Dis* 63:1260–1263
19. Lo GH, LaValley M, McAlindon T et al (2003) Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. *JAMA* 290:3115–3121
 20. Petrella RJ, Cogliano A, Decaria J (2008) Combining two hyaluronic acids in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. *Clin Rheumatol* 27:975–981
 21. Pollard MA, Cermak MB, Buck WR et al (2007) Accuracy of injection into the basal joint of the thumb. *Am J Orthop* 36:204–206
 22. Mandl LA, Hotchkiss RN, Adler RS et al (2006) Can the carpometacarpal joint be injected accurately in the office setting. *J Rheumatol* 33:1137–1139
 23. Roux C, Fontas E, Breuil V et al (2007) Injection of intra-articular sodium hyaluronidate (Sinovial) into the carpometacarpal joint of the thumb (CMC1) in osteoarthritis. A prospective evaluation of efficacy. *Joint Bone Spine* 74:368–372