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Corticosteroid Compared with Hyaluronic Acid Injections for the Treatment of Osteoarthritis of the Knee

A PROSPECTIVE, RANDOMIZED TRIAL

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Background: Although both corticosteroid and hyaluronic acid injections are widely used to palliate the symptoms of knee osteoarthritis, little research involving a comparison of the two interventions has been done. We tested the hypothesis that there are no significant differences between Hylan G-F 20 (Synvisc) and the corticosteroid betamethasone sodium phosphate-betamethasone acetate (Celestone Soluspan) in terms of pain relief or improvement in function, as determined by validated scoring instruments.

Methods: One hundred patients with knee osteoarthritis were randomized to receive intra-articular injection of either Hylan G-F 20 or the corticosteroid, and they were followed for six months. The patients treated with Hylan G-F 20 received one course of three weekly injections. The patients treated with the corticosteroid received one injection at the time of enrollment in the study, and they could request one more injection any time during the study. An independent, blinded evaluator assessed the patients with the Western Ontario and McMaster University Osteoarthritis Index (WOMAC), a modification of the Knee Society rating system, and the visual analog pain scale.

Results: Both the group treated with the corticosteroid and the group treated with Hylan G-F 20 demonstrated improvements from baseline WOMAC scores (a median decrease from 55 to 40 points and from 54 to 44 points, respectively; $p < 0.01$ for both). The scores according to the Knee Society system did not significantly improve for the patients who received the corticosteroid (median, 58 to 70 points; $p = 0.06$) or for those who received Hylan G-F 20 (median, 58 to 68 points; $p = 0.15$). The scores on the visual analog scale improved for patients receiving Hylan G-F 20 (median, 70 to 52 mm; $p < 0.01$) but not for the patients who received the corticosteroid (median, 64 to 52 mm; $p = 0.28$). However, no significant differences between the two treatment groups were found with respect to the WOMAC, Knee Society system, or visual analog scale results. Women demonstrated a significant improvement in only one of the six possible outcome-treatment combinations (the WOMAC scale), whereas men demonstrated significant improvements in five of the six outcomes (all measures except the Knee Society rating system).

Conclusions: No differences were detected between patients treated with intra-articular injections of Hylan G-F 20 and those treated with the corticosteroid with respect to pain relief or function at six months of follow-up. Women demonstrated significantly less response to treatment than men did for both treatments on all three outcome scales. Such significant gender-related differences warrant further investigation.

Level of Evidence: Therapeutic study, Level I-1b (randomized controlled trial [no significant difference but narrow confidence intervals]). See Instructions to Authors for a complete description of levels of evidence.

Although 200,000 total knee arthroplasties are performed each year in the United States¹, this group represents only a small minority of patients with knee arthritis.

Most patients avoid surgery by using a variety of nonoperative treatments, including oral analgesics, nonsteroidal anti-inflammatory drugs, or any of several types of intra-articular injections.

Intra-articular injections of corticosteroids and hyaluronic acid each have been compared with placebo injections or nonsteroidal anti-inflammatory drugs, or both, in patients with osteoarthritis. Although some studies have described mixed results with those treatments²⁻⁵, others have demonstrated favorable results in terms of pain relief and function for hyaluronate-based products including Hylan G-F 20 (Synvisc) as well as for corticosteroid injections⁶⁻¹⁰. The few studies to date that have attempted to compare hylan-based products with corticosteroid injections were limited by incomplete follow-up or small numbers of patients, and all of these studies that we are aware of have been funded by the manufacturer of the hyaluronate-based product in question¹¹⁻¹³.

We report the results of a prospective, blinded, randomized study comparing the efficacy of intra-articular injections of the corticosteroid betamethasone sodium phosphate-betamethasone acetate (Celestone Soluspan; Schering, Kenilworth, New Jersey) and Hylan G-F 20 (Synvisc; Wyeth-Ayerst Pharmaceuticals, Philadelphia, Pennsylvania) in 100 patients with osteoarthritis of the knee. We tested the null hypothesis that there are no significant differences between intra-articular injections with either Hylan G-F 20 or the corticosteroid in terms of pain relief or function as determined by validated scoring instruments for knee pain and function.

Materials and Methods

Study Site, Randomization, and Patients

This single-center, randomized, blinded, prospective clinical trial was approved by the medical center's institutional review board. All patients, seen in the practices of the two senior surgeons, who satisfied the inclusion criteria and did not meet any of the exclusion criteria were offered enrollment until the planned number of 100 patients was reached. Patients were enrolled between July 2000 and July 2001.

Inclusion criteria were an age of more than eighteen years, radiographic evidence of symptomatic osteoarthritis of the knee, and dissatisfaction with prior attempts at nonoperative management modalities, which variably included nonsteroidal anti-inflammatory drugs, oral analgesics, nutritional supplements, physical therapy, and knee braces. For the purposes of this study, symptomatic osteoarthritis was defined as pain with weight-bearing at the tibiofemoral and/or the patellofemoral articulation together with one or more of the following radiographic signs at the painful articulation: loss of cartilage thickness, osteophyte formation, subchondral sclerosis, or cysts. This group of patients represents those who, prior to this study, would have been offered an intra-articular injection of some type as a temporizing measure to try to avoid knee surgery.

Patients were excluded from the study if they were pregnant or lactating or if they demonstrated signs of so-called bone-on-bone arthritis on any radiograph. Weight-bearing anteroposterior, weight-bearing anteroposterior so-called notch view, weight-bearing lateral, and patellar skyline radiographs were made for all patients prior to enrollment. Patients were also excluded if they had radiographic evidence of chondrocalcinosis or if the physical examination demonstrated an in-

sufficiency of the collateral ligament, an insufficiency of the anterior or posterior cruciate ligament with concomitant symptomatic giving-way of the affected extremity, or a current infection in the affected extremity. Additional exclusion criteria were a history of crystalline arthropathy or inflammatory arthritis, neuropathic arthropathy, an intra-articular knee injection with any corticosteroid or any hyaluronic acid preparation within the previous three months, and allergy or hypersensitivity to any of the study medications or to eggs, feathers, avian proteins, or chickens.

Randomization was performed with use of a computerized random-number algorithm; this process created 100 study cards that listed either Synvisc or Celestone Soluspan, which then were placed in sealed, opaque envelopes by personnel from the hospital's Department of Clinical Investigation. Envelopes were opened only when it was determined that the patient was eligible for study inclusion, and only after she or he had provided informed consent for study participation. Randomization was stratified by age (less than sixty-five years or sixty-five years and greater) and by gender. The opening of an envelope was considered the point of enrollment. All envelopes and study cards were accounted for at the conclusion of the study.

Data Collection and Primary

Outcome Variables

All data collection was performed by a study nurse who was blinded to the treatment received by each patient and who was skilled in the administration of the study outcome instruments. The study nurse recorded all data using a palmtop computer with programmable database software (version 3.1, Pendragon Forms; Pendragon Software, Buffalo Grove, Illinois). Only the principal investigator had access to the data file in order to maintain patient confidentiality.

Demographic data, including height, weight, body-mass index, side of involvement (left, right, or both knees), and age, and the use of nonsteroidal anti-inflammatory drugs during the study period were recorded. No attempt was made to discourage the use of nonsteroidal anti-inflammatory drugs during the study period, since patients were presumed to have a number of providers who might have inadvertently prescribed the medications, and since a large variety of over-the-counter medications also are available to patients. Rather, use of nonsteroidal anti-inflammatory drugs was tracked with use of the pharmacy database. All patients who receive care in this clinic are able to get both prescription and over-the-counter medications at no charge from the institutional pharmacy, so it is likely that all—or nearly all—of the use of nonsteroidal anti-inflammatory drugs during the study period was accurately tracked.

The findings on the initial radiographs were graded by one of the investigators as demonstrating mild, moderate, or severe arthritis. Each of the three compartments (medial tibiofemoral, lateral tibiofemoral, and patellofemoral) was graded, and the worst grade was recorded. Mild arthritis was defined as minimal (<25%) estimated loss of apparent joint space on any radiograph and/or evidence of osteophyte

formation. Arthritis was classified as moderate when up to 75% of the cartilage thickness was lost; typically, subchondral changes and more noticeable osteophyte formation also were present in these knees. Severe arthritis was defined as evidence of near-total loss of the joint space on any radiograph; however, if bone-on-bone arthritis was visible on any radiograph, the patient was not considered eligible for inclusion in the study.

The modified (100-point) Knee Society clinical rating scale, the Likert-scaled Western Ontario and McMaster University Osteoarthritis Index (WOMAC), and the 100-mm visual analog pain scale were the outcomes instruments used to assess the response to treatment. The WOMAC was used as a self-administered questionnaire in accordance with the developers' instructions¹⁴. With the Knee Society clinical rating scale, a score of <60 points indicated a poor result; 60 to 69 points, a fair result; 70 to 84 points, a good result; and 85 to 100 points, an excellent result¹⁵. With use of the WOMAC, a lower score represented a better outcome; the possible values ranged from 0 (best score) to 96 (worst score) based on the three subdomains of pain, stiffness, and difficulty in performing daily activities. The visual analog scale, which also was administered by the patient, ranged from 0 to 100 mm, with lower numbers representing less pain and higher numbers representing more pain. All three instruments were used at the time of enrollment in the study prior to any injection and then again at three and six months after the initial injection. Patients were queried about adverse treatment reactions at the same time-points.

Patients were encouraged to wait a full month following the final injection of Hylan G-F 20 (six to seven weeks following the initial injection) in order to give the product ample time to begin to demonstrate efficacy. None of the patients withdrew before that amount of time had lapsed. Patients who elected to withdraw from the study were considered treatment failures but were still followed for six months to make sure that no late adverse reactions took place. However, their scores were not included in the analysis, since all patients who withdrew had additional treatments, including other injections, arthroscopic surgery, or knee arthroplasty. The six-month follow-up period began for all patients on the date that the first injection was administered.

Intra-Articular Injections

Hylan G-F 20 was administered in accordance with the manufacturer's recommendations as a course of three weekly injections. Each injection was given with use of the manufacturer's prefilled 2-mL syringe, which contained 16 mg of hydrated gel in buffered physiologic sodium chloride solution of pH 7.2. Prior to the administration of Hylan G-F 20, knee effusions were aspirated into a separate syringe; the same needle was left in place, and the syringe that had been prefilled with Hylan G-F 20 was used for the injection. Following the three injections, no additional injections were permitted in patients randomized to this treatment group.

The corticosteroid was given as a single injection of 2 mL of betamethasone sodium phosphate-betamethasone acetate

mixed in 4 mL of Marcaine (bupivacaine) and 4 mL of lidocaine. Patients who were randomized to receive the corticosteroid could request and receive a second injection of the same preparation at any time during the study period. Knee effusions were not aspirated prior to injection of the corticosteroid.

Because of the obvious differences in the administration of Hylan G-F 20 and the corticosteroid^{11,12}, no attempt was made to blind the patients to the treatment assignment.

All injections were performed in a similar manner by one of the attending knee surgeons involved in the trial. The patient was placed in the supine position, the knee was prepared in a sterile fashion, and a needle was placed superolaterally into the suprapatellar pouch. Ethyl chloride spray (Gebauer's Ethyl Chloride; Gebauer, Cleveland, Ohio) was used immediately prior to the injection for patient comfort, and all injections were performed with a 22-gauge needle, unless an aspiration was performed prior to injection, which was done with an 18-gauge needle that was then left in place for the injection. Patients were encouraged to refrain from strenuous activity for a day following the intra-articular injections.

Statistical Methods

SPSS for Windows software (version 10; SPSS, Chicago, Illinois) was used for data management and statistical analysis. Because histograms of the data indicated that the variables had non-normal distributions, nonparametric statistical methods were used to analyze the data. The Friedman test was done separately for each study group to test for changes over time with respect to non-nominal variables. The Mann-Whitney test was used to compare the study groups at each time-point with respect to non-nominal variables. Comparison of the study groups with respect to gender was done with the chi-square test of association. The level of significance was set at 0.05 for all statistical tests. No one-sided statistical tests were done. Because the data were not normally distributed, median values (which were not affected by outliers) are presented rather than means.

For the purposes of this study, one knee per patient was analyzed. Patients who requested treatment of both knees were randomized in the standard fashion and were treated with the same product in both knees. Data then were gathered in the standard prospective, blinded fashion at all required time-points according to the study protocol. However, for purposes of analysis, since two knees in the same patient cannot be analyzed statistically as independent specimens, patients who received treatment bilaterally underwent an additional randomization step to determine which knee would be included. To ensure that bias did not result from the random selection of a single knee for analysis, all analyses were repeated twice, first with use of the best knee outcome at each time-point for each outcomes instrument and then with use of the worst knee outcome at each time-point.

Inclusion of at least thirty-six subjects per group ensured at least 80% power to detect significant differences between groups treated with corticosteroid and Hylan G-F 20 if the probability that an observation in one group was less than an

TABLE I Baseline Demographic and Clinical Parameters

Treatment	Age (yr)	Weight (kg)	Body-Mass Index (kg/m ²)	Female Patients (%)	Percentage of Patients Using Nonsteroidal Anti-Inflammatory Drugs
Corticosteroid*	64 (40-83)	86 (40-143)	29.3 (17-58)	56	56
Hylan G-F 20*	66 (39-79)	86 (48-141)	28.8 (21-51)	52	64
P value	0.97	0.96	0.82	0.69	0.41

*The values are presented as the median, with the range in parentheses.

observation in the other group was 0.691, based on a two-sided Mann-Whitney test with a level of significance of 0.05. Power calculations were performed with use of nQuery Advisor software (version 2.0; Statistical Solutions, Boston, Massachusetts).

Results

Baseline Demographics and Clinical Parameters

Fifty patients per treatment group had baseline measurements. When patients who withdrew from the study were excluded from the analyses of the changes over time, data were available for forty-two patients in the corticosteroid group and thirty-eight in the Hylan G-F 20 group at baseline; for forty and thirty-seven patients, respectively, at three months; and for forty-one and thirty-six patients, respectively, at six months (one patient in the corticosteroid group did not return to the office at three months but did return at six months for the final follow-up examination).

No significant differences between the treatment groups were found with respect to age, gender, weight, body-mass index, use of nonsteroidal anti-inflammatory drugs during the study period, or side of involvement (Table I). A significant difference was detected between the two groups with respect to the radiographic severity of the disease ($p = 0.007$), with more

patients with moderate arthritis in the Hylan G-F 20 group (twenty-nine of fifty; 58%) than in the corticosteroid group (fourteen of fifty; 28%) and more patients with mild and severe arthritis in the corticosteroid group (32% had mild and 40% had severe arthritis) than in the Hylan G-F 20 group (14% had mild and 28% had severe arthritis). Despite the difference in the baseline data with regard to the apparent radiographic severity, no significant difference between the corticosteroid group and the Hylan G-F 20 group was found with respect to the baseline (pretreatment) outcome scores ($p = 0.94$ for the WOMAC scores, $p = 0.78$ for the Knee Society scores, and $p = 0.18$ for the visual analog scale scores). With the numbers available, further analysis of the subgroups (with use of radiographic scores to define the subgroups) did not affect the comparative results between the treatment groups.

In the corticosteroid group, twenty-four patients (48%; thirty-three knees) opted to receive a second injection of the corticosteroid during the study period.

Improvements from Baseline Within the Groups (Table II)

The WOMAC scores improved from baseline for both the patients treated with the corticosteroid (median, 55 to 40 points; $p < 0.01$) and for those treated with Hylan G-F 20 (median, 54

TABLE II Changes in Median Outcomes Scores over Time

Treatment	WOMAC (points)	Knee Society Rating System (points)	Visual Analog Scale (mm)
Corticosteroid			
Before treatment	55	58	64
3 mo	42	72	52
6 mo	40	70	52
P value*	<0.01	0.06	0.28
Hylan G-F 20			
Before treatment	54	58	70
3 mo	41	69	45
6 mo	44	68	52
P value*	<0.01	0.15	<0.01

*P values refer to changes over time within each treatment group, based on the Friedman test; p values of <0.05 were considered significant. Note that no significant differences between treatment groups were detected by any of the three outcomes instruments at either follow-up interval, according to the Mann-Whitney test ($p = 0.29$ to 0.61 at three months and $p = 0.69$ to 0.98 at six months).

TABLE III Subanalysis by Gender for Changes in Median Outcomes Scores over Time

Gender	WOMAC (points)	Knee Society Rating System (points)	Visual Analog Scale (mm)
Female			
Corticosteroid			
Before treatment (n = 24)	60	56	59
3 mo (n = 24)	48	62	57
6 mo (n = 23)	48	59	68
P value*	0.16	0.72	0.73
Hylan G-F 20			
Before treatment (n = 22)	54	53	69
3 mo (n = 22)	46	68	46
6 mo (n = 22)	36	70	45
P value*	0.01	0.39	0.08
Male			
Corticosteroid			
Before treatment (n = 18)	54	66	67
3 mo (n = 16)	30	85	46
6 mo (n = 18)	38	86	36
P value*	<0.01	0.02	<0.01
Hylan G-F 20			
Before treatment (n = 16)	54	62	70
3 mo (n = 15)	28	74	37
6 mo (n = 14)	54	67	64
P value*	<0.01	0.17	0.02

*P values refer to changes over time, based on the Friedman test; p values of <0.05 were considered significant.

to 44 points; $p < 0.01$). The scores on the Knee society rating system did not significantly improve for the patients treated with the corticosteroid (median, 58 to 70 points; $p = 0.06$) or for those treated with Hylan G-F 20 (median, 58 to 68 points; $p = 0.15$). The scores on the visual analog scale improved for the patients in the Hylan G-F 20 group (median, 70 to 52 mm; $p < 0.01$) but not for those in the corticosteroid group (median, 64 to 52 mm; $p = 0.28$). Even when significant improvements were seen, the clinical magnitude of these responses was only modest. The WOMAC scores—although significantly better than baseline for both treatment groups—did not improve in either group beyond the middle one-third of the scale at any time-point, which is where both groups began. When both knees of the patients who were treated bilaterally were included by analyzing the best and worst outcomes for such patients, the results were very similar to those described above.

Comparison of the Corticosteroid and Hylan G-F 20 Groups

No significant differences between the group treated with the corticosteroid and that treated with Hylan G-F 20 were found with respect to the results on the WOMAC index, Knee Society rating system, or visual analog scale at the six-month follow-up evaluation ($p = 0.98, 0.69, \text{ and } 0.94$, respectively). When minimum and maximum values for each outcomes in-

strument were analyzed in order to include both knees of the patients who had treatment bilaterally, no significant differences between the groups at either time-point following treatment with corticosteroid or Hylan G-F 20 were found with respect to the WOMAC, Knee Society rating system, or visual analog scale results.

Gender Differences (Table III)

Women demonstrated a significant improvement in only one of the six possible outcome-treatment combinations (the WOMAC scale for the patients treated with Hylan G-F 20), whereas men demonstrated significant improvements in five of the six combinations (all measures except the Knee Society rating system for the patients treated with Hylan G-F 20). These gender-related differences could not be explained by differences in age or disease severity. When these analyses were repeated with use of the best-case and worst-case results for both knees of each patient who was treated bilaterally, similar results were obtained.

Treatment Failures

Twenty (20%) of the 100 patients withdrew from the study because of a lack of treatment efficacy. They included twelve (24%) of the fifty patients in the Hylan G-F 20 group and eight (16%) of the fifty patients in the corticosteroid group;

the difference was not significant ($p = 0.32$). One patient in the Hylan G-F 20 group withdrew because an acute local reaction developed within twenty-four hours after an injection. The reaction was treated with aspiration of a large effusion of straw-colored synovial fluid and intra-articular administration of the corticosteroid (betamethasone), and the symptoms were relieved. There were no acute local reactions in the corticosteroid group. A total of three patients (two in the Hylan G-F 20 group and one in the corticosteroid group) were lost to follow-up. There were no infections in this series.

Discussion

The present study demonstrated only modest treatment effects from baseline for both Hylan G-F 20 and the corticosteroid and no significant differences in outcome between the two treatment groups, despite an 80% statistical power to detect clinically relevant differences.

In a prospective, randomized study, Jones et al. reported that patients who received hyaluronic acid injections (Hyalgan; Fidia S.p.A., Abano Terme, Italy) for the treatment of inflammatory knee arthritis had less pain at six months of follow-up than did patients who received the corticosteroid triamcinolone hexacetonide¹¹. Only sixty-three patients were enrolled in that study, and forty-three (68.3%) of them withdrew most commonly because of worsening of the symptoms—before the six-month final follow-up evaluation. In addition, when those authors applied an intent-to-treat analysis that included all of the patients who had withdrawn, no significant differences were detected between the group treated with hyaluronic acid and that treated with the corticosteroid. Outcomes assessment in that report was limited to the visual analog scale.

The study by Leardini et al. is the only other randomized clinical trial, as far as we know, in which hyaluronic acid was compared with a corticosteroid (6-methyl prednisolone acetate)¹². They also concluded that hyaluronic acid was superior to the corticosteroid, particularly in terms of the duration of pain relief. The authors stated that they considered the hyaluronic acid product to be a potential “therapeutic breakthrough.” However, that study included a total of only forty patients, the follow-up period was limited to two months, and as in the previous study¹¹, apart from the visual analog scale, no validated outcomes instruments were used.

To our knowledge, the present report is the largest prospective, randomized trial involving a comparison of any hyaluronic acid product with any corticosteroid. It is also the first study of this type to use validated disease-specific outcomes instruments, such as the WOMAC index or the Knee Society rating system, and it is also the first comparative trial involving Synvisc, the most widely used intra-articular hyaluronic acid product in the United States, and a corticosteroid. The present study was independently funded.

The present report probably represents an optimistic scenario for Hylan G-F 20, since patients with evidence of bone-on-bone arthritis on weight-bearing radiographs were excluded; previous studies have found hyaluronic acid injections in this group of patients to be of minimal benefit^{16,17}. We used a simple radio-

graphic grading system, rather than the Ahlback classification¹⁸ or similar grading scales that have been used in prior studies^{8,16,17}. The Ahlback classification was not used because three of the four stages include knees with a completely obliterated joint space.

The present study identified potentially important gender-related differences in treatment response for both the patients treated with Hylan G-F 20 and those treated with the corticosteroid. Women had significantly less response to both treatments; this difference was not attributable to differences in age or disease severity. Whether this finding represents a true biological difference or gender bias in outcomes assessment is an important question that warrants further study.

In order to comply with the Declaration of Helsinki, the present study did not include a placebo group. The Declaration states: “The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.”¹⁹ Both Hylan G-F 20 and corticosteroid injections have been demonstrated to be effective and clinically acceptable^{2,3,5,9,10,16,20-26}, and both have been found to be superior to placebo injections^{8,9}. In view of those findings, the addition of sham injections to the study design of the present report would have increased the risks to study participants out of proportion to any scientific benefit that might have resulted.

Data collection in the present study was carried out by a blinded, independent, experienced study nurse; however, neither the patients nor the treating physicians were blinded to the treatment used. The authors of two prior studies in which a hyaluronic acid product was compared with a corticosteroid commented on the difficulties associated with attempting to “blind” either the treating physician or the patient by using placebo injections^{11,12}. However, it seems likely that patient and physician awareness of the treatment used would have favored the newer, more heavily-marketed treatment (Synvisc) if it had any effect at all.

Although the groups were well matched at baseline in terms of demographic parameters, including age, gender, weight, and body-mass index, differences were detected between the Hylan G-F 20 group and the corticosteroid group with respect to the radiographic severity of the disease. The distribution of the knees—more knees had moderate osteoarthritis in the Hylan G-F 20 group than in the corticosteroid group and more knees had mild and severe osteoarthritis in the corticosteroid group than in the Hylan G-F 20 group—was such that it was unlikely to have substantially impacted the outcome. The fact that no significant differences between patients randomized to either treatment group were detected with respect to the scores on the WOMAC, Knee Society rating system, or visual analog scale at baseline tends to support this view; moreover, further subgroup analysis, with use of radiographic scores to define the subgroups, did not affect the comparative results between the Hylan G-F 20 and the corticosteroid group. To our knowledge, no radiographic grading system for osteoarthritis of the knee has undergone interobserver and intraobserver reliability testing; this should be considered a limitation for any study that draws inferences between radiographic grades and outcome, including the present report. The absence of a val-

idated system is particularly a concern if radiographs are not corrected for magnification and are performed with use of fluoroscopic guidance. However, bone-on-bone arthritis on any radiograph precluded inclusion in the present trial in order to avoid prejudicing the results against treatment with Hylan G-F 20^{16,17}.

Both Hylan G-F 20 and the corticosteroid provided patients with modest improvements in function, but no significant differences between these treatments were observed at three or six months. Given the additional pain and the potential risk associated with the three-injection course of Hylan G-F 20, and given the approximately 100-fold difference in pharmacy cost at our institution, we do not consider Hylan G-F 20 a first-line treatment for patients with osteoarthritis who are considering intra-articular knee injections for palliation of symptoms. ■

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