Intra-Articular Hyaluronans: A Review of Product-Specific Safety Profiles

Max I. Hamburger, Sharad Lakhanpal, Pekka A. Mooar, and David Oster

Background and Objectives: **Intra-articular (IA) hyaluronans (HAs) are indicated for pain relief of osteoarthritis (OA) of the knee. Hyalgan (sodium hyaluronate), Supartz (sodium hyaluronate), and Synvisc (hylan G-F 20) are Food and Drug Administration–approved HA products. They are derived from rooster combs; Hyalgan and Supartz are naturally derived (unmodified); Synvisc is chemically modified to increase its molecular weight. This article reviews and updates the safety data for IA HAs used for the treatment of knee OA.**

Methods: **References were taken from Medline through July 2002; respective product information services and information from the searchable United States Food and Drug Administration Manufacturer and User Facility Device Experience Database also were used.**

Results: **All products demonstrated favorable safety profiles in clinical trials and practice compared to other standard therapies for management of OA knee pain. The most common adverse event associated with HAs is mild injection site pain and swelling. Each product has had rare reports of pseudogout and anaphylactoid reactions. Product-specific adverse events, severe acute inflammatory reactions (pseudoseptic knee), in patients receiving Synvisc have been reported. One such patient developed antibodies to chicken proteins and hylan, suggesting an immunologic basis for the severe acute inflammatory reaction. Data from an animal study support a possible immunogenic difference between Synvisc and Hyalgan.**

Conclusions and Relevance: **Overall, HA therapy is a safe treatment for OA knee pain, although there may be interproduct variability in safety profiles.**

INDEX WORDS: Hyaluronans; immunogenicity; osteoarthritis of the knee; safety.

OSTEOARTHRITIS (OA) is a common chronic disease of the joints, characterized by the loss of cartilage, bone remodeling, and degradation, which results in joint instability and failure. The intra-articular (IA) injection of hyaluronans (HAs) is an American College of Rheumatology–recommended approach to the treatment of pain in patients with knee OA, and is indicated when the patient has failed to obtain adequate pain relief from simple analgesics, or when nonsteroidal anti-inflammatory drug–related side effects contraindicate this option (1).

The purpose of this article is to review and update safety data for IA HA products used for the treatment of OA knee pain, and to present data that appear to differentiate the safety profiles of Hyal-

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Table 1: Hyaluronan Products Currently Marketed in the US for OA Knee Pain

Product	Properties	Weekly Dose	Manufacturer (US Distributor)
Hyalgan*	MW, 500-730 kd	3 or 5 × 20 mg	FIDIA Pharmaceutical Corp, Washington, DC
	Not chemically crosslinked <1% protein		(Sanofi-Synthelabo Inc)
Synvisc†	≈80% MW, 6000 kd	3 × 16 mg	Genzyme Biosurgery, Ridgefield, NJ
	≈20% gel; indeterminate MW, >6000 kDa		(Wyeth-Ayerst, Philadelphia, PA)
	Chemically crosslinked with formaldehyde and vinylsulfone (↑ MW), then purified		
	<1% protein		
Supartz‡	620–1170 kd	5 × 25 mg	Seikagaku Corp, Tokyo, Japan (Smith and Nephew, Inc)
	Not chemically crosslinked		
	<1% protein		

Abbreviation: MW, molecular weight.

*Premarketing approval application approved for marketing in the US May 1997.

†Premarketing approval application approved for marketing in the US August 1997.

‡Premarketing approval application approved for marketing in the US January 2001.

gan (sodium hyaluronate; Fidia Pharmaceutical Corporation, Padua, Italy) and Synvisc (hylan G-F 20; Biomatrix, Inc, Ridgefield, NJ), the 2 HA products currently marketed in the United States (US) for the treatment of OA. Recently, a third HA, Supartz (Seikagaku Corporation, Tokyo, Japan) also was approved by the Food and Drug Administration (FDA), and although some discussion is made of this product, there is very little postmarketing data in the US regarding this product.

METHODS

This review was based on a Medline literature search through July 2002, and on a search of the US FDA Manufacturer and User Facility Device Experience (MAUDE) Database by using the terms "Hyalgan," "Synvisc," "Supartz," "sodium hyaluronate," and "hylan."

RESULTS

HAs for the Treatment of OA

HAs are polysaccharides composed of N-acetyl glucosamine and glucuronic acid found in many extracellular tissues, including synovial fluid, aqueous humor, and cartilage. Hyalgan and Synvisc are 2 FDA-approved HA products that have been marketed as devices in the US since 1997. A third product, Supartz (marketed as Artz or Artzal outside of the US), received FDA approval in 2001 (Table 1). These products are IA injections for relief of pain in knee OA in patients who have failed to respond adequately to conservative nonpharmacologic therapy and to simple analgesics such as acetaminophen. Although Supartz is now marketed in the US and additional HA products currently are marketed outside the US, this review focuses primarily on the safety profiles from controlled clinical trials, clinical postmarketing experience, and the Summary of Safety and Efficacy provided with the respective product applications to the FDA of Hyalgan and Synvisc. We did not consider or review the shown clinical efficacy of these HAs.

Hyalgan is a viscous solution of the sodium salt of HA with a molecular weight in the range of 500 to 730 kd. The product is naturally derived from rooster combs without chemical modification; presumably, HAs in this form may resemble normal human HA (synthesized as molecules of 2×10^5 or 2×10^6 d molecular weight) and they would then undergo natural crosslinking by endogenous

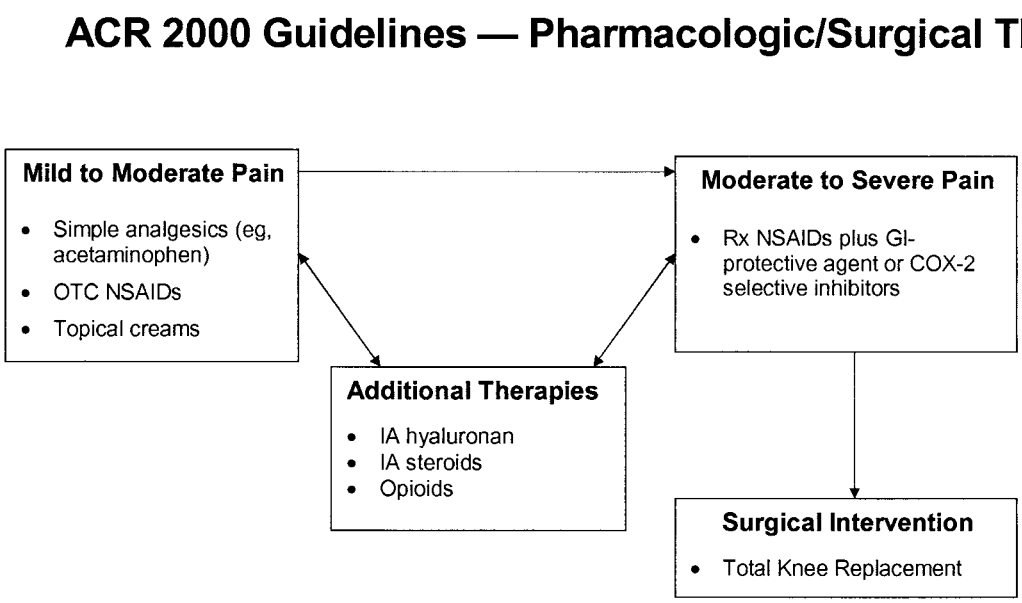

Fig 1. Current American College of Rheumatology recommendations for pharmacologic treatment of OA of the knee (2). Recommendations vary for patients with mild, moderate, or severe disease. OTC, over the counter; Rx, prescription; TKR, total knee replacement.

hyaladherins found in the synovial fluid (2). Synvisc (hylan G-F 20) is a viscous mixture of chemically crosslinked HA to increase molecular weight, composed of approximately 80% hylan A (molecular weight, ≃6000 kd) and approximately 20% hylan B (gel matrix of indeterminate molecular weight) (3). In the case of hylan, rooster comb preparations are first treated with formaldehyde and vinylsulfone as exogenous crosslinking agents, and then the preparation is purified (4). The molecular weight of crosslinked HA slightly exceeds that found in normal synovial fluid, and it was originally hypothesized that, because of the enhanced viscoelasticity, crosslinking also may improve clinical efficacy for the treatment of OA. Although the clinical data evaluating this hypothesis are controversial (5,6), the majority of the published clinical reports do not support the notion that the higher molecular weight ($>5 \times 10^5$ d) is related to efficacy (7). Please refer to an in-depth discussion of the possible contribution of HA molecular weight to its therapeutic action (8).

Each of the products marketed in the US is safe and efficacious for the treatment of knee OA (6,9-15). The most common adverse events associated with their use are injection site pain and swelling. These reactions are typically mild and resolve either untreated or with minimal local therapy. The FDA-approved indication(s) for use of all 3 HAs specify that therapy should be considered in the treatment of pain in knee OA in patients who have failed to respond adequately to conservative nonpharmacologic therapy and to simple analgesics (eg, acetaminophen). Recently, the American College of Rheumatology Guidelines for treatment of OA pain (Fig 1) have adopteda treatment recommendation that incorporates HA therapy (1). Product-specific safety and tolerability clinical trial data are summarized in the following sections.

Hyalgan Safety and Tolerability: Clinical Trials

The efficacy and safety of IA Hyalgan were investigated in an international clinical development program of more than 40 placebo-controlled, active-controlled, open-label, and postmarketing studies carried out in the US, United Kingdom (UK), Germany, France, Austria, Italy, Spain, Poland, the Slovak Republic, and Argentina (16). A selected number of the published reports are shown in Table 2. The results have strongly supported the safety and tolerability of Hyalgan. In the largest controlled trial of HAs conducted in the US, Alt-

Table 2: Summary of US and International Trials Evaluating the Safety of Hyalgan

Study	Country/Design	Patients, n	Brief Safety Results
Altman & Moskowitz, 1998 (14)	US/multicenter, blinded, double-dummy, randomized, saline- and NSAID-controlled; 5 weekly Hyalgan injections	456	GI AE > in naproxen group Local injection site pain > in Hyalgan *v* control
Carrabba et al, 1995 (49)	Italy/single-center, randomized, placebo- and arthrocentesis-controlled; 1, 3, or 5 weekly Hyalgan injections with a 6-month follow-up	100	All regimens well tolerated, AE mild and transient No serious AE
Dougados et al, 1993 (9)	France/multicenter, blinded, placebo-controlled, 4 weekly Hyalgan injections	110	Well tolerated, equal to control No serious AE
Huskisson & Donnelly, 1999 (15)	UK/multicenter, blinded, randomized, saline-controlled, 5 weekly Hyalgan injections	100	Well tolerated, equal to control Injection site reactions similar in placebo and active treatment groups
Henderson et al, 1994 (17)	UK/randomized, saline-controlled, double-blind, 5 weekly Hyalgan injections	91	More poorly tolerated than placebo Pain and swelling of knee in 47% Hyalgan patients *v* 22% placebo patients
Listrat et al, 1997 (50)	France/randomized, single-blind, no-treatment controlled, 3 weekly injections with course repeated every 3 months (totaling 9 injections)	36	Well tolerated No serious AE 8 of 20 Hyalgan patients reported pain limited to during or immediately after at least 1 injection
Kotz & Kolarz, 1999 (42)	Austria/multicenter, open-label, randomized, baseline-controlled, 1 year follow-up; 5 weekly Hyalgan injections; second treatment course for patients (15) requiring additional pain relief	108/15	Well tolerated No serious AE 8 of 20 Hyalgan patients reported pain limited to during or immediately after at least 1 injection
Scali, 1995 (41)	Argentina/open-label study, 5 weekly Hyalgan injections, repeat every 6 months regardless of need	110	Well tolerated No serious AE
Kazimir et al, 1998 (19)	Slovak Republic/postmarketing, 3 or 5 weekly injection	1233	Well tolerated No serious AE

Abbreviations: AE, adverse event; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

man and Moskowitz (14) reported on a 26-week, randomized, double-blind study that compared IA Hyalgan with naproxen therapy (500 mg, twice daily) or with IA saline control injections and placebo pills (Table 2).

The most frequent adverse events associated with Hyalgan in this pivotal trial are shown in Table 3. There were significantly more gastrointestinal adverse events associated with naproxen than with Hyalgan or saline control, whereas a significantly higher percentage of patients receiving HA reported injection site pain than did those receiving saline injections or mock-injections plus naproxen (Table 3), and more HA patients withdrew from the study because of injection-site pain (6 of 164, 4%) than patients in the placebo (1 of 168, 0.6%) or naproxen (1 of 165, 0.6%) groups ($P = .06$). With the exception of withdrawals

Table 3: Summary of Adverse Events in US Pivotal Trial of Hyalgan

Adverse Event	Hyalgan, n (%)	Placebo, n (%)	Naproxen, n (%)
No. of patients randomized	164	168	163
Gastrointestinal complaints	48 (29)	59 (36)	68 (41)*
Injection-site pain	38 (23)†	22 (13)	14 (9)
Headache	30 (18)	29 (17)	17 (10)
Local skin reactions	23 (14)	17 (10)	29 (18)
Local joint pain/swelling	21 (13)	22 (13)	10 (6)
Pruritus	12 (7)	7 (4)	7 (4)

NOTE. Data from Altman and Moskowitz (14).
*$P = .087$ *v* placebo; $P = .031$ *v* Hyalgan.
†$P < .01$ *v* placebo.

because of gastrointestinal adverse events (statistically significant in the naproxen group), none of the subsequent analyses of covariates identified any difference between the groups based on withdrawn patients.

With the exception of 4 reports of severe knee swelling or effusion, 1 each in the placebo- and naproxen-treated patients, and 2 in patients receiving Hyalgan, the adverse events reported in the study were generally transient. No clinically significant laboratory findings were noted, nor were any drug interactions reported. A recent report of similar design conducted in the UK showed a similar safety and efficacy profile (15). Additional findings of excellent tolerability were obtained in a number of clinical trials, listed in Table 2. It should be noted that, in a single study involving 91 patients (17), Hyalgan was more poorly tolerated than placebo; pain and swelling of the knee was noted in 47% of patients treated with Hyalgan, compared with 22% of patients treated with saline injections (Table 2). This study also failed to establish the effectiveness of Hyalgan above that of the saline-treated group, although both groups significantly improved from baseline.

Hyalgan Safety and Tolerability: Postmarketing Surveillance

Product labeling. Hyalgan has been marketed in Italy since 1987, and in 32 countries since then, with approximately 10 million injections given; the product has not been withdrawn from any country for reasons related to safety or to effectiveness (16). Postmarketing surveillance has indicated that most adverse events were related to local symptoms such as mild pain, swelling or effusion, and warmth or redness at the injection site. According to the current labeling, there have been 2 reports of anaphylactoid reactions and 3 cases of allergic reaction, which all resolved with discontinuation of treatment. In 1 of the cases of anaphylactoid reaction, the patient was treated with transfusion and crystalloids and recovered within minutes; information regarding the necessity of any medical treatment in the other cases is not available. Seven cases of fever were reported, of which 3 were associated with a local reaction; pyogenic arthritis was reportedly ruled out by results of cultures in these cases. These events resolved with discontinued use. One incident of hypotensive crisis was reported, which resolved, and treatment was continued (18).

Clinical practice. A published postmarketing study from the Slovak Republic evaluated data from a total of 1233 patients with knee OA who received a total of 5048 injections of Hyalgan (most received 3 or 5 injections) (19). Hyalgan was well tolerated in this population, with only 17 adverse events reported. These included local reaction to puncture (5), exudation in the articular space (6), local swelling (2), gastric discomfort (2), and allergic exanthema (1).

Pseudogout. Despite the excellent tolerability profile of Hyalgan shown in clinical trials and observed in clinical experience, there has been at least 1 published case study of a patient with calcium pyrophosphate dihydrate (CPPD) arthritis (pseudogout) presumably resulting from an IA injection of Hyalgan (20); 2 additional reports did not specify which HA product was used (21,22). These reactions are difficult to quantitate because they are spontaneous reports; however, they appear

Table 4: US FDA MAUDE (June 1998 to March 2002): Spontaneous Synvisc and Hyalgan Adverse Event Reports

Product	Adverse Event	Reports, *n* (%)
Hyalgan		
	SAIR/possible SAIR*	6/32 (19)
	Infection/possible infection	5/32 (16)
	Allergic/urticaria/rash	4/32 (13)
	Anaphylactoid reaction	1/32 (3)
	Other (hypotension, tachycardia, chest pain, respiratory failure, cellulitis [ankle], meniscus lesion, seizure, pancytopenia, death due to fever and sepsis judged not related to Hyalgan)	16/32 (50)
Synvisc		
	SAIR/possible SAIR†	26/67 (39)
	Infection/possible infection	21/67 (31)
	Allergic/urticaria/rash	7/67 (10)
	Anaphylactoid reaction	1/67 (1)
	Other (deep vein thrombosis; thrombocytopenia, pseudogout, empyema, myalgia, complaint, urinary frequency, 1 death due to cardiovascular disease and pneumonia, 2 deaths due to multiple injections of Synvisc/lidocaine in one case with and one case without corticosteroids; deaths judged not related to Synvisc	12/67 (18)

NOTE. Data from reference 37.

Reports, accessed from the US FDA MAUDE Database (37) by using the search words "Synvisc," "hylan," or "Hyalgan," were all voluntary and anecdotal in format, filed by health care professionals, distributor, or manufacturer. Only cases involving the indication of knee OA were considered. In some cases, the same case was reported more than once; these were counted as 1 case only. Assignment of adverse event category was based on author interpretation of the narratives and/or conclusion of the reporting party.

*Possible SAIRs included cases that were either very poorly documented or did not have most of the characteristics of a SAIR. Four of the Hyalgan-associated cases were considered possible SAIRs because of the effusion or inflammatory response noted, but 3 were poorly documented with regard to the severity and/or characteristics of the event; 1 involved swollen ankle and tibia, contralateral to the injected knee.

†One event was considered a possible SAIR that involved swelling of entire leg, and 3 were either poorly documented or did not have most of the characteristics of a SAIR. In some of the cases considered to be SAIRs, the event was reported as possible infection but the characteristics of an SAIR were present and there were either no laboratory tests performed or the results of the laboratory tests were not reported.

to be rare given the total number of injections administered. They are characterized by severe inflammation of the knee with pain and loss of function, occurring between 5 and 48 hours after the injection. These reactions are characterized by the presence of CPPD crystals in the synovial fluid aspirate. The condition resolves within a few days after initiation of nonsteroidal anti-inflammatory drug therapy.

Additional postmarketing information regarding Hyalgan was accessed from the US FDA MAUDE database (Table 4), and is discussed in the section on US FDA MAUDE Database reports.

Synvisc Safety and Tolerability: Clinical Trials

Synvisc also has been shown to be safe and effective in numerous clinical trials. In 7 controlled or open-label clinical trials of Synvisc reported in support of premarket approval involving 511 patients and 1711 injections, 7% of patients (2.3% of injections) reported knee pain and/or swelling after injections (6,10-12,23). Ten of these patients required arthrocentesis and removal of joint effusion, 2 received IA steroids, and 2 received nonsteroidal anti-inflammatory drugs (1 of whom also received arthrocentesis). One patient was treated with ar-

Table 5: Summary of US and International Trials Evaluating the Safety of Synvisc

Study	Country/Design	Patients, n	Brief Safety Results
PMA study #1: Adams et al, 1993; Scale et al, 1994 (10,12,23)	German/single-center, double-blind, saline-controlled, 2 16-mg injections 14 days apart	48	No serious AE 1 local AE
PMA study #2: Adams et al, 1993; Scale et al, 1994 (10,12,23)	German/single-center, double-blind, saline-controlled, 3 weekly 16-mg injections	30	No serious AE 1 local AE
PMA study #3: Adams et al, 1993 (10,23)	German/multicenter, double-blind, 3 weekly 16-mg injections	110	No serious AE Only local AE
PMA study #4: Adams et al, 1993 (10,23)	German/open-label, 3 weekly 16-mg injections	144	No serious AE Only local AE
PMA study #5 (23)	US/multicenter, double-blind, arthrocentesis-controlled, 3 weekly injections	94	No significant differences in numbers or types of AE between Synvisc and control
PMA study #6: Adams et al, 1995 (11,23)	Canada/double-blind, arthrocentesis-controlled, 3 weekly 16-mg injections ± concomitant NSAID therapy *v* NSAID alone	102	Transient local reaction in 3 patients after Synvisc resulting in 1 withdrawal Well tolerated
Wobig et al, 1999 (51) report of results from 2 of 4 arms of study in PMA submission (5)	Germany/multicenter, double-blind, 3 weekly 16-mg injections *v* Artzal	70	No serious AE 2% AE *v* 1% AE for Artzal
Lussier et al, 1996 (13)	Retrospective study of patients treated by 5 Canadian clinicians over 2.5 years	336	No systemic AE 3% generally mild and transient local AE per injection; 7% per joint; 8% AE per patient Incidence of AE related to injection technique
Puttick et al, 1995 (29)	Canada/retrospective study of patients treated by 3 rheumatologists	22	6 of 22 (27%) patients experienced SAIRs

Abbreviations: AE, adverse events; NSAIDs, nonsteroidal anti-inflammatory drugs; PMA, premarketing approval application.

throscopy. In 3 controlled trials with a total of 112 patients receiving Synvisc and 110 patients receiving either saline injection or arthrocentesis, there was no significant difference in the number or type of adverse events between treatment groups. Additional clinical trials of Synvisc, summarized in Table 5, have reported good tolerability. No Synvisc-related serious adverse events were reported; local adverse reactions tended to be transient and mild.

Synvisc Safety and Tolerability: Postmarketing Surveillance

Product label. Synvisc has been marketed in Canada and in Sweden since 1992 and 1995, respectively, and has been approved for marketing in the US since 1997. According to the most recent product information, the most common adverse events reported with Synvisc during postmarketing surveillance have been pain, swelling, and/or effusion in the injected knees (24). Although articular infections were not reported in any clinical trials, they have been reported rarely during clinical use (24). Adverse events that have been reported in clinical practice, but only rarely, include rash, hives, itching, fever, nausea, headache, dizziness, chills, muscle cramps, paresthesia, peripheral edema, malaise, respiratory difficulties, flushing, and facial swelling (24).

Clinical practice. A retrospective study evaluating Synvisc administered as 1537 injections to 336 patients in clinical practice in Canada (13) also indicated an excellent tolerability profile. Local adverse events were noted in only 28 patients (32 knees), with an overall rate of 2.7% events per injection, 7.0% per joint, and 8.3% per patient. No systemic adverse events were reported; most adverse events were characterized by pain and/or swelling of the injected joint, and were generally mild and transient.

Pseudogout. There have been 3 published reports of pseudogout or synovitis apparently related to Synvisc injections (25-27); again, 2 additional reports did not specify which HA product was used (21,22).

The mechanisms underlying the development of CPPD arthritis after HA injection are not understood. More work is needed to investigate the basis for and the frequency of this adverse reaction. At present, it is advisable for clinicians using these products to consider pseudogout as a possible, although rare, adverse effect when administering IA HAs, especially in patients with CPPD on radiographs, and to advise patients accordingly.

Severe acute inflammatory reactions. Despite the excellent tolerability profile of Synvisc observed in clinical studies and in some reports from clinical practice, the recently updated labeling for this product reflects a growing number of cases of severe pain and cellular effusion after its injection (24). These reactions appear to be clearly distinct from the rare anaphylactoid or other reactions that have been observed after HA injections for both products or for IA injections in general. Moreover, they have not been associated with the CPPD crystal deposition or pseudogout. Clinically, it may be difficult to immediately differentiate a severe acute inflammatory reaction (SAIR; or pseudoseptic knee) to Synvisc from a septic knee without culture reports.

A growing number of published reports of SAIRs in patients receiving Synvisc injections have drawn attention to possible qualitative differences within the HA class (28-35). Puttick et al (29) was the first to document this reaction in a retrospective review of all patients with knee OA treated with Synvisc in a clinical practice setting; a total of 22 patients received 88 injections in 28 knees. These investigators found that, after Synvisc injection (multiple lots), 6 of 22 (27%) patients had SAIRs characterized by pain, warmth, and swelling, lasting up to 3 weeks. The investigators ruled out CPPD deposition and septic joint in all cases. Only 1 patient had radiographic evidence of chondrocalcinosis. In each case, the patient had tolerated between 1 and 4 injections before having a reaction, although the reactions occurred within 24 hours after an injection. The reactions resolved, but generally required intervention such as aspiration or corticosteroid injections and work-up for possible septic knee.

One of the patients experiencing an SAIR, who continued to receive injections despite progressive reactions (treatment was efficacious for pain relief), developed serum antibodies to hylan and chicken proteins. Interestingly, no such antibodies were found in the synovial fluid (29). The study did not report whether any of the other patients were similarly tested. The investigators could offer no explanation for the higher incidence of adverse reactions with Synvisc compared with clinical or previous retrospective studies (Table 5). These reactions were associated with more than 1 lot of Synvisc, ruling out batch contamination as a reason for the frequency of the reactions. It has been hypothesized that these events may result from misplacement of the injections or from blockage of the synovial outflow by the viscous substances (3), but none of these explanations explain the total lack of such reactions in saline control patients or in patients receiving Hyalgan in controlled clinical trials. This explanation also does not take into account the finding that the reaction tends to require multiple injections, or findings of the elicitation of hylan- or chicken protein–reactive antibodies in 1 patient (29). Instead, the characteristics of the reaction are suggestive of an immune-mediated mechanism.

A second report (28) described 10 similar cases in 8 patients who received Synvisc in a large orthopedic practice. In each of these cases, the reaction required more than 2 injections; in half of the patients, the reaction occurred after the first injection of a second course of treatment. Examination of synovial fluid from the inflamed knees showed significant immune cell infiltrates, prompting the investigators to postulate that the patients may have undergone immunologic sensitization; macrophages were seen, suggestive of a foreign body response (Fig 2).

Two publications (30,32), in addition to the

SAIRs, reported 3 cases that also were characterized by fever, severe painful swelling of the knee, and immune cell infiltrate; at least 1 of these was considered by the physician to be a possible allergic response. Two case reports of bilateral symmetric SAIRs during Synvisc treatment also have provided further evidence that these represent a highly specific reaction to the product in susceptible individuals (31,33). Finally, 2 recent histologic studies showed granulomatous inflammatory reactions in patients experiencing SAIRs after receiving Synvisc injections (34,35). These periarticular and synovial reactions probably represent 1 manifestation of a continuum in the pathologic responses to Synvisc. Hylan used in dermatologic applications also has been reported to have similar reactions (36).

US FDA MAUDE Database Reports

A summary of voluntary adverse event reports pertaining to Hyalgan and Synvisc made to the US FDA from June 1998 to March 2002 is shown in Table 4 (37). Spontaneous adverse event reporting is difficult to quantitate outside the controlled setting of clinical trials. These reports cannot be used to predict adverse event rates, and often lack sufficient details to clearly define the nature of the reaction clinically. However, these reports do provide a qualitative evaluation of the adverse events reported.

The database that follows the adverse events reported to the Center for Diagnostics and Radiological Health is known as the MAUDE Database. The MAUDE reports, filed by health professionals, distributors, or manufacturers, are consistent with the high proportion of published SAIRs associated with the use of Synvisc but not with Hyalgan. Based on the differential previously outlined for SAIRs, there were 6 possible SAIRs reported with Hyalgan. Four of these cases were poorly documented and, therefore, could not definitively be characterized as an SAIR (eg, few or no details were provided regarding the severity, diagnostics performed, or characteristics of the event), and 1 was ruled out because the patient experienced ankle and tibial swelling, but not knee swelling. Of the 26 possible SAIRs in the Synvisc-treated patients, 22 appeared after a second or subsequent injection.

There were 2 reports of deaths in patients who had received multiple injections of Synvisc with lidocaine, but they were not considered related to Synvisc. Aside from these exceptional cases, other events for both products that occurred in more than 1 case were consistent with previously reported clinical and postmarketing findings; most frequently, these included infection and allergic reactions such as rash.

Hyalgan and Synvisc: Comparative Immunogenicity Studies

The SAIRs, "described previously that appear to be associated with Synvisc but not Hyalgan, coupled with the antibodies found in the serum of a patient after an SAIR (29), suggest the possibility that the 2 products may differ in their immunogenicity. Theoretically, this could be based on the chemical modification used in the manufacture of Synvisc, because crosslinking is known to enhance or to modify immunogenicity of antigens (38). In the Premarketing Approval Summary of Safety and Efficacy report for Synvisc (23), although immunogenicity in rodents was reported as negative, repeated administration of Synvisc in primates induced serum antibodies to hylan or to chicken proteins in approximately one third of

Fig 2. Immunogenicity of Hyalgan and Synvisc in rabbits. (A) Anti-HA and (B) anti–chicken protein antisera titration curves measured at study termination (week 29) for rabbits immunized with crude rooster preparation, Synvisc, or Hyalgan. Shown are the titration curves from a single representative rabbit for each immunization group. Sera were obtained from a bleed performed at study termination (week 29) after rabbits received a course of 7 subcutaneous injections over 24 weeks. Enzyme-linked immunoadsorbent assays were performed with serially diluted antisera (1:10 to 1:610) by using chicken protein reduction prepared by treated a crude rooster comb preparation with sheep testes hyaluronidase; these were absorbed to 96-well plates. The data points represent the means of duplicate wells. Blanks were wells that did not receive antisera dilution. CRP, crude rooster preparation; OD, optical density.

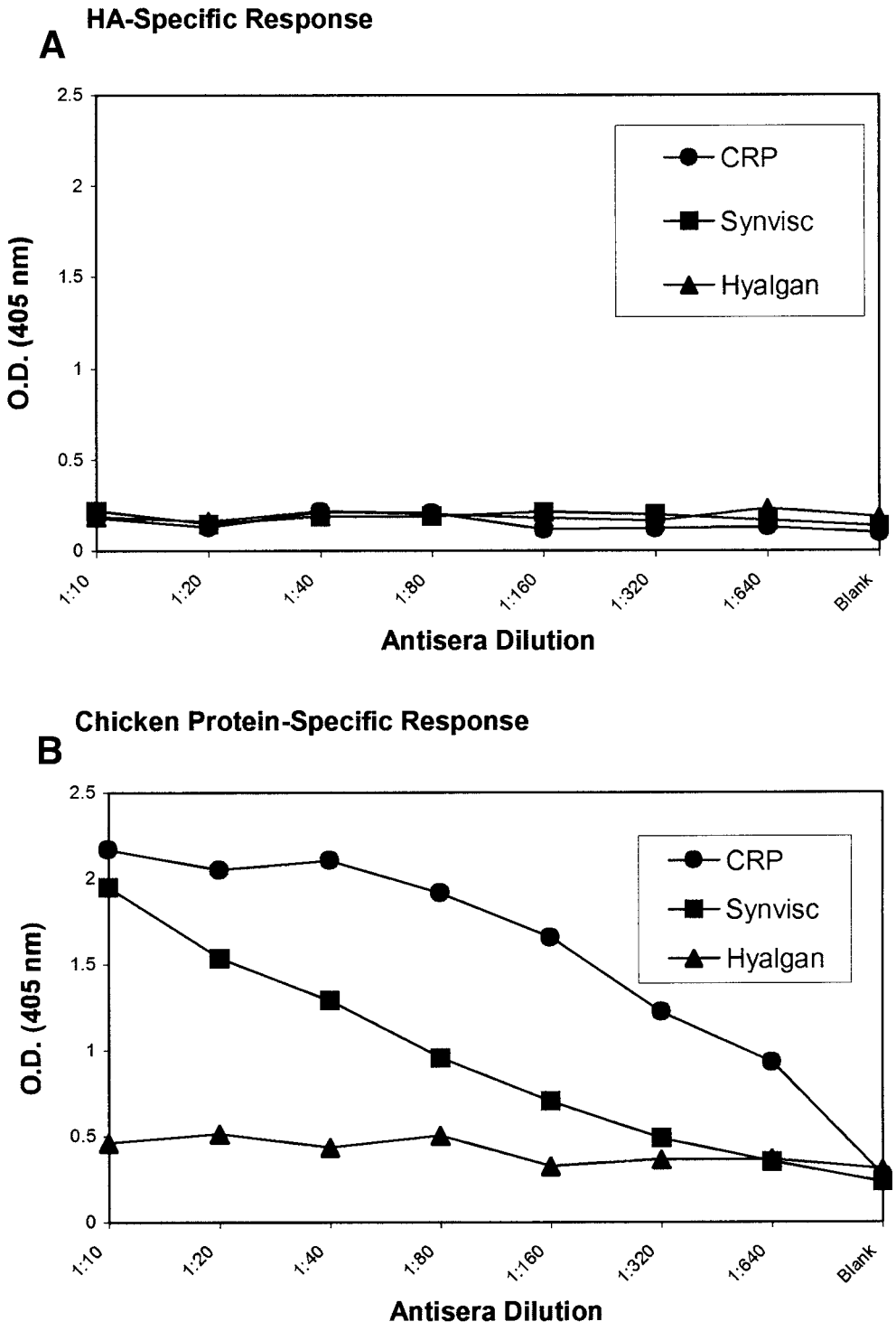
A
HA-Specific Response
O.D. (405 nm)
2.5
2
1.5
1
0.5
0
CRP
Synvisc
Hyalgan
1:10
1:20
1:40
1:80
1:160
1:320
1:640
Blank
Antisera Dilution
B
Chicken Protein-Specific Response
O.D. (405 nm)
2.5
2
1.5
1
0.5
0
CRP
Synvisc
Hyalgan
1:10
1:20
1:40
1:80
1:160
1:320
1:640
Blank
Antisera Dilution

Figure 2

animals tested (23). Long-term administration of Hyalgan to rats did not produce any evidence of induction of an antibody response (16), but no primate data were provided.

A recent study conducted in rabbits compared the immunogenicity of 2 finished products, Hyalgan and Synvisc, with that of a crude rooster comb extract (39). Four rabbits per group were immunized with Hyalgan, Synvisc, or the rooster comb preparation. None of the preparations elicited a significant antibody titer to HA when injected repeatedly. In contrast, crude rooster comb preparation– (4 of 4) and Synvisc- (3 of 4) immunized rabbits had detectable antibody titers to the chicken proteins contained within the crude rooster comb preparation. However, there were no chicken protein–specific titers observed in Hyalgan-treated rabbits. In an exploration of the biochemical basis for this immunologic finding, Western blot analysis of an HA-depleted sample of the crude rooster comb preparation indicated reactivity with a diffuse 6- to 8-kd band in blots developed by using either anti–crude rooster comb preparation or anti-Synvisc rabbit sera. No bands were detected by using sera from the Hyalgan-immunized rabbits. This biochemical finding is concordant with the evidence of nonimmunogenicity of Hyalgan as compared with Synvisc, and provides evidence of the nature of the qualitative difference between the 2 products (M.I.H., unpublished data). A recent report by Goomer et al (40) also has confirmed immunologic reactivity to hylan, in this case comparing the immune response to Synvisc with that to Supartz. In this study, guinea pigs responded to sensitization and subsequent challenge by Synvisc but not Supartz with active cutaneous anaphylactic and delayed type hypersensitivity reactions. Further work will be necessary to confirm whether these preclinical results are related to SAIRs in Synvisc-treated patients.

Safety of Repeated Treatment With HAs

Until recently, the product inserts for both Hyalgan and Synvisc each stated that the safety of repeat treatment courses has not yet been established (18,24). However, 2 long-term studies evaluating repeat treatment courses of Hyalgan and longer-term efficacy have led to a recent change in regulatory status and labeling for this product. Scali (41) evaluated the safety and efficacy of a total of 5 treatment courses, repeated every 6 months for more than 25 months. No serious local or systemic effects were seen after these repeated cycles of Hyalgan treatment, nor did any patient's condition deteriorate during this treatment period.

More recently, Kotz and Kolarz (42) examined the safety and efficacy of a single course of Hyalgan, compared with placebo, during a 12-month period in patients with OA, as well as that of a repeat course of 5 injections in a small number of patients who initially responded but required additional pain relief between 4 and 9 months after the first treatment course. A single treatment course with Hyalgan provided significant pain relief even after a 12-month follow-up. A repeat treatment course was effective for relieving pain and was well tolerated; no unexpected safety findings were observed. A recent study also has shown no adverse events after repeat treatment cycles of Hyalgan in 53 patients with knee OA. Patients received up to 8 treatment cycles, separated by a mean of 11 months between cycles; the mean number of cycles was 3.8 per patient (43). These published findings are now reflected in the labeling for Hyalgan, which no longer includes the statement (unlike the 2 other approved HA products) in the Precautions section of the full prescribing information: "The safety and effectiveness of repeat treatment has not been evaluated" (18).

A literature search showed no prospective published controlled studies detailing the safety of repeat courses of Synvisc, although the retrospective study reported by Lussier et al (13) included patients who had received up to 4 courses of treatment in the same knee, and 5 courses overall. Despite no reported serious consequences in this postmarketing study, the most recent prescribing information states: "The safety and effectiveness of repeat courses of therapy have not been established" (24). The collective results obtained in the premarketing approval submission in primates, the published report of serum antibodies to hylan in a patient with a SAIR, the rabbit immunogenicity studies, and the numerous published reports of SAIRs and soft tissue granulomatous reactions, may call into question the advisability of repeat injections. Studies of the immunoreactivity profiles of Synvisc or Hyalgan in patients receiving repeat courses could support or refute the notion that the product-specific SAIRs are immunologically based.

Supartz Safety and Tolerability: Clinical Trials

Although Supartz, a nonchemically modified HA product of 620 to 1170 kd, has been only recently marketed within the US, and its safety and tolerability have been investigated in a number of clinical trials (44-46). Overall, reports from the literature indicate that Supartz, administered in a course of five 25-mg IA injections, is well tolerated, with no serious adverse events or laboratory abnormalities noted.

According to the posted US Premarketing Approval Application and labeling information for this product (47,48), of 619 patients who received at least 1 injection, 5 allergic reactions have been reported, all of which were classified as mild to moderate. No anaphylactic reactions were observed. The most common adverse events noted (occurring in >4% of patients) were arthralgia, back pain, nonspecific pain, injection-site reaction, injection-site pain, and headache. Five allergic events occurred in patients receiving Supartz, which were classified as hay fever (2), reaction on face and neck, cutaneous reaction of forearms and knees, and an undefined mild allergy reaction. Additional postmarketing surveillance data in the US awaits future scrutiny as it accumulates.

DISCUSSION AND RELEVANCE

Results from both controlled clinical trials and clinical practice indicate that HA therapy has a favorable safety and tolerability profile. Other reviews and published reports also have established its clinical efficacy. Thus, IA HA provides an excellent therapeutic alternative, especially in patients with pain isolated to, or predominantly affecting, the knee joint, or for patients in whom other oral or IA medications may be contraindicated. However, a review of the published literature and voluntary safety reports to the FDA indicate that 1 HA product, Synvisc, has been associated with a disproportionately high frequency of SAIRs. These reactions may occur at a very low frequency with other HA products, such as Hyalgan and Supartz, but to our knowledge, no such reports have been published to date. The preclinical and clinical data supporting a hylan-specific and not a HA-specific reaction also do not support this notion. Thus, a product-specific evaluation of safety profiles indicates that differences between the products exist and should be considered, especially when considering repeat treatment in patients that had a favorable response. Further work is needed to determine the basis for SAIRs that occur with an apparently higher frequency in patients receiving Synvisc, compared with Hyalgan or Supartz, as well as the possible subclinical reactions that might occur within a degenerative joint in response to injections of hylan.

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