

A Retrospective Study of SUPARTZ® and Repeat Treatment for Osteoarthritis Pain in the Knee

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Summary

Osteoarthritis is one of the most common forms of arthritis, affecting up to 27 million Americans. OA is now being diagnosed in younger patients and as the baby-boomer population ages, cases of OA are expected to dramatically increase by 2030. One of the most commonly affected joints is the knee. Knee OA is usually treated with conservative, non-pharmacological therapy, analgesics, and corticosteroid injections. For patients who fail to respond to conservative treatments, and for patients who are non-surgical candidates, hyaluronic acids (HAs) injections are recommended.

In our retrospective study, we collected effectiveness data from 220 patients who had received repeat injections of SUPARTZ® (sodium hyaluronate) injectable joint fluid therapy for symptoms associated with knee OA. Repeat treatments of SUPARTZ® delayed the need for total knee arthroplasty (TKA) for up to four years in our patient population. Positive clinical results continue to outweigh a low incidence of reported adverse events (AEs).

Key Points

- Osteoarthritis is the most widespread form of joint disease now affecting younger groups of patients with expectations of millions of future cases as the population ages.
- In 2004, there were 454,652 TKAs performed, mainly for arthritis.¹
- The focus of the study was the effectiveness, duration, safety, and cost effectiveness of repeat treatments of SUPARTZ® to delay or eliminate the need for TKA.
- Study patients reported significant improvement in knee OA pain levels while being treated with SUPARTZ®.
- Results show that repeat treatments of SUPARTZ® delayed the need for TKA for up to four years.
- Similar studies may be beneficial to support future reimbursement costs and research for other joint areas affected by OA.

Introduction

According to the Arthritis Foundation, in 2005, as many as one in three adults currently suffer from joint symptoms of arthritis.² Arthritis remains one of the most prevalent chronic health problems in America and is the nation's leading cause of disability among Americans over age 15.

One of the most common forms of arthritis is osteoarthritis (OA). OA affects 27 million Americans with women affected more than men. It is the most widespread form of joint disease; worldwide estimates show that 9.6 percent of men and 18.0 percent of women older than 50 have symptomatic OA.³ As the population ages, the number of people with OA will increase dramatically. According to projections by the National Institutes of Health, by 2030, 20 percent of Americans—about 72 million people—

will reach their mid-60s and will be at high risk for the disease.”⁴

Conventional treatment options for knee OA include lifestyle changes; (weight loss and elimination of certain activities, heat and cold therapy, analgesic creams, and assistive mobility devices); low-impact exercises; (to minimize stiffness and optimize joint health); nutritional supplements, such as glucosamine

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Exhibit 1: Number of Series of Injections¹³

Number	Left	Right	Total
2	86	95	181
3	28	36	64
4	14	14	28
5	9	8	17
6	3	6	9
7	2	0	2
8	1	1	2
TOTAL	143	160	303

and chondroitin sulfate; (to protect against cartilage breakdown and provide mild anti-inflammatory effect); and medications, such as acetaminophen and NSAIDs (for pain relief).

When these treatments provide minimal or no benefit, more invasive procedures are offered, such as intra-articular corticosteroid injections, which are administered directly into the joint to decrease inflammation. Another injection treatment is viscosupplementation of hyaluronate, an FDA-approved fluid device, which increases a joint's fluid viscosity (thickness) and aids in the lubrication of the knee joint. "Viscosupplementation may be used to buy time before more aggressive surgical procedures are needed,"⁵ as well as to provide long-term relief in non-surgical candidates.

It has been more than 20 years and more than 170 million injections since the introduction of SUPARTZ[®] injectable joint fluid therapy in Japan in 1987. (SUPARTZ[®] was approved by the FDA in 2001 for use in the United States). Today, with the health and public healthcare system of millions impacted by OA worldwide, we are increasingly aware of the need to obtain more information about the effectiveness of SUPARTZ[®] for the relief of pain

associated with OA of the knee. There is an urgent need to learn about the effectiveness of repeat treatments of SUPARTZ[®] over time to determine if its effects will continue to provide safe, lasting results and delay or eliminate the need for TKA.

Several studies have been conducted on the different types of HAs for effectiveness in pain relief for knee OA patients with favorable results.⁶⁻⁹ Studies have also been conducted concerning the safety of using HAs regarding any AEs citing minor incidences.¹⁰⁻¹¹ In early 2008, a retrospective clinical study was conducted by Smith & Nephew, Inc. to learn more about not only about the effectiveness of SUPARTZ[®], but also about the duration of effectiveness, safety, and cost effectiveness of SUPARTZ[®] for the treatment of OA knee pain with a special interest in repeat injection series.

Materials and Methods

We collected data from five clinical sites in North Carolina on patients who had received a minimum of one repeat treatment series of injections of SUPARTZ[®] to document the status of OA patients before and after their injections; to determine an average time of duration of the effect of SUPARTZ[®]; to determine the effectiveness of the injections; to collect and classify any adverse events (AEs); and to assist the medical community in developing criteria to support reimbursement costs for repeat injections of SUPARTZ[®].

This retrospective study was approved by the Institutional Review Board through NEIRB. A site waiver was obtained for each of the five clinical sites to allow us to collect patient data without obtaining informed consent from each patient. The only personal data collected from each of the patients was their birth month and year.

Patient Population

Our patient population included 220 patients and 303 knee joints that had been treated with SUPARTZ[®] at five clinical sites. Because women are more likely than men to suffer from knee OA after age 50, our study patient population was 74.5

Exhibit 2: Pain assessments over injection series¹³

Pain Assessment Over Time	All Series	Last Series
Improved*	91.9%	92.5%
Did not improve	8.1%	7.5%

*"Improved" indicates that the pain level was rated "better" at sometime within the series and that there were no ratings of "worse" after that rating.

percent female and 25.5 percent male. The average age for patients included in the study was 70.9 years (range from 35 to 99 years).

Clinical retrospective data was collected on 220 patients and 303 knee joints. Criteria for inclusion required that all patients were at least 18 years of age with a confirmed diagnosis of OA and had received a minimum of one repeat treatment series of injections of SUPARTZ® into the affected knee. Diagnoses by incidence included: OA, Degenerative Joint Disease, Post-Traumatic Arthritis, and Rheumatoid Arthritis.

Baseline data was obtained on each patient that included basic demographics with medical, surgical, and joint involvement history. Approximately 82 percent of those patients had not had any previous surgery on the affected knee and only 15 percent were found to have had arthroscopy. Additionally, of the 303 treated knees, nearly 40 percent of patients had both knees treated with multiple injections of SUPARTZ®.

Devices and Procedures

SUPARTZ® (Seikagaku Corporation, Tokyo, Japan and distributed in the United States by Smith & Nephew, Inc., Memphis, Tenn.) is a sterile, viscoelastic, non-pyrogenic solution of highly purified, high molecular weight sodium hyaluronate having a pH of 6.8-7.8. Sodium hylauronate is a common constituent of the extracellular matrix of connective tissues and is extracted from chicken combs.

Sodium hyaluronic acid is a polysaccharide, which contains repeat disaccharide units of glucuronic acid and N-acetylglucosamine. SUPARTZ® is supplied in a single-use disposable plastic syringe. Each syringe contains 25 mg of sodium hyaluronate dissolved in a phosphate buffered saline (2.5 mL of 1.0 percent solution). Each pre-filled syringe is packed in a molded-blister packaging with a Tyvek sheet.

The current United States labeling for SUPARTZ® injections recommends a course of five intra-articular injections one week apart, and also indicates that some patients may benefit from three injections given at weekly intervals. However, as a general precaution, the benefit of less than three injections has not been established.

SUPARTZ® is administered directly into the knee joint. The skin and subcutaneous tissue can be anesthetized with a local anesthetic or a liquid freezing agent can be applied to numb the skin.

Over-the-counter pain medications are all that is required for most patients for any pain and swelling that may follow the injection.

The lead investigator/author (C.W.) chooses to prescribe SUPARTZ® to his patients because of its ease of use and the better results he has seen com-

Exhibit 3: Performance of TKA data by site¹³

Physician	Number knees wWith TKA (%)
Whitman	2/110 (1.8%)
Oweida	4/58 (6.9%)
Allen	2/40 (5.0%)
Comadoll	3/40 (7.5%)
Thomason	12/50 (24.0%)
TOTAL	23/303 (7.6%)

pared to other HA products.¹² After eight years of prescribing SUPARTZ®, he has found that it is less viscous which makes it easier to inject and develop a “feel” for when the needle is extraarticular. This enables the clinician to minimize undesired extraarticular placement of the material. The lower viscosity also allows the clinician to enter the patient’s joint when they are in the supine position with the injection going into the suprapatellar pouch from a superior-lateral approach.

Results and Discussion

Assessing the survivorship of SUPARTZ® joint fluid therapy, 303 knees were evaluated (see Exhibit 1) and a total of 835 series of injections were performed.

Pre-SUPARTZ® injections, approximately 94 percent of the patients rated their knee pain level as severe or moderate. Following repeat injections of SUPARTZ®, 92 percent of those patients evaluated demonstrated improvement in knee pain over time, leaving only 8 percent that did not improve, as shown in Exhibit 2.

Pain level ratings were assessed over a maximum of five injections in a series. Those patients showing improvement were found to show relief of knee pain following injections of SUPARTZ® in as early as 14.7 days (standard deviation = 9.0, range = 3 to 62 days). Patients that had additional series of injections after they experienced pain relief during a series were found to have a lasting effect of knee pain relief for over one year, with an average of 399.5 days (standard deviation = 277.3, range = 35 to 1597 days). This high standard deviation of 277.3 indicates that patients experienced knee pain relief at many different time intervals with an average relief of 399.5 days.

When looking at the 303 last series of injection’s pain ratings, there was a near statistical significant cor-

relation ($p=0.0569$) between performing TKA and the improvement or non-improvement in pain ratings.

For the 303 knees evaluated during the study, only 23 knees (see Exhibit 3) resulted in TKA. The minimum time to TKA was 0.51 years following the first injection and the maximum time was four years. The mean time to TKA was 1.99 years.

At the one-year post completion of a repeat injection series, the freedom from TKA was 99.0 percent, and at two years, it was a 94.7 percent.

Adverse Events (AEs)

The overall safety of each patient was assessed through the collection of AEs during their course of treatment beginning with the patient's first injection of SUPARTZ[®]. AEs were collected and classified as follows: related to the injection, possibly related to the injection, or not related to the injection. Events were categorized as severe, moderate, or mild.

Categories of AE severity assessed were as follows: severe; (significantly limits the subject's ability to perform routine activities despite symptomatic therapy and requires medical or surgical treatment or results in hospitalization) moderate; (interferes with routine activity but responds to symptomatic therapy or rest), and mild; (noticeable to the subject, but does not interfere with routine activity).

There were 26 total reported AEs (25 possibly related and one definitely related to the SUPARTZ[®] injections) and none of them were severe. Of the five moderate AEs reported, only one moderate AE was classified as being definitely related to the SUPARTZ[®] injection; a patient experienced post-injection pain that interfered with walking for three days and required bed rest. With the occurrence number in parentheses, the remaining four moderate AEs were possibly related to the injections and included increased knee pain (2), swelling (1), stiffness (1), and fainting (1).

Twenty (20) mild AEs were reported as being possibly related to the injection. With the number of occurrences in parentheses, the types of all 26 AEs reported (moderate and mild) included ecchymosis of the skin (11), pain (8), swelling (3), stiffness (1), blistering (1), nausea (1), and fainting (1). Please note that some patients reported more than one AE in each knee. For example, three patients experienced both swelling and pain of the knee. Three patients experienced AEs in both knee joints. Overall, AEs definitely related to the SUPARTZ[®] injections occurred in less than 1 percent of the patients and were resolved spontaneously without medical intervention.

Many of the patients also noted improvement in the amount of overall stiffness of the affected knee joint; however, this data was not obtained from all patients.

Cost effectiveness

In addition to providing safe pain relief for longer periods of time and delaying the need for TKA, SUPARTZ[®] is also cost effective for the patient and their healthcare plan provider. For example, in a 2008 study conducted on the costs of viscosupplementations within different healthcare plan types, Yeaw et al. reported that the wholesale acquisition cost of five doses (one series) of SUPARTZ[®] injections was \$580.00.¹⁴ In comparison, in a recent study about TKA, the national average cost of a TKA in 2006 was reported as \$38,447, according to Cook et al.¹⁵ Even if the patient needed multiple SUPARTZ[®] injections, there are still significant savings versus the expense of TKA. Additionally, there are the savings related to using viscosupplementations, like SUPARTZ[®], instead of a patient having TKA at too early or late of an age. For example, as Waddell and Bricker state in their 2007 study of TKA, "In many cases, it may be desirable to delay TKA in younger patients because of the risk of hardware revisions, loosening from the bone, pain from overuse, or to delay or avoid the procedure altogether in older patients or patients with comorbidities who may increase their complications risk at surgery."¹⁶ As the population ages, future cases of knee OA will increase the treatment and economic challenges to the patients, physicians, and healthcare plan providers.

Conclusion

Our conclusion is that SUPARTZ[®] is safe and effective and that it delayed the need for TKA for almost four years in our patient population. Before receiving SUPARTZ[®] injections, approximately 94 percent of the patients rated their pain level as severe or moderate. After repeat injections, 92 percent of those patients evaluated demonstrated improvement in knee pain over time, leaving only 8 percent that did not improve. Our positive clinical results continue to outweigh a low incidence of only 26 reported AEs. AEs definitely related to the injection occurred in less than 1 percent of the patients and were resolved spontaneously without medical intervention.

Only 23 of the patients' knees required a TKA after having repeat SUPARTZ[®] injections. This data indicates significant cost savings associated with the lower treatment cost of SUPARTZ[®] injections versus TKA. Because significant clinical data gathered over a long-term basis on the number of repeat injections of SUPARTZ[®] may support its effectiveness over time, information from this study could be beneficial for multiple situations related to the support for reimbursement of the cost of repeat injections.

Many physicians are now treating knee OA in younger patients (age 50 and under), and using viscosupplementations for these patients earlier in the treatment process. With an earlier knee OA patient population and a large future population reaching their mid-sixties by 2030, alternatives to TKA, like SUPARTZ[®], will be highly desirable from a managed care perspective.

Additionally, our study results, along with the findings of other studies, may also be used to support future research projects for treatment of OA in other joint areas, such as the hand, hip, and shoulder.¹⁷

Our retrospective study includes a few shortcomings. The study was a medium-sized series so additional studies are needed to corroborate these findings in a larger patient population. A more detailed cost analysis would further emphasize the total savings associated with the SUPARTZ[®] injections.

This study was limited to a review of the medical records of patients who had received a minimum of one repeat treatment series of injections into the knee. Our study focused on patients treated with SUPARTZ[®] only. Finally, we should note that some patients will not experience any knee pain relief from any method. JMCM

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