

Original article

Medicoeconomic evaluation of hyaluronic acid for knee osteoarthritis in everyday practice: The MESSAGE study[☆]

Bernard Mazières^{a,*}, Hervé Bard^b, Marie Ligier^c, Isabelle Bru^d,
Geneviève Giret d'Orsay^d, Claude Le Pen^e

^a Rheumatology Department, Rangueil Teaching Hospital, Toulouse, France

^b Rhumatologist, European Georges Pompidou Teaching Hospital, Paris, France

^c Aremis Consultants, Neuilly-sur-Seine, France

^d Laboratoire Chiesi SA, Courbevoie, France

^e Dauphine University, Paris, France

Received 22 July 2006; accepted 15 January 2007

Available online 9 August 2007

Abstract

Introduction: Medicoeconomic data on treatments for osteoarthritis are scant. We investigated the impact of hyaluronic acid therapy on the cost of management of knee osteoarthritis. Our primary objective was to compare medical costs (admissions, outpatient visits, investigations, and treatments) and non-medical costs (sick leaves and transportation) from the perspective of the national health insurance system during the 3 months before and the 6 months after three intraarticular injections of hyaluronic acid. Our secondary objective was to evaluate treatment benefits in terms of pain, function, and quality of life.

Methods: Observational, multicenter, longitudinal, before-after study of the medical and economic effects of hyaluronic acid therapy for symptomatic knee osteoarthritis.

Results: Of the 296 assessable patients (mean age, 69 years; 30% with obesity; 65% women), only 5% of patients were withdrawn prematurely from the study. Significant improvements in the Lequesne index were found 3 and 6 months after treatment; the improvement was greater than 50% in over half the patients. Pain and quality-of-life scores improved significantly. Total cost of the disease decreased from €334 for the 3 pretreatment months to €295 and €233 for posttreatment months 1–3 and 4–6, respectively.

Conclusion: The costs of knee osteoarthritis decreased during the 6 months after Suplasyn[®] therapy, indicating that the cost of the medication was more than offset by the decreased need for other treatments. Concomitantly, clinical benefits were obtained. Under the conditions of everyday practice, hyaluronic acid may provide medical benefits at an acceptable cost.

© 2007 Published by Elsevier Masson SAS.

Keywords: Cost-benefit analysis; Medicoeconomic analysis; Knee osteoarthritis; Hyaluronic acid; Suplasyn[®]

1. Introduction

Knee osteoarthritis is a chronic disabling disease that has a major impact on quality of life and healthcare costs.

[☆] MESSAGE: Medico-économie de Suplasyn[®] dans l'Arthrose du Genou (Medicoeconomics of Suplasyn[®] in knee osteoarthritis).

* Corresponding author at: Service de Rhumatologie, CHU Rangueil, 1 avenue Jean Poulhès, 31059 Toulouse Cedex 9, France. Tel.: +33 561 322 723; fax: +33 561 322 934.

E-mail address: mazieres@cict.fr (B. Mazières).

Expenditures for knee osteoarthritis in France increased by 156% over the last decade, from 1 billion to 1.57 billion Euros per year [1,2]. Viscosupplementation with intraarticular hyaluronic acid is widely used in Europe and North America in patients with unresponsiveness and/or intolerance to acetaminophen and non-steroidal antiinflammatory drugs (NSAIDs) [3]. It is among the treatments listed in European recommendations for the management of knee osteoarthritis [4]. A 2006 Cochrane database review confirmed the efficacy of hyaluronic acid but also found evidence of variability across studies,

products, and follow-up durations [5]. Viscosupplements injected into the joint improve the rheological properties of the synovial fluid. Osteoarthritis is characterized by decreases in the amount and viscosity of endogenous hyaluronic acid. Injecting exogenous hyaluronic acid corrects these abnormalities.

French legislation requires that intraarticular hyaluronic acid injections be prescribed and administered by a rheumatologist, orthopedic surgeon, or physical rehabilitation physician. Because commercially available hyaluronic acid preparations for intraarticular injection are paid for in large part by the universal health insurance system in France, the Economic Committee for Healthcare Products (CEPS) has requested an evaluation of outcomes in treated patients.

Hyaluronic acid is highly purified hyaluronic acid obtained by ultrafiltration of hyaluronic acid produced by bacterial fermentation. In a 3-month trial versus a placebo and NSAID, hyaluronic acid was as effective as NSAID therapy in alleviating pain at rest, more effective in alleviating pain upon physical activity, well tolerated, and devoid of systemic effects [6].

The objective of this study was to determine whether hyaluronic acid therapy provided additional symptom relief over previous conventional treatments, thereby decreasing the use of healthcare resources and the cost of treatment over a 6-month period under the conditions of everyday practice.

2. Methods

2.1. Study design

This was an observational, multicenter, longitudinal, before-after study of the medical benefits and costs of viscosupplementation with hyaluronic acid (Suplasyn[®], Chiesi) in patients with symptomatic knee osteoarthritis managed by 101 office-based rheumatologists in France between April 2003 and January 2004. The sample of study rheumatologists was drawn at random from the entire population of rheumatologists in France who reported using viscosupplementation to treat patients with knee osteoarthritis.

Our primary objective was to compare the cost of knee osteoarthritis during the 3 months before viscosupplementation with three hyaluronic acid injections to the cost during the 6 subsequent months. Our secondary objective was to evaluate the clinical benefits and safety of hyaluronic acid therapy.

The study was approved by the appropriate ethics committee (CCPPRB Toulouse II). It was conducted in compliance with the recommendations of the *Association des Epidémiologistes de Langue Française* for data collection and processing.

2.2. Study patients

Participating rheumatologists informed their patients about the study orally and in writing. Inclusion criteria were age older than 18 years; knee osteoarthritis meeting American College of Rheumatology criteria [7]; and an inadequate response, as assessed by the patient and physician, to level 1 or 2 analgesics

or to NSAID therapy taken daily or on alternate days during the last 3 months. Patients were not included if they had an effusion in the target knee, a history of intraarticular glucocorticoid therapy within the last 3 months, a history of hyaluronic acid injection within the last year, scheduled surgery on the target knee, any of the usual contraindications to intraarticular injections, or known hypersensitivity to hyaluronic acid. Pregnancy was also a non-inclusion criterion.

2.3. Conduct of the study

The study was managed by an independent steering committee, and an independent company organized the study and conducted the statistical analyses.

At the first visit (V0), patients were asked about their treatment for knee osteoarthritis over the last 3 months and about the current status of their disease. Within the next month, three hyaluronic acid injections were administered in the target knee at intervals of 1 week (during visits V1 through V3). Patients were evaluated 3 months (V4) and 6 months (V5) after the last injection. Any additional visits required by the patient's disease during the study period were recorded.

We defined three periods for the evaluation: the pretreatment period (preT), which consisted of the 3 months preceding the first injection, was studied retrospectively; whereas the two posttreatment periods, which consisted of the first 3 months (postT-1) and months 4 through 6 (postT-2) after the last injection were studied prospectively. PreT ended with V0, postT-1 with V4, and postT-2 with V5. At each of these three visits, disease status and healthcare resource use were evaluated (Fig. 1).

2.4. Evaluation criteria

At the first visit (V0), the following data were collected: demographics, past history of health problems, co-morbidities, and procedures and criteria used to diagnose knee osteoarthritis.

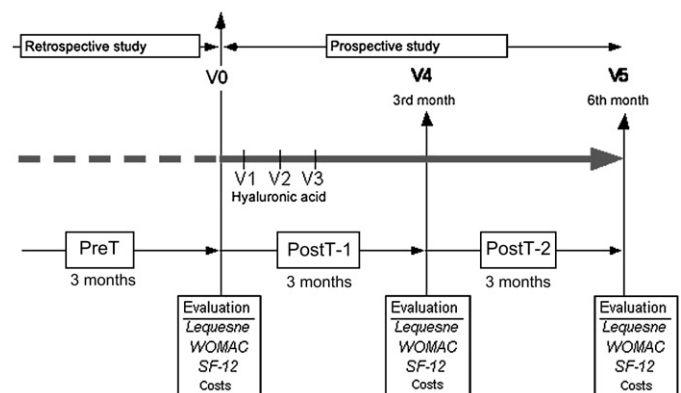


Fig. 1. Study flow chart. Evaluation of patients with knee osteoarthritis, retrospectively during the 3 months before viscosupplementation (preT) and prospectively during the first 3 months (postT-1) and fourth to sixth months (postT-2) after viscosupplementation. Patients were evaluated at visits V0 (immediately before viscosupplementation), V3 (end of postT-1), and V5 (end of postT-2). Suplasyn[®] was injected at visits V1 through V3.

2.4.1. Evaluation of medical benefits

At V0, the physician and patient evaluated disease activity on a 5-point scale ranging from 0 (inactive) to 4 (extremely active). The severity of the structural lesions was assessed by determining the Kellgren-Lawrence grade on an anteroposterior radiograph of both knees taken within the last 6 months [8].

At each of the three evaluation visits (V0, V4, and V5), questionnaires were completed to determine the Lequesne index [9] and the pain and function subscores of the Western Ontario and McMaster Universities (WOMAC) scale [10] with the 5-point Likert format. In addition, quality of life was assessed by determining the physical and mental component summaries on the 12-item Short Form questionnaire (SF-12) [11].

2.4.2. Evaluation of costs

Costs were evaluated from the perspective of the universal health insurance system, which covers much of the healthcare costs (including the cost of medications and medical devices) of all individuals residing in France. The cost of inpatient care was estimated from the nationwide hospital database (*Programme de Médicalisation des Systèmes d'Information*). To estimate the costs of rehabilitation center care and day-hospital joint lavage, we used the health insurance system reimbursement schedules for the Uniform Patient Groups 670 (rehabilitation) and 770 (outpatient arthroscopy), respectively. Similarly, reimbursement schedules for 2003 were used to estimate the costs of visits to general practitioners, rheumatologists, and other healthcare professionals; costs of investigations (e.g., laboratory tests and imaging studies); and costs of care by nurses and physical therapists.

Costs of medications were determined based on the proprietary or international non-proprietary name of each product, dosage, form, start and end dates, and retail price in the 2003 edition of the physician's drug compendium (Vidal dictionary). When the dosage was unknown, the mean dosage recommended in the Vidal was used. When the form used was unknown, we computed the mean cost of all available forms. The cost of the Suplasyn[®] injections was computed by adding the reimbursed costs of the product (114 Euros per injection) and the physician fee for performing each injection. Medical device costs were estimated as the cost of the device added to the cost of delivery when the device was purchased; for rentals, we multiplied the weekly rental fee by the number of weeks of use, and we added delivery costs where appropriate. To estimate spa therapy costs, we used the amounts reimbursed by the health insurance system for the spa therapy per se and the spa physician's fees; we did not have information on the amounts reimbursed for hotel services and transportation, which were paid in part out-of-pocket in proportion to the patient's income and were not recorded for this study.

Among non-medical costs, we estimated days of work lost and transportation costs. For employed patients, we multiplied the mean compensation per sick-leave day [12] by the number of days on sick leave after the first 3 days (for which no compensation is given). Transportation costs were estimated from reimbursements for ambulances and taxis per kilometer and from

the number of trips recorded in the patient's files. Total costs were computed as the sum of medical and non-medical costs.

2.5. Statistics

For this before-after study, we estimated the sample size needed to obtain acceptable precision in the comparison of total costs (medical and non-medical) before versus after hyaluronic acid therapy. We found that including 300 patients would provide 95% confidence intervals for cost estimates, different from zero, with standard deviations of up to 8-fold the mean cost (e.g., a mean cost of €1000 with a SD of up to €8000 would be significantly different from zero). Thus, 350 patients were required to ensure that 300 assessable patients would be available.

We assessed efficacy data and costs for each of the three periods (preT, postT-1, and postT-2). All patients for whom data were available were included in these estimates. For each variable, we computed the mean, standard deviation, median, and 95% confidence interval (95%CI). For each component of total cost, we estimated the mean cost per patient in each period. To compare mean efficacy data and costs between preT and postT-1, and between preT and postT-2, we used Student's *t*-test for paired samples. Statistical tests were performed using SAS V8.02 on a computer operated with Windows[™] (Microsoft, Redmond, WA).

3. Results

Of 310 included patients, 296 were assessable, i.e., received at least two hyaluronic acid injections followed by an evaluation at V4. Among them, 285 were evaluated at V4 and 275 at V5. Only 14 patients were withdrawn prematurely, for the following reasons: withdrawn by the investigator after study inclusion ($n = 9$), injections given too late after V0 ($n = 1$), worsening of the symptoms ($n = 1$), surgery ($n = 1$), skin allergy at the injection site ($n = 1$), and patient request ($n = 1$).

3.1. Description of the study patients at inclusion (Appendix)

Of the 296 patients, 192 (65%) were women. Mean age was 69 ± 10 years (range, 36–88 years). Mean body mass index was 28 ± 5 kg/m², and 30% of men and women were obese (body mass index ≥ 30 kg/m²).

A single knee was affected in 188 (63.5%) patients and both knees in 108 (36.5%) patients. Mean symptom duration was 4.8 ± 5.3 years. Other sites affected with osteoarthritis were the hands (44% of patients), hips (16%), spine (66%), and other joints (10%). Radiographs showed medial femorotibial osteoarthritis in 92% of cases. The Kellgren-Lawrence grade was 2 or 3 in 73% of patients. Radiological evidence of chondrocalcinosis was seen in 39 (13%) patients. Disease activity was usually assessed as moderate to severe by both the patient and the physician.

Mean time from V0 to the first hyaluronic acid injection was 16 ± 13 days (median, 14 days) and mean interval between

injections was 8 ± 3 days (median, 7 days). The injections were given at the superolateral corner of the patella in 60% of cases, with the knee extended in 66% of cases.

3.2. Clinical outcomes (Table 1)

The Lequesne index was significantly lower at V4 and V5 than at V0. The proportion of patients with a 3-point or greater decrease in the Lequesne index was 52% at V4 (3 months after the injections) and 57% at V5 (6 months after the injections). The WOMAC pain and functional impairment scores were significantly decreased at V4 and V5, compared to V0. Significant improvements in the SF-12 quality-of-life score were found at the same time points.

3.3. Health resource utilization and cost of the disease

3.3.1. Admissions related to knee osteoarthritis

Seven admissions occurred during preT, for arthroscopy ($n = 4$), meniscectomy ($n = 1$), joint lavage ($n = 1$), and evaluation of knee pain ($n = 1$). The total cost was €3,999, yielding a mean per patient of €13.5 for the overall population of

296 patients. During postT-2, there were four admissions, for joint lavage ($n = 1$), osteotomy ($n = 1$), single-compartment arthroplasty ($n = 1$), and total knee arthroplasty ($n = 1$). The total cost was €10,637 and the mean cost per patient was €38.7.

3.3.2. Physician visits (Table 2) related to knee osteoarthritis

Visits to general practitioners occurred for 43% of patients during preT compared to only 6% and 7% during postT-1 and postT-2, respectively. In addition to the six visits required by the study protocol, 24 (8%) patients had 38 rheumatologist visits during preT, 3 (1%) patients had 3 visits during postT-1, and 11 (4%) patients had 17 visits during postT-2. The mean number of visits per patient was 1.13 (334 visits by 296 patients) during preT compared to only 1.08 and 1.04 during postT-1 and postT-2, respectively. All patients but 1 had three visits for the injections; 1 patient received only two injections.

The number of visits to physicians in other specialties was 24 during preT, 3 during postT-1, and 11 during postT-2. Most of these visits were to orthopedic surgeons.

Table 1
Effect of viscosupplementation on pain, function, and quality of life in 296 patients with knee osteoarthritis

	V0 (pretreatment)	V4 (3 months)	V5 (6 months)	Difference V0/V4	Difference V0/V5
<i>Lequesne Index</i>					
N. of patients	296	285	275	285	275
Mean \pm SD	11.03 \pm 3.86	8.10 \pm 4.64	7.68 \pm 4.74	2.94	3.28
Median	10.5	7.5	6.5		
Min–Max	2.5–22	0–23	0–22		
<i>t</i> (Student)				14.08	13.81
<i>P</i>				<0.0001	<0.0001
<i>WOMAC pain score</i>					
N. of patients	294	285	275	284	274
Mean \pm SD	9.7 \pm 3.1	6.7 \pm 3.9	6.0 \pm 3.8	2.89	3.60
Median	10	6	6		
Min–Max	1–17	0–18	0–17		
<i>t</i> (Student)				12.97	14.62
<i>P</i>				<0.0001	<0.0001
<i>WOMAC function score</i>					
N. of patients	293	285	275	283	274
Mean \pm SD	31.1 \pm 12.0	22.3 \pm 14.0	19.9 \pm 14.0	8.7	10.9
Median	31	20	17		
Min–Max	2–60	0–56	0–60		
<i>t</i> (Student)				12.24	13.50
<i>P</i>				<0.0001	<0.0001
<i>SF-12 Physical component</i>					
N. of patients	288	273	261	269	256
Mean \pm SD	33.8 \pm 7.6	39.3 \pm 9.1	40.3 \pm 9.2	–5.4	–6.3
Median	32.9	40.0	41.3		
Min–Max	15.6–57.7	19.1–59.1	18.8–58.6		
<i>t</i> (Student)				–9.91	–11.13
<i>P</i>				<0.0001	<0.0001
<i>SF-12 Mental component</i>					
N. of patients	288	273	261	269	256
Mean \pm SD	41.8 \pm 10.5	45.1 \pm 10.4	45.8 \pm 10.2	–3.1	–3.7
Median	41.8	47.4	48.0		
Min–Max	18.6–64.4	16.6–67.2	18.6–66.4		
<i>t</i> (Student)				–4.84	–5.36
<i>P</i>				<0.0001	<0.0001

Table 2
Healthcare service utilization

Healthcare service used	PreT*	PostT-1**	PostT-2***
	296	285	275
<i>Rehabilitation center care</i>			
N. of patients (%)	0	0	1 (0.4)
<i>Physician visits</i>			
General practitioners (%)	126 (43)	18 (6)	20 (7)
Total number of visits	275	34	36
Mean number of visits per patient	0.9 ± 1.3	0.1 ± 0.5	0.1 ± 0.5
<i>Rheumatologists</i>			
N. of patients (%)	296 (100)	285 (100)	275 (100)
Total number of visits	334	288	292
Mean number of visits per patient	1.1 ± 1.0	1.1 ± 0.4	1.0 ± 0.3
<i>Other specialists</i>			
N. of patients (%)	24 (8)	3 (1)	11 (4)
Total number of visits (including orthopedic surgeons)	24 (18)	3 (2)	11 (9)
Mean number of visits per patient	0.1 ± 0.5	0.01 ± 0.1	0.1 ± 0.3
<i>Investigations</i>			
N. of patients (%)	184 (62)	9 (3)	16 (6)
Imaging studies (%)	157 (53)	4 (1)	12 (4)
Mean number per patient	1.2 ± 1.5	0.1 ± 0.5	0.1 ± 0.5
<i>Health professionals other than physicians</i>			
<i>Nurses</i>			
N. of patients (%)	184 (62.2)	9 (3.2)	16 (5.8)
Mean number of sessions per patient	26.2 ± 16.2	ND	33.0 ± 21.0
<i>Physical therapists</i>			
N. of patients (%)	45 (15.2)	18 (6.3)	21 (7.6)
Mean number of sessions per patient	38.8 ± 5.0	26.7 ± 4.5	26.4 ± 3.7
<i>Spa therapy</i>			
N. of patients (%)	0	3 (1.1)	4 (1.5)
<i>Medical devices</i>			
N. of patients (%)	23 (7.8)	15 (5.3)	13 (4.7)
Walking sticks	18	12	8
Wheelchair	2	0	2
Walker	2	1	0
Knee wrap	1	1	3
Knee brace	0	1	0

*PreT: 3 months before treatment with three intraarticular injections of Suplasyn®. **PostT-1: first 3 months after treatment with three intraarticular injections of Suplasyn®. ***PostT-2: months 4 through 6 after treatment with three intraarticular injections of Suplasyn®.

3.3.3. Investigations (Table 2) related to knee osteoarthritis

Imaging studies contributed most of the investigations. Few patients underwent laboratory tests (blood cell counts, renal function tests, or liver function tests).

3.3.4. Care from health professionals other than physicians and use of medical devices (Table 2)

This category comprised care from nurses and physical therapists, as well as spa therapy. The number of patients who required physical therapy decreased after the injections. An even larger decrease occurred in the number of patients requiring care from nurses. Medical devices were used by less than 10% of patients.

3.3.5. Medications (Table 3)

Medications included NSAIDs, analgesics, symptomatic slow-acting drugs for osteoarthritis (Sy-SADOAs), and proton pump inhibitors. Compared to preT, reductions in the percentage of patients who used medications were 39.1% for NSAIDs, 19.2% for analgesics, 5.6% for Sy-SADOAs, and 10.6% for proton pump inhibitors. The result was a 31% decrease in the cost of medications between preT and postT-2.

The health insurance system in France categorizes hyaluronic acid therapy as a medical device and reimburses 65% of the cost of the product and 70% of the cost of the injections, yielding a total cost of €96.05 from the perspective of the health insurance system for the three injections.

3.3.6. Non-medical costs (Table 4)

Hyaluronic acid therapy was followed by decreases in both the number of patients on sick leave and sick-leave duration. Table 5 reports the corresponding costs and the total costs. Compared to preT, total cost per patient was lower during

Table 3

Medication use, with the mean cost per patient from the perspective of the national health insurance system

Medications	PreT*	PostT-1**	PostT-2***
	296	285	275
<i>NSAIDs</i>			
N. of patients (%)	202 (68.2)	122 (42.8)	80 (29.1)
Mean number of medications per patient	1.1 ± 0.3	1.2 ± 0.5	1.1 ± 0.4
Mean cost per patient (€)	26.4 ± 31.9	20.9 ± 33.7	14.2 ± 30.3
<i>Analgesics</i>			
N. of patients (%)	203 (68.6)	167 (58.6)	135 (49.4)
Mean number of medications per patient	1.1 ± 0.3	1.3 ± 0.6	1.2 ± 0.4
Mean cost per patient (€)	20.3 ± 21.1	19.6 ± 24.7	16.6 ± 26.4
<i>Sy-SADOAs</i>			
N. of patients (%)	107 (36.1)	97 (34.0)	84 (30.5)
Mean number of medications per patient	1.0 ± 0.2	1.1 ± 0.3	1.0 ± 0.2
Mean cost per patient (€)	7.9 ± 12.5	7.9 ± 12.5	6.8 ± 11.6
<i>Proton pump inhibitors</i>			
N. of patients (%)	57 (19.3)	35 (12.3)	24 (8.7)
Mean number of medications per patient	1.0 ± 0	1.1 ± 0.2	1.1 ± 0.3
Mean cost per patient (€)	9.5 ± 25.2	9.7 ± 27.8	6.5 ± 22.6
<i>Other</i>			
N. of patients (%)	35 (11.8)	37 (12.3)	28 (10.2)
Mean number of medications per patient	1.9	2.1	2.5
Mean cost per patient (€)	6.3 ± 1.6	6.0 ± 1.7	4.0 ± 1.1
<i>TOTAL</i>			
N. of patients (%)	296 (100)	239 (83.6)	212 (77.1)
Mean number of medications per patient	2.3 ± 1.2	2.1 ± 1.7	1.5 ± 1.4
Mean cost per patient (€)	70.4 ± 54.7	64.3 ± 64.0	48.4 ± 55.6

*PreT: 3 months before treatment with three intraarticular injections of Suplasyn®. **PostT-1: first 3 months after treatment with three intraarticular injections of Suplasyn®. ***PostT-2: months 4 through 6 after treatment with three intraarticular injections of Suplasyn®. NSAIDs: non-steroidal antiinflammatory drugs; Sy-SADOAs: symptomatic slow-acting drugs for osteoarthritis.

Table 4
Non-medical costs from the perspective of the national health insurance system

Costs	PreT (n = 296)	PosT-1 (n = 285)	PostT-2 (n = 275)	ΔPreT/PostT-1 (n = 285)	ΔPreT/PostT-2 (n = 275)
<i>Transportation</i>					
N. of patients (%)	2 (0.7)	1 (0.35)	2 (0.73)		
Mean number of trips per patient	1.5	1	1.5		
Mean distance traveled per patient (km)	5	60	103		
Mean cost per patient (€)	0.21	0.25	1.51	0 <i>P</i> = 0.934	-1.3 <i>P</i> = 0.192
<i>Sick leaves</i>					
N. of patients (%)	11 (3.7)	8 (2.8)	7 (2.5)		
% of employed patients	17	14	12		
Total number of days off work	765	649	606		
Mean duration per patient (days)	70 ± 38	81 ± 23	87 ± 12		
Mean cost for the overall population (€)	100.2	88.9	86.2	3.0 <i>P</i> = 0.875	9.0 <i>P</i> = 0.712
Mean cost for all employed patients	463.6	429.3	388.7		
Total non-medical costs (€)	100.44	89.13	87.73	3.0 <i>P</i> = 0.876	7.7 <i>P</i> = 0.752

*PreT: 3 months before treatment with three intraarticular injections of Suplasyn[®]. **PostT-1: first 3 months after treatment with three intraarticular injections of Suplasyn[®]. ***PostT-2: months 4 through 6 after treatment with three intraarticular injections of Suplasyn[®].

postT-1 and significantly lower during postT-2. The mean savings was €101 per patient.

4. Discussion

Our observational study reflects the use of hyaluronic acid therapy in everyday practice. However, it shares the limitations inherent in all observational studies. The modalities for collecting follow-up data were less stringent than during

clinical trials. Nevertheless, only 7% of patients were prematurely withdrawn from the study, and there were few missing data.

All the clinical efficacy criteria (pain, function, and quality of life) were significantly improved 3 months after hyaluronic acid therapy compared to the 3 previous months, and further improvements in pain and function were achieved during the fourth through sixth month after hyaluronic acid. Although our study design precluded the inclusion of a control group,

Table 5
Recapitulation of costs per patient in Euros from the perspective of the national health insurance system

N	PreT (n = 296)	PosT-1 (n = 285)	PostT-2 (n = 275)	ΔPreT/PostT-1 (n = 285)	ΔPreT/PostT-2 (n = 275)
Inhospital care	13.51	0	38.68	13.68 <i>P</i> = 0.9	25.18 <i>P</i> = 0.34
Rehabilitation center care	0	0	6.63	—	ns
Physician visits	42.805	20.714	20.794	22.091 <i>P</i> < 0.0001	22.011 <i>P</i> < 0.001
Suplasyn [®] therapy		96.05			
Investigations	49.81	5.44	5.74	43.8 <i>P</i> < 0.0001	44.2 <i>P</i> < 0.0001
Health professionals (physicians excluded)	55	18.23	22.91	37.1 <i>P</i> = 0.0003	35.3 <i>P</i> = 0.002
Devices	2.06	0.95	2.04	ns	ns
Medications	70.4	64.3	48.4	6.2 <i>P</i> = 0.21	22.0 <i>P</i> < 0.0001
Medical costs excluding investigations	183.78	200.20	139.47	16.42 <i>P</i> = 0.30	44.31 <i>P</i> = 0.22
Total medical costs	233.59	205.64	145.20	27.95 <i>P</i> = 0.11	88.38 <i>P</i> = 0.02
Non-medical costs	100.44	89.128	87.73	11.315 <i>P</i> = 0.81	12.71 <i>P</i> = 0.79
Total cost	334.03	294.76	232.80	26.3 <i>P</i> = 0.308	98.6 <i>P</i> = 0.030

*PreT: 3 months before treatment with three intraarticular injections of Suplasyn[®]. **PostT-1: first 3 months after treatment with three intraarticular injections of Suplasyn[®]. ***PostT-2: months 4 through 6 after treatment with three intraarticular injections of Suplasyn[®]. ns: non-significant difference.

a Lequesne-index decrease greater than 2 is considered clinically meaningful. In our study, the mean Lequesne index decreases were 2.94 and 3.28 after 3 and 6 months, respectively. In addition, the index diminished by 3 points or more in over half the patients.

These clinical improvements were achieved despite reductions in physician visits and medical costs. The reductions were statistically significant for several components of care such as medications and physical therapy. Decreases occurred in both the number of patients on medications and the number of medications used per patient. The number of investigations was smaller after than before the injections. However, this result should be interpreted with caution, as persistent symptoms despite conventional therapy may lead to knee radiographs being obtained before hyaluronic acid therapy.

Few cost-benefit studies have been reported for osteoarthritis or hyaluronic acid injections. From a theoretical model based on epidemiological, clinical, therapeutic, and economic data in the literature on knee osteoarthritis, Waddell et al. concluded that introducing hyaluronic acid therapy led to a 16% reduction in direct medical costs over a 3-year period [13]. Yen et al. [14], in contrast, found no cost savings from adding hyaluronic acid to a treatment strategy for knee osteoarthritis. In two other studies, introducing hyaluronic acid resulted in additional costs but significantly improved quality of life [15,16]. The modest cost increase was consistent with a recommendation to use hyaluronic acid. Different hyaluronic acid preparations were administered in these studies, and differences in safety and/or efficacy may exist across preparations [17]. Kahan et al. [18] compared costs in 500 patients given standard treatment with or without hyaluronic acid. Total cost per patient over the 9-month follow-up was €829 in both groups, but outcomes were significantly better in the group given hyaluronic acid. The cost of the hyaluronic acid injections was offset by decreases in the use of other treatments. The criteria used for cost estimates in this earlier study [18] were the same as in our study. We obtained a similar total cost of €862 per patient over the 9-month study period, which constitutes evidence of external validity. In Italy, the direct annual cost of knee osteoarthritis was estimated at €934 and the indirect cost at €1236 per patient [19]. In our study, extrapolating the data from the pretreatment period to 1 year yielded a mean cost per patient of €932 from the perspective of the health insurance system.

Appendix

Demographic, social, and clinical parameters at study inclusion in the 296 study patients ($n = 296$).

Place of residence ($n = 295$)

Urban (>50,000 population): 127 (43%)

Semi-rural (20,000–50,000 population): 73 (25%)

Rural (<20,000 population): 95 (32%)

Self-sufficiency ($n = 294$)

Independent without assistance: 268 (91.2%)

Independent with assistance: 25 (8.5%)

Retirement home without health professionals: 1 (0.3%)

Health insurance ($n = 296$)

National health insurance only: 98 (33.0%)

National health insurance + complementary private insurance: 198 (66.9%)

Job category

Farmer: 25 (8.4%)

Artisan, retailer, head of company: 34 (11.5%)

Executive, professional: 48 (16.2%)

Employee: 102 (34.5%)

Unemployed: 53 (17.9%)

Factory worker: 15 (5.1%)

Foreman: 5 (1.7%)

Other: 14 (4.7%)

Occupational status

Full-time paid job: 53 (17.9%)

Part-time paid job: 5 (1.7%)

Retired for health reasons: 9 (3.0%)

Retired at the normal age: 187 (63.2%)

Unemployed: 27 (9.1%)

Unpaid job: 9 (3.0%)

Other: 6 (2.0%)

Kellgren-Lawrence grade

Grade 1: 35 (11.8%)

Grade 2: 96 (32.4%)

Grade 3: 119 (40.2%)

Grade 4: 46 (15.6%)

Evaluation of disease activity ($n = 295$)

By the patient

None: 2 (0.68%)

Mild: 29 (9.83%)

Moderate: 134 (45.42%)

Severe: 130 (44.07%)

Very severe: 0 (0%)

By the physician

None: 1 (0.34%)

Mild: 31 (10.51%)

Moderate: 167 (56.61%)

Severe: 95 (32.20%)

Very severe: 1 (0.34%)

References

- [1] Le Pen C, Reygrobelle C, Gerentes I. Financial cost of osteoarthritis in France. The "COART" France study. *Joint Bone Spine* 2005;72: 567–70.
- [2] Gupta S, Hawker GA, Laporte A, Croxford R, Coyte PC. The economic burden of disabling hip and knee osteoarthritis (OA) from the perspective of individuals living with this condition. *Rheumatology (Oxford)* 2005;44:1531–7.
- [3] Dictionnaire Vidal 2003.
- [4] Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCIIT). In: *Ann Rheum Dis*, 62; 2003. 1145–1155.
- [5] Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2006;19. CD005321.
- [6] Petrella RJ, DiSilvestro MD, Hildebrand C. Effects of hyaluronate sodium on pain and physical functioning in osteoarthritis of the knee. *Arch Inter Med* 2002;162:292–8.
- [7] Altman R, Brandt K, Hochberg M, Moskowitz R, Bellamy N, Bloch DA, et al. Design and conduct of clinical trial in patients with osteo-arthritis:

- recommendations from a task force of the Osteoarthritis Research Society. Results from a workshop. *Osteoarth Cartilage* 1996;4:217–43.
- [8] Kellgren JH, Lawrence JS. Radiological assessment of osteoarthritis. *Ann Rheum Dis* 1957;16:494–502.
- [9] Lequesne MG, Mery C, Samson M, Gerard P. Indexes of severity for osteoarthritis of the hip and knee. *Scand J Rheumatol* 1987;65:85–9.
- [10] Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip and knee. *J Rheumatol* 1988;15:1833–40.
- [11] Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol* 1998;51:1171–8.
- [12] CRAM de l'Ile de France. Indicateurs Statistiques, Edition 2002/2003.
- [13] Waddell D, Rein A, Panarites C, Coleman PM, Weiss C. Cost implications of introducing an alternative treatment for patients with osteoarthritis of the knee in a managed care setting. *Am J Manag Care* 2001;7:981–91.
- [14] Yen ZS, Lai MS, Wang CT, Chen LS, Chen SC, Chen WJ, et al. Cost-effectiveness of treatment strategies for osteoarthritis of the knee in Taiwan. *J Rheumatol* 2004;31:1797–803.
- [15] Allhoff P, Graf von der Schulenburg JM. Cost-effectiveness of conservative therapy of knee joint osteoarthritis [Article in German]. *Z Orthop Ihre Grenzgeb* 1998;4:288–92.
- [16] Torrance GW, Raynauld JP, Walker V, Goldsmith CH, Bellamy N, Band PA, et al. A perspective, randomized, pragmatic, health outcomes trial evaluation the incorporation of hylan-20 into the treatment paradigm for patients with knee osteoarthritis (part 2 of 2): economic results. *Osteoarthritis Cart* 2002;10:518–27.
- [17] Mullins CD. Response to Torrance, et al (letter). *Osteoarthritis Cart* 2003;11:377–8.
- [18] Kahan A, Lléu PL, Salin L. Prospective randomized study comparing the medicoeconomic benefits of Hylan GF-20 vs. conventional treatment in knee osteoarthritis. *Joint Bone Spine* 2003;70:276–81.
- [19] Learadini G, Salaffi F, Caporali R, Canesi B, Rovati L, Montanelli R. Italian Group for Study of the Costs of Arthritis. Direct and indirect costs of osteoarthritis of the knee. *Clin Exp Rheumatol* 2004;22:699–706.