Adv Ther (2016) 33:2200–2210
DOI 10.1007/s12325-016-0433-3

ORIGINAL RESEARCH

Potential Impact of Biologically Derived Hyaluronic Acid on Quality of Life in Patients with Knee Osteoarthritis in the United States

Jeffrey Rosen · Parag Sancheti · Anke Fierlinger · Faizan Niazi · Herman Johal · Asheesh Bedi

Received: August 10, 2016 / Published online: November 3, 2016

ABSTRACT

Introduction: Knee osteoarthritis is one of the leading causes of disability in the world. Intra-articular hyaluronic acid (IA-HA) is a treatment modality that provides a minimally invasive treatment option for the management of osteoarthritis-related symptoms. This study examined the current and potential economic impact of using a biologically derived, high molecular weight hyaluronic acid preparation (Euflexxa) on the US population for the management of knee osteoarthritis.

Methods: A model was developed to estimate the total number of patients with symptomatic knee osteoarthritis in the US in 2015, distributed by Kellgren–Lawrence (K–L) grade, and the number of people living with total knee arthroplasty (TKA). The potential utility of Euflexxa was applied to this model population to determine the current and potential impact of the treatment as the total number of quality adjusted life years (QALY) saved within the US population.

Results: There are approximately 12 million people currently suffering from symptomatic knee osteoarthritis in the US, and approximately 5 million living with TKA. It was estimated that, with a target treatment group of K–L grades 2–3, there are approximately 4 million patients eligible for treatment with a high molecular weight intra-articular hyaluronic acid injection. With current use, it is estimated that Euflexxa can save 36,730 QALY/year among the US population, and

Enhanced content To view enhanced content for this article go to http://www.medengine.com/Redeem/5217F060447ECE97.

J. Rosen (✉)
Department of Orthopaedics and Rehabilitation, New York Presbyterian Queens, New York, NY, USA
e-mail: Jeffrey.Rosen@nyumc.org

J. Rosen
Department of Clinical Orthopaedic Surgery, Weill Medical College of Cornell University, New York, NY, USA

P. Sancheti
Sancheti Institute for Orthopaedics and Rehabilitation, Pune, Maharashtra, India

A. Fierlinger · F. Niazi
Ferring Pharmaceuticals Inc., Parsippany, NJ, USA

H. Johal
Division of Orthopaedics, Department of Surgery, Centre for Evidence-Based Orthopaedics, McMaster University, Hamilton, ON, USA

A. Bedi
Department of Orthopaedic Surgery, University of Michigan, Ann Arbor, MI, USA

has the potential to save an additional 369,181 QALY/year if used by all eligible patients. ***Conclusions***: This study demonstrates that more widely used, biologically derived, high molecular weight IA-HAs, such as Euflexxa, have the potential to save a substantial number of QALYs among the US population with symptomatic knee osteoarthritis.
Funding: Ferring Pharmaceuticals Inc.

Keywords: Economic; Euflexxa; Hyaluronic acid; Knee; Orthopaedics; Osteoarthritis

INTRODUCTION

Knee osteoarthritis (OA) is a chronic, progressive disease that continues to be one of the leading causes of disability among active patients in the USA. Knee OA results in a decrease in quality of life for those suffering from the disease, as well as a large financial burden on health care systems and society [1, 2]. The prevalence of symptomatic knee OA in the USA was estimated to be 9.9 million in 2010, and it is estimated that among older adults in the USA, there are over 10 million quality of life years lost annually because of knee OA [3, 4].

A number of treatment methods are available for managing the symptoms of knee OA. Non-surgical treatments may incorporate changes in diet and exercise, ambulatory aids, simple analgesics, and non-steroidal anti-inflammatory drugs (NSAIDs), while more invasive treatments may include intra-articular injections and surgical interventions like total knee arthroplasty (TKA). Many patients diagnosed with OA may have comorbidities precluding them from some of the available treatment options [5]. There are also patients that may not demonstrate an adequate response to non-surgical treatments and are unwilling or medically unsuitable to undergo surgical interventions [6]. Experts argue that it is essential to prolong the period of time between the decline of conservative treatment efficacy and surgical intervention, as having TKA at a younger age may increase the likelihood of requiring a revision, leading to increased costs and possible complications [7]. It is therefore important to consider treatment options available that may alleviate symptoms related to knee OA and delay the need for primary TKA in order to reduce the likelihood of requiring a revision TKA.

The use of intra-articular hyaluronic acid (IA-HA) as a treatment method for knee OA presents a non-surgical option for symptom relief which may provide better results than other conservative treatment options [8, 9]. Evidence also suggests that the use of IA-HA preparations may safely delay the time to arthroplasty [10, 11]. The IA-HA preparation Euflexxa (1% sodium hyaluronate) has been shown to be a cost-effective method of treating the symptoms associated with knee OA; however, the current and potential economic impact of this form of treatment on the US population has yet to be determined [12].

The purpose of this study is to determine the current and potential impact that a biologically derived high molecular weight IA-HA (Euflexxa) may have on quality adjusted life years (QALY) if used more widely for patients suffering with knee OA.

METHODS

Ethics Statement

This article does not contain any new studies with human or animal subjects performed by any of the authors.

Study Scope and Model Generation

We modelled the total number of patients in the USA (2015) with symptomatic knee OA, distributed across Kellgren–Lawrence (K–L) OA severity grades, and the current number of patients with TKA. Using these estimates, we projected the total number of eligible patients who may benefit from the use of Euflexxa versus conventional care in the USA.

The model was developed to provide an estimate for the prevalence of symptomatic knee OA in the USA in 2015. Estimates for the prevalence of symptomatic knee OA in the USA were obtained from the American Academy of Orthopaedic Surgeons (AAOS) [3], and estimates on the incidence of knee OA, prevalence of TKA, and incidence of TKA were obtained from the published literature [13–15] (Table 1). The portion of the population who have undergone a TKA was omitted from the model, given that they have already received definitive knee OA treatment and would no longer be eligible to benefit from an IA-HA injection. As incidence data was sourced from 1995, the prevalence per 100,000 person/years was taken and adjusted for the age and sex distribution for 2015 [13]. It was estimated that there were 9.9 million people with symptomatic knee OA in the USA in 2010, and that the annual incidence of symptomatic knee OA in the US is approximately 770,000 (Table 1).

The distribution of patients with knee OA by K–L severity grades was obtained from a large observational study on knee OA involving 3021 people surveyed in the US population [16]. The majority of studies examining IA-HA involved participants with K–L grades of 2–3, so the percentage of the symptomatic OA population with K–L grades 2 and 3 was calculated to determine the total number of patients eligible to benefit from IA-HA injections. Patients across all K–L levels who had not received a TKA or were currently using IA-HA were considered eligible to receive appropriate conventional care. The current use of Euflexxa and other IA-HA products was obtained through the IMS claims data for 2014 [17].

The mortality rate corresponding to the demographics of the model population was used, under the previously validated assumption that mortality amongst the OA population is similar to that of the general US population [18–20]. Data on utility scores for the healthy US population was obtained from the literature [21].

The changes in health state of patients receiving treatment was reported in terms of a utility score, represented in QALYs, a frequently used quality of life measurement in health economic analyses. QALYs are determined by using utility values that represent desired health states which, for a single patient, vary from 0 (indicating death) to 1 (indicating perfect health) [22]. In order to determine the impact of a treatment, the number of eligible patients for the treatment was multiplied by the increase in utility score resultant from that treatment.

Total QALYs saved within the population of patients with symptomatic knee OA in the USA for 1 year was calculated for the following three scenarios: (1) all eligible patients with knee OA receiving no treatment versus current Euflexxa use; (2) current Euflexxa use versus use in all eligible patients with knee OA; and (3) all eligible patients with knee OA receiving no treatment versus all eligible patients receiving Euflexxa.

OA Prevalence and TKA Prevalence Calculations

The prevalence of symptomatic knee OA in the USA for the year 2015 was estimated according to the formula

Table 1 US OA demographic values

Variable	Past estimates (year)	2015 estimate
US symptomatic knee OA prevalence	9,900,000 (2010)[a]	12,338,273
US OA incidence	768,494 (1995)[b]	605,598
US TKA prevalence	4,000,000 (2013)[c]	5,240,455
US TKA incidence	671,374 (2012)[d]	–
US death rate in adults >35	1.026% (2007)[e]	–
K–L grade 1	30.0% (2009)[f]	2,130,382
K–L grade 2	27.3% (2009)[f]	1,939,724
K–L grade 3	29.2% (2009)[f]	2,074,428
K–L grade 4	13.4% (2009)[f]	953,283
Total eligible patients	–	4,014,153
Current Euflexxa use	276,168 (2014)[g]	276,168
Current other IA-HA use	962,185 (2014)[g]	962,185
Total eligible non-HA users	–	3,051,968

[a] AAOS, 2010
[b] Oliveria, 1995 [13]
[c] Weinstein, 2013 [14]
[d] Healthcare Cost and Utilization Project, 2015 [15]
[e] Centers for Disease Control and Prevention, 2015 [18]
[f] Multicenter Osteoarthritis Study, 2010 [16]
[g] IMS, 2014 [17]

$$f^5(x) = (x+y) - (x+y) \times z$$

where x is the 2010 symptomatic knee OA prevalence, y is the symptomatic knee OA incidence, and z is the US death rate for adults over 35.

A similar formula was used to estimate the prevalence of TKA in the US population:

$$f^2(a) = (a+b) - (a+b) \times z$$

where a is the 2013 TKA prevalence, b is the TKA incidence, and z is the US death rate for adults over 35.

Both of these formulas are nested formulas, where the number of times the formula is nested corresponds to the superscript number. The nested formula takes the preliminary prevalence, adds the incidence, and subtracts the death rate to gain the prevalence for the following year. This new prevalence is then the starting point for the next iteration of the formula, which is repeated for the number of times specified.

Treatment

The treatment option examined in this study is the high molecular weight IA-HA injection Euflexxa. In a randomized controlled trial (the FLEXX trial), Altman et al. examined this preparation over two courses of three injections, with 6 months between each course of treatment [23]. As a comparator, we used appropriate

conservative care (henceforth referred to as "appropriate care"), which was defined as all non-IA-HA treatments (NSAIDS and other analgesics, physiotherapy, weight loss, ambulatory aids), and abstracted the data from a randomized controlled trial by Torrance et al. [24].

Utility Score Calculations

Baseline and treatment utility scores for Euflexxa over the course of a year were abstracted from Hatoum et al. [12], plotted, and the area under the curve between the two treatments was calculated for the total QALYs gained over 1 year. To model those receiving no treatment, baseline scores were extrapolated over a year with the assumption that their condition would neither worsen nor improve. Utility score information for appropriate care was obtained from Torrance et al., which compared baseline utility scores to scores following one year of appropriate care [24]. Utility scores for the US population across different age groups were abstracted from previously published EQ-5D data [22]. Since patients who receive IA-HA as a treatment method also receive aspects of appropriate care in addition to the injections, the QALY of appropriate care was subtracted from the QALY of the IA-HA preparation to account for gains potentially attributed to the use of appropriate care.

Economic Impact Calculation

The current and potential impact of each treatment was calculated by multiplying the utility score of the treatment for one person over the course of a year by the number of people currently using, or eligible to use the treatment, respectively. The current impact of Euflexxa was determined by comparing the current use of Euflexxa to no use. The potential impact of Euflexxa was determined by modelling the utility of all eligible patients using Euflexxa and comparing it to the modelled utility of both current use and no use.

Sensitivity Analysis

Sensitivity analysis was conducted to evaluate the robustness of the results, and to provide confidence intervals to account for potential variation in both the population of eligible patients and the efficacy of the treatment. This was evaluated by performing a two-way sensitivity analysis by increasing and decreasing both the number of eligible patients and the utility score of Euflexxa by ±20%.

Sensitivity analysis was also performed to provide insight into potential uncertainties in certain input domains. The current use of Euflexxa was determined from IMS claims data in 2014; however, as this value may have either increased or decreased in 2015, a two-way sensitivity analysis was performed on the current use of Euflexxa. In addition, there is some uncertainty as to whether the mortality rate of persons with OA is similar to or higher than that in the general population [18–20, 25]. In order to consider this uncertainty, a two-way sensitivity analysis was performed adjusting the mortality rate.

RESULTS

Knee OA Prevalence in the USA

The estimate for the number of people with symptomatic knee OA in the USA in 2015 is therefore approximately 12.3 million. The model estimated the prevalence of patients who have received a TKA in the USA to be approximately 5.2 million, which left 7.1 million people in the USA with symptomatic

knee OA who have not received a TKA. The number of patients with K–L 2–3 OA was determined to be 4.0 million, or roughly 32% of the population who have symptomatic knee OA [17]. To determine the number of patients eligible for Euflexxa injection, the number of patients receiving other forms of IA-HA were subtracted ($n = 962{,}185$), leaving 3.0 million eligible patients, of which 276,168 are currently using Euflexxa [18].

Utility Scores

A calculation of the area under the curve between baseline and treatment over 1 year for the use of Euflexxa indicated that there was 0.163 QALYs gained per year per person, while the effectiveness of appropriate care was determined to be 0.03 QALYs gained per person per year [24]. The QALYs gained per person per year for Euflexxa when accounting for the concomitant use of appropriate care was therefore considered to be 0.133 QALYs.

Current Impact of Euflexxa

Figure 1 shows the 1-year QALY for a healthy individual, an OA patient receiving no treatment, and an OA patient receiving Euflexxa, and for a 62-year-old (mean age of the FLEXX trial treatment group) [23]. The current estimate for the number of QALYs saved by Euflexxa is 36,730 QALY/year when comparing current use to no use (Table 2).

Potential Impact of Euflexxa

If all 3.0 million eligible symptomatic knee OA patients were to use Euflexxa, then an additional 369,181 QALY/year could be saved in addition to the current impact of Euflexxa. If all eligible patients were treated with Euflexxa, there would be a potential 405,911 QALY/year saved, when compared to not treating any eligible patients with Euflexxa (Table 2).

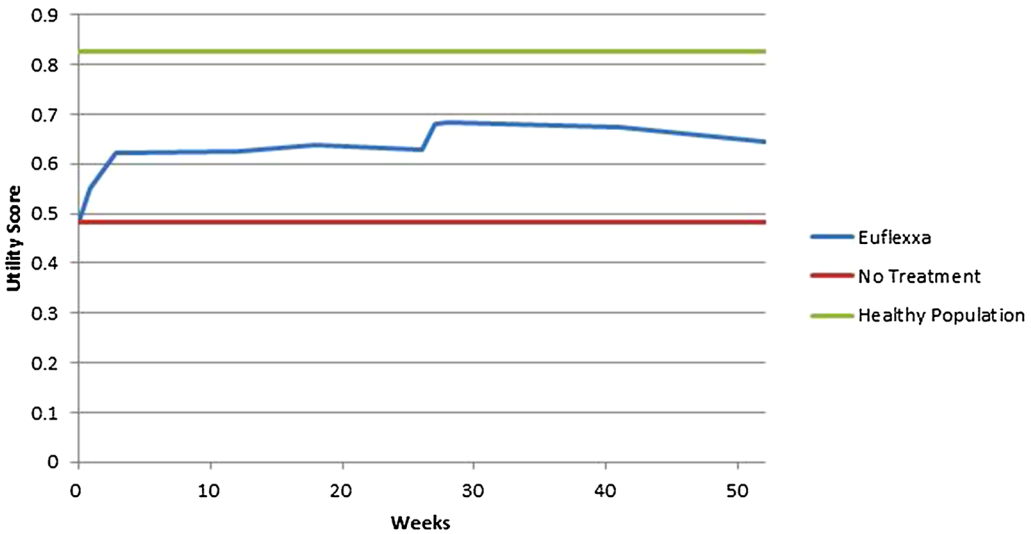

Fig. 1 QALY for healthy individual, OA patient receiving no treatment, and OA patient receiving Euflexxa (age 62)

Table 2 Impact of Euflexxa

Variable	Euflexxa	Appropriate care
Baseline utility	0.482	0.46
Post treatment utility	0.645	0.51
QALY gained	0.163	0.03
Current QALY gained per year (current use–no use)	36,730	–
Potential QALY gained per year (maximum use–no use)	405,911	185,074
Potential additional QALY gained per year (maximum use–current use)	369,181	–

Table 3 Sensitivity analysis

			Number of eligible patients	QALY and impact			
				High		Low	
				QALY	Impact	QALY	Impact
Euflexxa	Current use	High	331,401	0.1596	52,891	0.1064	35,261
		Low	220,934		35,261		23,507
	Additional	High	3,330,960		531,621		354,414
		Low	2,220,640		354,414		236,276
	Maximum	High	3,662,362		584,512		389,675
		Low	2,441,574		389,675		259,783
Appropriate care	Maximum	High	7,402,964	0.036	266,506	0.024	177,671
		Low	4,935,309		177,671		118,447

Comparison to Appropriate Care

The model determined that 6.2 million patients were eligible for appropriate care. The total number of QALY saved if all eligible patients were to use appropriate care was determined to be 185,074 QALY/year, less than half of the impact of Euflexxa.

Sensitivity Analysis

When evaluating the current use of Euflexxa, the modelled value of 36,730 QALY/year saved ranged from 23,507 to 52,891 QALY saved, when both the number of eligible patients and the utility score of Euflexxa were adjusted by ±20% (Table 3). The range of values for the additional QALY/year saved, if all potential patients used Euflexxa, was 287,999–450,363 QALY/year for a potential total range of 324,729–487,094 QALY saved per year. The sensitivity analysis for the potential maximum QALY/year saved by appropriate care revealed that the impact ranged from 118,447 to 266,506 QALY/year.

The sensitivity analysis examining the current use of Euflexxa determined that for the modelled 276,168 patients the lower and upper limits of the sensitivity were 220,934 and 331,401, respectively. These limits

corresponded to the originally modelled 36,730 QALY/year adjusting to 44,076 QALY/year for the upper limit and 29,384 QALY/year for the lower limit. When examining mortality rate, it was found that a 20% decrease in the mortality rate increased the number of persons with symptomatic knee OA to 12,454,377 corresponding to 414,645 QALY/year saved, while an increase in the mortality rate led to a decrease in the persons with symptomatic knee OA to 122,223,078 and an impact of 397,247 QALY/year saved.

DISCUSSION

The purpose of this study was to evaluate the current and potential impact of a biologically derived, high molecular weight IA-HA preparation (Euflexxa) on the US population with symptomatic knee OA. Our model found that Euflexxa currently saves 36,730 QALY/year, and has the potential to save an additional 369,181 QALY/year if it was to be more widely administered.

Several studies have looked at the cost-effectiveness of various treatments [2, 12, 24], the lifetime medical costs of treatments [26, 27], and the impact of OA treatments in European countries [28]. To our knowledge, this is the first study to measure the current and potential impact of a symptomatic knee OA treatment modality with respect to the total number of QALYs saved per year across the entire US population. The lack of literature demonstrating the impact of other treatment methods makes it difficult to compare the impact of Euflexxa to other treatment modalities; however, we were able to compare our intervention to appropriate care, which covers all other forms of non-operative treatment.

Previous literature has shown that treatment of knee osteoarthritis with IA-HA, and specifically with biologically derived hyaluronic acid (Bio-HA), is a cost-effective treatment option over appropriate care [12, 24]. The results of this study also demonstrate a difference in the potential impact of these two treatment methods. While appropriate care had a larger eligible patient base compared to Euflexxa (50% versus 34% of all symptomatic knee OA patients, respectively), Euflexxa still demonstrated an overall larger impact on the symptomatic knee OA population by more than double (405,911 QALY/year to 185,074 QALY/year, respectively).

Several assumptions were made within this study which may be limitations of the accuracy of the model. The first assumption is that only patients with K–L 2 or 3 are eligible for the use of Euflexxa. It is possible for patients with K–L 1 and 4 to be prescribed IA-HA, and this assumption may underestimate the total number of patients who may benefit from the use of the treatment. Second, when comparing Euflexxa to appropriate care, two different studies were used, involving patients from different regions and at different times, meaning that the patient populations were not the same and which may result in some unwanted variation. In addition, the health utility index for patients receiving either Euflexxa or appropriate care was derived from different preference measures than the healthy population. This derivation from different initial measures may lead to some potential differences between the QALY scores between the patients with symptomatic knee OA and the healthy population. The utility score data from Hatoum et al. [12] included data from both the FLEXX trial and extension trial, although the extension was an open label investigation. This

creates a potential limitation, as the open label extension trial data may be subject to bias. Finally, there is a lack of information in the current literature regarding suboptimal adherence to an IA-HA injection regimen. For this reason, we used the available evidence for Euflexxa use, which demonstrated no issues with adherence; however, this may not be the case in clinical scenarios.

The present study is strengthened by the sensitivity analysis, which examines potential variation in both the population of eligible patients and the efficacy of the treatment method. The two-way analysis provides a range of the current and potential impacts on the US population based on up to a 20% increase or decrease in both the eligible population and the utility score of the treatment method.

CONCLUSION

This study has shown that, if more widely used, a biological fermentation-derived, high molecular weight IA-HA preparation, such as Euflexxa, has the potential to save substantial QALY per year within the USA; this is more than twice as much as appropriate care. Further studies examining the impact of additional treatment methods on the US population will allow further comparison between OA treatment strategies.

ACKNOWLEDGEMENTS

We would like to thank Steven Phillips and Mark Phillips of Global Research Solutions who provided medical writing services for this project, funded by Ferring Pharmaceuticals Inc, and for their help in developing and submission of the manuscript. This study and article processing charges were funded by Ferring Pharmaceuticals Inc. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Disclosures. Jeffrey Rosen: Serves on the Advisory Board for Ferring Pharmaceuticals Inc. Anke Fierlinger is a paid employee of Ferring Pharmaceuticals Inc. Faizan Niazi is a paid employee of Ferring Pharmaceuticals Inc. Asheesh Bedi is a consultant for Arthrex Inc., and stock/stock options with A3 surgical. Parag Sancheti and Herman Johal have nothing to disclose.

Compliance with Ethics Guidelines. This article does not contain any new studies with human or animal subjects performed by any of the authors.

Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Bitton R. The economic burden of osteoarthritis. Am J Manag Care. 2009;15(8 Suppl):S230–5.

2. Losina E, Daigle ME, Reichmann WM, et al. Disease-modifying drugs for knee osteoarthritis: can they be cost-effective? Osteoarthr Cartil. 2014;21(5):655–67.

3. American Academy of Orthopaedic Surgeons. Treatment of osteoarthritis of the knee: evidence based guideline 2nd Edition. AAOS. 2013.

4. Losina E, Walensky RP, Holt HL, et al. Ten million quality-adjusted life years lost due to knee osteoarthritis (OA) in the US elderly population: the role of obesity. The American College of Rheumatology Annual Scientific Meeting. 2008. https://acr.confex.com/acr/2008/webprogram/Paper2046.html.

5. Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet. 2013;382(9894):769–79.

6. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res. 2012;64(4):465–74.

7. Dy CJ, Marx RG, Bozic KJ, Pan TJ, Padgett DE, Lyman S. Risk factors for revision within 10 years of total knee arthroplasty. Clin Orthop Relat Res. 2014;472(4):1198–207.

8. Adams BYME, Atkinsont MH, Lussier AJ, et al. The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multicenter trial comparing hylan G-F 20 alone, hyland G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDS alone. Osteoarthr Cartil. 1995;3:213–25.

9. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis. Ann Intern Med. 2015;162:46–55.

10. Waddell DD, Joseph B. Delayed total knee replacement with hylan G-F 20. J Knee Surg. 2016;29(2):159–68.

11. Karatosun V, Unver B, Gocen Z, Sen A. Comparison of two hyaluronan drugs in patients with advanced osteoarthritis of the knee. A prospective, randomized, double-blind study with long term follow-up. Clin Exp Rheumatol. 23(2):213–218.

12. Hatoum HT, Fierlinger AL, Lin S-J, Altman RD. Cost-effectiveness analysis of intra-articular injections of a high molecular weight bioengineered hyaluronic acid for the treatment of osteoarthritis knee pain. J Med Econ. 2014;17(5):326–37.

13. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis Rheum. 1995;38(8):1134–41.

14. Weinstein AM, Rome BN, Reichmann WM, et al. Estimating the burden of total knee replacement in the United States. J Bone Jt Surg. 2013;95(5):385–92.

15. Healthcare Cost and Utilization Project (HCUP). Nationwide Inpatient Sample (NIS). Agency for Health Research and Quality: 2012. http://hcupnet.ahrq.gov. Accessed 7 May 2015.

16. Multicenter Osteoarthritis Study (MOST). University of California San Francisco; 2010. http://most.ucsf.edu/. http://hcupnet.ahrq.gov. Accessed 7 May 2015.

17. United States IMS Claims Data Q4-2014. http://www.imshealth.com/. Accessed 26 May 2015.

18. Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death 1999-2013 on CDC WONDER Online Database, released 2015. Data are from the Multiple Cause of Death Files, 1999–2013, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. http://wonder.cdc.gov/ucd-icd10.html. Accessed 26 May 2015.

19. Leigh JP, Fries JF. Arthritis and mortality in the epidemiological follow-up to the National Health and Nutrition Examination Survey I. Bull N Y Acad Med. 1994;71(1):69–86.

20. Liu R, Kwok WY, Vliet Vlieland TP, et al. Mortality in osteoarthritis patients. Scand J Rheumatol. 2015;44:70–3.

21. Weinstein MC, O'Brien B, Hornberger J, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR task force on good research practices—modeling studies. Value Health. 2003;6(1):9–17.

22. Craig BM, Busschbach JJV. Revisiting United States valuation of EQ-5D states. J Health Econ. 2011;30(5):1057–63.

23. Altman RD, Rosen JE, Bloch DA, Hatoum HT. Safety and efficacy of retreatment with a bioengineered hyaluronate for painful osteoarthritis of the knee: results of the open-label Extension Study of the FLEXX Trial. Osteoarthr Cartil. 2011;19(10):1169–75.

24. Torrance GW, Raynauld JP, Walker V, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 2 of 2): economic results. Osteoarthr Cartil. 2002;10(7):518–27.

25. Nuesch E, Dieppe P, Reichenbach S, Williams S, Iff S, Juni P. All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. BMJ. 2011;342:d1165.

26. Losina E, Paltiel AD, Weinstein AM, et al. Lifetime medical costs of knee osteoarthritis management in the United States: impact of extending indications for total knee arthroplasty. Arthritis Care Res (Hoboken). 2015;67(2):203–15.

27. Ruiz D, Koenig L, Dall TM, et al. The direct and indirect costs to society of treatment for end-stage knee osteoarthritis. J Bone Jt Surg. 2013;95(16):1473–80.

28. Li CS, Seeger T, Auhuber TC, Bhandari M. Cost-effectiveness and economic impact of the KineSpring® knee implant system in the treatment for knee osteoarthritis. Knee Surgery Sport Traumatol Arthrosc. 2013;21(11):2629–37.