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LETTER

Important Considerations When Determining the Cost-effectiveness of Viscosupplements in the Treatment of Knee Osteoarthritis: Letter to the Editor regarding Rosen, J., Sancheti, P., Fierlinger, A. et al. Adv Ther (2016) 33: 998. doi:10.1007/s12325-016-0331-8

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The economic costs of knee osteoarthritis (OA) and its treatment are important considerations for patients, physicians, and healthcare systems when making decisions about the management of knee OA, especially given the direct costs associated with total knee replacement (TKR) [1, 2], and the estimated increase in demand by 2030 projected for TKR in the United States (673% increase from 2005 for primary TKR) [3]. Viscosupplementation has been shown to delay the time to TKR [4–6], making it an attractive option for delaying or reducing healthcare costs due to TKR. However, users of the treatment have a number of Food and Drug Administration (FDA)-approved viscosupplementation products with potentially different cost-benefit impacts from which to choose. These include, among others, Euflexxa® (Ferring Pharmaceuticals Inc., Parsippany, NJ, USA), GelSyn-3™/Supartz™ (Bioventus, Durham, NC, USA), Hyalgan® (Fidia Pharma Inc., Parsippany, NJ, USA), Orthovisc® (DePuy Synthes, Warsaw, IN, USA), and Synvisc®/Synvisc-One® (Sanofi, Bridgewater, NJ, USA). The purpose of the study by Rosen et al. [7] was to indirectly evaluate the cost-effectiveness of different forms of intra-articular (IA) hyaluronic acid (HA) injections for the treatment of knee OA based on efficacy data that were extracted from a select set of randomized controlled trials and converted into utility scores. We have serious concerns regarding this approach, especially with some of the assumptions made by Rosen et al. [7] and in light of other available data not included in their analysis. Our concerns are outlined below.

First, the study selection approach the authors employed did not result in adequate representation of available viscosupplementation treatments. They conducted a systematic search for randomized controlled trials that each examined the use of IA-HA in knee OA and reported full Western Ontario and McMaster Universities Index (WOMAC) pain, stiffness, and functional outcome data in a 5-point Likert format at both baseline and 6-month follow-up. Their search yielded just five articles with information on only five products [one article each for

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Durolane (Bioventus, Durham, NC, USA), Euflexxa, Hyalgan, and Synvisc, and two for Supartz (one shared with Synvisc)]. This is a small, nonrepresentative sample for a cost-effectiveness analysis. In addition, this selection process excluded often-used products such as Synvisc-One, which had an average patient market share of 24.7% for the period of June 2015–May 2016 [8], thereby rendering the analysis incomplete. Ensuring that all available products are included in this type of study is particularly important when analyzing this market. Specifically, IA-HA products have different dosing-for-efficacy regimens (e.g., one injection vs three weekly injections for 6 months of symptom relief), which has a direct impact on cost—assuming comparable efficacy, six injections per year (three injections/6 months) is obviously three times the number of injections as two (one injection/6 months).

The importance of this omission can be demonstrated directly by comparing the calculated cost of Synvisc-One (one injection for 6 months of efficacy [9]) with that of Euflexxa (three injections for 6 months of efficacy [10]) in a specific population of commercial health plan covered lives (e.g., Blue Cross Blue Shield HighMark: 5.2 million [11]) using a single payer perspective similar to the approach taken by Rosen et al. [7]. Synvisc-One may also be more appropriate than Durolane to include in this analysis because, unlike Durolane, Synvisc-One is FDA-approved. Our model focuses on OA patients $\geq$60 years of age and assumes a conservative estimate (based on previous reports [4, 12]) that 20% of these patients will receive IA-HA treatment. Given that 18.5% of the US population is $\geq$60 years of age [13] and that the prevalence of knee OA is 37.4% among adults [14], this model yields 71,917 prospective patients. When our model is used to compare Synvisc-One and Euflexxa, it demonstrates that if the approximately 72,000 Americans who use viscosupplements to treat their knee OA in the model were to switch from Euflexxa to Synvisc-One, the savings benefit in switching from Euflexxa's annual cost of $4001.64 to Synvisc-One's annual cost of $3086.66 [annual out-of-pocket (defined as cost of treatment + cost of treatment administration)] would result in each patient saving $914.98 per year.

Our model includes the direct costs of the product itself and the cost of administration. However, patients may experience additional burden associated with direct as well as indirect costs attributable to an increased number of office visits for those additional injections. Patients would likely have to pay additional co-payments for those visits. Moreover, patients may experience higher indirect costs such as loss of salary due to utilization of work time for injection visits, the need to use employer-provided time off, and cost of travel to the physician. Our concerns with the Rosen et al. article [7] do not pertain solely to the exclusion of Synvisc-One from the analysis. It could be argued that it is not surprising the cost of a medication administered only twice a year is lower than that of a medication administered six times a year. However, when Euflexxa is compared with a 3-injection regimen of either Hyalgan or Supartz (as was used in Rosen et al. [7]) using our model, patients who switch from Euflexxa to Supartz would realize an annual savings of $592.56 and patients who switch to Hyalgan would save $709.92 per year.

Second, we have concerns regarding the methodology used to extract data from the selected studies. Because cost-effectiveness

evaluation is a comparison of incremental efficacy gained given cost, the efficacy data selected must be comparable. In the Rosen et al. analysis [7], however, the data from one of the five articles that met the selection criteria set forth by the authors, the Altman et al. article [15], was not used directly in their analysis. Rather, utility scores for Euflexxa were secondarily abstracted from a different article, Hatoum et al. [16], which is a cost-effectiveness analysis of the data in the Altman et al. article [15]. The data in Altman et al. [15] that were analyzed in Hatoum et al. [16] were also reported on a 100-mm visual analog scale rather than on the 5-point Likert scale format set forth as a requirement for the study selection, and were from both a randomized controlled study (as per the selection approach) and an open-label extension study that followed it. Given the different approaches used to convert efficacy data into utility data, it is difficult to interpret the baseline utility scores for the different products presented in Rosen et al. [7], which differ substantially. In addition to differences in data conversion contributing to differences in utility scores, variability may also result from efficacy differences among products in similar patient populations and/or similar efficacy but in varying patient populations. It is very difficult to reliably interpret the scores given in the article without information on factors that may contribute to variability in the analysis.

In conclusion, measuring cost-effectiveness depends on both cost and efficacy measures, which in the end depend on the integrity of the data used, how representative they are, and the model applied. A more direct, and therefore, more accurate approach, which has been used for other diseases ranging from pain and generalized anxiety disorders [17] to fibromyalgia [18], would be to assess health-related quality-of-life and utility measures directly as outcome measures in clinical trials. This would clarify the data collection and extraction processes, making comparisons easier to interpret within a real-world context for all users of the treatment. In considering cost-effectiveness of IA-HA treatments for OA, specifically, the issue becomes complicated by the delivery method needed for viscosupplementation. An increase in the number of injections is associated not only with the cost of the treatment and the cost of administration but also with additional direct costs (e.g., additional co-payments) and with indirect costs such as requiring time off from work. Therefore, these considerations must be included in a comprehensive evaluation of the cost-effectiveness of these products. Although Rosen et al. [7] acknowledge that this cost analysis represents "a single payer, base-case scenario," they do not fully acknowledge the complexity of this disorder and its treatment. For these reasons, we believe the overly confident conclusions drawn by the authors must be interpreted with caution, and we look forward to other investigative efforts to assist patients, physicians, and healthcare systems in choosing the best care for their patients with OA of the knee.

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