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Re: *Evidence supporting the value of high molecular weight hyaluronic acid for the care and treatment for patients with mild to moderate osteoarthritis of the knee.*

Dear Drs. Samitt and Whitney:

The purpose of this letter is to address negative payment decisions related to the use of high molecular weight hyaluronic acid (HMWHA) based upon the American Academy of Orthopedic Surgeon's (AAOS) Clinical Practice Guidelines (CPG) and Appropriate Use Criteria (AUC) published in 2013.

In the past 3 years, multiple published studies confirm that the "effect size" of HMWHA is effective in the treatment of mild to moderate OA. Recently, a review article published in JBJS, an orthopedic journal with the highest impact factor (see attachment), highlighted the fact that nearly all hyaluronic acid (HA) products were included in the AAOS evaluation where a conclusion was made that HA products were "no better than placebo" in the treatment of knee arthritis.

In contrast, recent literature supports a very different conclusion. For example, the Bannarru study from Annals of Internal Medicine in January, 2015 reviewed 137 studies representing 33,243 patients, the Percoppe study from the Journal of Arthroscopy published in April of 2015 reviewed 49 trials representing 6,962 patients, the Strand study published in May of 2015 reviewed 29 studies totaling 4,866 patients, the Campbell study published in November of 2015 involving 20,049 patients for a total of 65,120 patients treated in these summarized clinical trials. The conclusions drawn in these reviews were that HA provided clinical improvement in pain and function compared to all other modalities up to 26 weeks and that HA had large treatment effects between 4 and 26 weeks for pain and function compared to pre-injection values. The overall conclusion was that the most efficacious treatment modality was HA.

I have attached PDFs of 2 review articles, one of which has been accepted for publication in "Therapeutic Advances in Musculoskeletal Disease" entitled "Intra-articular Hyaluronic Acid in the Treatment of Knee Osteoarthritis-A Canadian Evidence-Based Perspective". The second PDF was published in "JBJS reviews" in 2016 entitled "Viscosupplementation in Knee Osteoarthritis: Evidence Revisited" as noted above. Highlighted in the abstract of this review article, "closer evidence around viscosupplementation (VS) favors clinically important reductions in pain among higher molecular weight and cross-linked formulations and is a safe option in patients with knee osteoarthritis". Of all the articles recently written regarding the usage of VS, this review article confirms that a "careful examination of the most recently published articles suggests that VS is a safe option with a clinical reduction in pain for younger patients with osteoarthritis in those formulations with higher molecular weights or hyaluronic acid cross-linking".

In the AAOS CPG, despite their encouragement that payment decisions should not be based upon their opinion of a "strong recommendation against" the usage of HA, it has now become the basis for payer's noncoverage decisions. During this process, only 14 articles were analyzed using a metric of determination published by Angst and Tubach termed "meaningful clinically important improvement" (MCII) as well as "meaningful clinically important difference" (MCID). In the 14 VS studies that were included in the AAOS analysis, 9 concluded that there was a statistically significant benefit of treatment vs. placebo. In the group of chosen studies, 7 included data which resulted in an improvement from baseline ranging from 36% to 64%. Of interest is that > 30% change from baseline meets the criteria for MCII for "meaningful improvement." Ironically, the percent improvement from baseline with VS is similar to that reported with NSAIDs and tramadol (18% to 45%) which were strongly recommended by the "osteoarthritis of the knee" CPG group. Also, the effect size (ES) of acetaminophen and oral NSAIDs is basically the same as VS and is < .20.

We believe that the study inclusion criteria for the CPG was unnecessarily limited. Only 14 studies were considered for review discounting an additional 13 studies published between 1996 & 2012, plus the meta-analysis from 2004(Wang) that reviewed 20 trials out of 647, the Cochrane databases from 2009 (Bellamy et al) and from 2014 (Evaniew et al) that respectively reviewed over 100 trials all of which showed improvement from baseline post injection from 30% to 69%. The most recent Cochrane review found "overall benefits to VS in comparison to placebo for pain, function & patient global assessment scores." Utilizing only a small subset of studies based upon the current methodology inclusion criteria created a bias in the analysis leading to non-coverage decisions for a technology that clearly has objective evidence-based benefits for the treatment of knee osteoarthritis.

There have been exciting new developments regarding the potential impact of viscosupplementation injections on the biochemistry of articular cartilage of the knee joint. A study published in 2015 by Shah & Kelly from the University of Pennsylvania (Journal of Orthopedics), noted increased quantities of Type II proteoglycan in the cartilage cells of patients with OA after injection with a high molecular weight, cross linked viscosupplement (HMWVS) compound. This was accomplished by evaluating the joint surfaces using T1 rho imaging MRI. The results of the study concluded that the articular cartilage biochemistry may actually improve in patients with OA after injecting HMWVS.

Another Level I study published by Wang and Hall in 2011 (BMJ, 2015) confirmed that lack of progression of OA occurs after 2 years of injections of HMWVS using results of MRI T2 mapping. In those patients that did not get HMWVS, their OA continued to progress. Ironically, in one of the first states that published a noncoverage decision for HA in 2013, the incidence of total knee arthroplasty increased by 500%. Furthermore, when Medicare in 2015 hired AHRQ (the agency for healthcare and quality) to perform an independent analysis of HA, they concluded that "HA may be considered for patients who have not responded adequately to nonpharmacologic measures". From an economic perspective, there is clear supporting evidence that HA can in fact delay the need for knee replacement making thousands of patients more "age-appropriate" for their first and only knee replacement sparing the system and the patient from revision knee replacement surgery during their lifetime. Recent data has confirmed that utilizing HMW VS can postpone TKA from 3.7 to 7.6 years (Waddell et al, 2016).

Based upon the preponderance of existing evidence, we believe that HMW VS is appropriate care and treatment for patients with mild to moderate osteoarthritis of the knee and from a value perspective, is ultimately advantageous for payers and patients alike. Thank you for your time and consideration.

Sincerely,



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