Delay to TKA in Patients Treated with a Multimodal Approach Using High Molecular Weight, Biologically Derived Hyaluronic Acid

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ABSTRACT: Background: The primary objective of this study was to determine the effect of single versus multiple rounds of intra-articular hyaluronic acid (IA-HA) in delaying the need for total knee arthroplasty (TKA) in patients with knee OA, and if additional benefits were seen when used in conjunction with other multimodal treatment options.

Methods: This study was a retrospective claims analysis of a large commercial database containing more than 100 million patients with continuous coverage from October 1, 2010 through September 30, 2015. Time to TKA for patients who received one course of Euflexxa (IA-BioHA) were compared to patients who received two or more courses of IA-BioHA and patients who received no IA-HA. Assessment of multimodal treatment effects was done between the following groups: IA-BioHA injections alone, IA-BioHA and bracing, IA-BioHA and corticosteroid injection, and IA-BioHA with both corticosteroids and bracing.

Results: A total of 26,727 patients were included in the analysis of treatment courses, and 31,034 in the analysis of multimodal treatment combinations. The use of IA-BioHA demonstrated a delay of TKA that was prolonged with repeated courses of treatment (1.411 years, interquartile range [IQR]: 1.44). The greatest delay to TKA was observed for the patients who had received all three treatment options (1.5 years, IQR: 1.52) in the multimodal analysis.

Conclusions: These results confirm that treatment of knee OA should consider the use of multimodal therapy instead of focusing on individual treatment options. Additionally, the use of repeated courses of IA-BioHA should be considered for prolonged benefit for patients with symptomatic knee OA.

KEY WORDS: knee, osteoarthritis, multimodal, hyaluronic acid, corticosteroid, bracing

I. INTRODUCTION

Knee osteoarthritis (OA) is a highly investigated area of health research due to its significant impact on functional disability, stiffness, and pain for patients, a well a large socioeconomic burden for patients and the healthcare system.[1,2] Patients are typically managed using a variety of nonpharmacologic and pharmacologic treatment options.[3,4] As the disease progresses to more advanced stages, surgical intervention may be required. In these cases, the knee joint can be treated by performing partial or total knee arthroplasty (TKA).[5]

In patients who have not progressed to the point where they require TKA, or are unwilling to undergo TKA, there is a need for effective treatments to relieve pain and improve function.[6] It may be advantageous to provide symptomatic relief for these patients, while also delaying TKA at their current stage of disease progression.[6] There are many nonsurgical treatment options available for the management of knee OA prior to the need for a knee replacement, including NSAIDs, bracing, corticosteroids, and intra-articular hyaluronic acid (IA-HA) injections. Current research typically aims to identify the superiority of these available

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treatment options in comparison to each other, yet a multimodal approach is often utilized by clinicians in the real-world treatment of knee OA.[7]

The use of IA-HA as a treatment option has been shown to be effective in reducing negative outcomes, such as pain, in patients with mild to moderate knee OA.[8,9] Differences in treatment effect have been demonstrated across the class of IA-HA products, with high molecular weight (HMW) IA-HA products demonstrating greater pain relief than low molecular weight (LMW) products.[10] Euflexxa (IA-BioHA) is one such HMW IA-HA that is biologically derived, forgoing the use of avian-derived molecules that are present in other IA-HA products.[11] A typical course of IA-BioHA consists of three injections administered over a three-week period. While most IA-HA evidence focuses on the initial course of treatment, some evidence has suggested that the beneficial effects of IA-HA may be prolonged, and even increased, following repeat courses of treatment.[12,13] These studies demonstrated that repeat courses of IA-BioHA had a dose–response relationship that not only prolonged pain improvement after the initial course but also further increased reductions in pain.[12,13]

The primary objective of this study was to determine the effect of IA-BioHA in delaying the need for TKA in patients with knee OA, both alone, and in multimodal treatment regimens. The analysis looked at the effect of IA-BioHA alone, with one round of injections, repeat rounds of injections, and if there were any additional benefits conferred when used in conjunction with other treatment options through the analysis of real-world evidence.

II. METHODS

A. Study Design

This study was a retrospective claims analysis of a large commercial database containing more than 100 million patients with continuous coverage from October 1, 2010 through September 30, 2015. The database included anonymous claims data for all OA patients seen within the aforementioned timeframe. The database contained HIPAA compliant de-identified data, and as a retrospective assessment of de-identified data, this investigation did not require ethics approval.

B. Eligibility Criteria

All patients with the diagnosis code for knee osteoarthritis and a treatment received prior to TKA were included. Exclusion criteria were as follows: patients without OA, patients with OA other than knee, patients with knee OA who had immediate TKA after diagnosis and no treatment, and patients with knee OA who had no treatment and no TKA. Patients were excluded if they received any other IA-HA treatment in the 12 months prior to treatment with IA-BioHA to reduce the effects of other IA-HA products on the assessed outcome. Eligibility was defined by ICD-9 codes. The ICD-9 codes that were included in our analysis of TKA were: ICD-9 711.x6, 712.x6, 715.x6, 716.x6, 717.x, 718.x6, 719.x6, 836.x, and 844.x.

C. Comparison Groups

Patients who received one course of IA-BioHA were compared to patients who received two or more courses of IA-BioHA, as well as those who did not receive any IA-HA treatment. Additionally, the assessment of multimodal treatment effects examined the following groups: IA-BioHA injections alone, IA-BioHA and bracing, IA-BioHA and corticosteroid injection, and IA-BioHA with both corticosteroids and bracing. IA-HA is recommended for treatment only after the use of NSAIDs no longer provides therapeutic relief, so most patients were assumed to have typically taken simple analgesics during their OA treatment regimen.

D. Data Analysis

Descriptive statistics of included patients were reported as counts and percentages for categorical data. Means and standard deviations were reported for continuous outcomes unless the data were not normally distributed. In this case, the median and interquartile range (IQR) were provided. The delay to TKA for patients who received single and multiple courses of IA-BioHA was assessed from the

time of the first IA-BioHA injection to provide insight into the delay that may be considered directly attributable to IA-BioHA. Additionally, analysis of delay to TKA was conducted from the time of first OA treatment code, an estimation of the time of diagnosis, for patients who received either one or at least two full courses of IA-BioHA to assess the overall delay period for these patients. Only patients who eventually required TKA were included, and patients who did not require TKA throughout the study period were not included in the analysis. Kaplan–Meier survival curves were provided to illustrate the differences in TKA rates between one course and multiple courses of IA-BioHA throughout the study timeframe. These groups considered all patients who received IA-BioHA, regardless of any other treatment options they may have received. To better understand the direct impacts of specific multimodal therapy regimens on the delay to TKA, a similar analysis was conducted for different multimodal treatment combinations. The assessment of time to TKA in patient subgroups receiving specific multimodal treatments was analyzed from the time of first OA treatment code. Kaplan–Meier survival curves were provided for the following groups: IA-BioHA injections alone, IA-BioHA and bracing, IA-BioHA and corticosteroid injection, and IA-BioHA with both corticosteroids and bracing.

III. RESULTS

A. Included Patients

The administrative database included 2,390,375 patients. Among these patients, 1,248,298 patients were diagnosed with knee OA and were over the age of 18, with no history of prior knee replacement. 563,103 patients did not receive an IA-HA treatment for their knee OA in the 12 months prior to treatment with IA-BioHA. Of these patients, 139,665 eventually had a TKA in the database timeframe (mean age of 56.11 ± 8.5, 57.6% female). A total of 19,004 patients within the database received one full course of IA-BioHA (mean age 55.5 ± 8.4, 61.7% female), and 7,723 patients received two or more courses of IA-BioHA (mean age 55.5 ± 7.9, 63.6% female). There were 10,183 patients who received only IA-BioHA (mean age 54.8 ± 8.9, 61.2% female), 699 patients who received IA-BioHA and a prescribed brace (mean age 53.7 ± 8.8, 48.2% female), 18,422 patients who received both and corticosteroid injection (mean age 55.9 ± 7.9, 64.0% female), and 1,730 patients who received corticosteroid injection and a prescribed brace (mean age 55.5 ± 7.9, 51.2% female).

B. Single vs. Multiple Courses of IA-BioHA

A summary of the number of TKAs and median time to TKA for those who eventually underwent TKA for course groups is provided in Table 1. The median time to TKA from the first injection for the one course group was 0.66 years (IQR: 0.87) and 1.411 years (IQR: 1.44) for the multiple course group. A Kaplan–Meier analysis of the TKA-free survival for treatment course groups is included in Fig. 1; the median time to TKA was 1.36 years (IQR: 1.58) for the one IA-BioHA course group and 1.91 years (IQR: 1.66) for the multiple course group. In comparison, the median time to TKA from the first OA treatment code was 0.38 (IQR: 0.95) for patients who received no IA-HA treatment.

TABLE 1: Time to TKA for patients who received single and multiple IA-BioHA courses

Treatment courses	Number of patients	Number of TKAs	Median years to TKA from first IA-BioHA injection (IQR)	Median years to TKA from first OA treatment code (IQR)
No IA-HA	563,103	139,665	NA	0.38 (0.95)
One course	19,004	5,061	0.66 (0.87)	1.36 (1.58)
Two or more courses	7,723	1,876	1.411 (1.436)	1.91 (1.66)

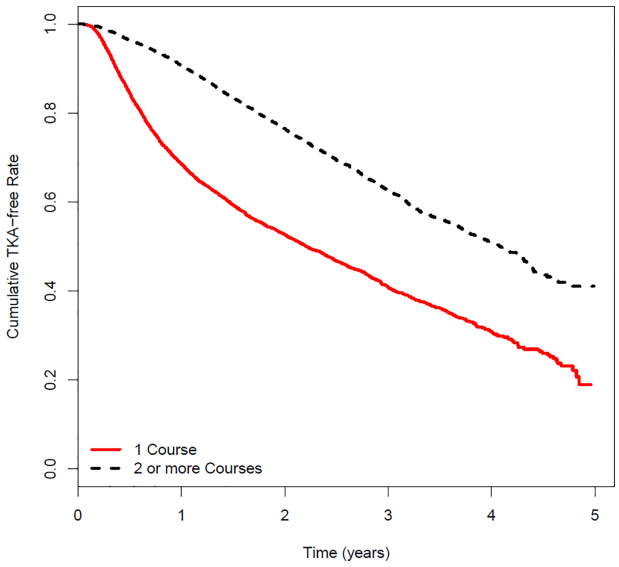

FIG. 1: Kaplan–Meier of treatment courses. Cumulative TKA-free rate over time from first IA BioHA injection in patients who received 1, or 2 or more courses of IA-BioHA.

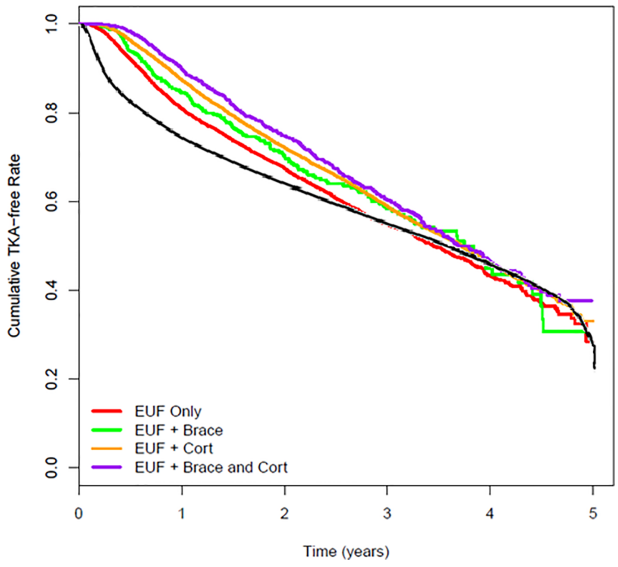

FIG. 2: Kaplan–Meier of multimodal groups. Cumulative TKA-free rate over time from first OA treatment in patients who received no IA-HA, IA-BioHA, IA-BioHA and a brace, IA-BioHA and corticosteroid, or IA-BioHA, a brace, and corticosteroid.

C. Multimodal Therapy

Table 2 includes a summary of the number of TKAs and the median time to TKA for each of the multimodal treatment groups. Of those that received a TKA, the median time to the event from first OA treatment code was longest for patients who received all three therapies (1.5 years, IQR: 1.52), followed by patients treated with IA-BioHA and corticosteroid (1.32 years, IQR: 1.48), IA-BioHA and a prescribed brace (1.1 years, IQR: 1.43), and IA-BioHA alone (0.89 years, IQR: 1.28). A Kaplan–Meier curve of the TKA-free survival for all groups is shown in Fig. 2.

IV. DISCUSSION

This study identified an additive pattern in which multimodal therapy regimens can prolong the time to TKA. Compared to the use of IA-BioHA alone, the delay to TKA was prolonged with the addition of bracing or corticosteroids, with the greatest benefit seen when all three treatments were used together. This study provides a novel approach to assessing multimodal treatment of knee OA with a large observational database, with findings that confirm those seen within assessments of other multimodal regimens.[7] This study additionally found that the

TABLE 2: Median time to TKA for multimodal treatment groups

Multimodal groups	Number of Patients	Number of TKAs	Median years to TKA from first OA treatment code (IQR)
No IA-HA	563,103	139,665	0.38 (0.95)
IA-BioHA only	10183	2263	0.89 (1.28)
IA-BioHA and knee brace	699	180	1.10 (1.43)
IA-BioHA and corticosteroid	18422	5026	1.32 (1.48)
All three treatments	1730	519	1.50 (1.52)

administration of IA-BioHA postponed the need for TKA, and continuing with IA-BioHA treatment beyond the first course may be of greater benefit within the patients who progressed to TKA. Previous investigations have identified the TKA delaying effects of repeated courses of IA-HA injection[9]; however, this study specifically addresses the differences in effect that are seen after repeated courses of IA-BioHA from real-world evidence. Repeated IA-HA injections have also been shown to increase symptom relief benefits, as pain and function improvements tend to be maintained – if not further improved – by additional courses of IA-HA.[12,13]

The findings of this study raise important considerations for clinical practice, as well as future research. There are two key findings that can be utilized within clinical practice from this study. First, a multimodal approach that utilizes IA-BioHA, corticosteroids, and bracing, can be used to optimize benefits for patients. Clinically, it may also be important to consider the use of IA-HA treatments, such as IA-BioHA, earlier in the OA disease progression to allow for repeated injection timing to be appropriate for a patient, prior to the patient progressing to a late disease stage. This may not only allow for patients to experience a greater delay until their need for TKA, but also significant and prolonged relief from pain and functional disability associated with knee OA.[9,14] From a research perspective, the findings of this study also have important implications. Currently, the majority of IA-HA evidence focuses on the initial treatment course of individual treatments. There have been far fewer studies that assess multimodal treatment approaches or follow patients for multiple treatment courses, particularly when assessing symptomatic outcomes such as pain and function.[13] To gain a better understanding of the treatment effects for patients receiving multimodal treatment and repeated courses of treatment, research endeavors should continue to collect patient data beyond their first IA-HA treatment course.

There are important strengths to consider regarding this study. First, the utilization of a large administrative database allows for the analysis real-world data on a scale that is not typically seen in randomized trial settings. This type of data may be more useful to the practicing clinician who will likely experience similar type of patient scenarios versus the more narrowly selected and treated subjects in randomized controlled studies. This current study provides a large enough sample to assess the progression of timing to TKA within patients who received varying multimodal treatment combinations for their knee OA. The differentiation between IA-HA product outcomes has been demonstrated, which makes this assessment of a single treatment valuable in distinguishing brand-specific results from class-specific assessments.[10]

There are also a number of key limitations to consider for this study. While observational data provides the opportunity to assess the treatment pathway and progression to TKA, this study design also poses challenges. First, the data provided within the database was taken at face value by the researchers, as data auditing for accuracy was not possible after the data had been anonymized and sent to the research team. Another important consideration is the inability to assess or determine the candidacy of included patients for TKA. Without specific assessments of disease progression, the requirement of TKA was considered as a sign of disease severity worsening. This may not always be the case, as some patients may face factors other than disease progression that result in them deciding to undergo, or not undergo/be ineligible for, TKA (job status, economics, family needs, etc.). The results of this study assume that patients who receive TKA have progressed to a severe stage of knee OA, which is a reasonable assumption for the majority of knee OA patients. Injection of HA in patients with severe OA is unlikely to be of benefit, based upon prior research, and may result in higher treatment failure. Addressing OA pain in the earlier stages may result in more robust outcomes and a longer delay for the need for TKA. This still poses as a limitation within this study, as direct disease severity data were not collected in the administrative database. Additionally, while the assessment of a multimodal approach suggests that the use of all three treatments provides the greatest benefit, it does not provide specific information regarding the optimal order of use for each of the treatments. Future studies may provide additional clarity on this. Despite these limitations, this project provides a detailed assessment of the

impact of single and multiple courses of a high molecular weight, biologically derived IA-HA product on patient delay to TKA from a large administrative database.

V. CONCLUSION

The results of this study highlight the clinical benefit of IA-BioHA within a multimodal approach to treatment of knee OA. The greatest delay to TKA was observed for patients who received all three treatment options, followed by the groups who received combined therapy of two interventions, and finally the group who received IA-BioHA alone. It is of note that a large proportion of patients were treated with both IA-BioHA and corticosteroids, which demonstrated improved results over IA-BioHA alone and also over IA-BioHA and bracing. The use of IA-BioHA demonstrated a delay in the need for TKA that was prolonged with repeated courses of treatment. These results confirm that treatment of knee OA should consider the use of multimodal therapy instead of focusing on individual treatment options. Additionally, the use of repeated courses of IA-BioHA should be considered for prolonged benefit for patients with symptomatic knee OA. Further research is needed to determine the optimal order and timing of the various multimodal treatments to maximize outcomes.

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