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Analysis for Prognostic Factors from a Database for the Intra-Articular Hyaluronic Acid (Euflexxa) Treatment for Osteoarthritis of the Knee

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Abstract

Introduction. Intra-articular hyaluronic acid (IA-HA) injections are a treatment for knee osteoarthritis (OA), although current literature provides mixed results with regard to their efficacy. We will review a randomized controlled trial (RCT) and subsequent extension trial in order to identify factors that are associated with outcomes in patients with knee OA who received IA-HA. *Methods*. We used data recorded by the FLEXX trial and extension trial for secondary analysis of potential prognostic factors. Linear regression was used to examine the predictors of outcomes at 6- and 12-month follow-up visits. *Results*. Sixty percent of all patients presented with a Kellgren Lawrence (K-L) grade 3. Patients with high baseline outcome scores and a K-L grade 3 demonstrated less response than individuals within an earlier stage of knee OA, although results for both K-L grade 2 and K-L grade 3 patients still showed benefit. Those with more severe radiographic change K-L grade 3 often had a better response with the second series of IA-HA injections. Significantly greater positive response in all outcomes was demonstrated for the patient subgroup classified as K-L grade 2, when compared with K-L grade 3 patients. *Conclusions*. The results demonstrate that IA-HA for knee OA was of greater benefit in those with less severe radiographic changes. However, those with more severe radiographic change often had a better response with the second course of IA-HA. Similar analyses are required in order to determine if these results are unique to Euflexxa, or if these results are consistent with other available IA-HA agents.

Keywords

knee, joint involved, osteoarthritis, diagnosis, intraarticular delivery, therapeutic delivery

Introduction

Knee osteoarthritis (OA) is the most common form of OA and it is increasingly prevalent and symptomatic in the elderly. Progressive intra-articular (IA) changes associated with the disease may result in significant pain and disability.[1] Socioeconomic implications such as cost of treatment, inability to work, and early retirement have a significant impact those affected by knee OA, and these direct and indirect costs can pose a large burden on society.[2] IA hyaluronic acid (IA-HA) injections are a treatment option for knee OA that serves to replenish the decreasing viscoelastic and biochemical properties of the synovial fluid.[3] Previous trials evaluating IA-HA have provided mixed results regarding efficacy; however, some evidence has shown greater therapeutic benefit for higher molecular weight IA-HA.[4] Variable results in current publications have resulted in inconsistent recommendations among clinical practice guidelines regarding the use of IA-HA for the treatment for OA of the knee.[5-7]

Further insight into the efficacy and safety of IA-HA is needed in order to determine the appropriate role of IA-HA for each individual with knee OA. In a previous study on prognostic factors, radiographic guidance of the IA injection predicted a more positive outcome for IA-HA therapy.[8]

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Further pre–IA injection prognostic studies need to be explored in order to identify additional prognostic factors associated with positive outcomes in patients treated with IA-HA. Conversely, identifying factors associated with a less than ideal outcome will help identify specific populations who respond less than ideally, to IA-HA. The objective of this study is to help clinicians determine the most appropriate patients for IA-HA therapy for OA of the knee.[8]

To help identify potential predictors of response to IA-HA, a detailed review will be performed on a previous randomized controlled trial (RCT).[9] and subsequent extension trial[10] of a biologically produced, high-molecular-weight HA treatment (Euflexxa, Ferring Pharmaceuticals Inc.). The initial study (FLEXX trial) randomized 588 patients with knee OA to 3 weekly IA injections of biologically derived HA (Bio-HA), or 3 weekly injections of IA saline. In the initial 26 week study, the Bio-HA group showed significantly greater improvement in the measured outcomes with a low incidence of adverse events.[9] The 26-week extension trial demonstrated the safety and supported the efficacy of reinjection of Bio-HA after an additional 26 weeks.[10] Both trials will be examined in an attempt to identify factors that may predict either a successful or less successful outcome in patients who received IA-HA.

Methods

The FLEXX Trial and Extension Trial

The FLEXX trial was conducted at 36 sites in the United States in accordance with the Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. The study took place from October 2006 to May 2008. Patients were included based on the following criteria: OA of the knee by American College of Rheumatology criteria; moderate to severe pain score of 41 to 90 mm recorded on 100 mm visual analog scale (VAS) immediately following a 50-foot walk; bilateral standing anterior-posterior radiograph demonstrating Kellgren and Lawrence (K-L) grade 2 or 3 OA (Grade 2: definite presence of osteophytes and definite joint space narrowing; Grade 3: multiple osteophytes present, definite joint space narrowing, some sclerosis, and possible bone deformity) of the target knee; ability and willingness to use only acetaminophen as the analgesic (rescue) study medication; unassisted walking 50 feet on a flat surface and going up and down stairs; and willingness and ability to complete efficacy and safety questionnaires.[9] All individuals within the FLEXX trial were eligible for inclusion within the extension trial.[10]

Prognostic Factors

We used data recorded by the FLEXX trial and extension trial for secondary analysis of potential prognostic factors. Baseline variables included in the analyses were treatment received, age, body mass index (BMI), sex, alcohol use, smoking status, severity of osteoarthritis (K-L grading scale), OA in contralateral knee, history of physical therapy, history of steroid injection, history of other injection, history of arthrocentesis, history of nonsteroidal anti-inflammatory drug (NSAID) treatment, baseline VAS pain, and Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain, stiffness, and disability scores. The outcome measures analyzed were VAS pain score recorded after a 50-foot walk, WOMAC pain, stiffness and disability subscale scores and global VAS pain score. Higher scores indicate worse outcomes on all of the outcome measures.

Data Analysis

Descriptive statistics were performed for the recorded baseline variables. Continuous variables were reported as a mean with standard deviation and compared using independent-samples *t* test. Categorical variables were reported as frequencies and relative frequencies and compared using a chi-squared test. Multivariable linear regression was used to examine the predictors of pain outcomes at 6- and 12-month follow-up visits. Coefficients with 95% confidence intervals (CIs) are reported. Distribution of the residuals and scatterplots of residuals against predicted values were examined for goodness-of-fit of the model. Multivariable logistic regression was performed for OMERACT OARSI response, and odds ratios with 95% CIs for the predictors and *P* value for the Hosmer-Lemeshow goodness of fit were reported. Means with 95% CIs were plotted for visual interpretation of the pain outcomes over time. Boxplots were plotted for the visual interpretation of the change in pain outcomes by Kellgren-Lawrence (K-L) grade. A *P* value of 0.05 was considered for statistical significance. SPSS software (www.IBM.com) was used for analysis.

Results

Demographics and Outcome Scores

The mean age of the participants was 61.5 years. On all, 63% of patients included in the study were women and 60% of all patients presented with a K-L grade 3 (**Table 1**). The mean primary outcome measure of pain after the 50-foot walk test for all patients was 55.1 on a 100-mm VAS scale at the time of randomization. This mean score decreased to 34 at 6 months, and to 25.6 at 12 months. The mean scores of secondary outcomes showed a similar decrease over the follow-up period. The scores from all of the outcome measures decreased within the first 3 weeks posttreatment, and plateaued until the 26-week follow-up. After receiving further treatment at week 26, a further

Table 1. Patient Characteristics.

	Saline (*n* = 295)	Euflexxa (*n* = 293)	Total (*n* = 588)
Age, years, mean (SD)	60.75 (10.3)	62.5 (10.6)	61.5 (10.5)
BMI, kg/m^2, mean (SD)	33.0 (7.4)	32.3 (7.4)	32.6 (7.4)
Current smoker, n (%)	40 (13.5)	34 (11.5)	74 (12.5)
Previously smoked, n (%)	84 (28.5)	101 (34.5)	185 (31.5)
Never smoked, n (%)	171 (58.0)	158 (54.0)	329 (56.0)
Sex, n (%)			
Male	109 (37.0)	108 (37.0)	217 (37.0)
Female	186 (63.0)	185 (63.0)	371 (63.0)
Target knee, n (%)			
Left	158 (53.6)	147 (50.2)	305 (51.9)
Right	137 (46.4)	146 (49.8)	283 (48.1)
Kellgren-Lawrence grade, n (%)			
2	115 (39.0)	120 (41.0)	235 (40.0%)
3	180 (61.0)	173 (59.0)	353 (60.0%)
Alcohol consumption, n (%)	133 (45.0)	124 (42.3)	257 (43.7%)
Baseline VAS score (mm) at 50 ft walk, mean (SD)	54.6 (21.8)	55.6 (22.0)	55.1 (21.9)
Baseline WOMAC score, mean (SD)			
Pain	54.0 (20.3)	52.3 (21.8)	53.2 (21.0)
Stiffness	57.7 (21.6)	57.4 (25.0)	57.6 (23.3)
Disability	53.5 (20.2)	53.8 (21.6)	53.6 (21.0)
Baseline global VAS score, mean (SD)	57.2 (19.7)	56.4 (21.6)	56.8 (20.7)
Baseline SF-36 score, mean (SD)			
Pain	49.8 (22.0)	50.2 (21.0)	50.0 (21.5)
Function	45.3 (24.0)	42.3 (25.2)	43.9 (24.6)
Health survey	47.5 (19.7)	46.2 (20.4)	47.0 (20.0)
Mean acetaminophen use, mean (SD)	18.6 (28.0)	15.0 (18.7)	16.8 (23.7)

BMI = body mass index; SF-36 = Short Form–36; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

decrease in scores was seen from weeks 26 to 40. After week 41, the outcome scores began to increase until the 52-week follow-up (**Fig. 1**).

A demographic comparison between patients with a K-L grade 2 ($n = 235$) and a K-L grade 3 ($n = 353$) demonstrated a significant difference in mean age (K-L grade 2, 59.28 ± 10.05 years vs. K-L grade 3, 63.20 ± 10.51 years, $P < 0.001$). There was also significant difference in mean BMI between K-L grade2 and K-L grade 3 (31.76 ± 7.31 vs 33.31 ± 7.48 kg/m^2, respectively; $P = 0.014$). All other demographic data were similar between patients with a K-L grade 2 and those with a K-L grade 3, including baseline outcome scores for target knee VAS pain at the 50-feet walk, WOMAC pain, stiffness, and disability, and global VAS assessment (**Table 2**).

Demographic and Disease Severity Prognostic Factors

Patients who received a saline injection had significantly higher ($P = 0.029$) VAS pain score after the 50-foot walk at 6-month follow-up than patients who received Euflexxa. Patients who had a higher baseline VAS pain score or a K-L grade 3 had a higher VAS pain score after the 50-foot walk at 6- and 12-month follow-up than patients who had a low baseline VAS score or a K-L grade 2. Older patients had a slightly more successful response to treatment with regard to VAS pain score after a 50-foot walk at 6- and 12-month follow-up than younger patients (coefficient = −0.3, $P = 0.029$). Women had a lower response than men at 6-month follow-up (coefficient = 7.1, $P = 0.021$), yet still significant. Patients with OA in the contralateral knee demonstrated significantly better results at 12-month follow-up with regard to VAS pain score after the 50-foot walk in the treated knee (**Table 3**).

A higher baseline WOMAC pain score, and a K-L grade 3 were associated with a higher WOMAC pain score at 6- and 12-month follow-up (**Table 4**). Saline injection and women were also associated with a higher WOMAC pain score at 6-month follow-up only (**Table 4**). A higher baseline WOMAC stiffness score was associated with a higher WOMAC stiffness score at 6 months. A higher baseline WOMAC stiffness score, and a K-L grade 3 were both associated with higher WOMAC stiffness scores at 6- and 12-month follow-up (**Table 5**). A higher baseline WOMAC disability and a K-L grade 3 were also associated with a

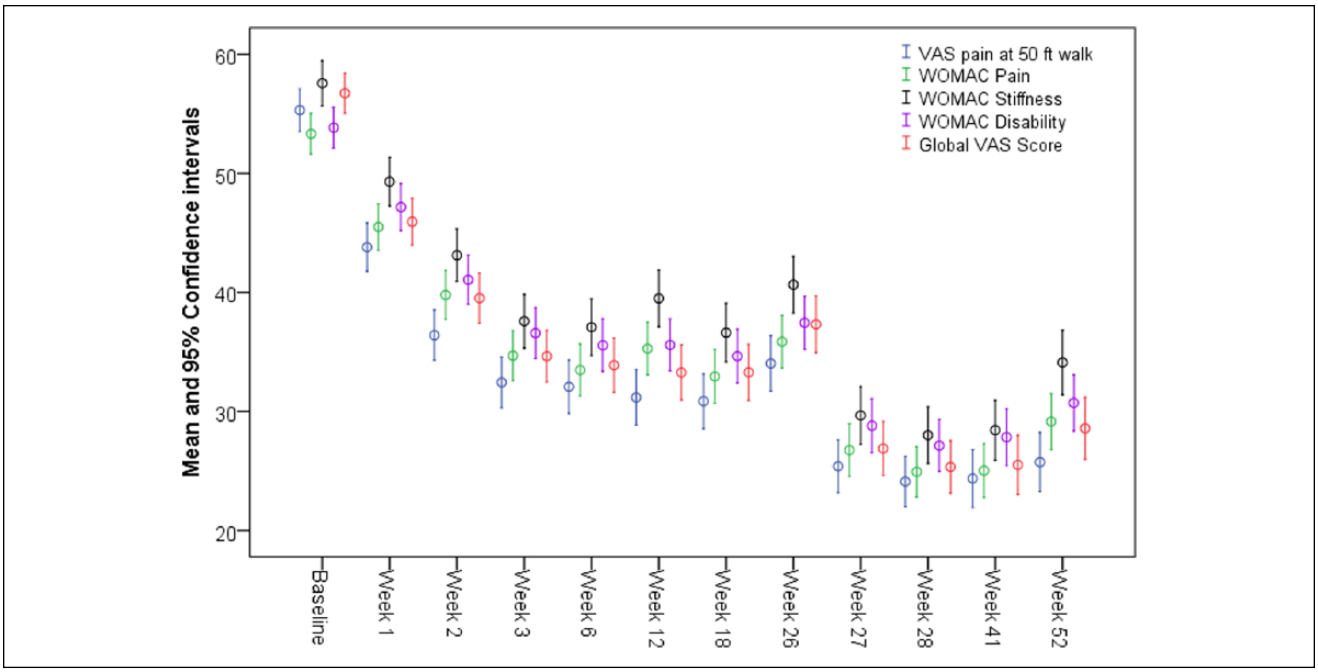

Figure 1. Mean Outcome Scores over Time.

Table 2. Baseline Characteristics by Kellgren-Lawrence (K-L) Grades.

	K-L Grade 2 (*n* = 235)	K-L Grade 3 (*n* = 353)	*P*
Age, years, mean (SD)	59.28 (10.05)	63.20 (10.51)	<0.001
BMI, kg/m^2, mean (SD)	31.76 (7.31)	33.31 (7.48)	0.014
Ever smoked, n (%)	101 (43.00)	158 (44.80)	0.671
Current smoker, n (%)	32 (13.60)	42 (11.90)	0.539
Men, n (%)	154 (65.50)	217 (61.50)	0.316
Alcohol consumption, n (%)	109 (46.40)	148 (41.90)	0.287
Target knee VAS pain at 50-ft walk, mean (SD)	56.17 (21.26)	54.43 (22.40)	0.349
WOMAC pain, mean (SD)	54.90 (21.76)	52.08 (20.56)	0.114
WOMAC stiffness, mean (SD)	57.80 (25.00)	57.47 (922.27)	0.866
WOMAC disability, mean (SD)	54.15 (21.87)	53.37 (20.33)	0.660
Global VAS, mean (SD)	57.47 (20.21)	56.39 (21.03)	0.538

BMI = body mass index; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

Table 3. Factors Associated with a High VAS Pain Score After a 50-Foot Walk at 6- and 12-Month Follow-up.[a]

	Coefficient (95% CI)	*P*
At 6 months		
Saline injection	6.2 (0.6, 12.0)	0.029
Baseline VAS pain score (mm) at 50 ft walk	0.2 (0.1, 0.4)	0.001
Kellgren-Lawrence grade 3	7.5 (1.5, 13.5)	0.014
Females	7.1 (1.1, 13.1)	0.021
Age	–0.3 (–0.6, –0.03)	0.029
History of steroid treatment	6.8 (0.1, 13.4)	0.044
History of arthrocentesis	–13.3 (–25.6, –1.1)	0.033
At 12 months		
Baseline VAS pain score (mm) at 50 ft walk	0.3 (0.1, 0.4)	<0.001
Kellgren-Lawrence grade 3	8.7 (2.5, 15.0)	0.009
Age	–0.3 (–0.6, –0.02)	0.033
OA in contralateral knee	–6.6 (–13.0, –0.2)	0.042

CI = confidence interval; OA = osteoarthritis; VAS, visual analog scale.
a Variables entered into the models were treatment received, sex, Kellgren-Lawrence grade, age, body mass index (BMI), smoking status, alcohol consumption, OA in contralateral knee, history of physical therapy, history of steroid injection, history of other injection, history of arthrocentesis, history of nonsteroidal anti-inflammatory drug (NSAID) treatment, and baseline VAS pain after 50-foot walk.

higher WOMAC disability score at 6- and 12-month follow-up, and saline injection and women were associated with higher scores at 6-month follow-up (**Table 6**). Saline was not provided within the extension trial, so the results could not be assessed at 12 months. A higher global VAS score and a K-L grade 3 were associated with higher global VAS scores at both 6- and 12-month follow-up. Additionally, younger patients and patients with unilateral knee OA were

Table 4. Factors Associated with a High WOMAC Pain Scores at 6- and 12-Month Follow-up.

	Coefficient (95% CI)	P
At 6 months		
Baseline WOMAC pain score	0.4 (0.3, 0.5)	<0.001
Kellgren-Lawrence grade 3	6.7 (1.4, 12.0)	0.013
Saline injection	5.6 (0.5, 10.8)	0.031
Females	5.5 (–0.1, 11.1)	0.052
At 12 months		
Baseline WOMAC pain score	0.38 (0.27, 0.50)	<0.001
Kellgren-Lawrence grade 3	9.3 (3.6, 15.0)	0.001

CI = confidence interval; WOMAC = Western Ontario and McMaster Universities Arthritis Index.
Variables entered into the models were treatment received, sex, Kellgren-Lawrence grade, age, BMI, smoking status, alcohol consumption, osteoarthritis (OA) in contralateral knee, history of physical therapy, history of steroid injection, history of other injection, history of arthrocentesis, history of nonsteroidal anti-inflammatory drug (NSAID) treatment, and baseline WOMAC pain score.

Table 5. Factors Associated with a High WOMAC Stiffness Scores at 6- and 12-Month Follow-up.[a]

	Coefficient (95% CI)	P
At 6 months		
Baseline WOMAC stiffness score	0.4 (0.2, 0.5)	<0.001
Kellgren-Lawrence grade 3	7.0 (1.2, 12.7)	0.018
History of steroid injection	6.8 (0.2, 13.5)	0.044
History of arthrocentesis	–16.9 (–29.0, –4.7)	0.007
At 12 months		
Baseline WOMAC stiffness score	0.4 (0.2, 0.5)	<0.001
Kellgren-Lawrence grade 3	10.6 (4.2, 17.0)	0.001

CI = confidence interval; WOMAC = Western Ontario and McMaster Universities Arthritis Index.
[a]Variables entered into the models were treatment received, sex, Kellgren-Lawrence grade, age, body mass index (BMI), smoking status, alcohol consumption, osteoarthritis (OA) in contralateral knee, history of physical therapy, history of steroid injection, history of other injection, history of arthrocentesis, history of nonsteroidal anti-inflammatory drug (NSAID) treatment, and baseline WOMAC stiffness score.

associated with slightly higher global VAS scores at 12-month follow-up only (**Table 7**).

Treatment History Prognostic Factors

Patients who had previously received steroid injection treatment prior to IA-HA administration demonstrated significantly higher ($P = 0.044$) VAS scores after a 50-foot walk test at 6-month follow-up, while patients who had previously received arthrocentesis demonstrated

Table 6. Factors Associated with a High WOMAC Disability Scores at 6- and 12-Month Follow-up.[a]

	Coefficient (95% CI)	P
At 6 months		
Baseline WOMAC disability score	0.5 (0.4, 0.6)	<0.001
Kellgren-Lawrence grade 3	6.0 (1.0, 11.0)	0.021
Saline injection	5.5 (0.6, 10.4)	0.027
Females	5.6 (0.3, 11.0)	0.038
At 12 months		
Baseline WOMAC disability score	0.45 (0.33, 0.5)	<0.001
Kellgren-Lawrence grade 3	8.1 (2.7, 13.6)	0.004

CI = confidence interval; WOMAC = Western Ontario and McMaster Universities Arthritis Index.
[a]Variables entered into the models were treatment received, sex, Kellgren-Lawrence grade, age, body mass index (BMI), smoking status, alcohol consumption, osteoarthritis (OA) in contralateral knee, history of physical therapy, history of steroid injection, history of other injection, history of arthrocentesis, history of nonsteroidal anti-inflammatory drug (NSAID) treatment, and baseline WOMAC disability score.

significantly lower ($P = 0.033$) VAS scores after a 50-foot walk test at 6-month follow-up (**Table 3**). Similarly, patients who had previously received steroid treatment ($n = 107$) prior to IA-HA administration demonstrated significantly higher WOMAC stiffness scores at 6-month follow-up, and patients who had previously received arthrocentesis ($n = 24$) demonstrated significantly lower WOMAC stiffness scores (**Table 5**) and global VAS assessment scores (**Table 7**) at 6-month follow-up. A significantly greater proportion of patients who were previously treated with steroid injection had a K-L grade 3 than patients who had not received previous steroid injection (71.96% vs. 56.5%, $P = 0.004$), which is a factor affecting the aforementioned results regarding the results of the steroid injection group.

OMERACT-OARSI Responders Analysis

The calculated odds ratios demonstrated a positive association between receiving Euflexxa injection and OMERACT-OARSI responders for VAS pain after the 50-foot walk and WOMAC pain subscale score at 6-month follow-up. It was shown that patients who received Euflexxa had 1.5 times better OMERACT-OARSI responders than patients who received saline for both VAS pain after 50-foot walk and WOMAC pain score. At 12-month follow-up, the only predictor of OMERACT-OARSI responders was high baseline VAS pain score after the 50-foot walk, as patients with a higher baseline score were more likely to categorize as an OMERACT-OARSI responder at the end of the extension trial (**Table 8**).

Table 7. Factors Associated with a High Global VAS Assessment Scores at 6- and 12-Month Follow-up.[a]

	Coefficient (95% CI)	*P*
At 6 months		
Baseline global VAS pain score (mm)	0.5 (0.3, 0.6)	<0.001
Kellgren-Lawrence grade 3	7.5 (1.8, 13.0)	0.010
Arthrocentesis	−14.7 (−26.2, −3.2)	0.012
At 12 months		
Baseline global VAS pain score (mm)	0.4 (0.3, 0.6)	<0.001
Kellgren-Lawrence grade 3	10.0 (3.7, 16.6)	0.002
Age	−0.3 (−0.6, −0.01)	0.026
OA in contralateral knee	−7.5 (−14.1, −0.9)	0.026

CI = confidence interval; OA = osteoarthritis; VAS = visual analog scale.
[a]Variables entered into the models were treatment received, sex, Kellgren-Lawrence grade, age, body mass index (BMI), smoking status, alcohol consumption, OA in contralateral knee, history of physical therapy, history of steroid injection, history of other injection, history of arthrocentesis, history of nonsteroidal anti-inflammatory drug (NSAID) treatment, and baseline global VAS assessment score.

Table 8. OMERACT-OARSI Responders.[a]

	Odds Ratio (95% CI)	*P*
50-ft walk VAS pain at 6 months		
Euflexxa injection	1.6 (1.0, 2.5)	0.033
Hosmer-Lemeshow goodness-of-fit *P* = 1.00		
50 ft walk VAS pain at 12 months		
Baseline VAS pain score	1.01 (1.0, 1.03)	0.024
Hosmer-Lemeshow goodness-of-fit *P* = 0.903		
WOMAC pain at 6 months		
Euflexxa injection	1.5 (1.0, 2.3)	0.046
Hosmer-Lemeshow goodness-of-fit *P* = 1.00		

CI = confidence interval; VAS, visual analog scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index.
[a]Variables entered into the models were treatment received, sex, Kellgren-Lawrence grade, age, body mass index (BMI), smoking status, alcohol consumption, osteoarthritis (OA) in contralateral knee, history of physical therapy, history of steroid injection, history of other injection, history of arthrocentesis, history of nonsteroidal anti-inflammatory drug (NSAID) treatment, and baseline VAS, WOMAC pain, WOMAC stiffness, WOMAC disability, or global VAS assessment score.

Mean Change in Outcome Scores by K-L Grades

Significantly greater reduction in all outcome assessments was demonstrated for the patient subgroup classified as K-L grade 2, when compared to patients with a K-L grade 3. These significantly greater differences in mean score reduction were demonstrated at both 6 and 12 months for VAS pain at 50-foot walk, WOMAC pain, stiffness, and disability subscales, and global VAS assessment (**Table 9**, **Fig. 2**). **Figure 2** demonstrates that the mean score for all pain and functional assessments for patients with K-L grade 2 or K-L grade 3 was reduced at 6- and 12-month follow-up times.

Discussion

It is apparent that the pain and functional scores decreased continually until the first 6 weeks and then somewhat increased by the end of the FLEXX trial, with mean reductions of 25.7 and 19.5 mm from baseline, respectively.[9] Similar trends of changes in the pain and function scores was shown for the extension trial, with additional mean reductions of 5.6 and 3.5 mm, respectively, although patients who participated in the extension trial started with lower mean pain and functional scores than the final visit of the FLEXX trial.[10]

In these studies of IA Bio-HA for OA of the knee, patients with K-L grade 2 and lower baseline demographics and outcome measures did better than those with K-L grade 3 and high baseline data, although both groups showed benefit. This suggests that those with less severe OA, and perhaps earlier disease, of the knee tend to have better responses to Bio-HA.

Previous publications have suggested a reduction of >19.9 mm (100 mm VAS) to be clinically meaningful.[11,12] This minimum clinically important difference was demonstrated by the 6-month follow-up in those with K-L grade 2, while reinjection at the 12-month follow-up was needed for those with K-L grade 3 to reach the minimum clinically important difference. For K-L grade 2 patients, a mean reduction of 25 scores was consistent for all outcome assessments, while this was not apparent for K-L grade 3 patients. These results are consistent with, and may partially explain, the results of the AMELIA trial, where some patients required more than one series of IA-HA injections to achieve benefit.[13]

Previous research has found that IA-HA treatment provides greater therapeutic benefit in the treatment of less severe OA in comparison with the treatment of more advanced or "late-stage" OA.[14,15] However, in other studies, disease severity was not specifically correlated to the efficacy of IA-HA treatment.[8] Our analyses agree with the former, as patients with a K-L grade 3 demonstrated higher values in specified outcome scores than patients with a K-L grade 2. Patients with a K-L grade 2 and K-L grade 3 had similar baseline outcome scores; however, a larger change from baseline was demonstrated across all outcome scores for patients with a K-L grade 2, when compared with those with a K-L grade 3.

Analyses presented within this report demonstrate that gender and age may also play a role in the outcome of IA-HA

Table 9. Mean Change in Outcome Scores for Kellgren-Lawrence (K-L) Grades at 6 and 12 Months.

	K-L Grade 2 (n = 235), Mean (95% CI)	K-L Grade 3 (n = 353), Mean (95% CI)	P
Mean change in VAS pain target knee			
6 months	–24.87 (–28.81, –20.93)	–17.19 (–20.55, –13.82)	0.004
12 months	–34.24 (–38.49, –29.98)	–27.22 (–30.94, –23.51)	0.016
Mean change in WOMAC pain			
6 months	–21.08 (–24.73, –17.43)	–13.22(–16.01, –10.43)	0.001
12 months	–29.44 (–33.26, –25.62)	–19.62 (–22.94, –16.31)	<0.001
Mean change in WOMAC stiffness			
6 months	–20.02 (–23.90, –16.15)	–14.09 (–17.36, –10.82)	0.023
12 months	–30.07 (–34.40, –25.75)	–19.46 (–23.28, –15.63)	<0.001
Mean change in WOMAC disability			
6 months	–19.39 (–22.88, –15.89)	–13.38 (–15.98, –10.78)	0.006
12 months	–28.55 (–32.42, –24.68)	–19.86 (–22.96, –16.76)	0.001
Mean change in global VAS assessment			
6 months	–23.21 (–27.08, –19.34)	–15.73 (–18.84, –12.61)	0.003
12 months	–33.29 (–37.58, –29.01)	–24.94 (–28.52, –21.36)	0.003

CI = confidence interval; VAS, visual analog scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

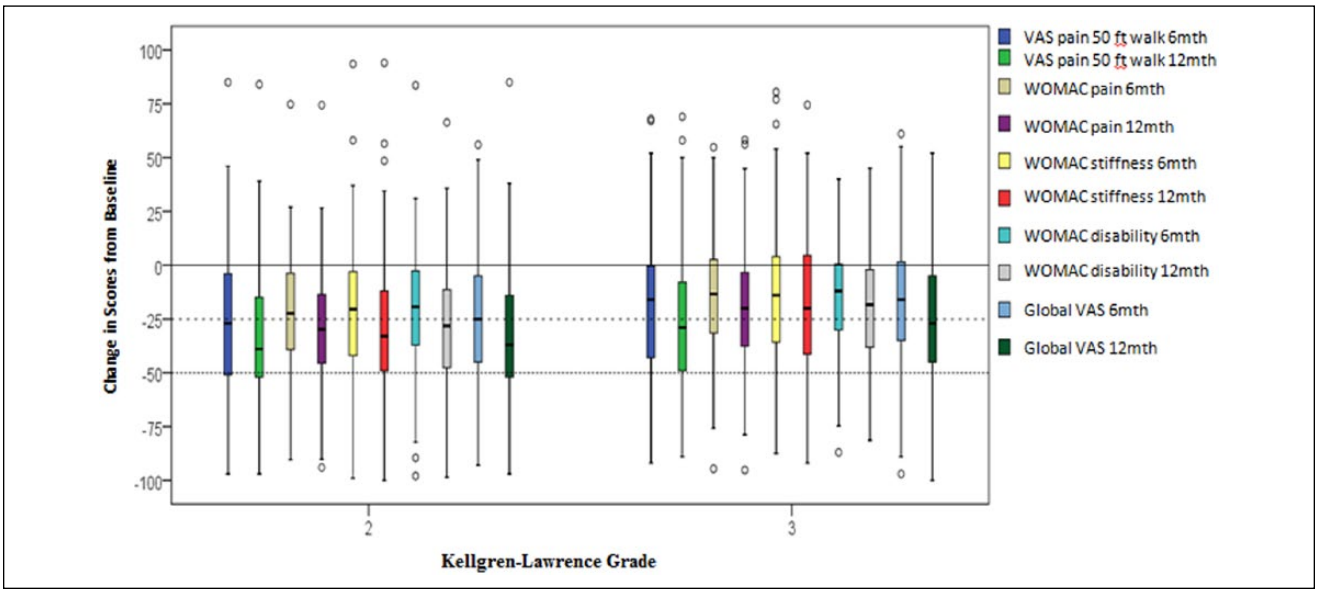

Figure 2. Mean change in pain and functional outcome assessments for Kellgren-Lawrence (K-L) grades at 6 and 12 months.

treatment. The analyses found that females had specific higher assessment scores at 6- and 12-month follow-up. The weak correlation between a younger age and a slightly worse response is not entirely clear, as our findings consistently suggested that treatment was significantly more successful for patients with earlier stages of OA (K-L grade 2 vs. K-L grade 3). The association to a greater response for all outcome variables is more closely correlated to K-L grade than to age; demonstrating that K-L grade is likely to be the prominent prognostic factor with respect to these two variables. The correlation between age and gender is not apparent within the current literature, making these findings of interest for future research to provide additional reporting of the potential correlation between age, gender, and IA-HA treatment outcomes. Patients with OA in the contralateral knee also demonstrated some significantly lower assessment scores at 12-month follow-up. This may suggest that the benefit of IA-HA was more obvious to the patient when the patient was able to compare the treated to the untreated knee with OA. These results differ from results of Orthovisc trials for FDA approval,[16] in which patients with contralateral knee pain demonstrated significantly worse results in a *post hoc* subgroup analysis, and were subsequently excluded from further analyses.[17] This comparison further illustrates

the variability in results based on products and their intrinsic characteristics, alluding to the notion that all HA products do not perform similarly.

This study is strengthened by its in-depth and thorough analysis of prognostic factors for the treatment of knee OA with IA-HA, specifically Euflexxa. This exploration of the FLEXX trail and extension database[9,10] for prognostic factors provides insight into the situations into where IA-HA treatment may be of greater benefit to patients, and should be considered in future IA-HA trial analyses to reinforce the findings from this report. This study is limited by its use of a single trial database. Because of the nature of the study design, we were only able to analyze the data that were originally collected. This prevented us from exploring radiographic factors that may provide prognostic value. Similar analyses are required for a variety of IA-HA products in order to determine the appropriateness of these results, as they may be specific to this study and not to IA-HA treatments in general.

Additionally, patients who had previously received steroid injections responded less to Bio-HA treatment, while patients who had previously received arthrocentesis demonstrated greater response to Bio-HA treatment. However, these findings are also not entirely clear, as we do not have data regarding the indication or frequency of use with respect to patients previously treated with steroid injection, such as the higher number of K-L grade 3 grade patients in this group, as well as other potential demographic differences between patients who had and had not previously received steroid injection or arthrocentesis. These results should be further investigated in future studies, as it would be of importance for health care professionals to understand how steroid injections or arthrocentesis affect the outcomes of future treatment using Bio-HA. It is important to understand potential prognostic factors when considering IA-HA as a treatment option in order to provide patients with an advantageous and informed treatment decision.

Conclusions

The results demonstrate that IA-HA for OA of the knee was of greater benefit in those with less severe radiographic changes. However, those with more severe radiographic change often had a better response with the second course of IA-HA. Similar analyses are required in order to determine if these results are unique to Euflexxa, or if these results are consistent with other available IA-HA agents.

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Trial Registration

Not applicable.

Declaration of Conflicting Interests

Roy Altman: Consultant for: Cytori, Dupuy, Ferring, Flexion, Iroko, McNeil, Novartis, Oletec, Pfizer, Q-Med, Rottapharm, Strategic Science & Technologies, Eva. Forough Farrokhyar: No conflicts of interest to declare Anke Fierlinger: Paid employee of Ferring Inc. Faizan Niazi: Paid employee of Ferring Inc. Jeffrey Rosen: Part of Ferring's speaker bureau and scientific advisory board.

Ethical Approval

Ethical approval was not sought for the present study because all data was obtained from a previously conducted trial. No patients were directly enrolled within this investigation.

Informed Consent

Informed consent was not sought for the present study because all data was obtained from a previously conducted trial. No patients were directly enrolled within this investigation.

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