

Assessment of the Health-Related Quality of Life Impact of EUFLEXA® (1% Sodium Hyaluronate) Using Short Form 36 (SF-36) Data Collected in a Randomized Clinical Trial Evaluating Treatment of Osteoarthritis Knee Pain

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Abstract

Background: Outcome measurements of clinical trials such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) have provided disease specific data on lower extremity osteoarthritis (OA). The impact of the disease, condition, or treatment on the dimensions of functioning and well-being has been supplemented by the use of general health-related quality of life (HRQoL) instruments.

Objective: To examine patients' general HRQoL measures using the Short Form 36 (SF-36) from the 26-wk double-blind, randomized, saline (IA-SA)-controlled FLEXX Trial and the 26-wk open-label Extension Study, which evaluated efficacy and safety of intra-articular (IA) injections of a bioengineered hyaluronic acid (HA [BioHA]) for treatment of OA knee pain.

Methods: HRQoL of participants treated with IA-BioHA in the FLEXX Trial was compared to patients' baseline HRQoL and to United States population and OA norms using the SF-36v2. This study evaluated the durability of improvement in physical health related domains of the SF-36 observed at week 26 of the FLEXX Trial by assessing the physical functioning scores at week 52 for patients who received a second course of 3 weekly injections of IA-BioHA during the FLEXX Trial Extension Study.

Results: Baseline SF-36 scores indicated significant physical limitations in patients enrolled in the FLEXX Trial relative to United States population and OA population norms. Changes between the SF-36 scores for IA-BioHA-treated patients at week 26 continued to improve following a repeat injection series through week 52, with a significantly lower bodily pain domain ($P=0.014$).

Conclusions: Patients treated with IA-BioHA in the FLEXX Trial experienced significantly greater improvement in physical functioning and disability at 26 weeks as measured by the SF-36. A repeat injection series of IA-BioHA resulted in further improvement towards United States population norms in their physical ability with a significant reduction in bodily pain from the end of the FLEXX trial to the end of the Extension Study (week 52).

Keywords: Osteoarthritis; Hyaluronic acid; Patient-related outcome measures; Knee pain; Health-related quality of life

Abbreviations: AE: Adverse event; BioHA: Bioengineered hyaluronic acid; BP: Bodily pain; CI: Confidence interval; ES: Effect size; GH: General health perceptions; HA: Hyaluronic acid; HRQoL: Health-related quality of life; IA: Intra-articular; IA-SA: Intra-articular buffered saline; MCS: Mental component summary; MH: Mental health; MID: Minimally important difference; OA: Osteoarthritis; OARSI: Osteoarthritis Research Society International; PCS: Physical component summary; PF: Physical functioning; RE: Role limitations due to emotional problems; RP: Role limitations due to physical health; SF: Social functioning; SF-36: Short Form 36; VAS: Visual analog scale; VT: Vitality; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Introduction

Osteoarthritis (OA) is associated with substantial pain and functional disability; in turn, these effects are associated with significantly decreased health-related quality of life (HRQoL) [1,2]. According to the United States Centers for Disease Control and Prevention (CDC), OA is one of the 5 leading causes of disability among

adults: 80% of OA patients have movement limitations of some kind, while 25% are unable to perform major daily activities [2]. Similarly, a review of the community burden of OA in Europe and the United Kingdom found that ~25% of individuals over 55 years of age reported significant knee pain annually, and 50% of these individuals reported associated disability. This analysis also found that 1.5% of adults over 55 years of age experienced severely disabling knee OA [3].

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Results from multiple clinical trials have shown that IA-HA is a safe and effective therapy for treatment of OA knee pain that provides sustained symptom relief following a single injection series [4-9]. Data from several clinical studies also show that patients may benefit from repeated injection series. In recent years, outcome measurements of clinical trials have expanded to include the assessment of the degree to which patients attain a more effective life by preserving function and restoring well-being. The impact of a disease, condition, or treatment on dimensions of functioning and well-being can be determined using a specific HRQoL instrument [10]. Although the efficacy of IA-HA for the relief of pain and disability caused by knee OA has been demonstrated, few studies have investigated the impact of IA-HA therapy on general HRQoL. Information about the HRQoL impact of a therapy may also be an important factor for determining the therapy's overall value from a health economics perspective [11-13].

The SF-36v2® Health Survey and its predecessor, the SF-36®, are among the most widely used health status assessment tools used in clinical trials [13]. There is substantial evidence for the effect of non-traumatic hip or knee disorders on general HRQoL as measured by the SF-36 [14]. Pooled estimates from 40 studies revealed that patients with hip and knee OA scored up to 2.5 standard deviations below reference population values, especially on the physical domains of the SF-36 [14]. In OA clinical trials, the bodily pain (BP) domain of the SF-36 is commonly used as one of the indicators for pain relief, and both the physical composite score (PCS) and physical function (PF) score of the SF-36 are commonly used as measures of disability [15]. A large population-based survey by Ware et al. reported considerable differences between healthy adults and OA patients in mean PCS (55.33 vs. 38.30), PF (54.76 vs. 38.81), and BP scores (55.59 vs. 39.83, respectively) [16].

This study investigated whether the clinical efficacy of IA-BioHA reported earlier also translates into significant improvement in patients' general HRQoL using the SF-36v2 (acute survey form with 7-day recall) and evaluated the durability of improvement in PF observed at week 26 of the FLEXX Trial by assessing the PF score at week 52 for patients who received a second course of 3 weekly injections of IA-BioHA during the FLEXX Trial Extension Study.

Methods

Data source and description of the FLEXX trial and extension study

The FLEXX Trial and the FLEXX Trial Extension study have been published elsewhere. Briefly, the FLEXX Trial was a randomized, double-blind, multicenter, IA-SA-controlled study investigating efficacy and safety of EUFLEXXA® (1% sodium hyaluronate) for the treatment of patients with mild to moderate knee pain from OA conducted in the United States [17]. The primary efficacy outcome measure was the difference in least-squares means between IA-BioHA and IA-SA in each subject's change in knee pain from baseline to week 26 on a 100-mm visual analog scale (VAS) following a 50-foot walk test. All adverse events (AEs) were recorded at each visit or interview to assess safety.

The FLEXX Trial Extension Study was a multicenter, open-label 26-week trial designed to assess safety of a repeated series of 3 weekly IA-BioHA injections. Patients who completed the FLEXX Trial and who elected to participate in the Extension Study remained without knowledge of whether they received IA-SA or IA-BioHA in the initial series of injections, and received either an initial course of IA-BioHA injections if they received IA-SA in the FLEXX Trial (n=219)

or a second course of IA-BioHA injections (n=214) [18]. SF-36 was evaluated at week 52.

Outcome measures and assessments

The SF-36v2 consists of a 36-item self-report inventory [16]. This patient-reported outcome measure assesses health-related limitations in eight domains: PF, role limitations due to physical health (role-physical, RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (role-emotion, RE), and mental health (MH). Two summary scores, the PCS and the mental component summary (MCS), can also be calculated from the eight domain scores (scale scores) [19]. SF-36 scores were measured using the acute form with 7-day recall at baseline (week 0) and at weeks 12 and 26 of the FLEXX Trial and at baseline (week 26) and completion (week 52) of the Extension Study.

Summary of findings from the FLEXX trial and extension study

At the end of FLEXX Trial, the intent-to-treat population included 295 patients in the IA-SA and 291 in the IA-BioHA groups. Sixty-three percent (63%) of the study population was female, with mean age of 61.6 years and body mass index of 32.7. At baseline of the FLEXX Trial (week 0), approximately 40% of patients in each group had Kellgren-Lawrence radiographic grade 2, and about 60% had radiographic grade 3 OA of the knee. Mean baseline pain scores were 54.7 and 55.6 in the IA-SA and the IA-BioHA groups, respectively. There were no statistical differences in demographics between the two groups at baseline [17].

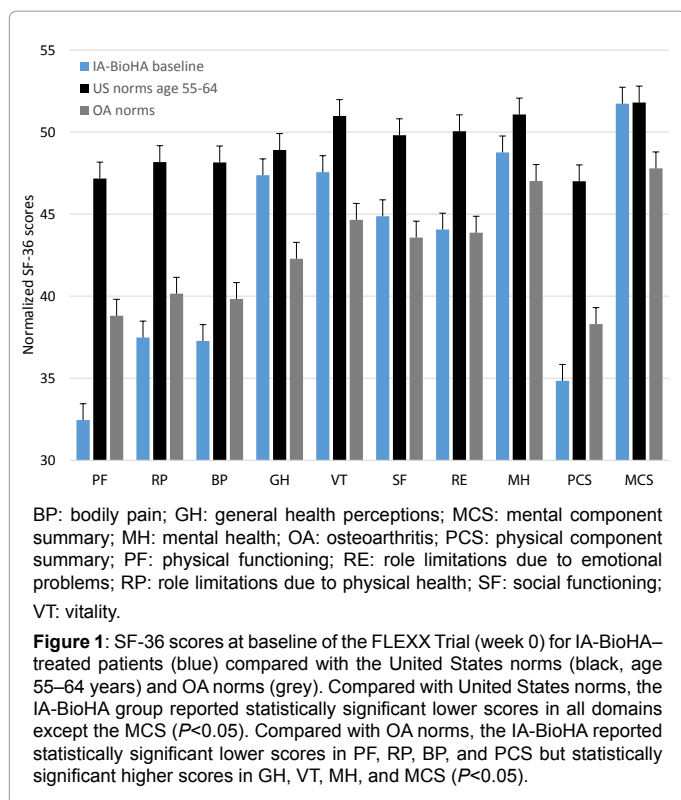
IA-BioHA therapy resulted in significant OA knee pain relief with a decrease in mean VAS scores of 25.7 mm at 26 weeks compared with 18.5 mm in the IA-SA group, a mean reduction of 53% for IA-BioHA and 38% for IA-SA from baseline ($P=0.002$) [17]. Subjects treated with IA-BioHA also experienced significant improvements in joint function, treatment satisfaction, and HRQoL. The IA-BioHA group also had a significantly higher proportion of patients who were Osteoarthritis Research Society International (OARSI) responders (67% vs. 59%, $P=0.0047$), with significant improvements in the change from baseline for both the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function subscale (difference of least-squares means of -4.3 mm, 95% confidence interval (CI), -7.9 to -0.7 mm, $P=0.019$) and patient global assessment (difference in least-squares means of -4.5 mm, 95% CI -8.6 to -0.3 mm, $P=0.035$) [17].

Three hundred seventy-eight (378) patients (87%) completed the Extension Study, including 187 subjects treated with IA-SA and 191 treated with IA-BioHA in the FLEXX Trial [18]. Results showed that a repeat injection series of IA-BioHA was safe and well-tolerated, and no patients reported a joint effusion over the course of the 52-week FLEXX Trial and Extension Study. Patients who received a second course of IA-BioHA treatment during the Extension Study experienced further improvement of 3.5 mm magnitude in VAS pain score between weeks 26 and 52, and patients who initially received IA-SA during the FLEXX Trial and were given a course of IA-BioHA in the Extension Study experienced a reduction in VAS score of 9.0 mm between weeks 26 and 52 [18].

Statistical Analysis

Data handling

Scores of the SF-36v2 acute form health survey were calculated based on the method described in the manual for the SF-36v2 health survey [16]. The half-scale rule was used to handle missing item



Variable	IA-BioHA (n=291)		
	Mean (SD)	ES*	% with \geq 3-point improvement
PF	4.77 (9.65)	0.49	51.8
RP	4.13 (10.49)	0.39	49.8
BP	3.85 (9.93)	0.39	53.7
GH	1.38 (6.22)	0.22	35.0
PCS	4.55 (8.50)	0.54	54.5

*Computed as mean/SD.

BP, bodily pain; ES, effect size; GH, general health perceptions; PCS, physical component summary; PF, physical functioning; RP, role limitations due to physical health.

Table 1: Change from baseline (week 0) in ES in the physical health domains of SF-36 scores for the IA-BioHA treatment group at week 26

response, with scores transformed to norm-based values using the United States general population [16].

Descriptive statistics and bivariate tests

Descriptive statistics were computed and reported for all subscales and two summary scores of the SF-36 at all study intervals. Student *t*-tests were performed to compare SF-36 scores for IA-BioHA treated patients at baseline (week 0) of the FLEXX Trial with the most recent United States norms for the 55- to 64-year-old age group and OA-specific norms [16]. Effect sizes (ES) of change from baseline scores to week 26 in the four domains related to physical health aspects of the SF-36 and its PCS were calculated using Cohen's *d* [20].

Pearson's correlation coefficients were calculated between change from baseline (week 0 of the FLEXX Trial) scores of the SF-36 with the pain score (100-mm VAS) following a 50-foot walk test, WOMAC scores, patient global assessment, and amount of rescue medication used at week 26. Student *t*-tests were used to compare the SF-36 scores between responders and non-responders in the IA-BioHA treatment group.

Results

Comparison of SF-36 scores for patients in the FLEXX trial at baseline (week 0) with United States and OA norms

All patients enrolled in the FLEXX Trial filled out the SF-36 survey at the specified intervals. Between 10% and 15% of patients left at least one item in the survey unanswered. At baseline (week 0) of the FLEXX trial, there were no significant differences between the IA-BioHA and IA-SA treatment groups in SF-36 scores. The SF-36 scores for the IA-BioHA-treated group were significantly lower than the United States norms in most of the eight domain scores and PCS (Student *t*-test, $P < 0.05$). This group experienced significantly greater physical disability than the United States norms: 14.7 (standard error, 0.63) points less than the United States norms in PF, 10.7 (0.64) points less in RP, 10.9 (0.59) points less in BP and 12.2 (0.61) points less in PCS (Figure 1).

SF-36 outcomes of patients treated with IA-BioHA in the FLEXX trial

At the completion of the FLEXX Trial (week 26), patients treated with IA-BioHA experienced statistically significant ($P < 0.05$) improvement in disability scores compared to baseline scores (week 0, mean [SD]) as measured by PF (+4.77 [9.65]), RP (+4.13 [10.49]), BP (+3.85 [9.93]), GH (+1.38 [6.22]), and PCS (+4.55 [8.50]). The IA-BioHA treatment group also showed significant improvement in two mental functioning domains, namely VT (+2.43 [8.09]) and SF (+2.17 [9.94], $P < 0.05$). Effect size at week 26 was the greatest for the IA-BioHA group in PCS (ES=0.54), followed by PF (ES=0.49, Table 1).

SF-36 outcomes following repeat injection of IA-BioHA in the FLEXX trial extension study

There were no significant differences between participants in the 52-week open-label FLEXX Trial Extension Study and nonparticipants in gender, age, or body mass index, and there were also no significant differences between the study participants and nonparticipants on any of the OA clinical endpoints or the SF-36 scores at the end of the FLEXX study period [18]. Change from baseline (week 0) in SF-36 scores to week 26 and week 52 showed improved PF in patients who received IA-BioHA as the initial course of treatment followed by another course at week 26. Moreover, patients continuing with IA-BioHA at week 26 had an additional reduction in pain, maintained their treatment effect to week 52, and also experienced an additional reduction in BP ($P = 0.014$; Table 2).

Discussion

In a landmark multinational study of the negative well-being impact associated with chronic conditions, arthritis was found to entail the highest negative impact on the SF-36 scores in the general population, more so than either chronic lung disease or congestive heart failure [21]. Pooled estimates from 40 studies revealed that patients with hip and knee disorders scored up to 2.5 SDs below their reference population norms, especially on the PF domains of the SF-36 [15]. Consistent with these findings, all participants in the FLEXX Trial showed lower SF-36 scores for PF at baseline compared with either a healthy population or OA population norms. The potential for relief of symptoms associated with knee OA symptoms with preparations such as IA-BioHA is important when one considers the detrimental impact of arthritis.

At the end of the 26-week FLEXX Trial, patients who received a series of 3 weekly injections of IA-BioHA experienced significant

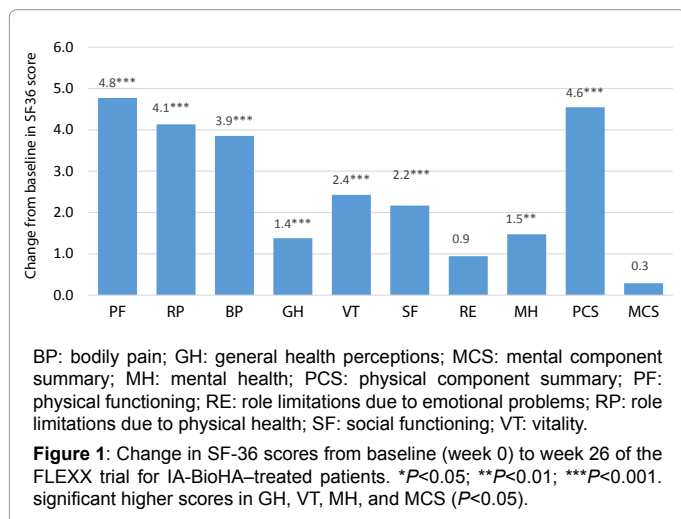
improvement from baseline in physical health-related scores, as measured by PF, RP, BP, GH, and PCS, and in 2 mental functioning domains, VT and SF. The results from this analysis demonstrate that these positive improvements in physical health were maintained for up to 52 weeks in patients who received an additional course of IA-BioHA treatment during the Extension Study. Patients with better outcomes on VAS pain scores following a 50-foot walk test, WOMAC scores, or patient global assessment also experienced significantly improved (higher) SF-36 scores (Figure 2).

Patients who received a repeated series of 3 weekly IA-BioHA injections 6 months after the initial treatment showed sustained improvement in physical ability and further relief from BP at 52 weeks.

SF-36 scale	Week number	Least squared mean of change scores from baseline (week 0)	Difference (SE)	P value
PF	26	4.73	0.03 (0.54)	0.955
	52	4.76		
RP	26	4.01	0.37 (0.63)	0.561
	52	4.38		
BP	26	3.79	1.61 (0.65)	0.014
	52	5.40		
GH	26	1.37	0.35 (0.46)	0.441
	52	1.72		
VT	26	2.44	0.59 (0.54)	0.274
	52	3.03		
SF	26	2.06	0.33 (0.64)	0.609
	52	2.38		
RE	26	1.06	0.47 (0.76)	0.539
	52	1.53		
MH	26	1.78	0.45 (0.57)	0.428
	52	2.23		
PCS	26	4.38	0.64 (0.52)	0.219
	52	5.02		
MCS	26	0.50	0.35 (0.57)	0.545
	52	0.85		

BP: bodily pain; GH: general health perceptions; MCS: mental component summary; MH: mental health; PCS: physical component summary; PF: physical functioning; RE: role limitations due to emotional problems; RP: role limitations due to physical health; SE: standard error; SF: social functioning; VT: vitality.

Table 2: Comparisons of the SF-36 change scores at weeks 26 and 52 in patients who received IA-BioHA during the FLEXX Trial and a repeat series of IA-BioHA in the Extension Study.



A meta-analysis of OA studies has shown that the treatment effect is usually larger when the follow-up duration is shorter [22]. For example, the ES on pain outcome was 0.54 in studies with less than 3 months follow-up, and 0.23 at 3 to 6 months. Repeated administration of IA-BioHA at 6 months after the initial treatment not only sustained the improvement in PF of the treated patients, but also resulted in significant improvement in the SF-36 BP domain at 52 weeks.

IA-BioHA-treated patients experienced significant clinical benefits not only in what are customarily regarded as OA-specific measures, but also in their general well-being measures. The clinical relevance of the positive general well-being impact of IA-BioHA is further highlighted with an earlier observation that the strongest improvements were clinically relevant by the strength of their relationships to OA disease severity [23]. There were significant correlations between the SF-36 domains measuring physical disability and most of the well-established OA clinical endpoints of the trial, thus reinforcing the responsiveness of the SF-36 to OA signs and symptoms [23]. Our results are also consistent with earlier studies in which some of the SF-36 domain scores were reported to differ significantly amongst patients with varying arthritic severity [23]. A treatment ES of around 0.5 is considered a relevant threshold for clinically meaningful effect [24]. In the current study, the improvements in PF domain and the PCS of the IA-BioHA group met this threshold at the end of the FLEXX Trial.

Ware and colleagues recommended a minimally important difference (MID) of 3 points as “a starting point for discussion” and described various implications of changes of such magnitude [16]. For instance, a 3-point reduction in PF could increase the risk of disability leading to inability to work by 38%, the risk of being hospitalized in the subsequent year by 13%, and the risk of 2-year mortality by ~31%. In the current study, we found that the IA-BioHA group achieved MID in most physical ability domains and their PCS score by week 26 (except in GH), whereas the IA-SA group only achieved MID in PF. Patients who continued with IA-BioHA in the Extension Study continued to report improvement in PF and physical ability and a significant reduction in BP.

Limitations of the Study

As part of the overall clinical trial design, this study shares the same limitations cited by Altman et al. [17]. Basically, the Extension Study was an open-label trial and lacked a control group. This aspect of the study design was necessary to ensure subject participation, as it is nearly impossible to enroll subjects in a long-term study if they are not guaranteed active therapy. The open-label design of the Extension Study was unlikely to have influenced patient-reported outcomes, especially because the subjects remained blinded to previous therapy. Moreover, the potential of study design biasing patients’ response is limited because we did not compare between the two treatment arms in the Extension Study. Rather, we focused only on the patients who received IA-BioHA in both the FLEXX Trial and the Extension Study to investigate the sustainability of the improvement in HRQoL from week 0 to week 52.

In spite of these limitations, patients treated with IA-BioHA showed improved PF at week 26, with sustained improvement at week 52 in patients who elected to receive an additional course of 3 IA-BioHA injections at week 26.

Conclusions

Patients with OA of the knee enrolled in this randomized controlled trial had significant physical disability as compared with the general

population or to the OA population norms. At the end of the 26-week FLEXX Trial, patients treated with IA-BioHA experienced significantly greater improvement in their PCS scores. These improvements were sustained for an additional 6 months for patients who completed the FLEXX Trial and elected to receive an additional course of 3 weekly injections of IA-BioHA. These findings are robust with significant correlations to the more specific OA measures and in their ability to discriminate treatment response.

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Author Contribution Statement

HTH obtained funding for the study and contributed to study concept and design, data analysis and interpretation, and drafting and revision of the article for important intellectual content. JER contributed to study concept and design. SJL provided statistical expertise and contributed to data analysis and interpretation and drafting of the article. ALF contributed to critical revision of the article for important intellectual content. RDA contributed to concept and design of the study, data analysis and interpretation, and critical revision of the article for important intellectual content. All authors provided final approval of the article.

Role of the Funding Source

Financial support for this study and for assistance with medical editing was provided by Ferring Pharmaceuticals Inc.

Competing Interests

Hind T. Hatoum, PhD is a paid consultant for Ferring Pharmaceuticals Inc., the marketer of one of the study drugs. Funding for the study was provided by Ferring Pharmaceuticals Inc. through a contract with Hind T. Hatoum & Company. Jeffrey E. Rosen, MD is a paid consultant for Ferring Pharmaceuticals Inc. Anke L. Fierlinger, MD is a paid employee of Ferring Pharmaceuticals Inc. Swu-Jane Lin, PhD is a paid consultant for Hind T. Hatoum & Company. Roy D. Altman, MD is a paid consultant for Ferring Pharmaceuticals Inc., Abbott Theralogix, LLC, Ortho-McNeil-Janssen Pharmaceuticals, Inc., Rotta Pharmaceuticals, Inc., Toltec Pharmaceuticals, LLC, Iroko Pharmaceuticals, LLC, and Novartis Pharmaceuticals Corporation, and also receives clinical trial funding from Ferring Pharmaceuticals Inc. and Novartis Pharmaceuticals Corporation.

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