

Unique aspects of pain reduction in osteoarthritis of the knee with LMWF-5A

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Abstract: Osteoarthritis of the knee (OAK) is a common form of arthritis that can lead to substantial pain and disability. This commentary highlights key aspects of the recently published phase 3 A Efficacy and Safety Study of Two Doses of Intra-Articular Injection of Ampion™ in Adults With Pain Due to Osteoarthritis of the Knee (SPRING) study. SPRING (NCT01839331) was a multicenter, randomized, vehicle-controlled, double-blind trial that evaluated the safety and efficacy of the low-molecular-weight fraction of 5% human serum albumin (LMWF-5A) for treatment of pain, measured by the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain scale, in patients with symptomatic OAK (N=329). Patients in this study reflected many characteristics of “real-world” individuals with OAK, with a broad range of disease severity and disability. The most important finding from this study was that treatment with a single intra-articular injection of LMWF-5A led to significant pain reduction in the patients with objective radiographic evidence of severe disease and joint deterioration (Kellgren-Lawrence grade 3; $P=0.04$ and Kellgren-Lawrence grade 4; $P=0.02$). The magnitude of pain reduction in the entire cohort treated with LMWF-5A was 42% from baseline and the treatment effect compared with vehicle control (estimated difference in WOMAC pain, -0.25 ; $P=0.004$) was also notable, especially relative to a previously reported study of hyaluronic acid, in which only a marginally significant treatment effect was observed (mean difference in WOMAC pain compared with control, -0.15 ; $P=0.047$). Significant improvement in physical function observed with LMWF-5A ($P=0.04$) was also noted and suggests that LMWF-5A may provide therapeutic benefit for those who are limited in the activities of daily living. Intra-articular injection of LMWF-5A was well tolerated, and the adverse event profile was similar to that of control. These results demonstrate significant benefit of LMWF-5A for patients with greatest disability (Kellgren-Lawrence grades 3 and 4) and highest therapeutic need who have limited pharmacologic options for relief of pain associated with OAK.

Keywords: human serum albumin, knee, osteoarthritis, pain, Kellgren-Lawrence

Introduction

Osteoarthritis is the most common form of arthritis and affects ~27 million people in the United States.¹ Osteoarthritis of the knee (OAK) occurs in ~12% of individuals older than 60 years,^{1,2} and ~60% of these patients may have moderate-to-severe OAK, which is associated with limitations in daily activities and loss of productivity.³ Osteoarthritis is usually a progressive disease that develops from failed repair of joint damage resulting from stresses that may originate from an abnormality in any of the synovial joint tissues.⁴ Pathological changes leading to the breakdown of cartilage and bone eventually result in substantial pain and disability.^{3,4} It has been proposed that

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osteoarthritis is not a single disease but a heterogeneous collection of subtypes, which can be characterized by joint inflammation.⁴

Current therapies for pain reduction in OAK include physical activity, weight loss, acetaminophen, nonsteroidal antiinflammatory drugs, intra-articular steroids, and hyaluronic acid (HA).⁵ Patients with pain uncontrolled by these treatments may eventually be eligible for knee surgery or replacement.⁶ Treatments such as intra-articular steroids can provide short-term pain reduction but may lose effectiveness over time and may not lead to improvements in physical function or stiffness.⁵ As the American Association of Orthopaedic Surgeons clinical practice guidelines could not recommend use of intra-articular steroids or HA,⁷ there is a need for an agent that would halt or reverse disease progression and provide antiinflammatory and analgesic benefits, especially for treatment of OAK in aging or obese patients.⁸ Burden of disease is especially high in the latter population, as it is estimated that OAK is associated with 1.86 quality-adjusted life-years lost for nonobese patients aged 50 to 84 years versus 3.50 for obese patients.⁹

Human serum albumin has been approved for treatment of burns and shock for more than 30 years, with favorable safety and tolerability.^{8,10} The low-molecular-weight fraction (<5,000 Da) of 5% human serum albumin (LMWF-5A) contains aspartyl-alanyl diketopiperazine, which may have antiinflammatory or immunomodulatory effects.^{8,11} Primary results from the SPRING study of LMWF-5A for pain reduction in OAK were recently published.⁸ This commentary highlights the unique aspects of this study of LMWF-5A in a heterogeneous “real-world” cohort of patients with moderate to severe OAK.

Commentary main text

Study design and methods

A Efficacy and Safety Study of Two Doses of Intra-Articular Injection of Ampion™ in Adults With Pain Due to Osteoarthritis of the Knee (SPRING) study (NCT01839331) was a multicenter, randomized, vehicle-controlled, double-blind trial to evaluate the safety and efficacy of LMWF-5A for treatment of pain in symptomatic OAK.⁸ Patients (N=329) were randomized to receive a 4 or 10 mL intra-articular injection of LMWF-5A or vehicle control (saline). At baseline, mean age of patients was ~62 years (range, 41–84 years); and 64% were female.⁸ Patients in SPRING reflected many characteristics of individuals with OAK that may not have been represented in previous clinical studies,^{12,13} including greater ethnic diversity (9% were nonwhite) and increased body mass index (mean, 33 kg/m²).⁸

The primary endpoint in SPRING was difference in pain reduction between LMWF-5A and control, measured by change from baseline in Western Ontario and McMaster Universities Osteoarthritis (WOMAC) A subscore at 12 weeks.⁸ Secondary endpoints included changes in physical function (WOMAC C) and pain with movement and at rest (WOMAC A). Safety assessments included incidence and severity of adverse events (AEs).⁸

Efficacy and safety

Nearly two-thirds of patients enrolled in SPRING had moderate (Kellgren-Lawrence [K-L] grade 3, 42%) or severe (K-L grade 4, 22%) symptomatic OAK,^{8,14} which differs from a pivotal trial of high-molecular-weight HA in patients with milder disease (K-L grades 2 and 3 only; K-L grade 4 was excluded).¹³ Patients with more severe disease are more likely to demonstrate joint deterioration that may be assessed more accurately.^{15,16}

The most important result in SPRING was the statistically significant pain reduction in patients with K-L grade 3 ($P=0.04$) and grade 4 (estimated treatment difference in WOMAC pain with LMWF-5A relative to control, -0.42 ; $P=0.02$).⁸ These results are noteworthy, given that this population has the greatest degree of joint damage, and significant effects have not been consistently demonstrated using other agents. For example, Chevalier et al reported that a single injection of HA led to a 31.3% pain reduction from baseline at 26 weeks.¹³ The effect observed with HA did not exceed a clinically meaningful threshold (-40.8%)¹⁶ and was associated with only a marginally significant difference compared with control (-0.15 ; $P=0.047$) in patients with less severe disease.^{12,13} Despite approval, the American Association of Orthopaedic Surgeons could not recommend HA for treatment of OAK.⁷

In SPRING, improvements in pain were observed with LMWF-5A in the overall cohort and across most subgroups.⁸ Significant clinical efficacy for pain reduction with LMWF-5A relative to control was observed as early as week 4 ($P=0.03$),⁸ an observation that has not been consistently demonstrated in previous studies of pain relief in OAK.^{12,13,17} Notable aspects were the clinically relevant¹⁶ magnitude of pain reduction (42% from baseline) and the significant effect compared with control (treatment difference, -0.25 ; $P=0.004$) observed with a single injection of LMWF-5A.⁸

Improvement in physical function (WOMAC C; $P=0.04$) was also demonstrated, suggesting LMWF-5A can provide therapeutic benefit in patients who may have substantial functional impairment.⁸ Moreover, the WOMAC C subscore may not capture all

aspects of improved function (eg, increased activity) that may positively affect quality of life for many patients.

Severity of OAK also may have influenced the treatment effects in this study, as a more pronounced placebo effect was observed in patients with milder disease (K-L grade 2), potentially leading to nonsignificant differences between LMWF-5A and control in this subgroup. Placebo effects are often observed in clinical studies of osteoarthritis;¹⁸ however, in SPRING, there was a consistent separation between treatment groups in patients with moderate-to-severe OAK (K-L grades 3 and 4), validating these results in a subgroup with objective radiographic evidence of joint damage.⁸

The overall safety profile of LMWF-5A was acceptable, and no serious drug-related AEs occurred. The percentage of AEs reported was similar in patients who received LMWF-5A (41%) or saline (47%).⁸

Potential limitations of the SPRING study include the relatively short follow-up time (12 weeks), which may not have captured the maximum difference between treatment groups. In addition, as efficacy measures could be affected by pain in the nontreated knee, bilateral disease was not evaluated in SPRING. Therefore, it was not possible to determine whether the treatment effect differed between patients with unilateral versus bilateral OAK. A planned phase 3 study with a longer observation period may assess the maximum treatment effect of LMWF-5A in OAK.

Conclusion

Results from the SPRING study exceeded expectations, given that a majority of patients enrolled had moderate to severe symptomatic OAK. There was a significant benefit of LMWF-5A for patients with objective radiographic evidence of OAK who have limited pharmacologic treatment options for pain associated with this disease.

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Disclosure

BM is a consultant for Ampio Pharmaceuticals, Inc. The author reports no other conflicts of interest in this work.

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