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ORIGINAL ARTICLE

The efficacy and safety of sodium hyaluronate injection (Adant®) in treating degenerative osteoarthritis: a multi-center, randomized, double-blind, positive-drug parallel-controlled and non-inferiority clinical study

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Abstract

Objective: To compare the efficacy and safety of two different sodium hyaluronate drugs in treating degenerative osteoarthritis (OA) of the knee.

Method: This randomized, multi-center, double-blind, positive-drug, parallel-controlled study included 229 patients aged ≥ 45 years who were clinically diagnosed with degenerative OA of the knee. The patients were randomly assigned to receive for 5 consecutive weeks a once-weekly intra-articular injection of the investigational drug Adant®, which is manufactured by fermentation, or the control drug Artz®, which is manufactured by extraction of cockscomb. The follow-up examinations were conducted 1, 2, 3, 4 and 6 weeks after the first injection. The primary efficacy parameter was the decrease in the visual analog scale (VAS) scores of pain on movement caused by load-bearing, and the secondary efficacy parameter was the decrease in the Lequesne index.

Results: The intra-articular injections of Adant® and Artz® produced a significant reduction in the VAS scores for pain on movement (50.4 and 50.3 mm, respectively) and in the Lequesne index. There were no significant differences in efficacy and safety between the two drugs and non-inferiority in VAS score decreases was confirmed.

Conclusion: The results of this study show that both Adant® and Artz® are effective for the treatment of OA and that there were no statistical differences between them in the VAS scores of pain on movement, Lequesne index or safety during the observation period with short-time follow up.

Key words: multi-center randomized controlled clinical study, osteoarthritis, sodium hyaluronate.

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INTRODUCTION

Sodium hyaluronate is a major component of joint fluid and cartilage matrix and has many physiological functions. In osteoarthritis (OA) and other types of

arthritis, the components of the synovial fluid change, resulting in reduced sodium hyaluronate concentration and joint hypofunction, which leads to articular cartilage erosion and damage, pain, and decreased range of motion.[1] Supplementing exogenous sodium hyaluronate can increase the sodium hyaluronate content of the synovial fluid to form a natural barrier that protects the cartilage matrix against further damage and disappearance, and improve the biological function of the synovial fluid, which significantly reduces pain. In addition to this mechanical action, different studies have confirmed that sodium hyaluronate interacts with inflammatory mediators and matrix turnover within the joint cells, reduces chondrocyte apoptosis and exerts a biosynthetic chondroprotective effect.[2–7]

Sodium hyaluronate shows a long-term carry-over effect on pain and function after administration, suggesting that it is a symptomatic slow-acting class compound (SYSADOA).[8,9] Recently, a study with the result that reveals repeated cycles of intra-articular injections of sodium hyaluronate not only improve OA in the knee symptoms during the in-between cycle period, but also exert a marked carry-over effect for at least 1 year after the last injection, was reported.[10] It has also demonstrated an exceptionally high safety profile over a long-term observation period.

Adant®, injectable sodium hyaluronate manufactured by microbial fermentation, has been administered in more than 35 countries since its launch in Japan in 1994 and received approval in China in 2012. Artz®, injectable sodium hyaluronate manufactured by the extraction of cockscomb, was the first sodium hyaluronate approved in China. Essentially both products exhibited similar biochemical and physical characteristics (formulation: 25 mg/2.5 mL aqueous solution) (molecular weight: from 0.6 to 1.2 million daltons), except the source of hyaluronic acid (HA: rooster comb extraction, Artz® and bacterial fermentation, Adant®) and manufacturing methods. The aim of this study was to compare the efficacy and safety of these two sodium hyaluronate drugs with the same standard treatment for degenerative OA of the knee.

METHODS

Ethics

This clinical trial was conducted in strict accordance with the code of ethics of the Declaration of Helsinki, the Chinese GCP (Good Clinical Practice) and relevant rules and regulations on medical studies involving human subjects.

Clinical trial approval No.: 2008L03646 by the China Food and Drug Administration.

Study design

The study was a randomized, multi-center, double-blind, positive-drug, parallel-controlled study.

Random allocation to the two treatment arms was based on a 2 : 2 (Adant®: Artz®) ratio, using a block size of 4. The drugs for investigation were randomized by stratified/stage randomization and numbered according to the random numbers generated by a computer. According to the order of enrollment, all patients were randomly distributed to the test or control group to receive for 5 consecutive weeks a once-weekly intra-articular injection of the investigational drug Adant® (Meiji Seika Pharma Co., Ltd., Tokyo, Japan), a 2.5 mL sodium hyaluronate injection containing 25 mg of sodium hyaluronate, or the control drug Artz® Dispo (Seikagaku Corporation, Tokyo, Japan), a 2.5 mL sodium hyaluronate injection containing 25 mg of sodium hyaluronate for 5 consecutive weeks. The investigators and patients were blinded to the groups and drugs to which they were assigned.

Follow-up examinations were conducted at 1, 2, 3, 4 and 6 weeks after the first injection (hereafter called weeks 1, 2, 3, 4 and 6, respectively).

The study protocol and informed consent form (ICF) of the clinical trial were reviewed and approved by the ethics committee of Peking University First Hospital.

The protocol for the research project has been approved by a suitably constituted Ethics Committee of the institution within which the work was undertaken, it conforms to the provisions of the World Medical Association's Declaration of Helsinki and informed consent has been obtained for all investigations on human subjects.

Inclusion/exclusion criteria

The main inclusion criteria were:

1. age $\geq$ 45 years and either sex
2. clinical diagnosis of degenerative OA of the knee after assessing the clinical examination, laboratory tests and radiography results
3. visual analog scale (VAS) score for pain on movement $\geq$ 30 mm
4. no history of apparent injuries
5. radiograph film of single-leg weight-bearing confirming OA of the knee, and
6. corresponding clinical symptoms and physical signs.

The main exclusion criteria were:

1 severe liver/kidney function impairment (aspartate aminotransferase > 1.5 × the normal value, alanine aminotransferase > 1.5 × the upper limit of normal [ULN], or creatinine > ULN)
2 intra-articular blood effusion
3 recent severe injury to the knee joint, congenital abnormality, bone tuberculosis or sequelae of pyogenic arthritis
4 other rheumatic diseases, and
5 use of anti-inflammatory analgesics or adrenocortical hormones within 3 weeks before the treatment or sodium hyaluronate preparations within the past 6 months.

Evaluation

Baseline characteristics (sex, race, age, height, weight, medical history, disease course, history of treatment, complications, medications, etc.) were recorded before the first injection.

The primary efficacy parameter was a decrease (measured in millimeters) in the VAS score of pain on movement caused by weight-bearing after treatment. The secondary efficacy parameter was a decrease in the Lequesne index (rest pain, movement pain, tenderness, knee joint swelling, morning stiffness and walking ability) after treatment.[11] In addition to these primary and secondary efficacy parameters, an overall four-level efficacy evaluation (cured, significantly effective, effective or ineffective) was performed according to the patients' answers to a questionnaire on their level of satisfaction with the therapeutic effects at the end of treatment.

Treatment safety and tolerability were evaluated based on the adverse event (AE) incidence and type.

Statistical methods

Sample size

The noninferiority test in VAS decreases as the primary efficacy indicator was determined based on data reported in the literature;[12] for a one-sided test, $\alpha = 0.025$, $\beta = 0.2$ (efficacy = 80%), and the pre-set common standard deviation S = 23 mm, $\delta = 10$ mm (approximately 1/2–1/3 of S). The calculated minimum sample size was 83 cases in each of the two groups, the test group and the control group. According to the requirement for the minimum number of cases specified in laws and regulations in China, and considering a 20% dropout, it was decided that 240 cases should be enrolled, 120 cases for each group.

Statistical analysis plan

The primary efficacy analysis was per-protocol set, because per-protocol cases have presented good compliance and completed the required contents of the raw data rather than an intention-to-treat set.

Statistical analysis software (SAS version 9.1.3, SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses for calculation. A two-sided test was adopted for all other statistical tests except the noninferiority test of the primary indicators; a *P*-value of 0.05 or less indicates that the tested differences are statistically significant, and a 95% confidence interval (CI) was used.

Subject data in the different groups obtained during each hospital visit are shown as mean ± SD or median (of the minimum and the maximum). A paired *t*-test was adopted to compare the pre- and post-treatment differences within the groups with the baseline values in the screening period.

RESULTS

Case distribution

The patients were recruited from April 2009 to November 2009. A total of 229 patients were enrolled in this study. The Artz® group had 113 patients of whom 105 completed the study, eight dropped out and none were eliminated. The Adant® group had 116 patients, of whom 108 completed the study, eight dropped out and none were eliminated (Fig. 1).

Pre-treatment baseline analysis

No statistically significant differences in sex, race, age, body height or body weight ($P > 0.05$) were observed between the Adant® and Artz® groups (Table 1). No statistically significant difference in vital signs ($P > 0.05$) was observed between the two groups, except for systolic blood pressure ($P < 0.05$). Concerning pre-treatment symptoms, no statistically significant differences in baseline individual symptoms, Lequesne total score, or VAS score ($P > 0.05$) were observed between the two groups.

Compliance analysis

Good compliance was observed for all patients in the two groups, excluding dropouts and eliminated cases.

Primary efficacy analysis

VAS decreases in per-protocol analysis

At week 6, the mean VAS score of the Artz® group ($n = 105$) decreased by 50.3 ± 21.22 mm and that of

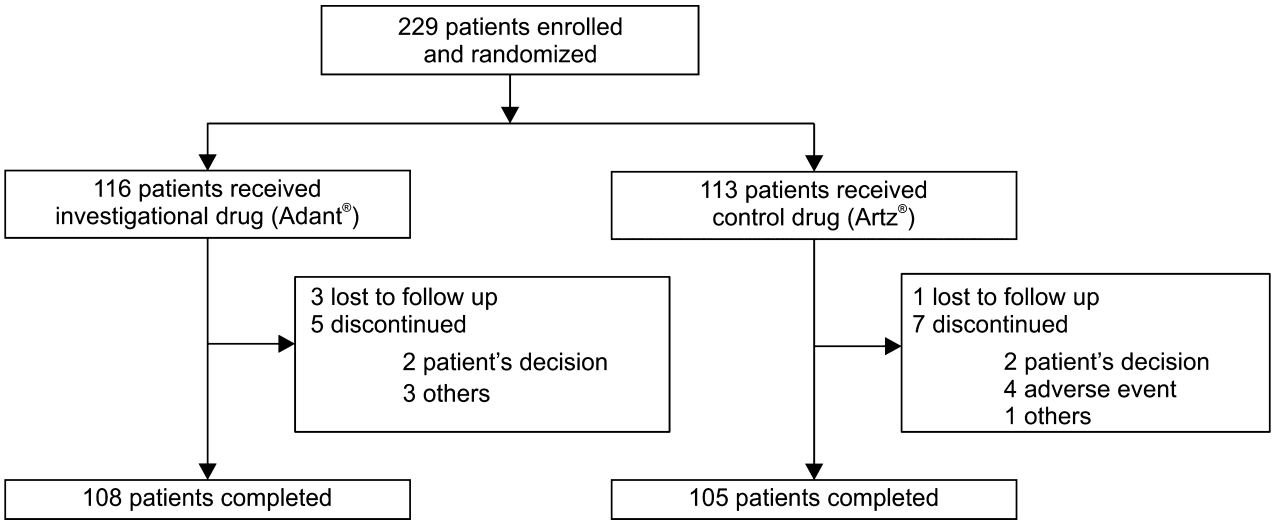

Figure 1 Case distribution.

Indicators	Adant®(n = 116)	Artz® (n = 113)	P-value
Sex (female), n (%)	93 (80.2)	84 (74.3)	0.292
Race (ethnic origin of Han), n (%)	115 (99.1)	110 (97.3)	0.365
Age (years), mean ± SD	61.87 ± 8.94	62.28 ± 8.52	0.721
Height (cm), mean ± SD	160.8 ± 7.93	161.4 ± 6.72	0.545
Weight (kg), mean ± SD	66.02 ± 10.76	65.97 ± 10.09	0.972

Table 1 Patient baseline characteristics by study group

the Adant® group (n = 108) decreased by 50.4 ± 20.77 mm. In both groups the change in the VAS score between pre- and post-treatment was statistically significant ($P < 0.01$). The difference between the two groups was not statistically significant ($P > 0.05$) and the Adant® group was noninferior to the Artz® group (non-inferiority margin: –10 mm; 97.5% CI: –5.772 to ∞) with respect to VAS score decreases (Fig. 2).

VAS decreases in intention-to-treat analysis (reference information)

Primary efficacy was evaluated in a per-protocol analysis; however, the results in an intention-to-treat analysis using the last observation carried forward were confirmed for reference. At week 6, the mean VAS score of the Artz® group (n = 113) decreased by 48.0 ± 23.39 mm and that of the Adant® group (n = 116) decreased by 49.2 ± 21.50 mm. The difference between the two groups was not statistically significant ($P > 0.05$) and the Adant® group was noninferior to the Artz® group (non-inferiority margin: −10 mm; 97.5% CI: −7.048 to ∞) with respect to VAS score decreases.

Measured VAS values

There were no statistically significant differences between the measured VAS values of the two groups obtained at the visit time points during the double-blind treatment period ($P > 0.05$).

Lequesne index decreases

At week 6, the mean Lequesne index of the Artz® group (n = 105) decreased by 6.10 ± 3.17 and that of the Adant® group (n = 108) decreased by 5.67 ± 3.24. In both groups, the mean difference in the Lequesne index between pre- and post-treatment was statistically significant ($P < 0.01$) and clinically significant; the mean Lequesne index of differences between the two groups were not statistically significant ($P > 0.05$; Fig. 3). The

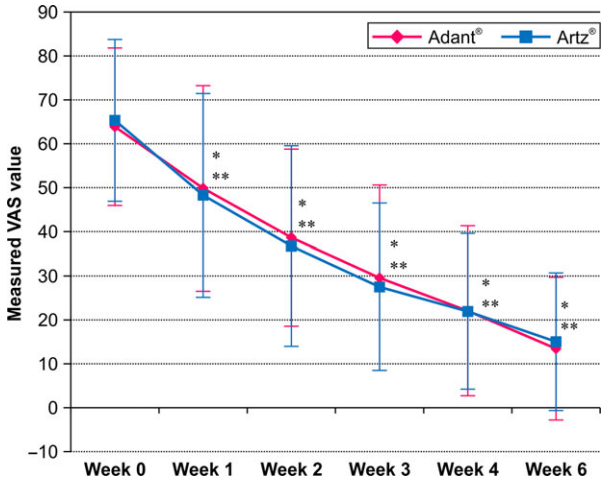

Figure 2 Diachronic analysis graphics of measured visual analog scale (VAS) values (mean ± SD, Per Protocol Set (PPS)). None of the differences between measured VAS values of the two groups obtained at the visit time points were statistically significant ($P > 0.05$). *Measured VAS value of Adant® group between pre- and post-treatment was statistically significant ($P < 0.01$). **Measured VAS value of Artz® group between pre- and post-treatment was statistically significant ($P < 0.01$).

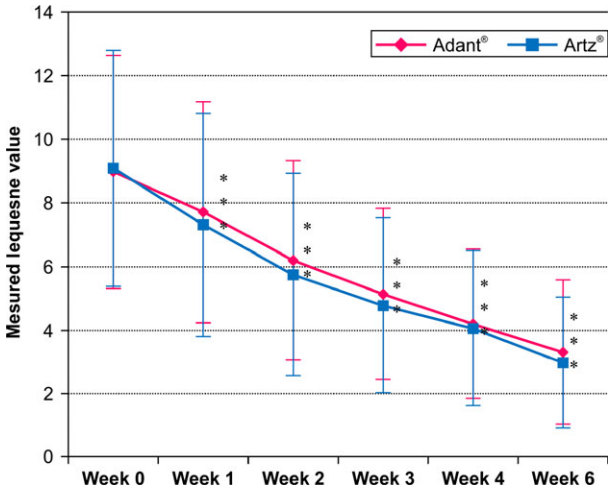

Figure 3 Diachronic analysis graphics of measured Lequesne values (mean ± SD, PPS). None of the difference between measured Lequesne values of the two groups obtained at the visit time points were statistically significant ($P > 0.05$). *Measured Lequesne value of Adant® group between pre- and post-treatment was statistically significant ($P < 0.01$). **Measured Lequesne value of Artz® group between pre- and post-treatment was statistically significant ($P < 0.01$).

two groups did not show clinically significant differences in efficacy.

Analysis of overall efficacy

Overall efficacy was analyzed based on the full analysis set, which included 218 of the 229 patients recruited. The proportion of patients who reported the treatment as cured, significantly effective or effective was 98.1% for the Artz® group and 98.2% for the Adant® group.

Safety analysis

Adverse events (AEs) and adverse reactions (ARs)

The safety set (SS) included 229 subjects. In the Artz® group, 26 subjects (23.0%) experienced AEs, of which six were judged as possibly related to the drugs, and the incidence of ARs was 5.3%. In the Adant® group, 21 subjects (18.1%) experienced AEs, two of which were judged as possibly related to the drugs, and the incidence of AR was 1.7%. Differences in the incidences of AEs and ARs between the two groups were not statistically significant ($P > 0.05$). There was one serious adverse event (SAE, hospitalization due to exacerbated symptoms of prostatic hyperplasia requiring trans-urethral holmium laser prostatectomy) that was judged to be unrelated to the drug used (Artz® group). ARs occurring in the clinical study included five cases of local pain (2.18% overall; one in the Adant® group and the other four in the Artz® group), two cases of swelling (0.87% overall; both in the Artz® group), and one case of a rash (0.44% overall; in the Adant® group).

DISCUSSION

Patients with OA are often clinically treated by the oral administration of non-steroidal anti-inflammatory drugs (NSAIDs). Despite their ability to ease symptoms, the chronic use of such drugs can cause gastrointestinal tract ulcers, kidney injuries and other side effects,[13] especially in middle-aged and elderly individuals. Corticosteroids administration is likely to worsen joint damage and accelerate degeneration of the articular cartilage, and the therapeutic effects of such drugs taper in just a few weeks.[14]

Intra-articular injection of sodium hyaluronate for the treatment of OA knee pain was first approved in Japan and Italy in 1987 and in the US in 1997. Since that time it has been shown to be a valuable treatment modality in the Clinical literature.[12,15–26] In both China and abroad, it has been shown that sodium hyaluronate injection is effective for the treatment of degenerative OA. In a recent meta-analysis using a Bayesian random-effects model, a total of 137 studies comprising 33 243 participants were identified in studying the comparative effectiveness of various treatments for

treating OA knee pain.[25] The authors concluded that HA treatment was the most effective (effect size of 0.63) and safest therapy. The excellent safety profile is particularly important in the elderly population who are prone to develop symptomatic knee OA given their preponderance of co-morbidities and susceptibility to adverse events.[24] While the precise mechanism of action of HAs is unknown they are thought to function as a mechanic barrier, lubricant and cushion as well as having direct anti-inflammatory and anti-analgesic properties. However, it is a quandary as to how, through either mechanism or a combination, they can elicit months of pain relief when the injected products are almost gone from the joint within 1–2 days.[27,28] A working hypothesis for which there is some preclinical and clinical data in support, is that the treatment 'primes' the biological regulatory pathways to restore the joint to a more normal status.

While this study does not include an intra-articular saline control, our study was designed to demonstrate the non-inferiority between two commercial products in use for more than 20 years and have been approved as being safe and efficacious in over 60 countries worldwide. As noted in prior publications and most recently confirmed by Bannuru *et al.*,[25] intra-articular saline injections are indeed an active intervention, and surprisingly, are as effective as twice daily celecoxib (Celebrex). Our strategic methodology for demonstrating non-inferiority is widely accepted as standard in clinical research. In selecting closely related treatment modalities for OA knee pain it is important to first establish a comparative effectiveness between products to guide judicious clinical decisions that might also be driven by other considerations, such as dosage form, ease of use, safety of repeat use, patient allergies and so on.

Production process of sodium hyaluronate is categorized as extraction, by taking animal tissues as the raw materials, and microbial fermentation. Almost all animal tissues contain various amounts of sodium hyaluronate, and cockscomb is the main raw material used for production, while microbial fermentation of sodium hyaluronate is also well-known. Compared with the extraction of animal tissues, microbial fermentation has the advantage of an unlimited production scale and a lack of animal proteins, which effectively avoids any risk of animal-based disease transmissions or allergenic reactions.

The results of this study show that both Adant® and Artz® are effective for the treatment of OA of the knee, and no statistically significant difference was seen between them in the decrease in the VAS scores of pain on movement and the Lequesne index. It also confirmed that Adant® was non-inferior to Artz® with respect to VAS score decrease during the observation period with short-time follow-up. The five-injection regimen of the drug (25 mg/2.5 mL) as the standard treatment cycle achieved excellent results as evidenced by reduced pain values (mm) at each visit after each injection. As well, age stratification analysis and disease stratification analysis of VAS efficacy also showed no statistically significant difference between Adant® and Artz®. The overall efficacy analysis also shows that most patients reported positive results. There were no serious adverse events judged to be related to the drug, reaffirming the safety of both Adant® and Artz®; however, since Adant® is manufactured by microbial fermentation and Artz® is manufactured by extraction of cockscomb, Adant® is more favorable in terms of both the production process and biological safety. In this study, it was also confirmed that there were no invalid reasons for dropout.

In addition to this study, there are several reports on clinical trials of Adant® that have demonstrated its efficacy and good safety profile in treating OA of the knee[10,26,29–32] as well as Artz,®[21–25] the first approved sodium hyaluronate product in China. In particular, one recent 3.5-year-long clinical trial for Adant® proved its long-term clinical efficacy.[10]

In conclusion, the sodium hyaluronate injection of Adant® is effective for treating degenerative OA, has a good safety profile with few adverse reactions and a preferable manufacturing process.

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AUTHOR CONTRIBUTIONS

Yang Xin and Cao Yongping: conceived and coordinated the study, collected the data at Peking University First Hospital and drafted the paper. Lin Jianhao and Sun Tiezheng: collected the data at Peking University People's Hospital. Sun Tiansheng and Yao Jianhua: collected the data at General Hospital of the Chinese PLA

Beijing Region. Hao Yongqiang and Xuan Liang: collected the data at Shanghai Ninth People's Hospital Affiliated to Shanghai Jiaotong University. Fan Weimin and Gu Xiaoyuan: collected the data at Jiangsu Provincial People's Hospital. Chen Ming: collected the data at Peking University First Hospital.

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