344

PREDICTION OF TOTAL KNEE REPLACEMENT IN A 6-MONTH MULTICENTRE CLINICAL TRILA WITH CHONDROITIN SULFATE IN KNEE OSTEOARTHRITIS: RESULTS FROM A 4-YEAR OBSERVATION

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Purpose: To identify predictive factors for the incidence of total knee replacement (TKR) during long-term follow-up of knee OA patients who formerly received treatment with chondroitin sulfate (CS) or placebo in a multicentre trial using clinical and quantitative magnetic resonance imaging (qMRI) data.

Methods: Knee OA patients participating in a previous 6-month randomized, double-blind controlled trial evaluating the impact of CS (400 mg b.i.d.; Condrosan®, Bioibérica, Spain,) vs. placebo who had serial MRI acquisitions of the symptomatic knee were recently contacted to evaluate retrospectively the incidence of TKR of the study knee. A sub-group of patients (n=70) who had taken all the study medication and had all clinical and MRI evaluations (according-to-protocol [ATP]) were selected for this post-hoc retrospective analysis. Of this cohort 51 patients were reachable for TKR incidence. The assessment was done blindly to treatment allocation with a standardized phone interview.

Results: The patients' mean age was 62.9 years, 61% were female and the average BMI was 30.6 kg[[Unsupported Character - /]]m^2. A total of 7 (6 target knees and 1 contralateral) TKRs (13.7%) were performed on this subpopulation in the timeframe of 3-4 years after completion of the original study. Interestingly, there were more TKRs performed within the placebo group (n=5) than the CS group (n=2) (71% vs. 29%, p=0.15, logistic regression). The predictors of long-term TKRs for the target knee were investigated by comparing the patients who had TKR (n=6) of the target knee to those who did not (n=45), using data at baseline or the change at 1 year. At baseline, the strongest predictors of TKR were WOMAC pain (p=0.02, logistic regression), stiffness (p=0.01) and function (p=0.04), bone marrow lesions of the medial tibial plateau (p=0.03), and C reactive protein level (p=0.03). Changes at 1 year in medial cartilage volume (p=0.05) and WOMAC stiffness (p=0.01) also predicted the occurrence of TKR.

Conclusions: These data demonstrate that, from a knee OA clinical trial, it is possible to predict a "hard" outcome such as TKR using clinical and qMRI data. Moreover, CS appeared to protect cartilage volume loss and improved clinical parameters.

345

COMPARISON OF ACETAMINOPHEN 1000 MG AND ACETAMINOPHEN 650 MG IN AN ACUTE PAIN MODEL: RESULTS FROM A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, EFFICACY AND SAFETY STUDY

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Purpose: Acetaminophen is recommended as a first line treatment for arthritis pain and 1000 mg is a widely used dose. The incremental benefit of acetaminophen 1000 mg versus 650 mg was questioned at a recent FDA Advisory Committee Meeting. To answer this question, a randomized, double-blind, placebo-controlled clinical trial was conducted to determine whether acetaminophen 1000 mg was more effective than acetaminophen 650 mg. The Dental Impaction Pain Model was chosen because of its proven validity, assay sensitivity, reliability, and reproducibility. The results from this model have been shown to be applicable to a wide variety of pain modalities. The model is widely accepted and utilized to evaluate dose-response and duration of effect of many prescription and over-the-counter analgesics.

Methods: Subjects were enrolled who required surgical extraction of up to 4 third molars with a minimum requirement of 1 full bony or 2 partial bony mandibular impactions. Subjects were randomly assigned a single dose of acetaminophen 1000 mg, acetaminophen 650 mg, or placebo when they had at least moderate pain and a Visual Analog Scale (VAS) score $\geq$50 out of 100 mm post-surgically. Pain intensity and pain relief were measured over 6 hours using a 100 mm VAS scale. Sum of Pain Intensity Difference (SPID) and Total Pain Relief (TOTPAR) scores over 6 hours (SPRID6) was the primary efficacy endpoint. Other key efficacy endpoints included Time to Rescue analgesic, stopwatch Time to Confirmed First Perceptible Relief and Meaningful Relief, and Subject's Global Evaluation. Spontaneous adverse events (AEs) were recorded throughout the study.

Results: All subjects (N=540) completed the study and were included in efficacy and safety analyses. Demographic and baseline characteristics were comparable among the 3 groups. Overall, the population was 52% female, age 16-30 years and 95% Caucasian. For the primary efficacy endpoint, SPRID6, acetaminophen 1000 mg demonstrated a 24% improvement compared to 650 mg (529.4 vs 427.3; p=0.001). Acetaminophen 1000 mg was also significantly superior to 650 mg ($p\leq0.002$) for SPID6, TOTPAR6, Time to Rescue analgesic, rescue rates through 4h (20% vs 32%) and 6h (29% vs 46%), and Subject Global Evaluation (49% vs 34% with very good or excellent ratings). Both active treatments were significantly superior to placebo ($p<0.001$) for these efficacy endpoints. The 2 active treatments were similar for times to Confirmed First Perceptible and Meaningful Relief. AEs were reported by 18.5% of subjects with no clinically important difference among the 3 treatment groups. No serious AEs were reported and no subjects discontinued due to an AE.

Conclusions: In this clinical trial, acetaminophen 1000 mg provided clinically meaningful and statistically significantly greater reduction in pain intensity and greater pain relief compared with acetaminophen 650 mg and placebo. In addition, acetaminophen 1000 mg required less use of rescue analgesic in treating acute pain compared with acetaminophen 650 mg and placebo. Significantly superior efficacy of acetaminophen 650 mg was also demonstrated compared to placebo.

346

A RETROSPECTIVE STUDY OF INTRA-ARTICULAR SODIUM HYALURONATE (MW 500-730 KDA) INJECTION FOR TRAPEZIO-METACARPAL JOINT OSTEOARTHRITIS

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Purpose: Hand osteoarthritis (OA) is a highly prevalent disease, and TMCJ is commonly targeted by OA. With respect to the long-term results, Hyaluronic Acid (HA) seems to be the better alternative in the treatment of TMCJ OA, even with a single injection. HA injections were found to be effective in reducing pain and improving fine hand function.

The purpose of this retrospective open-label study was to evaluate the efficacy and tolerability of i.a. injections of HA for the treatment of pain and disability due to TMCJ OA. Data from the study were discussed based on a review of the current news on the physiological effects of HA.

Methods: Fifty-eight patients, 50 W (86.2%) and 8 M (13.8%), aged between 40-75 ys, suffering from TMCJ OA and classified as K-L grades 2-3 as per standard X-ray, were included. The cases with known inflammatory arthritis, previous thumb trauma and intra-articular (i.a.) injections with corticosteroids were excluded. Primary endpoints were: pain (VAS), NSAID intake, radial and palmar abduction of thumb (degrees), pinch strength (Kg/hand dynamometer). Between Jan. 2000 and Dec. 2002 the patients received an i.a. injection of 0.8 ml of Hyaluronan saline, Hyalgan (10 mg/ml, MW 500-730 KDa)once weekly for three consecutive weeks, using a dorsolateral approach. Control examinations were carried out one, three and six months after the first treatment.

Results: Intra-articular HA injections significantly reduced spontaneous and provoked pain and improved hand function and motion range in comparison with baseline values. In particular after 1, 3 and 6 months following the first injection, the spontaneous and provoked pain revealed a statistically significant improvement ($p<0,0001$). In addition hand functionality, in particular pinch strength, showed a significant improvement after the treatment. NSAIDs intake also evidenced a statistically significant reduction against baseline ($p<0,017$). The adverse events occurring during the study (20.7%) are expected and related to local symptoms such as pain during or following the HA administration.