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THU0446

DIACEREIN PROVEN AS EFFECTIVE AS CELECOXIB IN REDUCING PAIN AND SYMPTOMS IN KNEE OSTEOARTHRITIS PATIENTS IN A MULTICENTRE DOUBLE-BLIND RANDOMISED STUDY (DISSCO)

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Background: There was a need to ascertain in a clinical trial the comparative efficacy of diacerein, an IL-1 inhibitor, vis-à-vis celecoxib, a COX-2 inhibitor, in relieving knee osteoarthritis (OA) symptoms.

Objectives: The primary outcome of this study was to show that diacerein is non-inferior to celecoxib in terms of pain reduction (WOMAC A pain subscale) after 6 months of treatment in moderate-to-severe symptomatic knee OA patients.

Methods: A randomised double-blind multicentre trial was conducted in four European countries (Spain, Belgium, Austria, Czech Republic) and in Canada evaluating treatment with diacerein versus celecoxib in patients with OA diagnosed according to ACR criteria, with KL grade 2-3 knee OA and moderate-to-severe pain (VAS pain score [0-100 mm] while walking on a flat surface $\geq$ 40 mm). Eligible patients were randomised to treatment for 6 months with either diacerein 50 mg once daily for the first month and twice daily thereafter, or celecoxib 200 mg once daily. The primary outcome was the change from baseline in WOMAC pain subscale (0-50 scale) after 6 months of treatment. Secondary outcomes included WOMAC function and stiffness, VAS pain, presence of joint swelling/effusion, rescue medication consumption, percentage of OMERACT-OARSI responders, and SF-36. A total of 380 patients were randomised in the study. The primary outcome assessment on the per protocol set (PPS) (n=288) was followed by sensitivity analysis on the ITT population (n=370). Exploratory statistical analysis on other efficacy criteria and safety were performed.

Results: The analysis of the PPS population showed that the adjusted mean change in WOMAC pain was -11.14 (SEM, 0.91) with diacerein (n=140) and -11.82 (0.89) with celecoxib (n=148). Diacerein met the non-inferiority criterion, as the upper bound of the 95% CI is inferior to the pre-specified non-inferiority margin of 5 (inter-group difference 0.67; 95% CI -1.83 to 3.18; p=0.597). The sensitivity analysis using the ITT population was supportive of those results. All other exploratory outcomes demonstrated no difference between the two treatment groups. The OMERACT-OARSI responder rate (PPS) at 6 months was similar in the diacerein (62.1%) and celecoxib (60.1%) groups. The incidence of adverse events related to drug treatment was in general low and balanced between groups. The only exception was a greater incidence of gastrointestinal side effects (diarrhoea) in the diacerein vs. the celecoxib group (10.2% vs. 3.7%, respectively), but accounted for 4.8% of permanent discontinuation in the diacerein group compared to 1.6% in the celecoxib group. In all but one patient, this diarrhoea was considered to be of a mild-to-moderate grade with complete resolution in all cases.

Conclusion: This clinical trial showed that in patients with moderate-to-severe knee OA pain, diacerein has comparable efficacy to celecoxib with respect to reducing pain and stiffness and improving function after 6 months in a clinically relevant manner. The drug also demonstrated a good safety profile with positive benefit to risk ratio.

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THU0447

THE RELATIVE EFFICACY OF TOPICAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND CAPSAICIN IN OSTEOARTHRITIS: MOVING FROM AVERAGE TREATMENT EFFECTS TO INDIVIDUAL TREATMENT PREFERENCES

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Background: Pain is an important issue for people with osteoarthritis (OA). Topical non-steroidal anti-inflammatory drugs (tNSAIDs) and capsaicin are recommended treatments, but reduce OA pain by different mechanisms.

Objectives: To [1] determine the relative efficacy of tNSAIDs and capsaicin in OA and [2] identify predictors of response that may allow tailoring of topical therapy to the individual.

Methods: Systematic literature searches were conducted up to 16/11/2015 for randomised controlled trials (RCTs) of tNSAIDs or capsaicin in OA. Placebo-controlled RCTs were pooled in conventional meta-analyses (CMA) for specific (difference between treatment and placebo) and overall (pain reduction in treatment arm) treatment effects. Bayesian network meta-analysis (NMA) compared treatments via placebo. RCT data custodians were contacted and an individual patient data meta-analysis (IPDMA) examined for predictors of response.

A pilot n-of-1 trial series (PNTS) examined treatment effects, patient preferences, and predictors of response. Participants with painful radiographic knee OA were allocated to three treatment cycles, each comprising four weeks treatment with 5% ibuprofen gel and 0.025% capsaicin cream in a random order.

Effect sizes (ES) are Hedges' g and 95% confidence interval (CI) or credible interval (CrI). Predictors of response were identified in regression modelling for treatment-by-covariate interactions (specific effect) or covariate associations (overall effect). 9 and 25 predictors were examined in IPDMA and PNTS, respectively.

Results: Of 63 tNSAID and 10 capsaicin RCTs identified, CMA and NMA analysed 21 tNSAID (n=6191) and five capsaicin (n=415) RCTs. The quality of evidence was moderate for tNSAIDs and very low for capsaicin. Overall treatment effects were large and likely clinically significant (tNSAIDs ES 1.23, 95%CI 1.06-1.41; capsaicin ES 1.05, 95%CI 0.52-1.57). tNSAIDs (all drugs/doses grouped) were superior to placebo (ES 0.31, 95%CI 0.20-0.41), but capsaicin was only effective at 0.025% concentration (ES 0.41, 95%CI 0.17-0.64; ES of all capsaicin RCTs 0.28, 95%CI -0.04-0.60). On average, tNSAIDs and capsaicin were equally effective (ES 0.04, 95%CrI -0.29-0.37).

IPD were provided for 15 (n=3889) tNSAID RCTs, including 11 (n=3140) placebo-controlled RCTs. No IPD were obtained for capsaicin. A significant but small interaction was observed between sex and tNSAID use for pain relief, with women reporting greater effect (11 RCTs, n=2939, p=0.023).

22 participants enrolled in the PNTS and completed 104 treatment periods. Clinically important pain relief ($\geq$ 1 on 0-10 numeric rating scale) was achieved in 64% of periods, with no difference in efficacy between treatments overall (p=0.271). Individual responses to treatment varied, with c.60% of people preferring one treatment over the other, but without clear predictors for the preference.

Conclusion: tNSAIDs and capsaicin may relieve OA pain, but treatment effects from group comparisons do not directly translate to treatment outcomes at an individual level. No baseline characteristics robustly determine which treatment is more likely to benefit an individual. Patients may benefit from trying both treatments to determine which is better for them.

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