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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 (≥ 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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THU0448 DISEASE BURDEN IN OSTEOARTHRITIS (OA) IS SIMILAR TO RHEUMATOID ARTHRITIS (RA) FROM THE PATIENT'S PERSPECTIVE, SLIGHTLY HIGHER IN RA AT PRESENTATION, SIMILAR ONE YEAR LATER, AND SLIGHTLY HIGHER IN OA TWO YEARS LATER AT ONE PRIVATE PRACTICE SETTING

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Background: Disease burden traditionally has been regarded as considerably greater in rheumatoid arthritis (RA) versus osteoarthritis (OA). However, recent reports of cross-sectional data indicate similar disease burden in OA vs RA according to MDHAQ/RAPID3 (multidimensional health assessment questionnaire/routine assessment of patient index data). One concern is that these findings may reflect only better treatment for RA, and initial disease burden may be considerably higher in RA vs OA.

Objectives: To analyze disease burden in patients with OA vs RA at baseline and 1- and 2-year follow-up according to MDHAQ/RAPID3 scores in routine care at a single rheumatologist private practice site.

Methods: All patients seen in routine care at this site complete an MDHAQ at each visit in the waiting area prior to seeing the rheumatologist. The MDHAQ includes three 0-10 scores for physical function, pain visual analogue scale (VAS), and patient global VAS, compiled into a 0-30 RAPID3, as well as 0-10 fatigue VAS, and 0-48 self-report painful joint count scores. Mean MDHAQ scores were compared in OA versus RA patients at 1st visit and visits 1 and 2 years later, using t tests, adjusted for age and body mass index (BMI) using analysis of variance (ANOVA).

Results: Among 101 OA and 175 patients with RA, at first visit, all MDHAQ scores except pain VAS were statistically significantly higher in RA vs OA, e.g., mean 0-30 RAPID3 was 11.9 in OA and 13.7 in RA. However, none of these differences appear clinically significant (Table). After 1-year, all scores were improved, but more in RA vs OA patients (Table), e.g., mean RAPID3 of 11.5 in OA and 10.9 in RA; no differences between OA and RA were statistically or clinically significant. After 2-years, mean RAPID3 was 11.9 in OA vs 9.0 in RA, indicating continued improvement in RA but little change in OA. All scores other than fatigue VAS were higher in OA, including the self-report painful joint count. Differences between OA and RA were explained only minimally by age and BMI.

Table. Mean MDHAQ scores in patients with primary OA or RA at 1st visit, and 1 or 2 years later

Mean scores at...	1st visit			1-year later			2-years later			P Change in OA vs RA	
	OA	RA	P	OA	RA	P	OA	RA	P	1 year	2 years
# patients	101	175		101	175		45	113			
RAPID3 (0-30)	11.9	13.7	0.03	11.5	10.9	0.50	11.9	9.0	0.02	0.004	0.0004
Function (0-10)	0.63	0.78	0.03	0.61	0.66	0.43	0.72	0.53	0.046	0.119	0.009
Pain (0-10)	5.0	5.5	0.16	4.9	4.3	0.43	4.7	3.6	0.03	0.004	0.004
PATGL (0-10)	4.8	5.6	0.01	4.6	4.4	0.54	4.9	3.7	0.009	0.005	0.0001
Fatigue (0-10)	3.9	4.9	0.008	3.7	4.0	0.43	3.6	4.0	0.41	0.073	0.359
Self-report painful JC 48 (0-48)	12.0	15.4	0.014	9.5	11.7	0.10	11.9	10.2	0.35	0.415	0.035

Abbreviations: MDHAQ=multidimensional health assessment questionnaire, OA=osteoarthritis, RA=rheumatoid arthritis, RAPID3=routine assessment of patient index data, PATGL= patient global assessment, JC=joint count

Conclusion: Most MDHAQ/RAPID3 scores were higher in RA than in OA at the first visit, indicating greater severity of RA, although OA was almost as severe. One year later, scores were similar with no statistically significant differences. Two years later, most scores were higher in OA. These findings likely reflect superior treatments for RA vs OA. At an individual level, patients with primary OA may have better or poorer status than other patients with primary RA. Nonetheless, at a group level, the severity of disease burden in OA appears almost as great as in RA, and becomes greater over the next 2 years, likely as a result of better treatment. The severity of OA is underrated, suggesting a need for increasing resources for research toward better treatment for OA.

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THU0449 EFFECT MODERATION OF ANALGESIC TREATMENT OUTCOMES BY DEPRESSION IN PERSONS WITH OR AT-RISK FOR SYMPTOMATIC KNEE OSTEOARTHRITIS

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Background: Depression often accompanies knee osteoarthritis (OA), exacerbates pain severity, and may negatively affect analgesic treatment outcomes.

Objectives: To determine whether depression moderates the effect of analgesics on pain severity in persons with or at-risk for symptomatic knee OA.

Methods: Participants (n=2059) were from the Osteoarthritis Initiative, with or at-risk for symptomatic knee OA, and had complete data on selected measures at baseline and four annual follow-up visits. Analgesic initiation (acetaminophen, non-steroidal anti-inflammatory drugs, opioids) was assessed at three annual follow-up visits in those who were not analgesic users at baseline. Depression was evaluated concurrent to assessment of analgesic use with the Center for Epidemiological Studies Depression (CES-D) scale using the corresponding CES-D screening threshold (CES-D score ≥ 16). Pain severity at the fourth annual follow-up visit was the outcome and measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale (rescaled range = 0-100). Time-invariant confounders measured at baseline were: age, gender, race, education, marital status, employment, health insurance, smoking, alcohol consumption, Charlson comorbidity index, and symptomatic knee OA status. Time-varying confounders measured at three annual follow-up visits were: WOMAC pain score, Kellgren-Lawrence grade, body mass index, physical performance, knee injuries, and knee injections. Structural nested mean models appropriate for evaluating time-varying effect moderation of dynamic treatments by evolving effect modifiers were implemented using an inverse-probability-of-treatment-weighting regression-with-residuals approach.

Results: In non-depressed participants, analgesic treatment effect at years one, two, and three on pain severity at year four was minimal (Figure 1). Time-specific associations in the non-depressed ranged from -1.18 (95% CI: -2.94, 0.59) to 0.81 (95% CI: -0.99, 2.61) and were not statistically significant. The persistent use of analgesics at years one and two ($\beta = -2.17$; 95% CI: -4.62, 0.27) or years one, two, and three ($\beta = -1.36$; 95% CI: -4.22, 1.50) did not increase the magnitude of the treatment effect in non-depressed participants. In contrast, time-specific associations in depressed participants increased during follow-up from 0.61 (95% CI: -9.17, 10.38) to -9.64 (95% CI: -17.96, -1.33), and the treatment effect of year three analgesic use on year four pain severity was statistically significant. The magnitude of the treatment effect increased from year one with persistent analgesic use at years one and two ($\beta = -5.75$; 95% CI: -20.65, 9.15) and years one, two, and three ($\beta = -15.39$; 95% CI: -33.99, 3.21). However, effect moderation was only significant concerning year three analgesic use, where the subsequent difference in treatment effect between depressed and non-depressed participants was -10.46 (95% CI: -18.97, -1.94).

Figure 1. Cumulative Effects (Treated vs. Untreated) of Analgesic Use on Pain Severity By Depression Status

Abstract THU0449 – Figure 1