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Symptomatic efficacy and safety of diacerein in the treatment of osteoarthritis: a meta-analysis of randomized placebo-controlled trials

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Summary

Objective: To estimate the efficacy and safety of diacerein as a pain-reducing agent in the treatment of osteoarthritis (OA), using meta-analysis of published randomized placebo-controlled trials (RCTs).

Methods: Systematic searches of the bibliographic databases Medline, Embase, Cinahl, Chemical Abstracts, Cochrane and Web of Science for RCTs concerning diacerein treatment of OA. Inclusion criteria: explicit statement about randomization to either diacerein or placebo, and co-primary outcomes being reduction in pain and improvement in function. Efficacy effect size (ES) was estimated using Hedges's standardized mean difference. Safety was measured *via* the risk ratio (RR) of patients having at least one episode of diarrhoea, or withdrawal due to adverse events. Trials were combined by using random-effects meta-analysis. Consistency was evaluated *via* the *I*-squared index.

Results: Six trials (seven sub-studies; 1533 patients) contributed to the meta-analysis, revealing a large degree of inconsistency among the trials ($I^2 = 56\%$) in regard to pain reduction: the combined ES was -0.24 [95% confidence intervals (CI): -0.39 to -0.08, $P = 0.003$], favouring diacerein. The statistically significant improvement in function ($P = 0.01$) was based on a small amount of heterogeneity ($I^2 = 11\%$), but presented a questionable clinical effect size (ES $= -0.14$). Risk of publication bias could not be excluded, and trials with duration of more than 6 months did not favour diacerein. There was an increased risk of diarrhoea with diacerein (RR $= 3.51$ [2.55–4.83], $P < 0.0001$), and some withdrawal from therapy following adverse events (RR $= 1.58$ [1.05–2.36], $P = 0.03$).

Conclusions: Diacerein may be an alternative therapy for OA for patients who cannot take paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) because of adverse effects or lack of benefit. However, it is associated with increased risk of diarrhoea, and the symptomatic benefit after 6 months remains unknown.

Key words: Diacerein, Placebo, Osteoarthritis, Knee, Hip, Meta-analysis.

Introduction

Osteoarthritis (OA) is a common joint disorder and may occur in any synovial joint in the body, although the condition is common in hands, knees, hips and spine[1]. The clinical problems, alongside the pathological and radiographic changes, include joint pain, short-term morning stiffness, restricted range of movement, and crepitus[2]. To manage symptoms of OA, patients and healthcare providers often resort to multiple approaches, including lifestyle modifications, medication, exercise, or surgery[3,4]. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed agents in the management of OA pain, although they are known to cause serious gastro-intestinal and vascular adverse events[5,6] without improving the underlying structural cartilage damage[4]. Disease-modifying therapy would therefore be preferential and beneficial to the patients. Disease-modifying OA drugs (DMOADs) remain to be developed in order to slow down disease progression and reduce the patients' symptoms (i.e., pain and limitations in daily activities due to poor physical function)[7,8].

There is strong evidence of a contribution of additional pro-inflammatory cytokines to cartilage degradation in OA[9–12]. One of these is interleukin-1 (IL-1) which stimulates the degradation process and suppresses cartilage-matrix synthesis, with the overall result of a severe degradation of cartilage and following appearance of conditions known to be characteristic of OA[13]. A further finding, which may increase the deleterious effect of IL-1, is that human OA cartilage may be more responsive to IL-1 than healthy cartilage[14,15]. Diacerein, an anthraquinone derivate, has, *in vitro* and *in vivo*, been shown to inhibit the production and activity of the cytokine interleukin-1β (IL-1β)[16,17]. This will prevent the IL-1β effect of reducing production of cartilage-specific macromolecules. Diacerein will equally diminish the IL-1β stimulated secretion of metalloproteinases and aggrecanases, and thereby prevent breakdown of cartilage by these enzymes[18]. A further potential advantage of using diacerein in OA treatment is, that diacerein does not

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affect the synthesis of prostaglandins[19] and does thereby not have a deleterious effect on the upper gastro-intestinal mucosa[20]. This is an important advantage compared to NSAID treatment.

There is some evidence that diacerein has both a symptomatic and a structural effect on cartilage, and clinical trials suggest that diacerein therapy significantly decreases OA symptoms when compared to placebo[21]. A Cochrane review, evaluating the efficacy and safety of diacerein in the treatment of knee and/or hip OA, concludes that diacerein therapy gives a small improvement of pain, but that the overall effect varies across studies, showing heterogeneity[22]. A divergent result from the Cochrane review is seen in another meta-analysis of diacerein treatment for OA of the knee and/or hip[23], where a high magnitude of pain relief is shown, using the Glass score [standardized mean difference (SMD)] as effect measure. Here, the issue of heterogeneity was not addressed[23].

As the existing meta-analyses on diacerein do not agree on magnitude of clinical efficacy, and as the influence of the heterogeneity on the effect size (ES) across trials was not adequately addressed[22,23], we decided to revisit the evidence for diacerein in the treatment of OA. This is especially important at a time where diacerein may be considered as a useful DMOAD, and where this may lead to a better formulation of diacerein with less adverse effects in the form of diarrhoea.

We performed a systematic review and meta-analysis of all available randomized placebo-controlled trials (RCTs) to determine the effects of diacerein on symptomatic efficacy and safety, and explore whether reported beneficial effects might be explained by biases affecting individual trials.

Materials and methods

Study selection, assessment of eligibility criteria, data extraction, and statistical analysis were performed based on a predefined protocol according to the Cochrane Collaboration guidelines (http://www.cochrane-handbook.org/).

RETRIEVAL OF PUBLISHED STUDIES

A thorough and comprehensive literature search for RCTs, all looking at the efficacy of diacerein therapy for knee and/or hip OA, was carried out with last search 15th December 2008. The following bibliographic databases were searched: MEDLINE *via* PubMed from 1950, EMBASE *via* OVID from 1980, CINAHL *via* EBSCO from 1981, Chemical Abstracts *via* Scifinder from 1907, and Web of Science from 1900, as well as The Cochrane Central Register of Controlled Trials, to identify all trials relating diacerein to OA. The search strategy used a combination of keywords and text words related to OA. These were combined with various names of the diacerein preparations (*Diacerein*, *Diacerhein*, *Rhein*, *Diacetylrhein*, *Anthraquinones* or *Diacetyilrhein*). We used similar strategies to identify previously published systematic reviews and meta-analyses[3]. In addition, we manually searched conference proceedings for the last 5 years and screened reference lists of all selected articles, including reviews.

INCLUSION AND EXCLUSION CRITERIA

We included randomized, controlled trials of patients with OA of the knee or hip that compared diacerein treatment with placebo. Two reviewers (EMB, PKS) independently evaluated reports for eligibility. Disagreements were resolved by discussion (HB). No language restrictions applied.

QUALITY ASSESSMENT: RISK OF BIAS

Empirical studies show that inadequate quality of trials may distort the results from meta-analyses[24]. Therefore, influence of quality of included studies should be included in meta-analyses[25]. Two of the reviewers (EMB, RC) independently assessed (*i*) randomization followed by concealment of treatment allocation, (*ii*) blinding, and (*iii*) adequacy of statistical analyses (i.e., proper intention-to-treat [ITT] analysis). Randomization and concealment of allocation was considered adequate if the investigators responsible for patient selection were unable – prior to allocation – to suspect which treatment was next. Blinding was considered adequate if participants and key study personnel ensured complete lack of knowledge of treatment allocation, and that it was unlikely that the blinding had been broken. Analyses were considered adequate if all randomized patients were analyzed in the group to which they were randomly allocated, regardless of the treatment received (ITT principle). Any *modified* ITT population/analysis would be categorized as unclear. The assessment of each entry involved answering a question, with answer 'A' indicating low risk of bias (=adequate handling), 'B' indicating unclear (either lack of information or uncertainty concerning the potential for bias), whereas 'C' refers to an inadequate handling of the item (i.e., high risk of bias *per se*). Disagreements were resolved by consensus.

DATA EXTRACTION AND OUTCOME MEASURES

Data from the included trials were extracted independently by two reviewers (PKS and RC). In the case of disagreement, a third reviewer (EMB) helped to reach a consensus. A standard data-extraction form was developed for data collection. The following information was systematically extracted as characteristics of the studies for each of the k randomized trials, and handled in a customized Microsoft Excel spreadsheet: Demographic baseline variables, study duration, dosage, attrition, and report of intention-to-treat analysis. The core-outcome data in each study consisted of the sample size of the placebo and the experimental group, the number of events in each group, the values of continuous outcomes, and their SDs at the end of the study, or the change scores. The pre-specified primary outcome was pain reduction. The secondary outcome was disability (including the *Lequesne Impairment Index*), while adverse effects were assessed as reported cases of diarrhoea and the number of withdrawals following *any* adverse event. Studies using a 2×2 factorial design were handled as two mutually independent (sub-) studies, and presented separately in the forest plots and analyses as based on different patients.

STATISTICAL ANALYSIS

Whenever possible, we used results from the ITT analysis. For the continuous outcomes, pain and disability, we calculated the SMD for each study[26] corresponding to Cohen's d-value[27]. The corresponding variance (SE^2) was calculated based on the individual study SMD and the number of patients included in each group ($SE^2 = 1/N_E + 1/N_C + SMD^2/[2 \times \{N_E + N_C\}]$)[26]. As the unadjusted (Cohen's) SMD in principle does not treat the variance (SE^2) as an estimate[28], we applied (i.e., *via* multiplication) the Hedges's bias-correction ($J = 1 - 3/[4 \times df - 1]$; i.e., $df = N_E + N_C - 2$) by default, adjusting for small sample bias[29]. The ESs (i.e., SMDs) were signed so that negative values ($SMD < 0$) indicated a benefit of diacerein treatment. The Risk Ratio (RR) was used as the outcome measure for tolerability and safety, as the RR is on average more consistent than the Risk Difference, and the alternative relative effect measure – the odds ratio (OR) – is often misinterpreted[30]. We estimated the Number Needed to Treat in order to *harm* a patient (NNH), with 95% CI on the basis of the combined RR value, applying the overall event rate in the placebo group as a proxy for baseline risk.

All results are given with 95% CI. We computed homogeneity statistics to evaluate the agreement of the individual trial results with a fixed-effect meta-analytic summary[31]. However, we used standard random-effects meta-analysis[32] as default option, whereas the fixed-effect analysis was applied for sensitivity analyses. We calculated the I^2 statistic[33], which describes the percentage of total variation across trials that is attributable to heterogeneity rather than to chance[34]: I^2 values below 25%, from 25% to 50%, and from 50% to 75% correspond to low, moderate, and high between-trial heterogeneity, respectively[34]. We performed a number of pre-specified sensitivity analyses: subgroup analyses stratifying the available trials according to risk of bias, and continuous variables at trial-level were included in pre-specified REstricted Maximum Likelihood (REML)-based (i.e., random-effects) meta-regression models[35]. We performed analyses using SAS software (version 9.1.3, by SAS Institute Inc., Cary, NC, USA)[36,37].

Results

CHARACTERISTICS OF TRIALS

Figure 1 shows the selection process of eligible studies from the first recovered references. From the retrieved 166 references, 133 were discarded based on title, abstract, reference type, being *in vitro* studies, letters, etc. The remaining 33 studies were scrutinized for possibility of inclusion and for possible eligible studies given in their reference lists[20–23,38–66]. Among these, two papers were excluded as

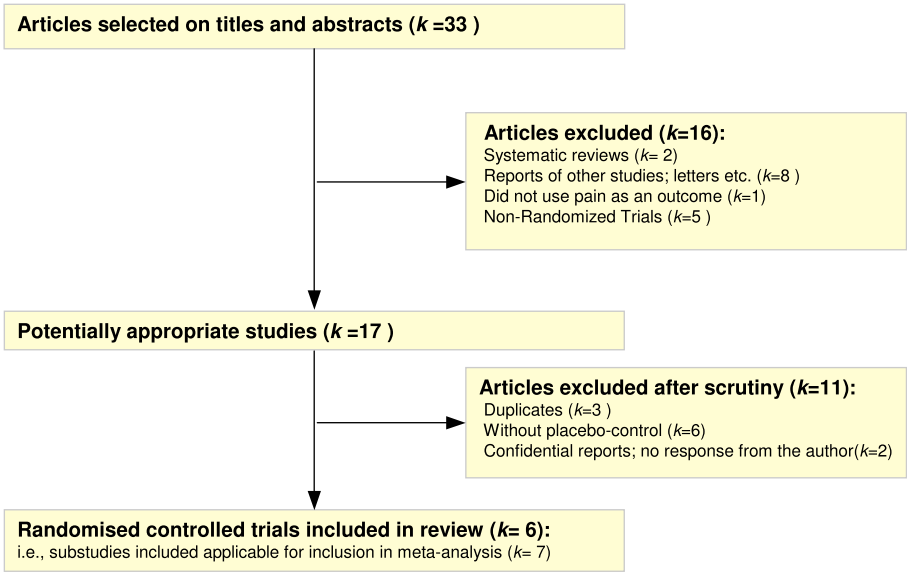

Fig. 1. Flow chart showing the search strategy and further selection of trials.

a consequence of being reviews[22,23], and eight for being reports on other studies (letters, etc.)[38–40,42–46]. One study was another part of an included study (The ECHODIAH Cohort)[41], and five were excluded as a consequence of using a non-randomized study design[20,47,49–51]. Amongst the remaining 17 studies, three were excluded due to being duplicates of other published studies[48,52,53], six due to not being placebo-controlled[54–59], and two due to being confidential reports where no response was received when contacting authors and publishing source[65,66]. The remaining six trials[21,60–64] were considered eligible for inclusion in the meta-analysis. Four of these studies were supported fully or partly by the manufacturer Negma Pharma, France[61–64].

In total, the included trials allocated and analyzed 1533 patients (median, 170 [range, 142–493]) to diacerein or a placebo-control group (Table I). Three trials included patients with OA of the knee only[21,60,61], one trial[64] included patients with OA of the knee or the hip, and two trials[62,63] included patients with OA of the hip only. The average age of the patients was similar across trials, with averages ranging between 61 years and 65 years (median, 61 years), and the percentage of women ranged from 55% to 78% (median, 63%). The study by Nguyen *et al.*[62] used a 2×2 factorial design defining four mutually independent treatment groups [E1] 'Diacerein' vs [C1] 'Placebo', and [E2] 'Diacerein & Tenoxicam' vs [C2] 'Placebo & Tenoxicam', respectively. In the study by Pelletier *et al.*[61], three different diacerein dosages were compared to the same placebo group. We included the standard dose (100 mg/day) compared to the placebo group in the meta-analysis. Finally, the study by Pham *et al.*[60] tested the efficacy/safety of a hyaluronic acid compound when compared to either diacerein or placebo in a masked, double-dummy design.

EFFICACY

Figure 2(A) shows the ES in pain reduction with diacerein vs placebo. Pooling the data from the six individual trials (7 sub-studies), reporting pain as an explicit outcome, produced a combined ES of −0.24 (95% CI: −0.39 to −0.08, $P = 0.003$), supporting efficacy of diacerein as opposed to placebo. The result is based on studies showing a large amount of heterogeneity ($I^2 = 56.3\%$). In comparison, the fixed-effect analysis resulted in a slightly reduced combined ES of −0.20 (data not shown), possibly indicating *some* small-study bias. Figure 2(B) shows the ES in the Lequesne Index reduction with diacerein vs placebo. Pooling the data from the seven sub-studies reporting Lequesne produced a statistically significant combined ES of −0.14 (95% CI: −0.25 to −0.03, $P = 0.010$), potentially supporting efficacy of diacerein treatment compared to placebo. The result is based on studies showing a small amount of heterogeneity ($I^2 = 11.4\%$). Choosing a fixed-effect model instead resulted in a combined ES of −0.14 (data not shown), indicating robustness independently of the default model setting, as expected from the small amount of inconsistency ($I^2 < 25\%$).

Table II presents results from stratified analyses. Estimates of ESs varied to some degree depending on adequacy of the concealment of allocation ($P = 0.21$). Apparently there was no difference between joints when comparing hip-only with knee-only studies ($P = 0.60$). As illustrated in Fig. 3, the study duration seemed to be a relevant study-level covariate, enabling a reduction in the between-study variation, with only studies of no more than 6 months duration showing efficacy. Based on funnel plots – plotting ESs on the vertical axis against their SEs on the horizontal axis – resulted in a reduced between-study variation ($\tau^2 = 0.0153$). Therefore, chance is, that some publication bias is present, i.e. the larger the study the less pronounced clinical efficacy *per se*.

Personal information from the investigators of the ECHODIAH study reveals that there is no long-term statistically significant effects of diacerhein (effects measured after 3 years), and that they have no short-term data available.

SAFETY

Every healthcare intervention comes with a risk, large or small, of harmful or adverse effects. As presented in Fig. 4(A), there was a significantly increased risk among patients allocated to diacerein to have episodes of diarrhoea when compared to placebo, with a $RR = 3.51$ (95% CI:

Table I
Characteristics of eligible trials

Study	Year	Risk of bias	Dose of diacerein	Control group	Trial duration (months)	Total *N*	Women (%)	Joint affected	Age (years)	Outcomes assessed	Definite sample size	
											N_E	N_C
Nguyen	1994a	A/A/A	2 × 50 mg/day	Placebo	2	146	80 (54.8%)	Hip OA	64.0 ± 10.5	VAS pain Lequesne Index	75	71
Nguyen	1994b	A/A/A	2 × 50 mg/day (+Tenoxicam)	Placebo and Tenoxicam	2	142	84 (59.2%)	Hip OA	60.9 ± 10.5	VAS pain Lequesne Index	67	75
Lequesne	1998	B/B/B	2 × 50 mg/day (+Diclofenac)	Placebo & Diclofenac	6	183	N.A.	Knee OA: 113 Hip OA: 70	61.5 ± 10.7	VAS pain Lequesne Index	90	93
Pelletier	2000	A/A/B	2 × 50 mg/day	Placebo	4	236	181 (76.7%)	Knee OA	64.4 ± 8.3	VAS pain WOMAC	110	124
Dougados	2001	A/A/B	2 × 50 mg/day	Placebo	36	521	N.A. (60.0%)	Hip OA	62.6 ± 6.9	VAS pain Lequesne Index (X-rays)	246	247
Pham	2004	A/B/A	2 × 50 mg/day (+I.A. Saline)	Placebo & I.A. Saline	12	170	111 (65.3%)	Knee OA	64.7 ± 7.7	VAS pain Lequesne Index	85	85
Pavelka	2007	A/A/B	2 × 50 mg/day	Placebo	3	168	131 (78.0%)	Knee OA	63.7 ± 8.2	WOMAC pain WOMAC disability	82	83

Data are number (%) or mean ± SD. *Risk of Bias* was assessed as (1) sequence generation and concealed allocation? (2) Blinding of participants, personnel and outcome assessors? (3) Adequate reporting of incomplete outcome data? (A = adequate, B = unclear, C = inadequate). Total *N*: all randomized individuals. N_E and N_C are the number of patients included in the analyses in the experimental and control group (i.e., diacerein and placebo), respectively. N.A.: data not available.

Fig. 2. Efficacy forest plot of trials comparing diacerein with placebo in OA patients presented as SMDs for (A) pain and (B) disability. Every square represents the individual study's effect measure with 95% CI indicated by horizontal lines. Square sizes are proportional to the precision of the estimate. The overall estimate from the meta-analysis and its CI are shown at the bottom of each subplot, represented as a diamond (random-effects model).

2.55–4.83, $P < 0.0001$). Based on the combined risk of having an incident case of diarrhoea in the placebo group of 81 (10.4%) among 778 patients, the NNH = 4 (95% CI: 3–7); i.e. one in four patients would have diarrhoea if diacerein is used instead of placebo. Considering adverse events in general, Fig. 4(B) shows a slightly increased risk of withdrawal from diacerein therapy due to adverse events compared to placebo, with a $RR = 1.58$ (95% CI: 1.05–2.36, $P = 0.027$). With 56 (7.2%) among 778 patients withdrawing from placebo therapy as a consequence of adverse events, the NNH was 24 (95% CI: 11–278) for patients with diacerein; i.e., one in 24 patients would withdraw because of adverse events related to the use of diacerein. Thus, based on the empirical evidence, the most important safety issue associated with use of diacerein will be the increased risk of diarrhoea – which will be expected to occur in every fourth patient initiating therapy.

Discussion

The earlier meta-analyses looking at the efficacy of diacerein in OA treatment, do both include the same studies as included here, except that Rintelen[23] only had a congress abstract available instead of a completed study in one case[21], and Fidelix[22] had no access to this. Our patient

Table II
Results of the stratified meta-analyses

Variable	Total trials, *k*	ES, SMD	(95% CI)	τ^2	I^2	*P*-value for interaction
All sub-studies	7	−0.24	(−0.39 to −0.08)	0.023	56.3	–
Concealment of allocation						
Adequate	6	−0.20	(−0.35 to −0.04)	0.019	46.0	0.21
Unclear	1	−0.47	(−0.87 to −0.07)			
Patient blinding						
Adequate	5	−0.24	(−0.44 to −0.05)	0.030	73.3	0.93
Unclear	2	−0.23	(−0.54 to 0.09)			
Intention-to-treat analysis						
Adequate	3	−0.18	(−0.44 to 0.09)	0.028	69.6	0.56
Unclear	4	−0.28	(−0.48 to −0.07)			
Affected joint						
Hip	3	−0.16	(−0.38 to 0.07)	0.022	53.8	0.60
Knee	3	−0.24	(−0.48 to −0.01)			

k = number of sub-studies (data points). τ^2 = Tau-squared (between-study variance); I^2 = inconsistency index (measuring heterogeneity).

material is in this respect larger than in the Fidelix analysis[22]. Rintelen did though have access to two unpublished reports which we, despite of several attempts, have not been able to get access to. The patient number is therefore higher in Rintelen's study, but we do consider these reports with some suspicion, since they suddenly seems to be manufacturer's secret. The extra included studies in the two meta-analyses were all concerned with a comparison of diacerein with other treatment, mainly NSAIDs, and this is outside our aim with this work, since we wish to see, if diacerein could be a valid alternative to others. The focus in the present study was in that respect slightly different from the

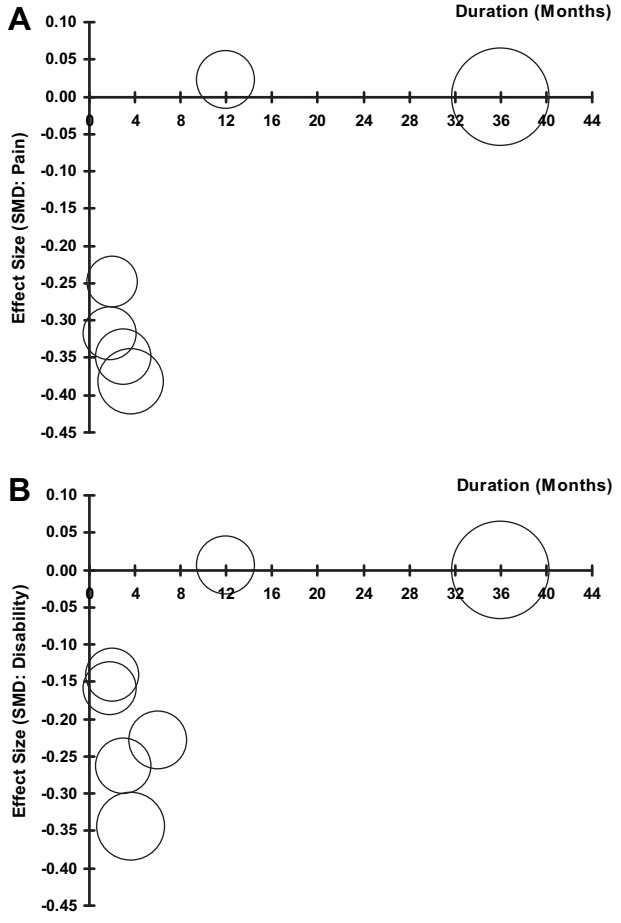

Fig. 3. ESs as a function of study duration. ESs on the vertical axis are plotted against the study duration on the horizontal axis. Size of every circle is proportional to the precision of each efficacy estimate. The solid line indicates the predicted treatment magnitude and direction; using an REML-based model.

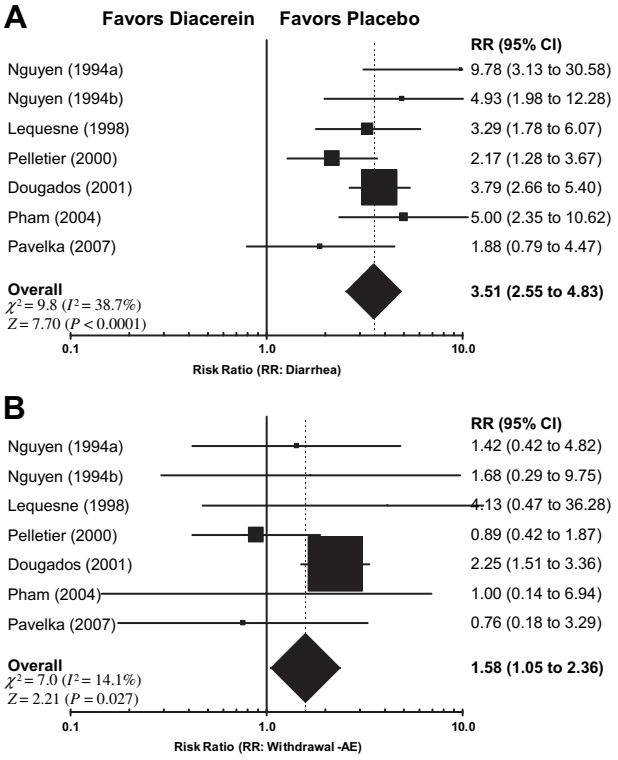

Fig. 4. Safety forest plot of trials comparing diacerein with placebo in OA patients presented as RR's for (A) diarrhea and (B) withdrawal due to any adverse events. Every square represents the individual study's effect measure with 95% CI indicated by horizontal lines. Square sizes are proportional to the precision of the estimate. The overall estimate from the meta-analysis and its CI are shown at the bottom of each subplot, represented as a diamond (random-effects model).

earlier meta-analyses, where we wished to look at diacerein as a suitable drug in its own right.

The main result of our analysis was the finding of a small efficacy of diacerein therapy for OA, showing a small reduction of pain in accordance with both of the earlier meta-analysis[22,23]. When exploring the observed heterogeneity, it was evident that efficacy was only present in the trials with less than 6 months duration. For trials with more than 6 months of therapy, diacerein intake did not show a significant effect on pain reduction. In the present analysis of diacerein, the analysis of heterogeneity between studies showed some inconsistency. Based on modified funnel plots, one may conclude that chance is that some publication bias is present, i.e., the larger the study the less pronounced clinical efficacy *per se*. It is anticipated that only with more large-scale trials will we be able to answer what the true efficacy of diacerein in pain therapy is. Diacerein intake did not result in an improvement of physical function in trials with more than 6 months of treatment. This outcome did not have the same problem with heterogeneity between studies as seen for the pain outcome. The result is in accordance with Rintelen[23], but not with Fidelix[22], and one may speculate if the larger patient number has helped to show this very small effect. Whether diacerein has a longer-term effect (>6 months) for pain and physical function is worth considering in further investigations.

Tolerability assessments revealed the superiority of placebo over diacerein concerning diarrhoea, an adverse effect noticed in all six included studies[21,60–64]. It is worth mentioning though, that none of the studies attempted to characterize or grade the loose stools reported (frequency, watery/formed, severity, etc.). The diarrhoea caused by diacerein intake could be linked to IL-1β inhibition. IL-1β is known to increase at the beginning of dysentery in pigs[67] and in *Escherichia coli* caused diarrhoea[68], and increased IL-1β is also seen in connection with irritable bowel syndrome[69]. The cytokine is thought to be part of the system triggering immune responses towards infections in the gut[68]. An inhibition of IL-1β may therefore make the diacerein-treated individual less able to fight off common gut infections, giving the higher incidence of diarrhoea observed in the diacerein group, when compared to the placebo group. There is though, no description of the severity of the diarrhoea in the studies, and it is therefore not possible to assess, if some diacerein drug types are more likely to give a milder form and therefore be more tolerable for the patients.

OA is the most common type of arthritis in older adults[70,71] with up to 40% of those aged over 65 showing symptomatic knee or hip OA[3]. If diacerein with its preferential risk/benefit ratio had the potential of being as efficient in pain treatment as NSAIDs, it would be an important alternative for people who are contraindicative to NSAIDs. Like effects of other therapies applied in OA[72,73], the effect of diacerein may wear off after some time. The reason for the time-dependent effect remains unknown. Whether this is related to the non-specific treatment effects[4], a narrow therapeutic window, or OA per se, have yet to be determined.

Diacerein does give an increased risk of experiencing diarrhoea, with one in four suffering this inconvenience. With a risk of various more severe adverse effects of NSAIDs, including cardiovascular, severe gastro-intestinal, hepatotoxicity, and nephrotoxicity events, as well as rare events of adverse effects on the central nervous system[74]. Diacerein may be more suitable for the elderly patients, or people at high risk of GI bleeding and cardiovascular co-morbidities.

Diacerein may have symptom-modifying effects in OA. However, it causes diarrhoea. Diacerein may be recommended as an alternative therapy to NSAIDs, especially for people at high risk of GI bleeding and cardiovascular diseases.

Conflicts of interest

The funding agencies (The Danish Rheumatism Association and The Oak Foundation) had no role in study design, data collection, data synthesis, data interpretation, writing the report, or the decision to submit the manuscript for publication. None of the authors is affiliated with or funded by any manufacturer of diacerein. RC is statistical editor in the Cochrane Collaboration (CMSG and PHRG); this is not a Cochrane review.

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