

A Meta-analysis of Controlled Clinical Studies With Diacerein in the Treatment of Osteoarthritis

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Background: This systematic meta-analysis on randomized controlled trials with diacerein was performed to provide an evidence-based assessment of its symptomatic efficacy in the treatment of osteoarthritis.

Methods: Electronic databases were searched for randomized controlled trials with diacerein. A manual review of the literature, abstracts, and posters was also conducted. Unpublished final reports were obtained from the manufacturer. Only studies performed in knee and/or hip osteoarthritis were chosen for review. Study inclusion, quality scoring, and data extraction were performed by 2 reviewers independently. Objectives for analysis comprised pain, function, escape medication use, global efficacy, and safety ratings by patients and investigators. Specific study periods, such as the active treatment period and the treatment-free follow-up period (when present), were analyzed. Statistical analyses were based on the intention-to-treat principle as far as possible, and acknowledged tests were used for data analysis.

Results: A total of 23 studies were identified, 19 of which were included. Diacerein was significantly superior to placebo during the active treatment phase (Glass score, 1.50 [95% confidence interval, 0.80-2.20]). Both diacerein and nonsteroidal anti-inflammatory drugs (NSAIDs) were similarly efficacious during the treatment period; however, diacerein, but not NSAIDs, showed a carryover effect, persisting up to 3 months after treatment, with a significant analgesic-sparing effect during the follow-up period (Glass score, 2.06 [95% confidence interval, 0.66-3.46]). Tolerability assessment revealed no differences between diacerein and NSAIDs, although the latter showed more severe events.

Conclusion: This systematic meta-analysis provides evidence for the symptomatic efficacy of diacerein in the treatment of knee and hip osteoarthritis, with reasonable tolerability.

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OSTEoARTHRITIS IS THE MOST common affliction of synovial joints in Western populations,¹ with the large, weight-bearing joints such as the hip and the knee being the most affected. Clinical manifestations comprise fluctuating joint pain, swelling, stiffness, and loss of motion. The main objectives in the management of osteoarthritis are to reduce symptoms and improve functionality. Another major objective is to reduce or even halt the progression of structural changes and, thereby, to delay or even avoid the need for prostheses.

Therapeutic measures consist of non-pharmacological (eg, patient education and physical therapy), pharmacological (eg, the use of analgesics, nonsteroidal anti-inflammatory drugs [NSAIDs], and symptomatic slow-acting drugs in osteoarthritis [SYSADOA]), and ultimately, surgical treatments (orthopaedic surgery, including joint replacement).²⁻⁴

Drugs belonging to the SYSADOA group are of increasing interest because

some have been shown to be effective in improving symptoms and also in reducing cartilage degradation in osteoarthritis,^{5,6} with a reasonable safety profile. These drugs have a slow onset of efficacy and a prolonged residual effect once treatment is stopped.⁷ However, the efficacy and safety of such drugs must be proved by randomized controlled trials (RCTs) over long periods of observation in a sufficiently large number of patients. Moreover, in keeping with the definition of a SYSADOA, the carryover effect of such drugs should be assessed for some time after treatment discontinuation. Almost all of the trials investigating SYSADOAs performed to date can be regarded as noninferiority trials from a statistical viewpoint because too few patients were included to allow unambiguous conclusions.

We therefore carried out a meta-analysis of RCTs with diacerein, a SYSADOA with interleukin 1 β (IL-1 β) inhibitory properties in osteoarthritis, to provide an evidence-based assessment of its potential efficacy in light of the lack of a

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Item	Score
Was the Study Described as Randomized (This Includes Words Such as Randomly, Random, and Randomization)?	0/1
Was the Method Used to Generate the Sequence of Randomization Described and Was It Appropriate (eg, Table of Random Numbers and Computer Generated)?	0/1
Was the Study Described as Double Blind?	0/1
Was the Method of Double Blinding Described and Was It Appropriate (eg, Identical Placebo, Active Placebo, and Dummy)?	0/1
Was There a Description of Withdrawals and Dropouts?	0/1
Deduct 1 Point if the Method Used to Generate the Sequence of Randomization Was Described and if It Was Inappropriate (Patients Were Allocated Alternately, or According to Date of Birth or Hospital Number, for Example).	0/-1
Deduct 1 Point if the Study Was Described as or Double Blind but the Method of Blinding Was Inappropriate (eg, Comparison of Tablet vs Injection With No Double Dummy).	0/-1

Figure 1. Jadad score calculation.

sufficient number of large, multicenter RCTs. Meta-analytic techniques constitute an acknowledged method to provide insights into the potential therapeutic properties of a compound by analyzing combined data from several independent RCTs.

The objective of this systematic meta-analysis of RCTs with diacerein was to compare the efficacy and safety of diacerein vs placebo or active treatments in patients with osteoarthritis of the hip and/or knee. Two periods were analyzed: the active treatment phase and the treatment-free follow-up phase, if present.

METHODS

LITERATURE SEARCH

We carried out a literature search for RCTs published from 1985 through 2004. Electronic databases (PubMed, MEDLINE, EMBASE, Google, Yahoo, and AltaVista) were searched using the terms *diacerein*, *diacerein*, *diacetylrhein*, and *rhein*, according to medical subject headings (MeSH) Browser and “related links.” Recent arthritis journals and personal files were hand searched for publications, posters, or abstracts. The reference lists in review articles were cross-checked. In addition, a complete list of abstracts, posters, publications, and copies of unpublished clinical study reports were obtained from the manufacturer.

SELECTION

Trials were selected if they included patients with osteoarthritis of the knee and/or hip, if the study had a randomized controlled design, if the comparative treatment was specified, and if there were extractable data on relevant outcome measures to improve the homogeneity of the analysis. Only studies in German, French, and English were selected.

Prior to the review of the RCTs, the reviewers (B.R. and B.F.L.) underwent formal training on review methods and the Jadad scale by the statistician (K.N.). Each selected study was independently assessed by both reviewers who were blinded to the authors, the date of publication, and the journals in which they were published. Duplicate studies were identified based on similarities in the study design, number of patients, and results obtained, and only the publication with the most extract-

able data was retained. We did not contact authors because the recent studies contained the required data, while the earlier studies with missing data were too old for raw data retrieval.

QUALITY ASSESSMENT AND DATA ABSTRACTION

A detailed prospective statistical analysis plan was developed under blind conditions using acknowledged standards for the extracted data.^{8,9} The methodological quality of the RCTs was assessed using the validated Jadad scale.¹⁰ In this procedure, a numerical score between 0 and 5 is assigned as a measure of the study design/reporting quality (0=weakest, 5=strongest) and is calculated using the 7 items described in **Figure 1**. To assess the potential for bias, the method of randomization, concealment of allocation, the blinding of study investigators and patients, handling of dropouts and withdrawals, and the availability of intention-to-treat (ITT) analysis were evaluated. The availability of unpublished reports, which constitute the most frequent cause of publication bias in our experience, contributed to this assessment.

The following parameters were also recorded:

- Duration of first active treatment period after randomization (in months);
- Duration of treatment-free follow-up periods (in months);
- Year of publication or internal study report;
- Type of publication, categorized as published in a scientific journal or congress report and/or whether a detailed internal report was used for this meta-analysis;
- Study type, categorized as randomized placebo controlled or reference drug controlled;
- Patients recruited per treatment group;
- Availability of ITT results.

The primary variables were pain (mostly using a 100-mm visual analog scale) and function (WOMAC [Western Ontario and McMaster Universities Index], Lequesne Index, or similar¹¹); in addition, comedication, consumption of analgesics or NSAIDs, global efficacy assessment (subjective ratings by patients or investigators), and global safety assessment (subjective ratings by patients or investigators) were recorded. Our null hypotheses was that diacerein was equal to any comparator group for any of these 5 variables. Data abstraction was performed individually by the reviewers and checked by the statistician.

STATISTICAL ANALYSES

Glass scores (standardized mean differences) were calculated for the study variables and corrected for small sample size bias using exact methods. The inverse normal method was used for statistical assessment (significance level, $P < .05$) of pooled results using exact weighting techniques. The results were assessed for robustness (sensitivity analysis) based on 2 different weighting methods for the Glass scores. The weights based on the Jadad method were prospectively defined as the primary method for decision making. Global alpha risk (type I error) control was made using the Bonferroni-Holm procedure. The statistical analyses were based on the ITT principle as far as possible and, when studies presented both per-protocol and ITT results, the ITT results were used.

All studies were assessed for homogeneity of the primary variables at baseline. We relied on the pooled analysis of the inverse normal method because the number of possible covariable criteria were very low, preventing the use of a more sophisticated statistical model. There was no systematic testing for heterogeneity because no commonly acknowledged meth-

ods exist for this.¹² Heterogeneity assessments were based on nonoverlapping, 2-sided 95% confidence intervals (CIs).

RESULTS

Twenty-three identified RCTs (20 published as full articles, abstracts, or posters and 3 unpublished) complied with the inclusion criteria (**Figure 2**). Of these, 2 studies^{13,14} were duplicates and only 1 study¹⁴ was retained because it was more appropriate for data extraction. One study¹⁵ was excluded for major methodological problems, while another¹⁶ was excluded because it had no extractable data on diacerein. A fourth study¹⁷ was excluded because it only reported inpatient changes. Thus, 19 studies with a total of 2637 recruited patients (1328 diacerein-treated patients and 1309 patients in the comparator groups) were included in the meta-analysis (**Table 1**). Of these, 8 (42%) were placebo controlled and 11 (58%) were active (mainly NSAID) controlled; 42% of the studies were conducted in patients with knee osteoarthritis, 11% in those with hip osteoarthritis, and 47% dealt with both osteoarthritis localizations. Data on the follow-up period were available in 11 (58%) of 19 studies, and this either lasted 1 (5 studies), 2 (4 studies), or 3 months (2 studies). Details on the study design, participants' characteristics, intervention, treatment duration, duration of follow-up period, variables analyzed, and Jadad score are given in Table 1.

The interrater reliability for the 19 studies selected showed identical results for the Jadad weights in 16 studies and a difference of just 1 point in 3 studies, thus showing a considerable degree of robustness. The average Jadad score was 3.2 points (Table 1), indicating an overall, above-average quality of the RCTs as assessed by the 2 reviewers with a high degree of congruence.

The Jadad-weighted (JW) and sample size-weighted (n-wtd) Glass scores (95% CIs) are given in **Table 2**. Glass scores greater than 0.8 are commonly regarded as clinically relevant.

EFFECTS OF DIACEREIN ON PAIN

At the end of the active treatment vs placebo period, the JW Glass score for the effect of diacerein on pain was 1.50 (95% CI, 0.80 to 2.20), and the n-wtd pooled result was 1.31 (95% CI, 0.49 to 2.14) (**Figure 3A**). Both methods show a statistically significant superiority of diacerein over placebo at this time point.

At the end of the follow-up period, the JW Glass score for the effect of diacerein on pain was 2.67 (95% CI, 1.27 to 4.07), while the n-wtd pooled score was 2.71 (95% CI, 1.32 to 4.10). At this time point, the effect of diacerein was found to be significantly better than placebo, regardless of the weighting method applied, indicating a carryover effect after treatment interruption.

There were no significant differences between diacerein and standard treatments (mostly NSAIDs) for the effect on pain at the end of active treatment (JW-pooled Glass score, -0.35 [95% CI, -1.11 to 0.41]; n-wtd result: -0.01 [95% CI, -0.76 to 0.74]) (Figure 3B). At the end of the follow-up period, however, the JW-pooled Glass score,

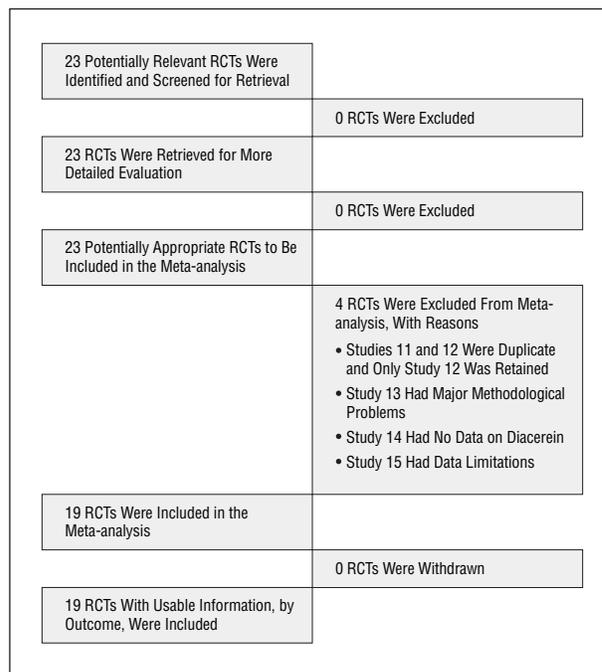


Figure 2. Selection of trials for inclusion in the meta-analysis. RCTs indicates randomized controlled trials.

compared with active treatment, was 2.13 (95% CI, 1.32 to 2.93), and the n-wtd score was 2.27 (95% CI, 1.42 to 3.11) (Figure 3C). At this time point, diacerein was significantly better than active treatment, regardless of the weighting method, also indicating a carryover effect.

EFFECTS OF DIACEREIN ON FUNCTION

The JW-pooled Glass score for changes in functional impairment at the end of the active treatment vs placebo period was 1.49 (95% CI, 0.78 to 2.19), while the n-wtd-pooled Glass score was 1.08 (95% CI, 0.26 to 1.91) (**Figure 4A**), indicating a statistically relevant superiority of diacerein. A comparison of diacerein vs placebo at the end of the follow-up period was not possible owing to insufficient data.

Both the JW (0.12 [95% CI, -0.68 to 0.93]) and n-wtd (0.73 [95% CI, -0.10 to 1.55]) (Figure 4B) scores indicated comparable effects of diacerein and NSAIDs on function. However, at the end of the follow-up period diacerein was superior to the comparator treatments (JW-pooled Glass score, 2.58 [95% CI, 1.71 to 3.45]; and n-wtd-pooled Glass score, 2.85 [95% CI, 1.90 to 3.81]).

ESCAPE MEDICATION INTAKE (ANALGESICS OR NSAID)

Both weighting methods revealed no differences between placebo and diacerein with respect to comedication consumption during active treatment (Table 2), probably because of marked heterogeneities for this parameter. The JW-pooled Glass score at the end of the follow-up period compared with placebo was 2.06 (95% CI, 0.66 to 3.46), indicating a statistically significant superiority of diacerein.

Table 1. Studies Included in the Meta-analysis

Study No.	Source	Study Design	Patients, No./ Age, Mean ± SD, y	Inclusion Criteria	Control	Treatment Duration, mo	Treatment-Free Follow-up Period	Variables Analyzed	ITT	Mean Jadad Score
1	Pelletier et al, ¹⁸ 2000	MC, R, DB, PLC, 4 arms	484 (382 F)/ 64.5 ± 8.65	Age, 40-80 y; knee OA (ACR); pain (≥35-mm VAS), KL I-III	Placebo	4	NR	POM (VAS), WOMAC (A, B, C), EM, GE, GS, AE	Yes	5
2	Lequesne et al, ¹⁹ 1998	MC, R, DB, PLC	183 (123 F)/ 61.5 ± 10.9	Age, 35-80 y; EULAR criteria for knee or hip OA; pain (≥30-mm VAS)	Placebo	6	2	POM, LI, flares, responders, EM, GE, GS, AE	Yes	3
3	Tang et al, ²⁰ 2004	MC, R, DB, DD	223 (183 F)/ 59.8 ± 8.18	Age, 40-65 y; knee OA (ACR); pain (≥40-mm VAS), KL II-III	NSAID	3	1	POW, WOMAC C, JE, EM, GE, GS, AE	Yes	5
4	Louthrenoo et al, ²¹ 2004	MC, R, DB, DD	171 (146 F)/ 54 ± 7.0	Age, 40-65 y; knee OA (ACR); pain (≥40 mm on 2 items of WOMAC A); KL II-III	NSAID	4	2	Pain (WOMAC A), WOMAC (B, C, total), EM, GE, GS, AE	Yes	3
5	Dougados et al, ⁶ 2001	MC, R, DB, PLC	507 (304 F)/ 62.5 ± 6.8	Age, 50-75 y; hip JSW, 1-3 mm; hip pain; LI 3-12 points	Placebo	36	NR	JSW, LI, pain	Yes	5
6	Nguyen et al, ²² 1994	MC, R, PLC and NSAID controlled, 4 arms	288 (164 F)/ 62.5 ± 10.5	Hip OA (LI, ACR); KL grade I-III; pain (≥40 mm VAS)	Placebo, NSAID	2	NR	POM, LI, EM, GS, GE, AE	Yes	4.5
7	Mantia, ²³ 1987	R, DB	38 (20 F)/60.5	Painful knee and/or hip OA (KL II-III)	NSAID	3	1	Pain, JM, AE	No	3
8	Portioli, ²⁴ 1987	MC, R, DB	69 (61 F)/61	Age, 18-75 y; painful hip or knee OA; KL grade II-III painful hip or knee OA	NSAID	3	1	Pain, JF, EM, GS, GE, AE	No	3.5
9	Mordini et al, ²⁵ 1986	R, DB	30 (No details)	Age, 18-75 y; KL grade II-III painful hip or knee OA	NSAID	2	1	Pain, JF, EM, GE, AE	No	2
10	Mattara, ²⁶ 1985	MC, R, DB	32 (No details)	Age, 18-75 y; KL grade II-III painful hip or knee OA	NSAID	3	1	POAM, POPM, POL, JF, EM, AE	No	2
11	Pietrogrande et al, ²⁷ 1985	R, SB	50 (29 F)/61.1	Age, 18-70 y; KL grade II knee OA	NSAID	1	NR	Pain, JF, JM, GE, AE	No	0
12	Fioravanti and Marcolongo, ²⁸ 1985	R, DB	30 (21 F)/52.3	NR	NSAID	2	2	Pain, JF, AE	No	2
13	Marcolongo et al, ²⁹ 1988	R, DB	95 (75 F)/57.8	Age, 38-75 y; hip and/or knee OA	NSAID	2	2	SP, NP, POAM, POPM, JM, GE, AE	No	0
14	Pham et al, ³⁰ 2004	Prospective, MC, R, DB, PLC	301 (207 F)/ 64.7	Knee OA (ACR); pain (>30 mm), KL I-IV; JSW >2 mm	Placebo, NRD101 (hyaluronic acid compound)	12	NR	Pain, LI, EM, GE, AE	Yes	4
17	Schulitz, ³¹ 1994	R, DB, PLC	80 (13 F)/ 47.5 ± 13.3	Age, 18-75 y; active knee OA; KL II-III	Placebo	3	NR	Pain, LI, SI, JM, EM, GE, AE	No	5
18	Ascherl, ³² 1994	MC, R, DB, PLC	111 (60 F)/ 55.3 ± 12.3	Age, 18-70 y; painful knee OA; KL II-III; restricted mobility; LI ≥8	Placebo	6	NR	LI, POP, PAR, POM, EM, GE, TOL, AE	Yes	5
19	Chantre et al, ¹⁴ 2000	MC, R, DB	122 (67 F)/ 61.7	Age, 30-79 y; painful (>50 mm VAS) OA of hip or knee; KL I-III	HP	4	NR	SP, FD, LI, EM, GE, AE	Yes	5
21	Fagnani et al, ³³ 1998	MC, R, open, pragmatic	207 (149 F)/ 66.5	Hip and/or knee OA (radiography), requiring NSAIDs; analgesics or SYSADOA	Standard treatment	6	3	Pain, LI, NSAID, EM	Yes	1.5
22	Pavelka et al, ³⁴ 2005	MC, R, DB, PLC	168 (132 F)/ 63.5	Age, 40-75 y; knee OA with pain (>40 mm on >2 items of WOMAC A), KL II-III	Placebo	3	3	WOMAC (A, B, C, total), SF-36, GE, TOP, JE, EM, AE	Yes	4

Abbreviations: ACR, American College of Rheumatology; AE, adverse events; DB, double-blind; DD, double-dummy; EM, escape medication; EULAR, European League Against Rheumatism; F, female; FD, functional disability; GE, global efficacy; GS, global safety; HP, *Harpagophytum procumbens*; ITT, intention to treat; JE, joint effusion; JF, joint function; JM, joint mobility; JSW, joint space width; KL, Kellgren-Lawrence grade; LI, Lequesne Index; MC, multicenter; NP, night pain; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; PAR, pain at rest; PLC, placebo controlled; POAM, pain on active movement; POL, pain on load; POM, pain on movement; POP, pain on pressure; POPM, pain on passive movement; POW, pain on walking; R, randomized; SB, single blind; SF-36, 36-Item Short Form Health Survey; SI, Schulitz Index; SP, spontaneous pain; SYSADOA, symptomatic slow-acting drugs in osteoarthritis; TOL, tolerability; TOP, tenderness on palpation; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Index.

Table 2. Summary of Results

Result	GS	n-wtd GS	n-wtd 95% Lower CL	n-wtd 95% Upper CL	JW GS*	JW 95% Lower CL	JW 95% Upper CL
Pain during active treatment	Diacerein vs placebo	1.31	0.49	2.14	1.50	0.80	2.20
Pain during active treatment	Diacerein vs NSAID	-0.01	-0.76	0.74	-0.35	-1.11	0.41
Pain during dechallenge period	Diacerein vs placebo	2.71	1.32	4.10	2.67	1.27	4.07
Pain during dechallenge period	Diacerein vs NSAID	2.27	1.42	3.11	2.13	1.32	2.93
Function during active treatment	Diacerein vs placebo	1.08	0.26	1.91	1.49	0.78	2.19
Function during active treatment	Diacerein vs NSAID	0.73	-0.10	1.55	0.12	-0.68	0.93
Function during dechallenge	Diacerein vs placebo	NR	NR	NR	NR	NR	NR
Function during dechallenge	Diacerein vs NSAID	2.85	1.90	3.81	2.58	1.71	3.45
Escape medication during active treatment	Diacerein vs placebo	-0.16	-1.28	0.96	0.80	-0.08	1.69
Escape medication during active treatment	Diacerein vs NSAID	-0.30	-1.31	0.70	-1.03	-2.11	0.06
Escape medication during dechallenge period	Diacerein vs placebo	1.94	0.55	3.33	2.06	0.66	3.46
Escape medication during dechallenge period	Diacerein vs NSAID	2.68	1.54	3.82	3.26	1.97	4.55
Global efficacy	Diacerein vs placebo	1.20	0.38	2.02	1.43	0.73	2.13
Global efficacy	Diacerein vs NSAID	2.23	1.43	3.03	1.43	0.62	2.24
Global safety	Diacerein vs placebo	-2.16	-2.99	-1.34	-1.51	-2.21	-0.81
Global safety	Diacerein vs NSAID	-0.55	-1.30	0.20	0.09	-0.66	0.85

Abbreviations: CL, confidence limit; GS, Glass score; JW, Jadad-weighted; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; n-wtd, sample size-weighted.

*The JW GSs reflect the primary weighting method based on study and data quality.

No significant differences were observed between diacerein and NSAIDs regarding additional analgesics during the active treatment period (Table 2). However, at the end of the follow-up period, diacerein was found to be significantly superior (JW Glass score, 3.26 [95% CI, 1.97 to 4.55]).

GLOBAL EFFICACY RATINGS BY PATIENTS

The interpretations for this parameter should be considered with caution because major heterogeneities were observed in the studies. The JW Glass score for patients' global efficacy rating at the end of active treatment was 1.43 (95% CI, 0.73 to 2.13) for diacerein vs placebo, while the n-wtd score was 1.20 (95% CI, 0.38 to 2.02), indicating the superiority of diacerein.

Compared with active treatment, the JW Glass score for global efficacy ratings at the end active treatment was 1.43 (95% CI, 0.62 to 2.24), while the n-wtd score was 2.23 (95% CI, 1.43 to 3.03) (Figure 4A). Surprisingly, both methods showed statistically significantly better patients' global efficacy ratings for diacerein at termination of active treatment.

PATIENTS' TOLERABILITY RATINGS

The JW (-1.51 [95% CI, -2.21 to -0.81]) and the n-wtd (-2.16 [95% CI, -2.99 to -1.34]) Glass scores for tolerability ratings indicated a statistically significant inferiority of diacerein vs placebo, whereas there was no statistically significant difference between diacerein and NSAIDs, although the latter showed more severe events.

Summarizing the tolerability results, a reasonable safety profile of diacerein can be observed, even after long-term administration as in the 3-year Evaluation of the Chondromodulating Effect of Diacerein in Osteoarthritis of the Hip (ECHODIAH) trial.⁶ The most frequent adverse effect was mild to moderate diarrhea, which usu-

ally appeared early during treatment and resolved on continuing treatment. In most patients, this did not result in treatment interruption. On average, about 39% of the patients in the diacerein group and 12% in the placebo group experienced at least 1 episode of loose stools and/or diarrhea, while 18% of the diacerein-treated and 12% of the placebo-treated patients complained of abdominal pain, with 2.7% interrupting treatment at a dosage of 100 mg/d of diacerein because of diarrhea.¹⁸ The other frequent adverse effect was a clinically irrelevant darker urine coloration.⁶ Pruritus and skin rash occurred in a few cases,⁶ whereas NSAID-specific adverse events, such as in the upper gastrointestinal tract or with respect to the cardiovascular system, did not appear more frequently than in the placebo group.

COMMENT

The use of diacerein for the treatment of osteoarthritis is still under—sometimes controversial—discussion. Its postulated modes of action, all indicating IL-1 β antagonism, make the drug an interesting option for the treatment of osteoarthritis not only for symptom relief but also for structure modification. Studies in different animal models³⁵⁻⁴¹ showed that diacerein consistently moderated cartilage loss in osteoarthritis. In humans, the ECHODIAH trial⁶ showed a reduction in the progression of hip osteoarthritis in the diacerein-treated patients compared with the placebo group.

Overall, this meta-analysis provides evidence for statistically significant and clinically relevant efficacy of diacerein on improvement of pain and function in patients with hip and/or knee osteoarthritis. The large number of patients included in this meta-analysis gives the basis for well-founded conclusions to be drawn.

Considering the pain relief results, one has to consider that complete withdrawal of analgesic comedica-

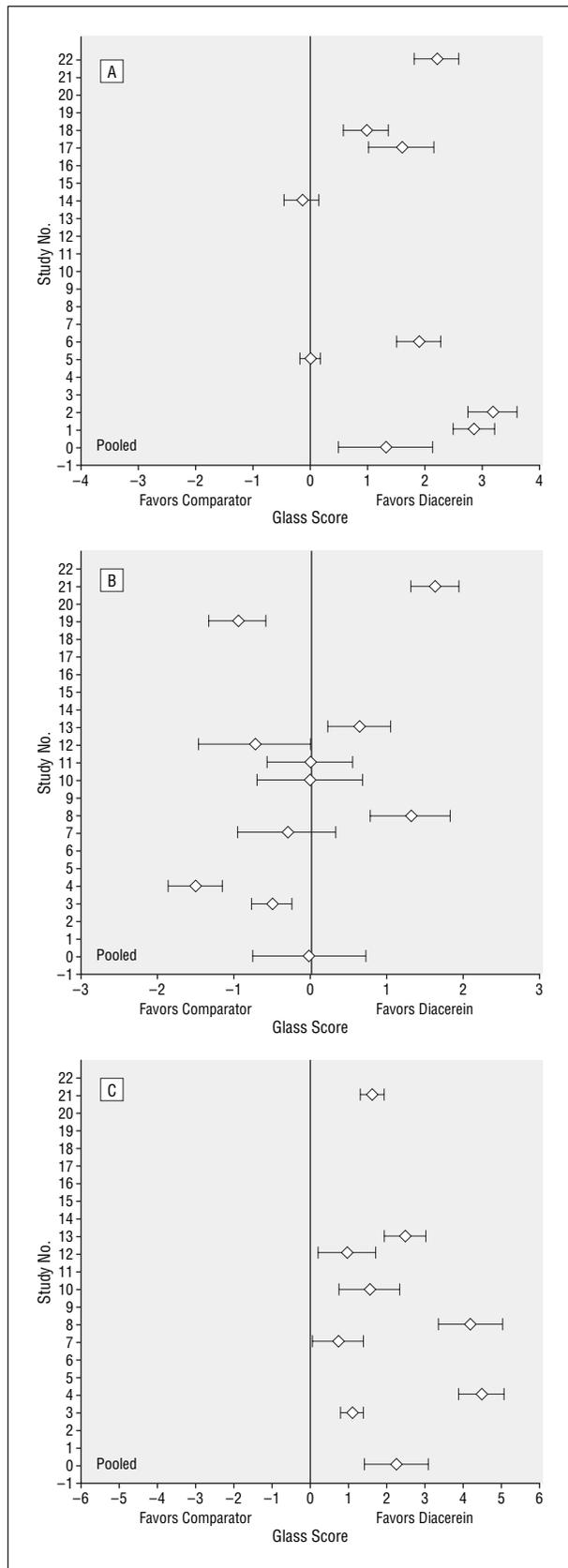


Figure 3. Pain (sample size-weighted Glass score) at the end of active treatment vs placebo (A), at the end of active treatment vs standard treatment (mostly nonsteroidal anti-inflammatory drugs) (B), and at the end of the dechallenge period vs standard treatment (mostly nonsteroidal anti-inflammatory drugs) (C). Error bars indicate 95% confidence intervals. See Table 1 for study number.

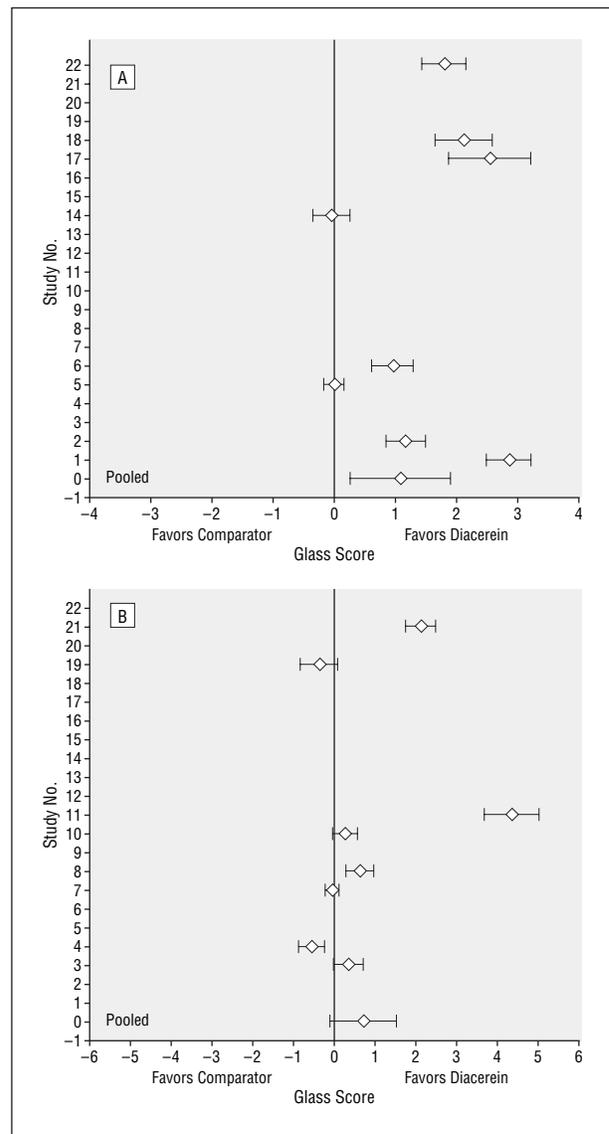


Figure 4. Function (sample size-weighted Glass score) at the end of active period vs placebo (A) and at the end of active treatment vs standard treatment (mostly nonsteroidal anti-inflammatory drugs) (B). Error bars indicate 95% confidence intervals. See Table 1 for study number.

tion was not possible during the studies analyzed. In most of the trials, acetaminophen, which is also considered an appropriate treatment modality for moderate osteoarthritis,^{3,4} was allowed as an escape medication in both the diacerein and control groups, and the amount taken was recorded by the patient in a diary. However, although mean intake of acetaminophen was similar during the active treatment period, its consumption increased significantly in the NSAID-treated patients, but not in the diacerein group, during the treatment-free follow-up period.

After the end of treatment, SYSADOAs are supposed to have a carryover effect.⁷ In this meta-analysis, we found evidence for this carryover effect with respect to pain and consumption of escape medication in all subanalyses performed, not only in the individual trials but also in the pooled population, and not only compared with placebo^{18,19} but also with active treatment modalities com-

prising diclofenac sodium,^{20,23} tenoxicam,²² piroxicam,^{21,27} and naproxen.²⁴ Given the fact that all selected studies had a randomized, controlled, parallel-group design, these findings indicate a positive impact of diacerein on the clinical status of patients with osteoarthritis.

The patients' global tolerability ratings at the end of active treatment showed no statistically significant differences between other active treatments and diacerein. However, as expected, a significant inferiority of diacerein vs placebo was observed, also indicating reproducibility of the results obtained here.

The risk-benefit ratio associated with long-term use of NSAIDs and analgesics is well documented in the literature,^{24,42-44} but clinical studies on the use of NSAIDs for more than 6 weeks in patients with osteoarthritis are rare.^{24,45} Nonsteroidal anti-inflammatory drugs, particularly the selective cyclooxygenase-2 inhibitors, are known to exert a higher risk for thromboembolic disorders such as myocardial infarction or stroke.⁴⁶ In this context, it is important to consider that most patients affected by osteoarthritis also experience disorders, or at least risk factors, of the cardiovascular system and that according to the European Agency for the Evaluation of Medicinal Products⁴⁷ and the Food and Drug Administration,⁴⁸ NSAIDs should be administered at the lowest possible dose for the shortest period. In contrast, cardiovascular adverse events in patients treated with diacerein can be considered very rare. In France, over a period of 11 years (from September 1994 to November 2005) and with more than 14 million prescriptions of diacerein, only 9 cases of cardiovascular adverse events with diacerein were spontaneously reported (information collected by the Drug Safety Department, Negma-Lerads, Toussus-Le-Noble, France). In particular, no acute coronary syndrome or myocardial infarction was reported. Thus, with respect to tolerability, diacerein may have some advantages compared with long-term application of NSAIDs.

Meta-analyses are commonly hampered by incongruencies with respect to the comparability of different studies in different patient populations.⁴⁹ In our investigation, however, a high degree of consistency was observed with respect to the results in all publications analyzed regarding the improvement of symptoms and tolerability in patients treated with diacerein. The methodological quality of the publications showed some differences, but 8 of them were published in peer-reviewed journals (average impact factor, 4.1), and the results of the other available studies were similar.

Even if a positive publication bias led to overestimation of therapeutic efficacy, it can be concluded that the pooled data still show beneficial effects of diacerein compared with placebo.

CONCLUSIONS

For diacerein, this meta-analysis provides evidence for a superiority over placebo and an equality with NSAIDs with respect to improvement in pain and function during the active treatment period in patients with osteoarthritis of the hip and/or knee. Moreover, diacerein was superior to placebo and NSAIDs during the follow-up pe-

riod with an NSAID-sparing effect, indicating that the drug has a carryover effect.

Tolerability assessments revealed the superiority of placebo over diacerein, with no differences between diacerein and NSAIDs. Given these results, a trial powered to ultimately prove the usefulness of diacerein as a symptom-modifying drug in osteoarthritis can be expected to give similar results.

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Author Contributions: Dr Leeb, as the principal investigator, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Correction

Error in Figure. In the Original Investigation by Rintelen et al titled "A Meta-analysis of Controlled Clinical Studies With Diacerein in the Treatment of Osteoarthritis" published in the September 25, 2006, issue of the ARCHIVES (2006;166:1899-1906), an error occurred in Figure 2 wherein the 4 randomized controlled trials excluded from the meta-analysis were incorrectly referenced. A corrected figure appears below.

23 Potentially Relevant RCTs Were Identified and Screened for Retrieval	0 RCTs Were Excluded
23 RCTs Were Retrieved for More Detailed Evaluation	0 RCTs Were Excluded
23 Potentially Appropriate RCTs to Be Included in the Meta-analysis	4 RCTs Were Excluded From Meta-analysis, With Reasons <ul style="list-style-type: none"> • References 13 and 14 Were Duplicate and Only Reference 14 Was Retained • Reference 15 Had Major Methodological Problems • Reference 16 Had No Data on Diacerein • Reference 17 Had Data Limitations
19 RCTs Were Included in the Meta-analysis	0 RCTs Were Withdrawn
19 RCTs With Usable Information, by Outcome, Were Included	

Figure 2. Selection of trials for inclusion in the meta-analysis. RCTs indicates randomized controlled trials.