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ORIGINAL ARTICLE

Diacerein for the treatment of rheumatoid arthritis in patients with inadequate response to methotrexate: a pilot randomized, double-blind, placebo-controlled add-on trial

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Abstract

Objective To evaluate the efficacy and safety of diacerein in patients with rheumatoid arthritis (RA) who are methotrexate inadequate responders (MTX-IR).

Method In this pilot, multicenter, double-blind, placebo-controlled trial, MTX-IR RA patients were randomized to either diacerein or matching placebo as add-on treatment to MTX for 24 weeks. Efficacy and safety were evaluated every 4 weeks until week 28. Primary and secondary efficacy endpoints were the percentage of patients achieving the ACR20 criteria and a moderate EULAR response at week 24, respectively.

Results Forty patients were equally randomized to both study treatments; 16 and 19 participants completed the study in the diacerein and the placebo arms, respectively. Baseline characteristics were similar in both groups, except that tender joint count, DAS28-ESR score, and non-steroidal anti-inflammatory drug consumption were higher in the placebo arm. The ACR20 response at week 24 was similar in the diacerein and placebo groups (65% vs 45%, $P = .20$). However, treatment response according to the EULAR criteria was better in patients taking diacerein (75% vs 25% of moderate response, $P = .002$). In the 35 patients with assessments through week 28, diacerein was superior to placebo in ACR20 at weeks 24 and 28 (both 81% vs 47%, $P = .04$). Incidence of adverse events was comparable in both arms, with only chromaturia being more common with diacerein than placebo (40% vs 10%, $P = .03$).

Conclusions These preliminary results show the potential benefits of diacerein on pain, joint function, and disease activity in MTX-IR RA patients.

Trial registration ClinicalTrials.gov Identifier: NCT01264211

Key Points

- *Diacerein has shown positive effects on rheumatoid arthritis symptoms.*
- *A good safety profile of diacerein has been observed when it was administered as add-on therapy to methotrexate in patients with rheumatoid arthritis.*

Keywords Diacerein · Disease activity · Methotrexate · Randomized controlled trial · Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease primarily affecting the joints. When improperly managed in the early stage of the disease, it can lead to progressive joint destruction, deformities, disability, impaired quality of life, and premature mortality [1]. Currently, conventional synthetic (cs) disease-modifying anti-rheumatic drugs (csDMARDs) should be prescribed to patients as soon as RA is diagnosed [2], either in monotherapy or combination therapy, in order to achieve disease remission or low disease activity [3]. Methotrexate (MTX) is generally the first treatment choice. In case of csDMARD treatment failure, targeted therapy with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) should be introduced [2]. However, there are concerns about their associated risk of specific side effects, in particular serious infections [4].

Diacerein is an anthraquinone derivative which has demonstrated efficacy and safety as an oral, symptomatic slow-acting drug in osteoarthritis (SYSADOA) [5]. Unlike non-steroidal anti-inflammatory drugs (NSAIDs), diacerein does not inhibit prostaglandin synthesis. Therefore, it does not have direct side effects on the upper gastrointestinal tract or on the renal and cardiovascular systems [6, 7]. In vitro studies have shown that diacerein decreases the production and activity of pro-inflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α [8, 9]. It also inhibits IL-1β-induced nuclear factor (NF)-κB activation and decreases synoviocyte matrix metalloproteinase (MMP)-13 production [10]. Such cytokines and proteinases induce inflammation and tissue degradation synergistically and are known to play an important role in the pathophysiology of RA [11]. In vivo, diacerein has been shown to inhibit and attenuate progression of joint destruction in a mouse model of spontaneous polyarthritis [12] and in a TNF transgenic mouse model of inflammatory arthritis [13]. As a result, it was postulated that diacerein may provide additional benefit to RA patients that are on a stable MTX regimen, along with a favorable safety profile. The objective of this proof-of-concept study was to investigate efficacy and safety of diacerein as add-on therapy in patients who still have active RA despite treatment with MTX.

Patients and methods

Ethical considerations

This trial was conducted in accordance with the Good Clinical Practices and was compliant with the principles of the 1983 Declaration of Helsinki. Ethics approval was provided by the Institutional Review Boards of the four participating centers. The study is registered in Clinicaltrials.gov National Institute of Health trial register (NCT01264211).

Study design

This was a randomized, double-blind, placebo-controlled, parallel-group, phase II study conducted in patients with RA attending the rheumatology clinic of four university hospitals in Thailand. Patients who proved to be eligible during the screening (week-4) and baseline (week 0) visits were consecutively randomized at baseline to receive either diacerein or placebo as add-on treatment to oral MTX for 24 weeks. The randomization scheme was 1:1, with a block size of 4, stratified by center. The randomization table was generated by Statmed SARL (Villemoirieu, France) using a validated in-house software. After enrolment and start of treatment at baseline, patients were examined for efficacy and safety every 4 weeks through 24 weeks of treatment and for a final follow-up 4 weeks later (week 28). Patients who prematurely discontinued were not replaced.

Patients

Eligible were adults (18–65 years old) diagnosed with RA according to the 1987 revised classification criteria of the American College of Rheumatology (ACR) [14] for at least 3 months and no more than 2 years, and with global functional status of class I–III [15]. RA had to be treated with MTX for ≥ 12 weeks with a stable weekly dose of 10–20 mg for ≥ 4 weeks before randomization. The disease had to be active despite MTX treatment, i.e., the Disease Activity Score 28 (DAS28) [16], calculated using the erythrocyte sedimentation rate (ESR) at screening and baseline had to be > 4.0 and not to have changed in-between both visits by ≥ 0.6 [17]. In addition, tender joint count (TJC, per 68 joints) and swollen joint count (SJC, per 66 joints) had both to be ≥ 6 at screening and baseline visits. All patients had to be abstinent from alcohol throughout the study, and women of childbearing potential had to use adequate contraceptive methods.

Patients were excluded if they have had active inflammatory arthritis other than RA, active immunodeficiency, recurrent infections or an infection requiring hospitalization, or treatment with intravenous/oral antibiotics within 4/2 weeks prior to screening. Further exclusion criteria were uncontrolled medical conditions (e.g., diabetes mellitus, asthma, cardiopulmonary disease), inflammatory intestinal disease (e.g., ulcerative colitis, Crohn's disease), intestinal (pseudo-) obstruction, painful abdominal syndrome or persistent diarrhea (> 3 stools/24 h), significant liver disease (cirrhosis, insufficiency, serum aminotransferases > 1.5 times the upper limit of normal, positive hepatitis B surface antigen, or hepatitis C antibodies tests), significant blood abnormalities (hemoglobin ≤ 8.5 g/dl, hematocrit ≤ 28.5%, white blood cell count ≤3000/mm^3, platelets ≤100,000/mm^3), ESR < 28 mm/h, or significant impaired renal function (serum creatinine > 1.6 mg/dl).

The following treatments had to be stopped prior to randomization: rituximab by 24 weeks; other bDMARDs: azathioprine and cyclosporine by 12 weeks; leflunomide, parenteral/oral gold, intra-articular depot-corticosteroid by 8 weeks; and other csDMARDs: oral corticosteroids (daily dose equivalent to > 10 mg prednisone) by 4 weeks. Chronic treatment with antihistamines, antidepressants, or tranquilizers should not have been initiated within the previous 12 weeks.

Treatments

All patients received basic therapy with oral MTX 10–20 mg/week. Prescribed dosage had to be stable throughout the study unless the patient did not tolerate it. Folate supplementation (5 mg/day) was prescribed before and throughout the study. Patients were randomized to receive either diacerein orally or matching placebo for 24 weeks. Both were given as one capsule per day with the evening meal for the first 4 weeks and as two capsules per day, one with breakfast and one with the evening meal, for the remaining 20 weeks, corresponding to daily diacerein doses of 50 and 100 mg, respectively.

Oral NSAIDs and corticosteroids up to an equivalent dosage of 10 mg/day prednisone as well as physical therapy were allowed, if patients were on stable dose regimens for ≥ 4 weeks prior to randomization and those were maintained throughout the study. In the presence of active synovitis, aspiration of the synovial fluid was allowed for each patient once. Within 2 weeks from such an aspiration, scheduled assessments of the affected joint were to be skipped. No intra-articular corticosteroid injection was allowed throughout the study. Rescue pain medication was paracetamol (500 mg tablets) at maximum daily doses of 2 g; daily consumption was to be recorded and rescue medication was not allowed within 12 h prior to any visit.

Outcome measures

The primary efficacy endpoint was the percentage of patients fulfilling ACR20 response criteria after 24 weeks of treatment [18]. The secondary efficacy endpoint was the percentage of patients achieving at least a moderate response according to the European League Against Rheumatism (EULAR) criteria based on the change from baseline in the DAS28-ESR score at week 24 [17]. Additional endpoints determined at each follow-up visit (week 4 to 28) were the percentage of patients (i) fulfilling ACR20, ACR50, and ACR70 response criteria [18]; (ii) achieving a minimal clinically important improvement (MCII) ≥ 15 mm or a patient acceptable symptom score (PASS) < 41 mm on patient assessment of pain using a 100-mm visual analog scale (VAS) [19]; (iii) and changes from baseline to week 28 in the DAS28-ESR score, Health Assessment Questionnaire (HAQ), ESR, C-reactive protein (CRP) levels, and use of rescue medication. Other endpoints included patient and physician global assessment of disease activity on a 100 mm VAS, and patient assessment of pain (100 mm VAS). Joint evaluation (i.e., TJC and SJC) and physician global assessment of disease activity were performed by the same experienced rheumatologist throughout the study.

Safety endpoints were the incidence, type, intensity, and relatedness to treatment of adverse events (AEs) and serious AEs (SAEs) [20], as well as any change in the general clinical examination, vital signs (body weight, heart rate, systolic/diastolic blood pressure), or laboratory values.

Statistical analysis

As this was a pilot study, sample size was arbitrarily fixed at 20 patients per treatment arm. The primary analysis of efficacy was performed on the intention-to-treat (ITT) population (all randomized patients), whereas the analysis of safety was conducted on the safety population (all treated patients). Baseline characteristics were analyzed using descriptive statistics: mean ± standard deviation, median, minimum-maximum. For inferential comparisons between the treatment arms, Chi-square test or Fisher exact test, and Student's t test or Wilcoxon-Mann-Whitney test were used, depending on the scale and distribution of data. In case of significant heterogeneity between the groups at baseline, an analysis of covariance or a multivariate logistic regression would be performed to assess the robustness of the primary result. Paired t test or signed rank test was used for comparisons within the treatment arms over time. Missing values after baseline were replaced using the last observation carried forward (LOCF) method. P value < .05 was considered statistically significant.

Results

Patient distribution

Participants were recruited in 4 study centers from November 2010 to September 2013, with the last patient completing the study in March 2014. Of the 45 screened patients, 40 were enrolled and randomized, and 20 were treated in each study arm. The ITT population and the safety population were identical. Of these patients, 16 completed the study in the diacerein and 19 in the placebo arm (completer population). Dropouts were related to increased disease activity and patient request (Fig. 1). One patient who participated in the study until week 4 presented a major protocol violation: < 8 weeks of diacerein treatment.

Pre-treatment baseline analysis

Demographic and disease characteristics of the randomized patients are shown in Table 1, while baseline efficacy

variables are presented in Table 2. All patients were of Asian race and baseline characteristics in both treatment arms were comparable, except that TJC (16.6 ± 9.3 vs 23.2 ± 9.6, $P = .02$), DAS28-ESR (6.2 ± 0.7 vs 6.8 ± 0.8, $P = .02$), and the proportion of patients taking NSAIDs (70% vs 95%, $P = .04$) were higher in the placebo arm. The only oral corticosteroid used was prednisolone. None of the participants had been previously treated with bDMARDs or tsDMARDs.

Efficacy analysis

Efficacy variables and response to treatment at week 24 are presented in Tables 2 and 3 for the diacerein and placebo patients of the ITT population. In the diacerein group, the percentage of patients achieving an ACR20 response continuously increased until week 24, while this increase was considerably slower and not consistent under placebo (Fig. 2). In the ITT population, differences between the treatment arms in the ACR20 response were significant at week 4 (diacerein: 25%, placebo: 0%, $P = .02$) and 16 (diacerein: 45%, placebo: 15%, $P = .04$), but not at the primary endpoint at week 24, where 65% of patients in the diacerein group vs 45% in the placebo group achieved ACR20 criteria ($P = .20$) (Fig. 2a, Table 3). As several baseline disease characteristics were not fully balanced between the two treatment arms, a multivariate analysis was needed to evaluate the relationship between the study treatment and the primary endpoint after adjusting for these confounding factors. Therefore, a multivariate logistic regression was built with the ACR20 response at week 24 as dependent variable, study treatment as independent variable, and baseline TJC (2 classes: < 11, ≥ 11) and DAS28-ESR (2 classes: ≤ 6 or > 6) as covariates. Without adjustment, results showed that odds of treatment response were 2 times higher in the diacerein than in the placebo group (odds ratio = 2.270, 95% confidence interval (CI) 0.636 to 8.106, $P = .21$). Although remaining not statistically significant, diacerein was still associated with a higher ACR20 response at week 24 compared to placebo after adjustment for baseline TJC and DAS28-ESR (odds ratio = 3.118, 95% CI 0.662 to 14.689, $P = .15$). In the completer population, the ACR20 response was significantly higher in the diacerein group than in the placebo group at weeks 24 and 28 (both 81% vs 47%, $P = .04$) (Fig. 2b).

Regarding the secondary endpoint in the ITT population, the percentage of patients achieving a moderate EULAR response at week 24 was significantly higher in the diacerein than in the placebo group (75% vs 25%, $P = .002$) (Table 3). However, for the DAS28-ESR itself, there was no significant difference in the change from baseline at week 24 between diacerein and placebo patients (Fig. 3a, Table 2); the intergroup difference was of 0.41 (standard error 0.40) with a 95% CI of −0.40 to 1.23. In the completer population, the change from baseline in DAS28-ESR was significantly higher in the diacerein group than in the placebo group from week 4 to 24 (Fig. 3); the intergroup difference in the change from baseline at week 24 was of 0.75 (standard error: 0.35) with a 95% CI of 0.03 to 1.47.

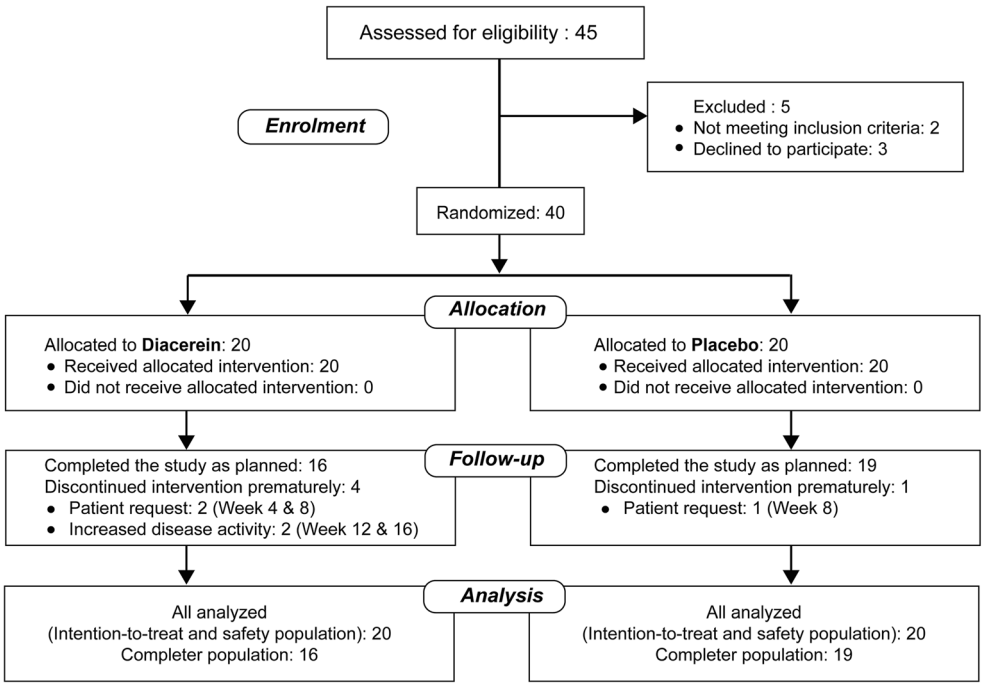

Fig. 1 CONSORT flow diagram. Study flow chart of enrolment, treatment allocation, follow-up, and analysis of patients in the study. ITT = intention-to-treat

Table 1 Baseline patient and disease characteristics (intention-to-treat population)

	Diacerein ($n = 20$)	Placebo ($n = 20$)	P value
Male sex, n (%)	4 (20)	4 (20)	> .99[a]
Age, mean (SD), years	45.0 (14.0)	51.1 (9.0)	.20[b]
Weight, mean (SD), kg	56.3 (9.0)	55.2 (8.8)	.69[c]
Height, mean (SD), cm	158.5 (6.7)	155.3 (6.0)	.12[c]
Any comorbidity, *n* (%)	12 (60)	11 (55)	> .99[a]
Hypertension, *n* (%)	4 (20)	6 (30)	.72[a]
Diabetes mellitus, *n* (%)	0 (0)	4 (20)	.11[a]
Dyslipidemia, *n* (%)	2 (10)	5 (25)	.41[a]
Others, *n* (%)	6 (30)	6 (30)	> .99[a]
Time since RA diagnosis, mean (SD), months	9.4 (5.2)	9.0 (6.6)	.46[b]
< 6 months, *n* (%)	8 (40)	10 (50)	.73[d]
6–12 months, *n* (%)	6 (30)	4 (20)	
> 12 months, *n* (%)	6 (30)	6 (30)	
Functional class of RA, *n* (%)			
I	2 (10)	1 (5)	> .99[a]
II	17 (85)	17 (85)	
III	1 (5)	2 (10)	
Serum rheumatoid factor positive, *n* (%)	15 (75)	19 (95)	.18[a]
Radiographic erosions, *n* (%)	10 (50)	9 (45)	.75[d]
MTX intake, mean (SD), mg/week	13.0 (3.4)	11.8 (2.4)	.30[c]
MTX treatment duration, mean (SD), months	6.9 (4.7)	7.3 (3.9)	.28[b]
Prednisolone users, *n* (%)	13 (65)	11 (55)	.52[d]
Prednisolone intake, mean (SD), mg/day	5.4 (2.1)	6.1 (2.1)	.59[b]
NSAID users, *n* (%)	14 (70)	19 (95)	*.04*[d]

MTX methotrexate, *n* number of patients, *NSAID* non-steroidal anti-inflammatory drug, *SD* standard deviation, *RA* rheumatoid arthritis

[a] Fisher exact test

[b] Wilcoxon-Mann-Whitney test

[c] Student's *t* test

[d] Chi-square test; significant results ($P < .05$) in italics

In the ITT population, the percentage of patients achieving an ACR50 response at week 24 was higher in the diacerein (40%, 95% CI 11% to 50%) than in the placebo group (15%, 95% CI 8% to 37%), but the intergroup difference was not statistically significant ($P = .08$); the ACR70 response was identical in both groups (both 5%, 95% CI − 6% to 16%, $P > .99$). However, significant differences in favor of diacerein vs placebo were reached at week 20 (80% vs 45%, $P = .02$) and week 24 (85% vs 50%, $P = .02$) for the PASS response criterion, whereas the differences did not achieve statistical significance for the MCII response criterion at any time point (Table 3). Changes from baseline at week 24 in HAQ ($P = .48$), ESR ($P = .36$), CRP ($P = .62$), and total paracetamol intake ($P = .33$) were in favor of diacerein although the difference with placebo was not statistically significant (Table 2). Among the other endpoints, significant differences for diacerein vs placebo were found regarding the change in TJC and SJC only at week 4 (-3.40 ± 6.56 vs 0.05 ± 6.08, $P = .02$ and -3.15 ± 3.82 vs -0.80 ± 3.02, $P = .04$, respectively). Although not statistically significant, the change from baseline in global disease activity (both assessed by the patient and the physician) and pain assessed by the patient were higher in the diacerein than in the placebo group (Table 2).

Safety analysis

The numbers of all patients with any treatment-emergent AEs by treatment group are shown in Supplementary Table 1. The percentage of patients reporting treatment-emergent AEs were similar in the diacerein (80%, 16 patients) and in the placebo arm (75%, 15 patients). The proportion of AEs considered treatment related were also comparable, i.e., 50% (10 patients) and 55% (11 patients), respectively. Two patients experienced an SAE: one patient in the diacerein group had a hip fracture and one patient in the placebo group reported a pharyngotonsillitis. Neither of these SAEs were considered

Table 2 Efficacy variables at baseline, at the end of treatment, and change from baseline at the end of treatment (intention-to-treat population)

	Baseline (week 0)			End of treatment (week 24)			Change (week 0 to week 24)		
	Diacerein ($n = 20$)	Placebo ($n = 20$)	P value	Diacerein ($n = 20$)	Placebo ($n = 20$)	P value	Diacerein ($n = 20$)	Placebo ($n = 20$)	P value
DAS28-ESR, mean (SD)	6.2 (0.7)	6.8 (0.8)	*.02*[a]	5.0 (1.4)	6.0 (1.2)	*.02*[a]	− 1.3 (1.4)	− 0.9 (1.2)	.12[b]
HAQ, mean (SD)	1.1 (0.6)	1.4 (1.0)	.30[b]	0.7 (0.81)	1.1 (0.8)	.09[b]	− 0.5 (0.7)	− 0.4 (0.6)	.48[b]
ESR, mean (SD), mm/h	74.0 (27.0)	87.9 (29.5)	.13[a]	62.5 (35.5)	84.3 (29.2)	*.04*[a]	− 11.5 (30.8)	− 3.6 (22.8)	.36[a]
CRP, mean (SD), mg/l	30.5 (37.1)	35.1 (26.0)	.30[b]	26.4 (36.4)	40.0 (66.8)	*.03*[b]	− 4.1 (27.5)	4.9 (61.9)	.62[b]
Total paracetamol intake, mean (SD), g/week	2.5 (3.3)	2.9 (3.1)	.36[b]	1.5 (1.9)	2.8 (2.7)	.09[b]	− 1.0 (3.2)	− 0.2 (2.1)	.33[a]
TJC (68 joints), mean (SD)	16.6 (9.3)	23.2 (9.6)	*.02*[b]	8.1 (8.3)	15.3 (10.1)	*.02*[b]	− 8.5 (11.0)	− 7.9 (10.3)	.87[a]
SJC (66 joints), mean (SD)	13.3 (6.3)	15.0 (7.2)	.45[b]	8.0 (6.7)	9.6 (6.7)	.30[b]	− 5.4 (7.4)	− 5.4 (6.9)	.98[a]
PGA, mean (SD), mm	44.6 (18.7)	55.4 (21.9)	.10[a]	29.5 (25.4)	41.5 (25.7)	.10[b]	− 15.1 (24.0)	− 14.0 (15.7)	.86[a]
PhGA, mean (SD), mm	44.2 (14.2)	48.7 (14.5)	.33[a]	29.8 (23.8)	35.8 (12.9)	.07[b]	− 14.4 (15.3)	− 12.9 (18.9)	.78[a]
Patient assessment of pain, mean (SD), mm	44.4 (23.5)	56.5 (22.9)	.11[a]	23.9 (22.7)	43.3 (24.0)	*.003*[b]	− 20.5 (24.0)	− 13.2 (19.2)	.20[b]

DAS28-ESR Disease Activity Score 28 calculated using the erythrocyte sedimentation rate, *ESR* erythrocyte sedimentation rate, *HAQ* Health Assessment Questionnaire standard disability index, *n* number of patients, *PGA* patient global assessment of disease activity, *PhGA* physician global assessment of disease activity. *SD* standard deviation, *SJC* swollen joint count, *TJC* tender joint count

[a] Student's *t* test

[b] Wilcoxon-Mann-Whitney test; significant results ($P < .05$) in italics

as related to the study treatment. Most frequent AEs were gastrointestinal disorders, which concerned 8 (40%) and 7 (35%) patients in the diacerein and placebo groups, respectively. Among those, the most common was diarrhea, reported by 4 patients (20%) in both groups. One case of aphthous stomatitis and one case of food poisoning were also described in each group. Other gastrointestinal AEs reported in the diacerein group included one dyspepsia, one gastro-esophageal reflux disease, and one hemorrhoidal hemorrhage. In the placebo group, one case of gastritis and one case of constipation were described. Overall, the most common, also most frequently considered treatment–related AE, was chromaturia, experienced by 8 patients (40%) in the diacerein group vs 2 patients (10%) in the placebo group ($P = .03$); it was always reported at the week 24 visit. In the diacerein group, 6 patients out of 13 ACR20 responders had urine discoloration vs 1 patient out of 9 in the placebo group. Neither laboratory test nor vital signs revealed any safety–relevant differences between the two groups. Clinically relevant abnormal liver tests were observed in placebo patients only.

Table 3 Treatment response at week 24 (intention-to-treat population)

	Diacerein ($n = 20$)	Placebo ($n = 20$)	P value
ACR20, *n* (%)	13 (65)	9 (45)	.20[a]
ACR50, *n* (%)	8 (40)	3 (15)	.08[a]
ACR70, *n* (%)	1 (5)	1 (5)	> .99[a]
Moderate EULAR, *n* (%)	15 (75)	5 (25)	*.002*[a]
MCII, *n* (%)	14 (70)	9 (45)	.11[a]
PASS, *n* (%)	17 (85)	10 (50)	*.02*[a]

ACR American College of Rheumatology; *EULAR* European League Against Rheumatism response (at least moderate response in Disease Activity Score 28 calculated using the erythrocyte sedimentation rate), *MCII* minimal clinically important improvement (diminution of ≥ 15 mm in patient's assessment of pain), *n* number of patients, *PASS* patient acceptable symptom score (< 41 mm in patient assessment of pain)

[a] Chi-square test; significant results ($P < .05$) in italics

Discussion

This randomized, double-blind, placebo-controlled study represents the first attempt to evaluate the effect of diacerein in patients with RA. The primary efficacy analysis on the ITT population showed that the difference in ACR20 response between the treatments was not statistically significant at 24 weeks, although a numerical advantage (about 20% of patients with ACR20 response) of the diacerein group vs the placebo group persisted during the entire treatment period. In contrast, for the 35 patients that had ACR20 assessments up to 28 weeks, the treatment effect of diacerein vs placebo was statistically significant at both 24 and 28 weeks, indicating that its effect persisted beyond the end of treatment. A similar carry-over effect has already been observed in clinical studies evaluating the effect of diacerein in patients with osteoarthritis [21–24]. The discrepancy between the results in the ITT and

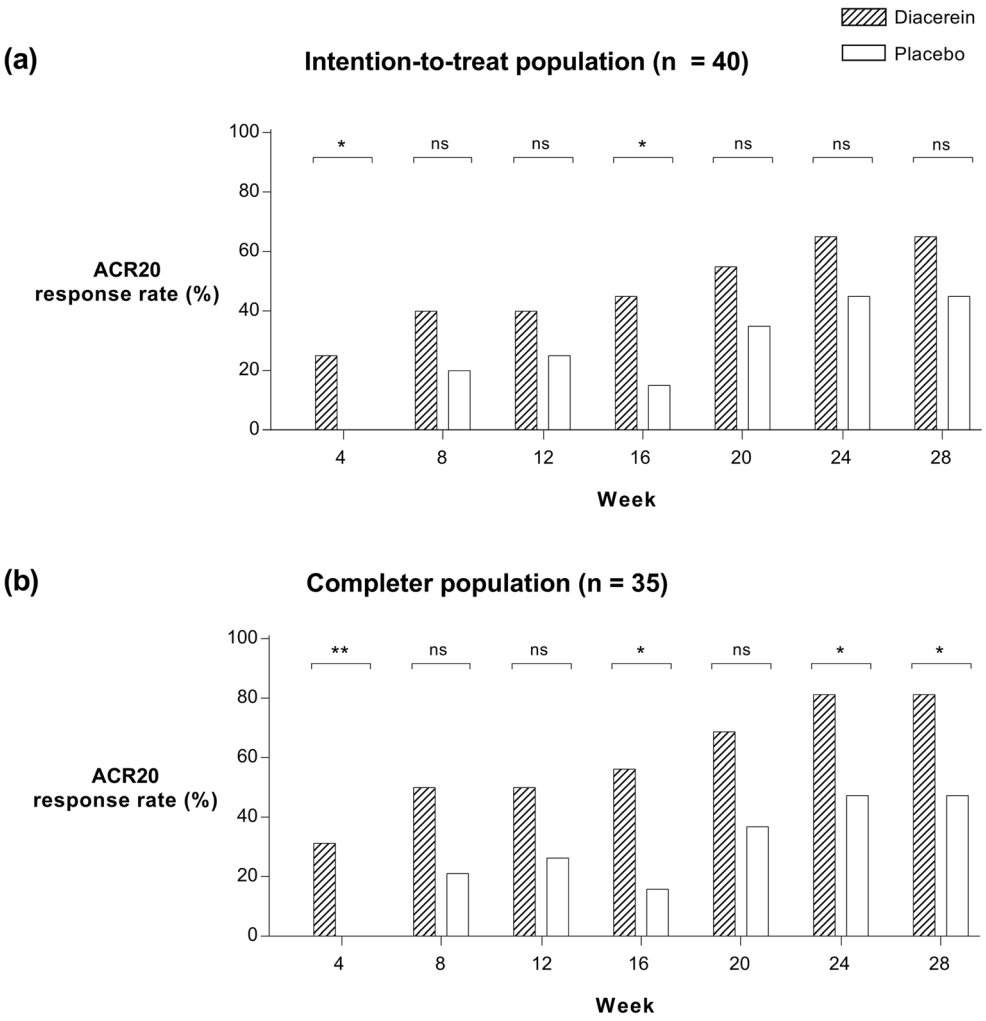

Fig. 2 ACR20 response from week 4 to week 28 (intention-to-treat and completer populations). Percentage of patients fulfilling ACR20 response criteria [18] **a** in the randomized patients ($n = 40$) and **b** in those completing the study ($n = 35$). ACR = American College of Rheumatology; ns = not significant; *$P < .05$; **$P < .01$ in Chi-square test

the completer population might be explained by the higher early discontinuation rate in the diacerein group (20%) than in the placebo group (5%). Among the participants who dropped out in the diacerein group, two patients were clear treatment failures (increased disease activity), but the remaining two left the study for personal reasons at week 4 and week 8, respectively. This is relatively early with regard to the mechanism of action of diacerein, and the treatment duration might have been insufficient to allow for an effect on efficacy variables, in particular TJC and SJC. As the LOCF method was used to replace missing data, this would have also influenced the results at week 24, in the ITT population.

Regarding the secondary efficacy endpoint of this study, the EULAR response at week 24 showed a highly significant intergroup difference, with 75% of patients in the diacerein group achieving a moderate or good response, as compared to 25% of patients in the placebo group. An additional clinically relevant endpoint, the achievement of the PASS criterion, was significant vs placebo at week 24, whereas the treatment groups did not differ in the MCII criterion. The reason why some patients achieved a moderate EULAR response whereas they did not fulfilled the ACR20 criteria may lie in the construct of the respective response criteria. While the ACR20 depends only on the percent change from baseline in several variables (TJC, SJC, along with ESR, CRP, patient assessment of pain, patient or physician global assessment of disease activity), the EULAR response is influenced not only by the improvement in DAS28-ESR but also by its value at a given time point. At week 24, the changes from baseline in DAS28-ESR were similar in both treatment arms, while DAS28-ESR was significantly higher in the placebo group than in the diacerein group, leading to a significant difference in the EULAR response.

Regarding the safety findings, diacerein treatment in addition to MTX was well tolerated in the study population of patients suffering from RA and patient dropouts were not related to AEs. The AE profile was comparable between the diacerein and placebo groups. In particular, diacerein did not

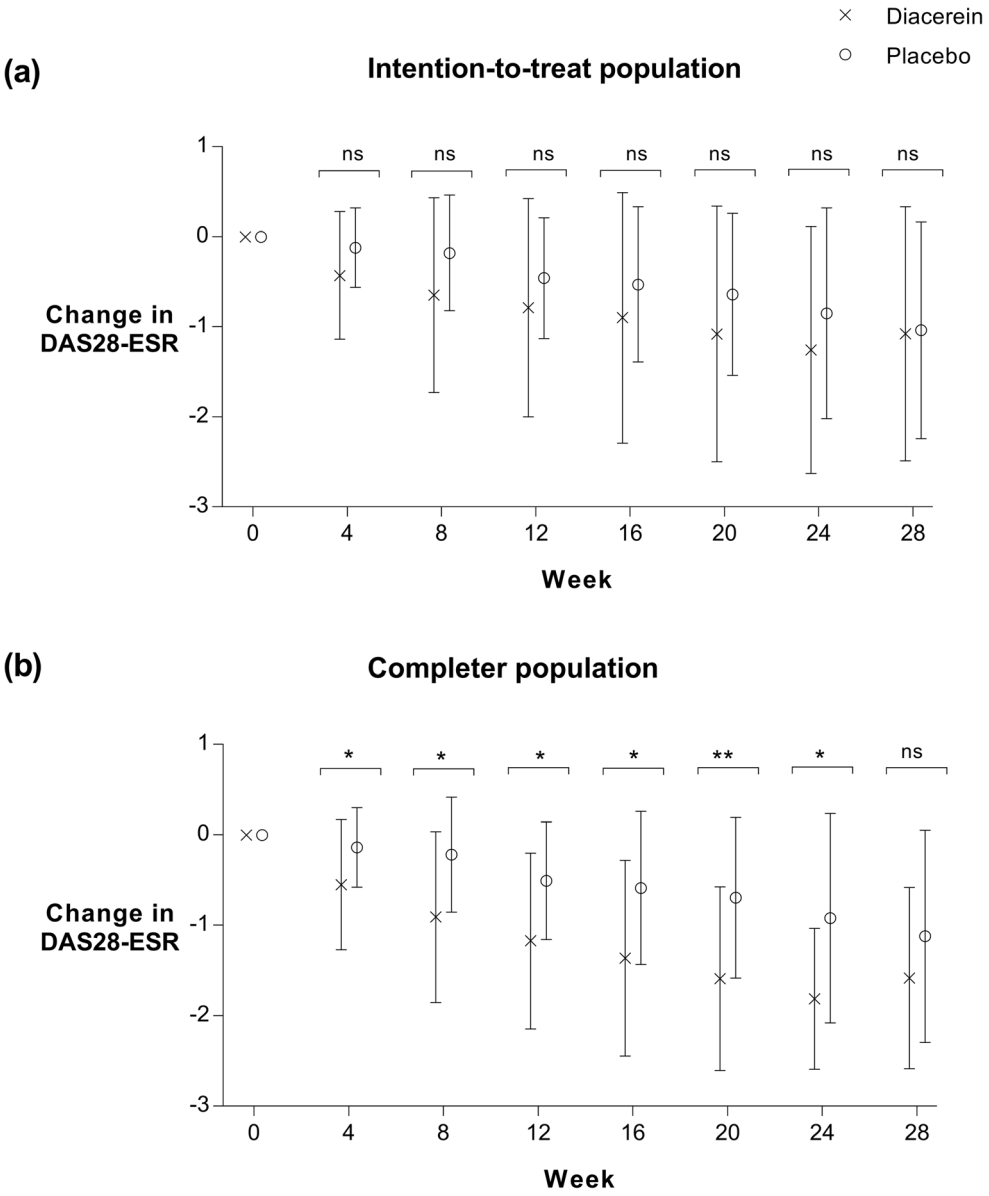

Fig. 3 Change of DAS28-ESR vs baseline from week 4 to week 28 (intention-to-treat and completer populations). Mean change from baseline in DAS28-ESR ± standard deviation **a** in the randomized patients ($n = 40$) and **b** in those completing the study ($n = 35$). DAS28-ESR = Disease Activity Score 28 calculated using the erythrocyte sedimentation rate; ns = not significant; $^{*}P < .05$; $^{**}P < .01$ in Student's t test

appear to increase the incidence of gastrointestinal complaints and clinically significant liver test abnormalities were only observed in the placebo group. The only AE that was significantly more common with diacerein than placebo was chromaturia, a well-known adverse reaction of diacerein of no clinical significance [6]. No SAEs were related to the study medication. No safety-relevant effects were seen in laboratory tests or vital signs.

One of the strengths of this study was the intervention of a single investigator per study center for the assessment of patient's joints, both this evaluating investigator and the patient being blind to the study treatment. Another strong point was the inclusion of a 4-week run-in period between screening and baseline visits during which DAS28-ESR had to be constant to ensure that patient's RA disease activity was stable. Besides, the main limitation of this study was the low sample size. Indeed, the trial could not be powered based on prior efficacy data and the sample size was arbitrarily fixed at 20 patients per treatment arm. This number was in the usual range of phase II trials and observed effects on the primary endpoint were expected to enable decision-making regarding further trials. However, the imbalance in the dropout rate between the treatment groups (diacerein, 20%; placebo, 5%) might have affected the results of the study. Another weakness of this trial, potentially also linked with the low sample size, is the intergroup difference in several baseline disease characteristics underlining a more active disease in the placebo group; its impact on the results seems to be limited, as shown by the multivariate analysis on the primary endpoint.

As this was a pilot study, the optimal dosage and the appropriate duration of diacerein treatment to have an effect on the clinical symptoms of RA were not known. Therefore, the standard dose regimen used in osteoarthritis was chosen in this trial (50 mg twice daily, i.e., approximately 2 mg/kg/day). It was reduced to half the dosage during the first 4 weeks of treatment to minimize the risk of gastrointestinal side effects. The decision to evaluate such a dose regimen was based on the results of two animal studies. In the first one, Tamura et al. [12] determined the effect of diacerein (3, 10, and 30 mg/kg/day), cyclosporine A (30 mg/kg/day) and vehicle, administered to male New Zealand black/KN mice 5 days/week during 7 months. The study showed that only diacerein at the dose of 30 mg/kg/day and cyclosporine A significantly inhibited arthritis progression. The retardation of radiographic progression was seen as early as 9 weeks after the first diacerein administration. The second animal study performed by Douni et al. [13] showed the effect of diacerein (2, 20, and 60 mg/kg/day), dexamethasone (0.5 mg/kg/day), MTX (1 mg/kg 3 times/week), and antihuman TNF antibody CB0006 (5 mg/kg/week) in the heterozygous Tg197 transgenic mouse with polyarthritis. The authors found significant improvements in clinical symptoms, radiographic progression, and histopathological findings after administration of diacerein (all dosage), dexamethasone, and antihuman TNF antibody, but not MTX. The primary endpoint was set at 24 weeks of treatment, in accordance with the "Points to consider" for conducting clinical trials in RA of the European Agency for the Evaluation of Medicinal Products (EMEA) that were in effect at the time when the study was designed [25]. The dosage of diacerein and the treatment duration chosen in this pilot clinical trial might have been not sufficient for alleviating RA symptoms, where the inflammatory process is much stronger than in osteoarthritis. An additional treatment arm with a higher diacerein dosage and a longer treatment follow-up should be considered in future trials.

Patients of this exploratory study were suffering from active RA of 3 months to 2 years duration since diagnosis. In the light of recent expert recommendations [26, 27], such a target population does not correspond to a population with early disease. While the ACR proposed a delay of not more than 6 months of disease/symptom duration to be qualified as early [27], the EULAR considers that duration of more than 1 year from symptom onset must not be considered as "early" anymore [26]. Thus, at least 60% of the patients included in this study (30% in each group) did not comply with the less stringent definition of early RA. Furthermore, regardless of disease duration, it has been established that patients previously treated with DMARDs usually respond to a lesser extent than DMARD-naïve [2]. The patients of this trial had an insufficient response to MTX therapy with a high disease activity according to DAS28-ESR. One might consider that the dosage of MTX in this study was relatively low (mean dose in the diacerein and the placebo group of 13.0 ± 3.4 and 11.8 ± 2.4 mg/week, respectively) when compared with the standard dose regimens used in Western Countries. However, the average body weight of the patients in this study was of about 55 kg, i.e., lower than in Caucasian populations. Thus, the MTX dosages were totally in line with those recommended by the Thai Rheumatism Association [28] and the MTX treatment could be considered as optimized. Nevertheless, a significant improvement vs baseline in several efficacy parameters was observed in the placebo group; we consider that this enhancement can hardly be explained by the placebo effect only and suggest that it could result from the MTX background therapy itself. Indeed, clinical trials in patients with early RA showed that the maximum response to MTX was usually obtained after 4 to 6 months of therapy [29]. Therefore, the MTX treatment duration prior to inclusion may have not been sufficient for the clinical effect to be fully established in 13 patients of the placebo group vs 9 of the diacerein group that took MTX for less than 6 months. In a future exploratory study, it would be interesting to evaluate diacerein in MTX-naïve patients, or at least in an early disease population.

In conclusion, this pilot study showed the potential benefits of using diacerein in the treatment of RA patients with insufficient response to MTX. Despite the ACR20 response was not significantly superior in the diacerein group than in the placebo group at week 24 (primary endpoint), it tended to be higher in patients treated with diacerein throughout the study. This trial also demonstrated that a higher proportion of patients treated with diacerein achieved a moderate EULAR response compared with patients in the placebo group. All other efficacy variables and treatment response criteria showed a trend in favor of diacerein, together with an acceptable safety profile. However, it is worth noting that the two treatment groups slightly differed in some disease characteristics at baseline, which might have had an influence on the results. The learnings of this pilot study in patients with RA should allow designing larger trials, with longer treatment duration and possibly higher drug doses, to further evaluate the efficacy of diacerein not only on the symptoms of RA but also its effect on joint structures.

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Data availability The data generated and/or analyzed during this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest Worawit Louthrenoo and Boonjing Siripaitoon received speaking honoraria from TRB Chemedica (Thailand) Ltd. Sabine Collaud Basset is an employee of TRB Chemedica International SA, Switzerland. Surasak Nilganuwong and Ratanavadee Nanagara declared no conflicts of interest.

Patient consent All patients gave their informed consent prior to enter the clinical trial, i.e., before they underwent any study procedure at the screening visit.

Ethics approval The trial was conducted in accordance with the Good Clinical Practices and was compliant with the principles of the 1983 Declaration of Helsinki. Ethics approval was provided by the Institutional Review Boards of the four participating centers. The study has been registered in the ClinicalTrials.gov National Institute of Health trial register (NCT01264211).

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