Efficacy and Safety of Diacerein in Patients With Inadequately Controlled Type 2 Diabetes: A Randomized Controlled Trial

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OBJECTIVE

To assess, in a randomized, double-blind, and placebo-controlled trial, the efficacy and safety of diacerein, an immune modulator anti-inflammatory drug, in improving glycemic control of patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Eighty-four patients with HbA_{1c} between 7.5 and 9.5% (58–80 mmol/mol) were randomized to 48-week treatment with placebo (*n* = 41) or diacerein 100 mg/day (*n* = 43). The primary outcome was the difference in mean HbA_{1c} changes during treatment. Secondary outcomes were other efficacy and safety measurements. A general linear regression with repeated measures, adjusted for age, sex, diabetes duration, and each baseline value, was used to estimate differences in mean changes. Both intention-to-treat (ITT) analysis and per-protocol analysis (excluding 10 patients who interrupted treatment) were performed.

RESULTS

Diacerein reduced HbA_{1c} compared with placebo by 0.35% (3.8 mmol/mol; *P* = 0.038) in the ITT analysis and by 0.41% (4.5 mmol/mol; *P* = 0.023) in the per-protocol analysis. The peak of effect occurred at the 24th week of treatment (−0.61% [6.7 mmol/mol; *P* = 0.014] and −0.78% [8.5 mmol/mol; *P* = 0.005], respectively), but it attenuated toward nonsignificant differences at the 48th week. No significant effect of diacerein was observed in other efficacy and safety measures. Diarrhea occurred in 65% of patients receiving diacerein and caused treatment interruption in 16%. Seven patients in the diacerein group reduced insulin dosage, whereas 10 in the placebo group increased it; however, mild hypoglycemic events were equally observed.

CONCLUSIONS

Diacerein reduced mean HbA_{1c} levels, with peak of effect at the 24th week of treatment. The drug was well tolerated and may be indicated as adjunct treatment in patients with type 2 diabetes, particularly in those with osteoarthritis.

The pivotal role of inflammatory pathways in the pathogenesis of type 2 diabetes and its associated long-term complications currently is well accepted (1). The two main physiopathological mechanisms underlying type 2 diabetes development and progression, namely defective pancreatic β-cell insulin secretion and peripheral insulin resistance, both have immunoinflammatory-mediated bases, particularly those involving the proinflammatory cytokine interleukin-1β (IL-1β) pathways (1,2). This

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evidence has led to proposals to target inflammatory pathways as potential treatment for type 2 diabetes (3,4).

Diacerein (1,8-diacetoxy-9,10-dioxodihydroanthracene-3-carboxylic acid), an anthraquinone derivative found in *Cassia* gender plants, has been indicated mainly for the symptomatic treatment of osteoarthritis (5,6). Although its specific mechanism of action is still unclear, diacerein is believed to act by its metabolite rhein as an immune modulator by mainly inhibiting the synthesis and activity of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), IL-6, and especially IL-1β, in several experimental models of osteoarthritis (7–10). In animal models of obesity and diabetes, diacerein has been demonstrated to downregulate IL-1β, IL-6, and TNF-α and their downward signaling in liver, adipose tissue, pancreatic islets, and muscle (11,12); to increase β-cell mass and insulin secretion by protecting β-cells from apoptosis (13,14); and to reduce peripheral insulin resistance, particularly in the liver and adipose tissue (12), resulting in improvements in glucose tolerance and lower fasting glycemia levels (11–14). Moreover, rhein has been shown to have beneficial effects in experimental diabetic nephropathy (15,16) and in diabetes-related nonalcoholic fatty liver disease (17,18). Despite this experimental evidence, only one previous clinical study (19) to our knowledge has assessed the effect of diacerein in patients with type 2 diabetes. The study was a randomized controlled trial (RCT) that showed potential beneficial effects of diacerein on improving glycemic control, reducing serum inflammatory biomarkers, and increasing insulin secretion. However, the study evaluated only a small sample of 40 drug-naive patients with recent-onset type 2 diabetes over a 60-day treatment period. Therefore, we conducted a nested RCT of patients with poorly controlled type 2 diabetes and high cardiovascular risk in an ongoing cohort—the Rio de Janeiro Type 2 Diabetes (RIO-T2D) cohort study—to assess the efficacy and safety of 1-year diacerein add-on treatment in improving glycemic control.

RESEARCH DESIGN AND METHODS

Design Overview

The study was a single-center, randomized (1:1), double-blind, parallel, placebo-controlled clinical trial nested within the RIO-T2D cohort conducted at a tertiary care university hospital to assess whether diacerein was superior to placebo in improving glycemic control of patients with poorly controlled type 2 diabetes. All participants gave written informed consent, and the local ethics committee had previously approved the study protocol (Rio de Janeiro, Brazil). Participants were randomly assigned after trial registration between October 2014 and January 2016, and the last patient visit occurred in January 2017.

Eligibility

Eligible participants were current adult RIO-T2D patients (≤75 years of age) with type 2 diabetes, with screening HbA_{1c} levels between 7.5% (58 mmol/mol) and 9.5% (80 mmol/mol), and on either stable oral or insulin treatment. The characteristics of the RIO-T2D cohort, its inclusion criteria, and its procedures and diagnostic definitions have been described previously (20–22). Exclusion criteria were pregnancy, concomitant life-threatening diseases, significant cognitive impairment, advanced renal failure (serum creatinine ≥177 μmol/L), chronic hepatic disorders (except nonalcoholic fatty liver disease), and major cardiovascular events in the previous 6 months. All eligible participants (n = 142) entered an 8-week run-in period where adherence to antidiabetic treatment was assessed by pill counting and direct observation of insulin administration.

Baseline Procedure

At the end of the 8-week run-in period, before randomization, all patients had fasting blood samples collected to assess HbA_{1c}, glycemia, serum lipids, creatinine, uric acid, liver function (alanine and aspartate aminotransferases, γ-glutamyl transferase, alkaline phosphatase, and albumin), and hematological/inflammatory indices (hematocrit, leukocyte and platelet counts, serum ferritin, and C-reactive protein). HbA_{1c} was measured by boronate affinity high-performance liquid chromatography (Premier Hb9210; Trinity Biotech, São Paulo, Brazil) certified by the National Glycohemoglobin Standardization Program. This assay has an intra- and interassay coefficient of variation <2% and a linear range of measurement from 3.8 to 18.5% and is highly specific with virtually no interference from common hemoglobin variants. No interference with diacerein is reported. A 24-h sterile urine sample was collected to assess 24-h albuminuria. Glomerular filtration rate was estimated by the Chronic Kidney Disease Epidemiology Collaboration equation (23). Clinical blood pressure (BP) was measured twice on two occasions (at screening and at the end of the run-in period) in the sitting position with a digital BP monitor (HEM-907XL; Omron Healthcare, Kyoto, Japan) and suitably sized cuffs. Body weight and height were also measured at screening and the end of the run-in period.

Randomization and Intervention

At the end of the run-in period, 84 patients were considered adherent to antidiabetic treatment, persisted with HbA_{1c} levels between 7.5% (58 mmol/mol) and 9.5% (80 mmol/mol), and were randomized to placebo (n = 41) or diacerein 100 mg/day add-on treatment as a single morning dosage (n = 43) for 48 weeks. One specialized nurse, who used sealed opaque envelopes in blocks of four, performed the randomization, which was stratified by sex, age (≤60, >60 years), and baseline HbA_{1c} level (7.5–8.4%, 8.5–9.5%). This nurse distributed the allocated medications but had no other contact with the participants. All other researchers, the attending physicians, and the participants were blind to allocated treatment.

Follow-up and Outcomes

Participants were followed by their attending physicians with a recommendation to keep antidiabetic, antihypertensive, and antilipidemic treatments unchanged throughout the 48-week period, except in case of hyperglycemic or hypoglycemic warnings. Participants were seen at the 4th, 8th, 12th, 24th, 36th, and 48th weeks by another specialized nurse who used a standard questionnaire to assess adherence to treatment by pill counting and adverse event occurrence and at the 12th, 24th, 36th, and 48th weeks by their attending physicians who repeated the same laboratory examinations except for 24-h albuminuria, which was repeated only at the 24th and 48th weeks. In case of gastrointestinal intolerance, participants were instructed to change their morning medication to the evening after dinner. They were instructed to monitor

daily fasting glucose levels and symptomatic events with glucometers. Hypoglycemia events were classified as mild if relieved by feeding or, if asymptomatic, with documented blood glucose <3.3 mmol/L (60 mg/dL) and as severe if requiring assistance (24). Researchers sent hypoglycemic warnings indicating a reduction in antidiabetic treatment to the attending physician if frequent (more than one per month) mild hypoglycemia events or any severe hypoglycemia event were observed at the 4th, 8th, 12th, 24th, 36th, and 48th week laboratory examinations. In the same way, hyperglycemic warnings indicating treatment intensification were sent whenever any HbA_{1c} >10% (86 mmol/mol) or fasting glycemia >13.9 mmol/L (250 mg/dL) was observed at the 12th, 24th, 36th, and 48th week laboratory examinations.

The primary outcome was the difference in change from baseline in HbA_{1c} during treatment between the placebo and diacerein groups. Secondary end points were changes in other efficacy and safety measurements, including fasting glycemia, serum lipids, renal and hepatic function parameters, hematological/inflammatory indices, clinic systolic and diastolic BPs, and body weight.

Statistical Analysis

Continuous data are described as mean (SD) or median (range), and categorical data are described as proportions. The original sample size calculation aimed to detect a difference of ≥0.4% in mean HbA_{1c} between the placebo and diacerein groups, with an estimated SD of 1.0%, an α-error of 0.05, and a statistical power of 0.80. A total of 200 randomized patients would be necessary. During the screening phase, it became clear that this number would not be achieved, so the protocol was amended to detect a minimum HbA_{1c} difference of 0.6%, dropping the necessary number to 90 patients (45 in each treatment arm). Differences in changes during treatment for each outcome were analyzed by general linear regression modeling, with the 12th, 24th, 36th, and 48th week measurements entered as repeated-measure dependent variables, the allocation group as a fixed-effect factor, and their respective baseline values, age, sex, and diabetes duration as adjusting random-effect covariates. This analysis allows adjusted comparisons of each time point measurement as well as adjusted estimations and comparisons of mean values and overall changes during the entire 48-week period between the placebo and diacerein groups. Results are presented as estimated mean values and changes from baseline, with their respective 95% CIs, for each treatment group and as the adjusted mean difference in changes between the placebo and diacerein groups. For analyses of changes in γ-glutamyl transferase, ferritin, and C-reactive protein, which had asymmetrical distributions, the variables were natural log-transformed before entering the regression model, and the results were then back-transformed. Graphical analysis of residuals confirmed assumptions of linear regressions. Missing values were <10% for all variable measurements, and they were handled by a multiple regression imputation strategy. Except for the placebo group participant who died in the 16th week of treatment, no other participant had a missing value for longer than a 12-week period. Both the intention-to-treat (ITT) analyses with all randomized participants and the per-protocol analysis excluding the 10 participants who interrupted the allocated treatment (n = 8 and 2 in the diacerein and placebo groups, respectively) were performed. All statistical analyses were performed with SPSS version 19.0 software (IBM Corporation, Chicago, IL), and a two-tailed $P < 0.05$ was regarded as significant.

RESULTS

Baseline Characteristics

Of the 512 patients on current follow-up screened, 142 entered the 8-week run-in period, and 84 were randomized to placebo (n = 41) and diacerein (n = 43) treatment (Fig. 1). Table 1 outlines the main baseline clinical and laboratory participant characteristics. Except for higher serum γ-glutamyl transferase levels and leukocyte count in the diacerein group, the groups were well balanced for the other characteristics. Most participants were obese women with longer (10 years) diabetes duration who already used insulin (77%) on a metformin background. Mean HbA_{1c} was 8.2% (66 mmol/mol) in both groups. No values were missing for HbA_{1c} and fasting glycemia during the study except for the deceased placebo group participant. Ten participants interrupted the allocated treatment (n = 8 and 2 in the diacerein and placebo groups, respectively) during the study (Fig. 1), and all who persisted on treatment had adherence of at least 80% on the basis of serial pill count.

Glycemic Control Change During Treatment

Table 2 and Fig. 2*A* and *B* show mean values and changes of HbA_{1c} and fasting glycemia according to allocated treatment. Diacerein group participants had a significantly lower mean HbA_{1c} level (mean difference in change −0.35% [3.8 mmol/mol]; P = 0.038) compared with the placebo group. This difference was most marked at the 24th week (−0.61% [6.7 mmol/mol], 95% CI −1.09 to −0.13; P = 0.014), but was attenuated at the 36th (−0.39% [4.3 mmol/mol], 95% CI −0.83 to 0.05; P = 0.086) and 48th (−0.26% [2.8 mmol/mol], 95% CI −0.75 to 0.22; P = 0.29) weeks. On per-protocol analysis (excluding the 10 patients who interrupted the allocated treatment), the overall difference between diacerein and placebo increased to −0.41% (4.5 mmol/mol) (95% CI −0.75 to −0.06; P = 0.023), as did the differences at the 24th (−0.78% [8.5 mmol/mol], 95% CI −1.32 to −0.25; P = 0.005) and 36th (−0.47% [5.1 mmol/mol], 95% CI −0.96 to 0.02; P = 0.058) weeks. Otherwise, no difference was found in fasting glycemia levels between the placebo and diacerein groups in either the ITT or the per-protocol analysis. Figure 2*C* shows the number of hyperglycemic warnings at each time point of the study. A total of 19 hyperglycemic warnings were observed on the basis of an HbA_{1c} >10% (86 mmol/mol) or a fasting glycemia >13.9 mmol/L (n = 12 and 7 in the placebo and diacerein groups, respectively). Figure 2*D* shows the number of hypoglycemic warnings during the study. A total of 16 hypoglycemic warnings were observed on the basis of frequent (more than one episode per month) mild hypoglycemic events (n = 7 and 9 in the placebo and diacerein groups, respectively). No severe hypoglycemic events were observed during the study. Supplementary Table 1 shows the cumulative number of participants who either increased or decreased their baseline antidiabetic treatment because of hyperglycemic or hypoglycemic warnings at each time point of the study. This change occurred exclusively in participants who

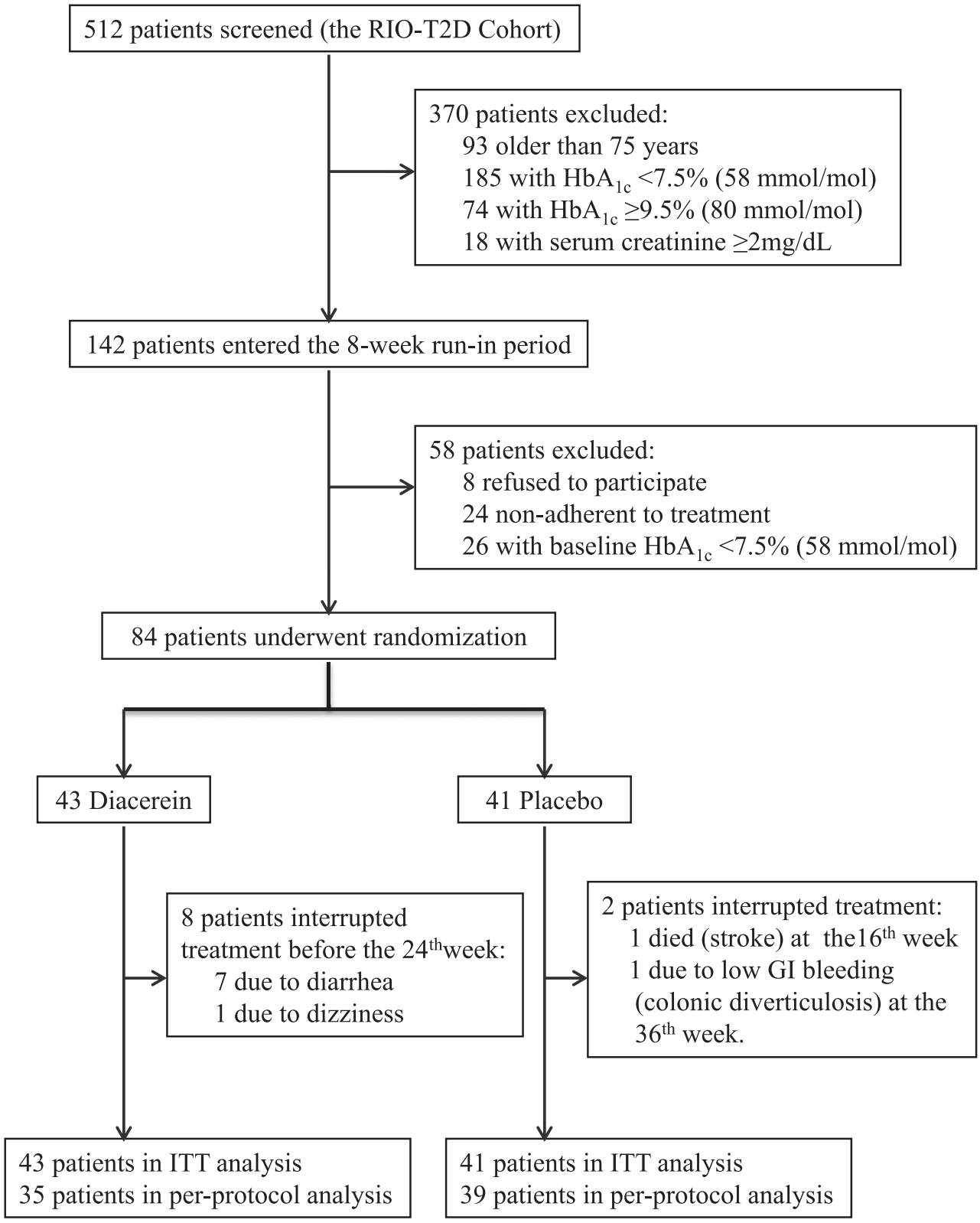

Figure 1—Study flowchart. Low GI, lower gastrointestinal tract.

used insulin. More participants in the diacerein group decreased insulin dosage (median insulin dose reduction 8 units/day, range 4–12), whereas more participants in the placebo group increased it (median insulin dose increase 10 units/day, range 4–16). No participant began a new antidiabetic medication during the study.

Table 1—Baseline characteristics of all participants and those randomized to placebo and diacerein treatment

Characteristic	All participants (n = 84)	Placebo (n = 41)	Diacerein (n = 43)
Age (years)	64.8 (7.2)	63.7 (7.9)	65.8 (6.3)
Male sex	21.7	20.0	23.3
Weight (kg)	79.6 (14.3)	77.3 (12.8)	82.1 (15.2)
BMI (kg/m^2)	31.8 (5.1)	31.3 (5.1)	32.3 (5.2)
Waist circumference (cm)	101 (9)	100 (11)	102 (8)
Physical activity	25.0	22.0	27.9
Diabetes duration (years)	10 (6–18)	9 (5–17)	12 (7–19)
Chronic diabetic complications			
Cerebrovascular disease	1.2	2.4	0
Coronary artery disease	14.7	13.5	15.8
Peripheral arterial disease	10.7	16.2	5.3
Retinopathy	23.3	22.9	23.7
Nephropathy	27.4	22.9	31.6
Peripheral neuropathy	17.6	19.4	15.8
Diabetes treatment			
Metformin	86.7	85.0	88.4
Sulfonylureas	19.3	15.0	23.3
DPP-4 inhibitors	7.2	5.0	9.3
Insulin	77.1	77.5	76.7
Aspirin	86.7	82.5	90.7
Statins	97.6	95.1	100
Arterial hypertension	85.3	89.2	81.6
SBP (mmHg)	139 (21)	138 (18)	139 (24)
DBP (mmHg)	75 (12)	73 (12)	77 (11)
Laboratory variables			
Fasting glucose (mmol/L)	8.4 (3.0)	8.5 (3.4)	8.2 (2.7)
HbA_{1c} (%)	8.2 (0.5)	8.2 (0.5)	8.2 (0.5)
HbA_{1c} (mmol/mol)	66 (5.5)	66 (5.5)	66 (5.5)
Total cholesterol (mmol/L)	4.2 (1.0)	4.1 (1.0)	4.2 (1.0)
HDL-C (mmol/L)	1.2 (0.3)	1.1 (0.3)	1.2 (0.3)
LDL-C (mmol/L)	2.4 (0.9)	2.4 (0.8)	2.3 (0.9)
TAG (mmol/L)	1.5 (0.7)	1.4 (0.7)	1.5 (0.6)
SCr (μmol/L)	88 (26)	88 (25)	88 (26)
GFR* (mL/min/1.73 m^2)	69 (19)	69 (19)	68 (19)
Uric acid (μmol/L)	315 (95)	321 (101)	309 (95)
Albuminuria (mg/24 h)	13 (7–30)	13 (6–32)	13 (7–27)
ALT (units/L)	44 (20)	43 (23)	45 (17)
AST (units/L)	28 (13)	28 (16)	27 (9)
GGT (units/L)	43 (30–62)	34 (27–54)	47 (38–94)
ALP (units /L)	97 (30)	92 (25)	100 (33)
Albumin (g/L)	38 (5)	39 (6)	38 (4)
Hematocrit (%)	38.7 (4.7)	38.6 (5.5)	38.8 (3.8)
Leukocyte count ($\times$ 10^9 cells/L)	8.1 (2.4)	7.5 (2.1)	8.6 (2.6)
Platelet count ($\times$ 10^9 cells/L)	226 (59)	225 (67)	229 (52)
Ferritin (μg/L)	94 (46–147)	103 (43–157)	91 (48–139)
CRP (mg/L)	4.5 (2.0–8.5)	4.4 (1.9–8.2)	4.8 (2.1–8.9)

Data are mean (SD), median (interquartile range), or percent. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; DBP, diastolic BP; DPP-4, dipeptidyl peptidase 4; GGT, γ-glutamyl transferase; GFR, glomerular filtration rate; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; SBP, systolic BP; SCr, serum creatinine; TAG, triacylglycerol. *Estimated by the Chronic Kidney Disease Epidemiology Collaboration equation.

Secondary End Points of Efficacy and Safety

Table 2 presents the other efficacy and safety secondary end points. No differences were found between the placebo and diacerein groups regarding changes in serum lipid levels, renal and liver function tests, hematological indices, and inflammatory markers. Particularly, nonsignificant reductions were found in albuminuria (mean −4 mg/24 h; P = 0.31) and serum C-reactive protein (−2.0 mg/L; P = 0.14) in the diacerein group. Parallel to HbA_{1c} reduction, C-reactive protein reduction also peaked at the 24th week examination (−2.9 mg/L [95% CI −6.5 to 0.6 mg/L]; P = 0.10). In addition, no differences were seen in changes in weight and mean BP levels between the diacerein and placebo groups, although a nonsignificantly 3-mmHg higher systolic and 2-mmHg higher diastolic BP were observed in diacerein-treated participants.

No serious adverse events were attributed to diacerein. Supplementary Table 2 shows the adverse events that occurred in ≥5% of the participants according to treatment group. Gastrointestinal symptoms, particularly diarrhea and nausea/vomiting, were the most frequent adverse events, occurring more frequently in the diacerein group mainly during the first 12 weeks of treatment. Twenty-eight (65%) participants in the diacerein group experienced at least one episode of diarrhea or loose stools; these were mostly self-limited and occurred mainly in the first 4 weeks of treatment (22 participants complained of diarrhea at the 4th week visit and only 12 at the 12th week, 5 at the 24th week, and 0 at the 36th and 48th week visits). Seven patients permanently interrupted diacerein treatment because of diarrhea between the 12th and 24th week of treatment. No differences were found in HbA_{1c} reduction between diacerein group participants with and without diarrhea.

CONCLUSIONS

This RCT evaluated the effects of diacerein compared with placebo as add-on 48-week treatment in patients with inadequately controlled, long-established type 2 diabetes. Diacerein reduced mean HbA_{1c} by 0.35% (3.8 mmol/mol) and 0.41% (4.5 mmol/mol) in the ITT and per-protocol analyses, respectively, compared with placebo. The magnitude of glycemic improvement was greatest at the 24th week of treatment (−0.61% [6.7 mmol/mol] and −0.78% [8.5 mmol/mol], respectively), but it was attenuated toward the 48th week. Otherwise, no effect on fasting glycemia levels was observed. Moreover, no significant effects of diacerein were observed regarding body weight, BP levels, serum lipid levels, renal and hepatic function, hematological indices, and serum inflammatory biomarkers, although a nonsignificant mean reduction in C-reactive protein of 2.0 mg/L was observed that also peaked (−2.9 mg/L) at the 24th week. The main

Table 2—Mean values during the 48-week treatment and adjusted differences in mean changes between placebo and diacerein for the primary and secondary outcomes

	Placebo		Diacerein		Adjusted difference	
Variable	During treatment	Change from baseline	During treatment	Change from baseline	in mean change	*P* value
Glycemic control						
HbA_{1c} (%)	8.39 (8.16 to 8.63)	0.19 (−0.04 to 0.43)	8.04 (7.81 to 8.27)	−0.16 (−0.39 to 0.07)	−0.35 (−0.68 to −0.02)	0.038
HbA_{1c} (mmol/mol)	68 (66 to 71)	2.1 (−0.4 to 4.7)	64 (62 to 67)	−1.7 (−4.3 to 0.8)	−3.8 (−7.4 to −0.2)	
Fasting glucose (mmol/L)	8.4 (7.7 to 9.1)	0.04 (−0.62 to 0.70)	8.4 (7.7 to 9.0)	0 (−0.64 to 0.64)	−0.04 (−0.96 to 0.88)	0.92
Lipids						
HDL-C (mmol/L)	1.2 (1.1 to 1.2)	0.01 (−0.05 to 0.07)	1.1 (1.1 to 1.2)	−0.03 (−0.09 to 0.03)	−0.04 (−0.12 to 0.05)	0.39
LDL-C (mmol/L)	2.4 (2.2 to 2.6)	0.05 (−0.15 to 0.25)	2.4 (2.2 to 2.6)	0.03 (−0.16 to 0.22)	−0.02 (−0.30 to 0.25)	0.86
TAG (mmol/L)	1.8 (1.6 to 2.0)	0.2 (−0.04 to 0.4)	1.9 (1.7 to 2.1)	0.2 (0.02 to 0.4)	0.1 (−0.2 to 0.3)	0.71
Renal						
SCr (μmol/L)	91 (87 to 94)	3.5 (−0.9 to 7.1)	90 (86 to 94)	2.6 (−1.8 to 6.2)	−0.9 (−6.2 to 5.3)	0.83
eGFR (mL/min/1.73 m^2)	67 (64 to 70)	−1.7 (−4.7 to 1.4)	67 (64 to 70)	−1.5 (−4.5 to 1.4)	0.2 (−4.1 to 4.4)	0.96
Uric acid (μmol/L)	300 (284 to 316)	−13 (−29 to 3)	295 (279 to 310)	−18 (−34 to −2)	−5 (−27 to 17)	0.65
Albuminuria (mg/24 h)	26 (21 to 30)	0 (−5 to 5)	22 (18 to 27)	−4 (−8 to 1)	−4 (−10 to 3)	0.31
Hepatic						
ALT (units/L)	41 (38 to 45)	−3 (−6 to 1)	44 (40 to 47)	−1 (−4 to 3)	2 (−3 to 8)	0.34
AST (units/L)	26 (24 to 28)	−1 (−3 to 1)	28 (26 to 29)	0 (−2 to 2)	1 (−1 to 4)	0.34
GGT (units/L)	61 (54 to 67)	2 (−5 to 8)	61 (55 to 67)	2 (−4 to 8)	0 (−9 to 9)	0.95
ALP (units/L)	95 (89 to 101)	−1 (−7 to 5)	91 (85 to 97)	−5 (−11 to 0)	−4 (−12 to 4)	0.33
Albumin (g/L)	37 (37 to 38)	−1 (−2 to 0)	38 (37 to 39)	0 (−1 to 1)	1 (0 to 2)	0.16
Hematological/inflammatory						
Hematocrit (%)	39.3 (38.4 to 40.3)	0.6 (−0.3 to 1.5)	39.3 (38.4 to 40.1)	0.6 (−0.3 to 1.4)	−0.1 (−1.3 to 1.2)	0.90
Leukocyte count (× 10^9 cells/L)	8.0 (7.7 to 8.4)	−0.03 (−0.4 to 0.3)	8.0 (7.6 to 8.3)	−0.09 (−0.4 to 0.3)	−0.06 (−0.6 to 0.4)	0.82
Platelet count (× 10^9 cells/L)	229 (223 to 235)	3 (−4 to 9)	232 (226 to 238)	6 (0 to 12)	3 (−5 to 12)	0.44
Ferritin (μg/L)	130 (103 to 157)	−13 (−40 to 13)	131 (106 to 157)	−12 (−37 to 13)	1 (−36 to 38)	0.94
CRP (mg/L)	7.9 (6.0 to 9.8)	1.1 (−0.8 to 2.9)	5.9 (4.0 to 7.8)	−0.9 (−2.8 to 0.9)	−2.0 (−4.5 to 0.7)	0.14
Vital signs/anthropometrics						
Weight (kg)	79.7 (79.1 to 80.3)	0.1 (−0.5 to 0.7)	79.4 (78.8 to 79.9)	−0.2 (−0.8 to 0.3)	−0.3 (−1.1 to 0.5)	0.42
SBP (mmHg)	139 (135 to 143)	−0.1 (−4.2 to 4.0)	142 (138 to 146)	2.9 (−1.0 to 6.9)	3.0 (−2.7 to 8.7)	0.30
DBP (mmHg)	75 (73 to 78)	0.4 (−2.1 to 2.8)	78 (75 to 80)	2.5 (0.1 to 4.9)	2.1 (−1.3 to 5.6)	0.22

Data are mean (95% CI). Values adjusted for their respective baseline values, age, sex, and diabetes duration from generalized linear mixed-effects modeling. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; DBP, diastolic BP; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyl transferase; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; SBP, systolic BP; SCr, serum creatinine; TAG, triacylglycerol.

adverse effect of diacerein treatment was diarrhea, which occurred in 65% of the patients and caused treatment interruption in 16% of them.

To our knowledge, only one previous RCT of diacerein treatment was performed in patients with type 2 diabetes (19). This study randomized 40 patients with recent-onset drug-naïve type 2 diabetes to 60 days' placebo ($n = 20$) or diacerein treatment and found significant reductions in mean HbA_{1c} (−1.3% [14.2 mmol/mol]), fasting glycemia (−1.1 mmol/L), and serum TNF-α and IL-1β levels accompanied by significant increases in first and late phases of insulin secretion as measured by a hyperglycemic-hyperinsulinemic clamp. The current study advances these preliminary findings on the efficacy of diacerein treatment to a larger group of patients with long-duration type 2 diabetes treated for a longer (1-year) period, hence increasing generalizability and clinical applicability. Other anti-inflammatory drug trials were performed in patients with type 2 diabetes (1,3), such as with hydroxychloroquine (25,26), IL-1β receptor blockade/antagonism (2,27–29), and salicylates (salsalate) (24). Most showed mean HbA_{1c} reductions compared with placebo in the range observed in the current study (0.3–0.8%) (1–3). The magnitude of mean HbA_{1c} reduction obtained with diacerein was arguably rather modest, but it was in the same range of the effects observed with dipeptidyl peptidase 4 inhibitors (30), which are approved and marketed as hypoglycemic drug treatment for type 2 diabetes.

Attenuation of diacerein effect on HbA_{1c} reduction was observed between the 6-month and 1-year treatments, which may be partially attributed to concomitant antidiabetic treatment changes, especially insulin dosage adjustments, that occurred mainly in the last half of the study, with more reductions in diacerein group participants and more increases in placebo group participants, thus decreasing estimates of diacerein efficacy. Nevertheless, diabetes disease progression and attenuation of drug efficacy might also have contributed. Moreover, most of the participants were already using insulin, so they should be considered as hyperglycemic insulin resistant. This characteristic may have led to less room for improvement in glycemic control of any new add-on treatment. Furthermore, almost all participants were using other drugs, such as metformin, statins, low-dose aspirin, and renin-angiotensin system blockers, which have potential pleiotropic anti-inflammatory actions (1) and might have contributed to a lesser effect of a specific anti-inflammatory therapy (1,2).

The observation of the lack of any effect of diacerein on fasting glycemia levels, although significantly reducing mean HbA_{1c}, is intriguing. We speculate that diacerein may have stronger effects on postprandial glycemia because of better β-cell function and increased hyperglycemia-induced insulin secretion, as suggested

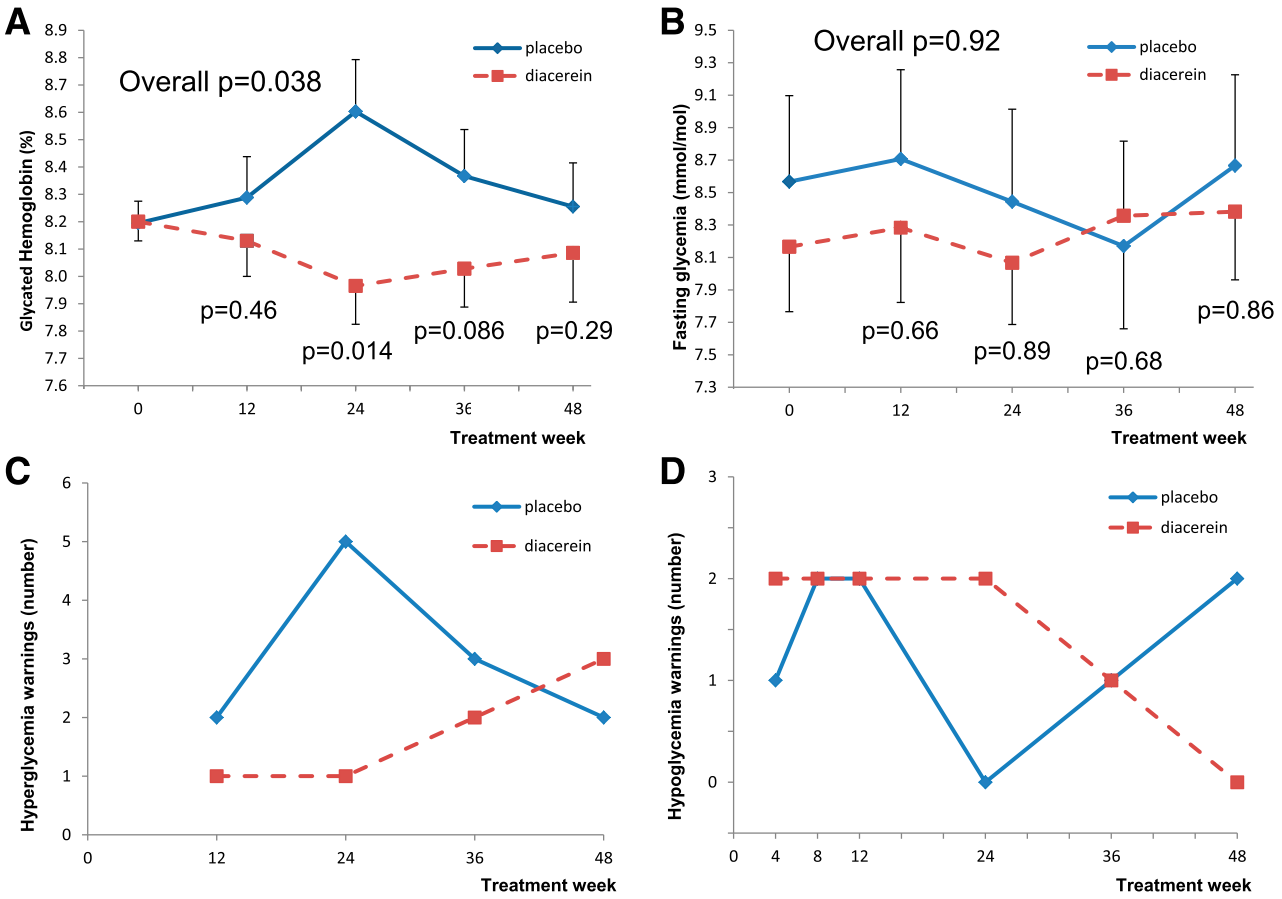

Figure 2—Changes in mean HbA_{1c} (*A*) and fasting glycemia (*B*) during placebo and diacerein treatments. Bars represent SEM. Numbers of hyperglycemic (*C*) and hypoglycemic (*D*) warnings during each time point for the placebo and diacerein treatments. (A high-quality color representation of this figure is available in the online issue.)

previously (13,14,19), than on fasting glycemia because of a lesser effect on nocturnal hepatic gluconeogenesis. However, in a comprehensive experimental study in mice with high-fat diet–induced obesity (12), diacerein improved both insulin secretion by reducing islet cell inflammation and peripheral insulin sensitivity by improving insulin signaling in liver and adipose tissue.

The most frequently observed adverse event of diacerein was diarrhea, which led to treatment interruption in 16% of the participants. This side effect of diacerein is well-known (5,6,31). Mild hypoglycemia events, which are also a relative measure of efficacy, occurred slightly more frequently in the diacerein group than in the placebo group, but all episodes were observed in participants who concomitantly used insulin. On the other hand, no worsening of albuminuria or increase in serum lipids, body weight, and BP levels, as reported during salsalate treatment (24), was observed in the current study. Furthermore, no change in renal and hepatic function tests and any hematological index was found. Because osteoarthritis is frequently associated with type 2 diabetes (32) and may result in several disabilities (33), diacerein may be the first-line treatment in place of salicylates or other nonsteroidal anti-inflammatory drugs in patients with osteoarthritis and type 2 diabetes because of its greater cardiorenal safety. Of note, the European Medicines Agency endorsed restrictions to diacerein use because of risks of severe diarrhea and hepatotoxicity in patients with previous liver disease (34). Moreover, diacerein is only established for hip and knee osteoarthritis treatment (5,6).

This study has some limitations. First, it still included a small number of patients, which restricts ascertainment of long-term diacerein efficacy and safety. Larger, possibly multicenter, RCTs are warranted. Second, no direct measure of β-cell function or peripheral insulin sensitivity was performed. Hence, no mechanistic inference (only speculated) on diacerein action can be made. Third, we lack information on physical activity changes during the study, which might have at least in part contributed to the beneficial effect of diacerein to glycemic control by improving osteoarticular symptoms. Finally, as previously discussed, this study enrolled patients with long-standing, inadequately controlled type 2 diabetes, most of whom were already on optimized treatment with insulin. Thus, the results cannot be generalized to patients with recent-onset diabetes on metformin monotherapy in whom the effect of diacerein on glycemic control is expected to be higher than we demonstrate here.

In conclusion, this RCT is the first to our knowledge to assess the effects of diacerein on glycemic control over a 48-week period. Diacerein reduced overall mean HbA_{1c} levels, with a peak effect at the 24th week of treatment but with attenuation toward the 48th week. The drug was well tolerated without serious adverse events (except for diarrhea) and may be indicated as adjunct treatment in patients with type 2 diabetes, particularly in those

with concomitant symptomatic osteoarthritis. However, larger RCTs with longer follow-up periods are needed to assess long-term cardiorenal safety as well as diacerein efficacy in preventing or reducing chronic macro- and microvascular diabetic complications (35).

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