

Efficacy and Safety of Avandamet or Uptitrated Metformin Treatment in Patients with Type 2 Diabetes Inadequately Controlled with Metformin Alone: A Multicenter, Randomized, Controlled Trial

Xiao-Ling Cai¹, Ying-Li Chen¹, Jia-Jun Zhao², Zhong-Yan Shan³, Ming-Cai Qiu⁴, Cheng-Jiang Li⁵, Wei Gu⁶, Hao-Ming Tian⁷, Hua-Zhang Yang⁸, Yao-Ming Xue⁹, Jin-Kui Yang¹⁰, Tian-Pei Hong¹¹, Li-Nong Ji¹

¹Department of Endocrinology and Metabolism, Peking University People's Hospital, Beijing 100044, China

²Department of Endocrinology and Metabolism, Shandong Provincial Hospital, Jinan, Shandong 250021, China

³Department of Endocrinology and Metabolism, First Hospital of China Medical University, Shenyang, Liaoning 110001, China

⁴Department of Endocrinology and Metabolism, Tianjin Medical University General Hospital, Tianjin 300070, China

⁵Department of Endocrinology and Metabolism, First Affiliated Hospital of School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310003, China

⁶Department of Endocrinology and Metabolism, Second Affiliated Hospital of School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310009, China

⁷Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China

⁸Department of Endocrinology and Metabolism, Guangdong General Hospital, Guangzhou, Guangdong 510080, China

⁹Department of Endocrinology and Metabolism, South Hospital, Guangzhou, Guangdong 510515, China

¹⁰Department of Endocrinology and Metabolism, Beijing Tongren Hospital, Beijing 100730, China

¹¹Department of Endocrinology and Metabolism, Peking University Third Hospital, Beijing 100191, China

Abstract

Background: At present, China has listed the compound tablet containing a fixed dose of rosiglitazone and metformin, Avandamet, which may improve patient compliance. The aim of this study was to evaluate the efficacy and safety of Avandamet or uptitrated metformin treatment in patients with type 2 diabetes inadequately controlled with metformin alone.

Methods: This study was a 48-week, multicenter, randomized, open-labeled, active-controlled trial. Patients with inadequate glycaemic control (glycated hemoglobin [HbA1c] 7.5–9.5%) receiving a stable dose of metformin (≥ 1500 mg) were recruited from 21 centers in China (from 19 November, 2009 to 15 March, 2011). The primary objective was to compare the proportion of patients who reached the target of HbA1c $\leq 7\%$ between Avandamet and metformin treatment.

Results: At week 48, 83.33% of patients reached the target of HbA1c $\leq 7\%$ in Avandamet treatment and 70.00% in uptitrated metformin treatment, with significantly difference between groups. The target of HbA1c $\leq 6.5\%$ was reached in 66.03% of patients in Avandamet treatment and 46.88% in uptitrated metformin treatment. The target of fasting plasma glucose (FPG) ≤ 6.1 mmol/L was reached in 26.97% of patients in Avandamet treatment and 19.33% in uptitrated metformin treatment. The target of FPG ≤ 7.0 mmol/L was reached in 63.16% of patients in Avandamet treatment and 43.33% in uptitrated metformin treatment. Fasting insulin decreased 3.24 ± 0.98 μ U/ml from baseline in Avandamet treatment and 0.72 ± 1.10 μ U/ml in uptitrated metformin treatment. Overall adverse event (AE) rates and serious AE rates were similar between groups. Hypoglycaemia occurred rarely in both groups.

Conclusions: Compared with uptitrated metformin, Avandamet treatment provided significant improvements in key parameters of glycaemic control and was generally well tolerated. Registration number: ChiCTR-TRC-13003776.

Key words: Avandamet; Efficacy; Type 2 Diabetes

INTRODUCTION

Type 2 diabetes is characterized by chronic hyperglycemia resulting in microvascular and macrovascular complications

which may contribute to an increased risk of early cardiovascular morbidity and early mortality. Now-a-days, the primary approach for type 2 diabetes management is steadily and continuously blood glucose control, with the aim of decreasing the risk of diabetic complications.^[1,2] A Diabetes Outcome Progression Trial (ADOPT),^[3] which compared three antidiabetic agents currently available

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Address for correspondence: Prof. Li-Nong Ji,
Department of Endocrinology and Metabolism, Peking University People's
Hospital, Beijing 100044, China
E-Mail: jiln@bjmu.edu.cn

for the treatment of type 2 diabetes, showed that in terms of glycemic control, rosiglitazone showed a long-term glycemic control. Since metformin and rosiglitazone act through different mechanisms, their combined use may be indicated in patients whose disease is poorly controlled with a maintenance dose of metformin. Studies^[3,4] have shown that rosiglitazone in combination with metformin can decrease glycated hemoglobin (HbA1c) while increase insulin sensitivity and improve β -cell function.

At present, China has listed the compound tablet containing a fixed dose of rosiglitazone and metformin, Avandamet, which may improve patient compliance. Data showed that, due to the increased number of patients with medication, it was very difficult to long-term adherence to their drug regimen. A compound tablet containing two different fixed dose drugs due to a different mechanism can reduce the number of medication, maintaining a more strict glycemic control, improving the compliance of patients with general. The aim of this randomized open study was to compare the efficacy and safety of Avandamet and up titrated metformin in patients uncontrolled with metformin alone.

METHODS

Study population

Patients aged 18–65 years who have been diagnosed with type 2 diabetes (defined according to World Health Organization criteria) inadequately controlled with metformin were considered for this 48-week, multicenter, randomized, open-label, parallel group study. Participants were recruited from 21 centers in China. The study was conducted in accordance with Good Clinical Practice guidelines and the 1996 version of the *Declaration of Helsinki*. Written informed consent was obtained from all participants. The study protocol and informed consent were approved by the ethics committee of Peking University People's Hospital according to local requirements. Participants with body mass index (BMI) ≥ 24 kg/m², 7.5% \leq HbA1c \leq 9.5%, 7 mmol/L \leq fasting plasma glucose (FPG) \leq 15 mmol/L at screening, receiving 0.75–1.0 g metformin alone at constant dosage for at least 6 weeks prior to entry were included in this trial.

Exclusion criteria included: (1) treatment with glucose-lowering agents other than metformin within 12 weeks before screening; (2) allergic to thiazolidinedione or their ingredients; (3) treatment with exogenous insulin or receiving insulin within 12 weeks before screening; (4) history of diabetic ketoacidosis; (5) hemoglobin disease or chronic anemia with the level of hemoglobin < 11.0 g/dl (male) or < 10.0 g/dl (female); (6) a history of kidney dysfunction with serum creatinine levels reaching 135 μ mol/L (male) or 110 μ mol/L (female); (7) alanine aminotransferase or aspartate aminotransferase > 2.5 times the upper limit of normal, suffering from hepatic disease; (8) type 1 diabetes, gestational diabetes, or other type of diabetes (Mody, *et al.*); (9) a history of ischemic heart disease or heart failure according to the New York Heart Association Classification

Class I–IV; (10) patients taking nitrates; (11) ongoing edema requiring pharmacological treatment; (12) systemic blood pressure > 170 mmHg or diastolic blood pressure > 100 mmHg while on anti-hypertensive treatment; (13) any chronic disease requiring continuous intermittent treatment with corticosteroids; (14) breastfeeding, pregnant or planning pregnancy women (women of childbearing age before interview one to use effective contraception for at least 1 month); (15) patients with abnormality during screening by the investigator judgement; (16) active drug or alcohol abuse within the last 6-month or any associated condition that could preclude completion of the study; (17) patients probably accept the iodinated contrast agent during study duration; (18) electrocardiogram with QTc > 500 ms or unadjusted QT > 600 ms; or patients with bundle branch block with QTc > 530 ms.

Study design

This was a 48-week, multicenter, randomized, open-label, parallel group study, consisting of a screening visit and 48-week of follow-up after randomization. In an open regimen, patients were randomized into two groups receiving Avandamet 4 mg/1000 mg or metformin 1500 mg as the initial daily dose. Four weeks later, for each treatment group, drug dosage was increased to the maximum dosage (8 mg/2000 mg of Avandamet or 2500 mg of metformin daily) according to the protocol. If FPG level > 7.0 mmol/L (126 mg/dl) and the maximum dosage was not reached, a dose increase was required at each visit; while a dose reduction was permitted if adverse events (AEs) occurred. The first patient was recruited on November 19, 2009 and the last patient completed follow-up visit on March 15, 2011. Registration number for this trial was ChiCTR-TRC-13003776 (<http://www.chictr.org/cn/proj/search.aspx>). The authors confirm that all ongoing and related trials for this drug/intervention are registered.

Study assessments

The primary efficacy outcome is the percentage of patients who reached the target HbA1c (HbA1c $\leq 7\%$) at week 48 in Avandamet treatment group and metformin treatment group. Hypothesis was made as that the between group difference more than 15% of the percentage of patients who reached HbA1c $\leq 7\%$ at week 48 suggested that superiority was reached. The secondary outcomes included: (1) Changes in HbA1c from baseline; (2) changes in FPG and prandial plasma glucose (PPG) from baseline; (3) percentage of patients reached HbA1c $\leq 6.5\%$ at week 48; (4) percentage of patients with the changes from baseline in HbA1c $\geq 0.7\%$ in Avandamet group and metformin group; (5) changes in fasting insulin from baseline.

All AEs were recorded and judged by an investigator as the severity and possible relationship to study medication. Safety laboratory assessments (hematology and biochemistry) and vital signs were assessed at each study visit. Mild-to-moderate hypoglycemia was defined if the patient had symptoms or a self-measured capillary glucose level (CG) < 63 mg/dl (3.5 mmol/L). Severe hypoglycemia was defined as any episode requiring assistance of another person with the CG

below 2.8 mmol/L, unless the clinical situation prevented obtaining CG measurement.

Vital signs and anthropometric measurements were recorded at each visit. HbA1c, fasting insulin and lipids profile were measured centrally at randomization and every 3 months. HbA1c was measured by high-performance liquid chromatography (Ultra2 HbA1c Detector, PRIMUS Corporation, USA). FPG, PPG, levels of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride were measured by immunonephelometry method (COBAS Integra 400 Plus System, Roche Diagnostics Ltd., Basel, Switzerland). Insulin level was measured by electrochemiluminescence immune assay (Elecsys 2010 System, Roche Diagnostics Ltd., Basel, Switzerland). All study drugs were withheld on the morning of testing. An outline of the study assessments at clinic visits was shown in Table 1.

Statistical analysis

SAS version 9.2 (SAS Institute Inc., USA) was used for all analyses. A sample size of 400 patients (200 Avandamet and 200 metformin-uptitrated) was required to ensure 85% power to detect a superiority difference of 15% in Avandamet treated patients who achieve the target HbA1c ($\leq 7\%$) to metformin-uptitrated treated patients (i.e., assuming in metformin monotherapy group 50% of patients at the end of the study achieving HbA1c $\leq 7\%$, 65% of patients in Avandamet group achieving HbA1c $\leq 7\%$ were needed) at the level of $\alpha = 0.05$ (two-sided). Assuming 15% of loss rate and 15% of screening failure rate, totally there were 554 patients needed to be screened and 471 patients needed to be randomized, to ensure that ultimately 400 patients complete the study.

Demographic and other baseline characteristics were analyzed using descriptive statistics. The primary endpoint, the percentage of patients who achieved the target HbA1c (HbA1c $\leq 7\%$) at week 48, was compared between Avandamet treatment group and metformin treatment group by Chi-square analysis. Other efficacy analyses for continuous variables were compared by using a one-way analysis of variance test while frequency of dichotomous variables was performed by Chi-square analysis.

This analysis was performed on the full analysis set (FAS). This group comprised all randomized patients who were treated with at least one dose of study medication, had a baseline HbA1c measurement and had at least one on-treatment HbA1c measurement. Safety analyses conducted on the treated patients' data set included all patients who received at least one dose of study medication. Chi-square test was used to compare the incidence of AEs between groups. Regression techniques were applied to assess the associations of variables with all continuous and categorical endpoints, respectively.

RESULTS

Study characteristics

Five hundred and eighty-eight patients who met the inclusion criteria were recruited for the study. At the end of run-in period, 398 patients who still met the inclusion criteria were randomly assigned into Avandamet treatment group and metformin treatment group, while 156 participants in Avandamet treatment group and 160 participants in metformin treatment group were included in the FAS [Figure 1]. Baseline characteristics of patients between Avandamet treatment group and metformin treatment group

Table 1: Outline of study assessments

| Assessment | Screening time (relative to baseline) | | | | | | |
|---|---------------------------------------|-------------|-------------|--------------|--------------|--------------|--------------|
| | V0 (0–7 day) | V1 (week 0) | V2 (week 4) | V3 (week 12) | V4 (week 24) | V5 (week 36) | V6 (week 48) |
| Vital sign | X | | X | X | X | X | X |
| Body weight | X | | X | X | X | X | X |
| Height | X | | | | | | |
| BMI | X | | | | | | |
| Waist and hip circumference | X | | | | X | | X |
| ECG | X | | | | X | | X |
| Complete blood count | X | | X | X | X | X | X |
| Urine analysis | X | | | | | | |
| B-HCG | X | | | | | | |
| FPG | X | | X | X | X | X | X |
| PPG | X | | | | X | | X |
| HbA1c | X | | | X | X | X | X |
| Lipid (TC, LDL-C, TG, HDL-C) | X | | | | X | | X |
| Hepatic function (ALT, AST, T-BIL, ALP) | X | | | | X | | X |
| Renal function (BUN, CRE) | X | | | | X | | X |
| FINS/CRP | | X | | | X | | X |
| AEs | | | X | X | X | X | X |

AEs: Adverse Events; BMI: Body mass index; ECG: Electrocardiogram; B-HCG: Beta-human chorionic gonadotropin; FPG: Fasting plasma glucose; PPG: Prandial plasma glucose; HbA1c: Glycated hemoglobin; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglyceride; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; T-BIL: Total bilirubin; BUN: Blood urea nitrogen; CRE: Creatinine; CRP: C-reactive protein; FINS: Fasting insulin.

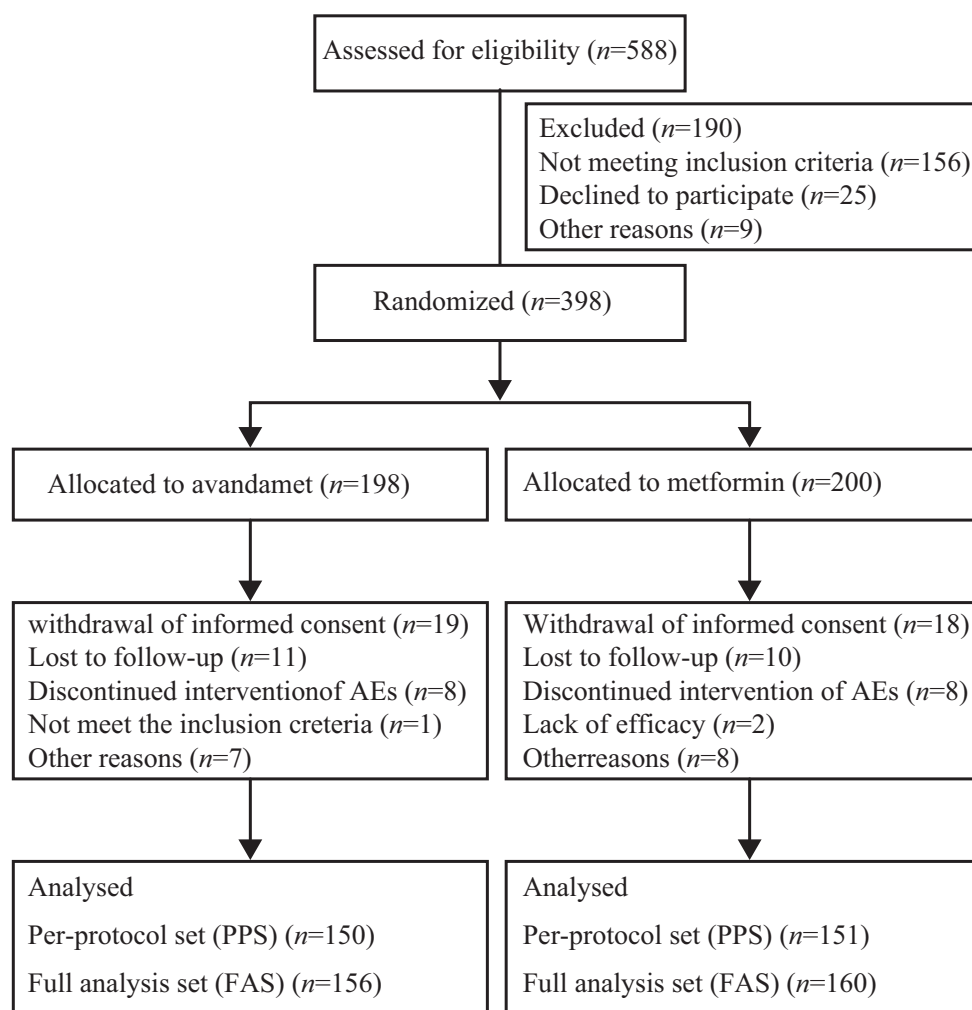


Figure 1: Flow diagram of this study.

were comparable except that the average duration of diabetes in Avandamet group was significantly longer than that in metformin group (3.56 ± 3.49 years vs. 2.73 ± 3.10 years, $P = 0.01$) [Table 2].

The percentage of patients who did not complete the study did not differ significantly between Avandamet group and metformin group (23.23% vs. 24.00%, $P > 0.05$). Baseline characteristics of the lost-to-follow-up patients did not differ from those who completed the study. Baseline characteristics of the lost-to-follow-up patients between Avandamet group and metformin group did not differ either. Data was shown in supplement material.

Glycemic control

The primary efficacy outcome is the percentage of patients reached $HbA1c \leq 7\%$ at week 48 in Avandamet group and metformin group. At the end of week 48, the percentage of patients who reached $HbA1c \leq 7\%$ was 83.33% in Avandamet group and 70.00% in metformin group ($P < 0.01$). However, according to the protocol, the significance for the superiority of Avandamet treatment to metformin treatment was not reached ($<15\%$). The percentage of patients who reached $HbA1c \leq 6.5\%$ in the two groups was 66.03% and 46.88% respectively ($P < 0.01$) [Table 3]. At week

Table 2: Baseline characteristics of the patients*

| Variables | Avandamet (n = 198) | Metformin (n = 200) |
|---------------------------|---------------------|---------------------|
| Age (years) | 51.38 ± 9.57 | 51.25 ± 8.84 |
| Gender (male, %) | 57.7 | 59.8 |
| Diabetic duration (years) | 3.57 ± 3.49 | 2.73 ± 3.10 |
| Body weight (kg) | 74.82 ± 11.18 | 74.67 ± 10.74 |
| Height (cm) | 165.92 ± 8.75 | 164.94 ± 8.62 |
| BMI (kg/m ²) | 27.10 ± 2.75 | 27.39 ± 3.06 |
| Waist circumference (cm) | 93.41 ± 8.15 | 93.48 ± 9.30 |
| SBP (mmHg) | 129.98 ± 13.62 | 129.61 ± 15.98 |
| DBP (mmHg) | 80.31 ± 9.72 | 80.97 ± 9.09 |

*Baseline characteristics were comparable between the two groups except for diabetic duration ($P = 0.01$). BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

48, the average level of $HbA1c$ in Avandamet group and metformin group was $6.78\% \pm 0.94\%$ and $7.03\% \pm 0.89\%$ respectively ($P < 0.01$), $HbA1c$ change from baseline at week 48 was $-1.49\% \pm 0.05\%$ and $-1.18\% \pm 0.09\%$ respectively ($P < 0.01$). Changes of $HbA1c$ during the 48-week were shown in Figure 2.

In terms of FPG, at week 48, the percentage of patients who reached $FPG \leq 6.1$ mmol/L was 26.97% in Avandamet group

Table 3: Comparisons of changes from baseline at week 48 between Avandamet and metformin

| Variables | Baseline | Week 48 | Adjusted changes from baseline | 95% CI | P |
|--------------------------------------|---------------|---------------|--------------------------------|--------------|-------|
| HbA1c (%) | | | | | |
| Avandamet | 8.26 ± 0.65 | 6.78 ± 0.94 | -1.49 ± 0.05 | -1.65, -1.32 | <0.01 |
| Metformin | 8.22 ± 0.60 | 7.03 ± 0.89 | -1.18 ± 0.09 | -1.33, -1.03 | |
| Patients reached HbA1c ≤6.5% (%) | | | | | |
| Avandamet | - | 66.03 | - | - | <0.01 |
| Metformin | - | 46.88 | - | - | |
| Patients reached HbA1c ≤7% (%) | | | | | |
| Avandamet | - | 83.33 | - | - | <0.01 |
| Metformin | - | 70.00 | - | - | |
| FPG (mmol/L) | | | | | |
| Avandamet | 9.03 ± 1.66 | 7.06 ± 2.18 | -1.98 ± 0.17 | -2.34, -1.62 | <0.01 |
| Metformin | 9.03 ± 1.90 | 7.66 ± 2.05 | -1.35 ± 0.11 | -1.72, -0.97 | |
| Patients reached FPG ≤6.1 mmol/L (%) | | | | | |
| Avandamet | - | 26.97 | - | - | >0.05 |
| Metformin | - | 19.33 | - | - | |
| Patients reached FPG ≤7.0 mmol/L (%) | | | | | |
| Avandamet | - | 63.16 | - | - | <0.01 |
| Metformin | - | 43.33 | - | - | |
| PPG (mmol/L) | | | | | |
| Avandamet | 13.69 ± 3.50 | 10.61 ± 3.17 | -3.0 ± 0.27 | -3.71, -2.48 | <0.01 |
| Metformin | 13.85 ± 3.38 | 11.86 ± 3.55 | -1.85 ± 0.27 | -2.44, -1.25 | |
| FINS (μU/ml) | | | | | |
| Avandamet | 13.75 ± 15.71 | 9.83 ± 12.97 | -3.24 ± 0.98 | -4.47, -2.01 | <0.01 |
| Metformin | 11.26 ± 8.88 | 10.79 ± 15.42 | -0.72 ± 1.10 | -3.25, 1.81 | |
| Body weight (kg) | | | | | |
| Avandamet | 75.20 ± 11.88 | 74.95 ± 12.89 | -0.09 ± 0.32 | -0.72, 0.55 | <0.01 |
| Metformin | 75.21 ± 10.74 | 72.66 ± 12.02 | -2.46 ± 1.03 | -3.55, -1.37 | |

CI: Confidence interval; HbA1c: Glycated hemoglobin; FPG: Fasting plasma glucose; PPG: Prandial plasma glucose; FINS: Fasting insulin; "-" means not applicable.

and 19.33% in metformin group without significance. The percentage of patients who reached FPG ≤7.0 mmol/L was 63.16% and 43.33% respectively ($P < 0.01$). At week 48, the average FPG was 7.06 ± 2.18 mmol/L and 7.66 ± 2.05 mmol/L respectively ($P < 0.01$) in the two groups, FPG change from baseline at week 48 was -1.98 ± 0.17 mmol/L and -1.35 ± 0.11 mmol/L respectively ($P < 0.01$). At week 48, the average PPG level was 10.61 ± 3.17 mmol/L and 11.86 ± 3.55 mmol/L respectively ($P < 0.01$), PPG decreased from baseline at week 48 was 3.09 ± 0.27 mmol/L and 1.85 ± 0.27 mmol/L respectively ($P < 0.01$) [Table 3]. Changes of FPG and PPG during 48 weeks were shown in Figure 2.

Fasting insulin

At week 24 and week 48, changes of fasting insulin from baseline in Avandamet group was -3.89 ± 1.01 μU/ml and -3.24 ± 0.98 μU/ml respectively, while in metformin group, changes of fasting insulin from baseline was -2.40 ± 0.98 μU/ml and -0.72 ± 1.10 μU/ml respectively. Comparisons between the two treatment groups showed significant difference both at week 24 and week 48. Changes of fasting insulin during 48 weeks were shown in Figure 2.

Body weight

At week 48, the average body weight was 74.95 ± 12.89 kg in

Avandamet group and 72.66 ± 12.02 kg in metformin group. Body weight decreased from baseline in the two groups was 0.09 ± 0.32 kg and 2.46 ± 1.03 kg respectively ($P < 0.01$).

Lipid profile

At week 48, changes of cholesterol from baseline in Avandamet group and metformin group were 0.33 ± 1.09 mmol/L and -0.23 ± 0.99 mmol/L respectively, with significant difference ($P < 0.01$). Changes of triglyceride from baseline in Avandamet group and metformin group were -0.05 ± 1.52 mmol/L and -0.32 ± 1.80 mmol/L respectively, with significant difference ($P < 0.05$). Changes of HDL-C from baseline in Avandamet group and metformin group were 0.09 ± 0.36 mmol/L and 0.02 ± 0.29 mmol/L respectively, with significant difference ($P < 0.01$). Changes of LDL-C from baseline in Avandamet group and metformin group were 0.27 ± 0.94 mmol/L and -0.05 ± 0.80 mmol/L respectively, with significant difference ($P < 0.01$).

C-reactive protein

At week 48, changes of hypersensitive C-reactive protein (CRP) from baseline in Avandamet group and metformin group were -1.06 ± 4.10 and -0.35 ± 6.50 respectively, with significant difference ($P < 0.01$).

Safety and tolerability

Over 48 weeks, both treatment regimens were

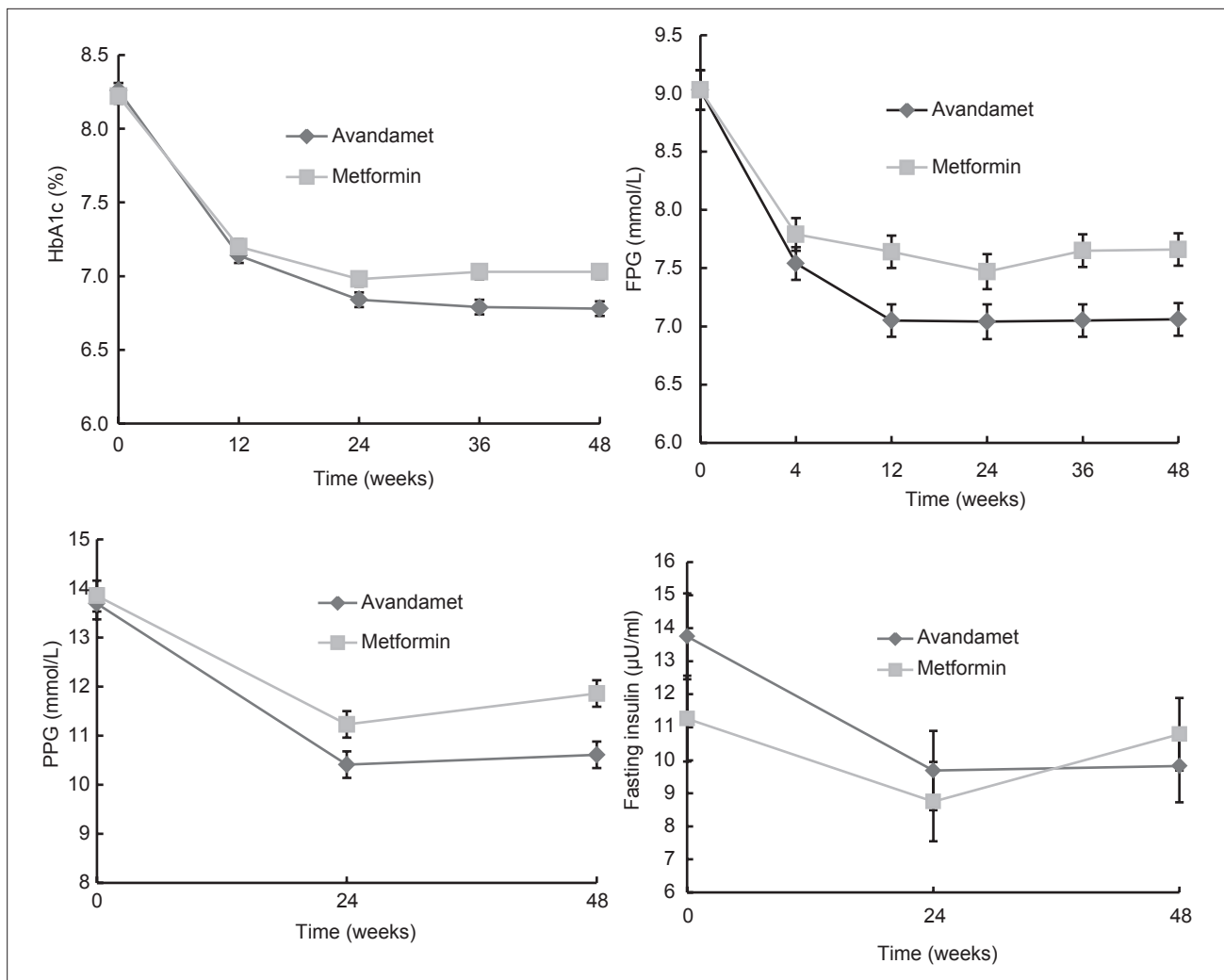


Figure 2: Changes of glycated hemoglobin, fasting plasma glucose, prandial plasma glucose and fasting insulin during 48 weeks in Avandamet group and metformin group.

generally well tolerated. The proportion of patients experiencing any AE (including hypoglycemia) was 24.24% (Avandamet-treated patients) and 31.50% (metformin-treated patients). AE frequency was comparable between groups. Serious AE (SAEs) were comparable between groups (1.52% in Avandamet-treated patients vs. 2.00% in metformin-treated patients, $P > 0.05$) [Table 4]. The most commonly reported AEs (occurring in $>5\%$ of Avandamet-treated patients vs. metformin-treated patients) were abdominal discomfort (7.1% vs. 9.5%, $P > 0.05$), dyslipidemia (7.6% vs. 8.5%, $P > 0.05$), upper respiratory tract infection (6.6% vs. 6.5%, $P > 0.05$), edema (6.6% vs. 0.5%, $P < 0.01$), diarrhea (3.5% vs. 11.5%, $P < 0.01$) and constipation (4.5% vs. 0.5%, $P < 0.01$). Hypoglycemic rate in Avandamet group was 0.51% while 2.00% in metformin group ($P > 0.05$). There were no clinically meaningful drug effects on any laboratory safety parameter. There were no cases of heart failure in either treatment group, but two occurrence of angina pectoris in Avandamet treated patients. One is a 61-year-old female patient who was incharged into hospital for the treatment of angina pectoris with the investigator

judgement as probably correlated with study drug and discontinued Avandamet treatment. Another is a 51-year-old female patient who was incharged into hospital with the investigator judgement as probably not correlated with study drug and continued Avandamet treatment. Both patients recovered and discharged from hospital soon. No death in both groups.

DISCUSSION

The aim of this randomized open study was to compare the efficacy of Avandamet and up titrated metformin in patients uncontrolled with metformin alone in a Chinese population. Avandamet treatment for 48-week in patients poorly controlled with metformin alone led to statistically significant and clinically relevant reductions in HbA1c, FPG and PPG. Compared with metformin up titrated treatment, Avandamet treatment also led to statistically significant more reductions in HbA1c FPG and PPG. Treatment with Avandamet also showed trends toward a greater proportion of patients achieving HbA1c $<7\%$ as well as achieving HbA1c $<6.5\%$. Results concluded from this study were

Table 4: AEs, hypoglycemia between the two groups (n)

| Variables | Avandamet (n=198) | Metformin (n=200) | P |
|--|----------------------|----------------------|-------|
| AEs - number of patients | | | |
| Total AEs | 48 | 63 | 0.09 |
| Cardiovascular disease | | | |
| Palpitation | 3 | 1 | 0.13 |
| Dyslipidemia | 15 | 17 | 0.88 |
| Chest tightness | 2 | 2 | 0.98 |
| Gastrointestinal events | | | |
| Constipation | 9 | 1 | 0.00 |
| Fatty liver | 0 | 3 | 0.22 |
| Liver dysfunction | 5 | 8 | 0.56 |
| Abdominal discomfort | 14 | 19 | 0.50 |
| Diarrhea | 7 | 23 | 0.002 |
| Blood system events | | | |
| Thrombocytosis | 0 | 1 | 0.60 |
| Increase of white blood cell | 2 | 1 | 0.59 |
| Leukopenia | 6 | 0 | 0.05 |
| Anemia | 2 | 3 | 0.83 |
| Respiratory events | | | |
| Upper-respiratory infection | 13 | 13 | 0.98 |
| Bronchitis | 0 | 1 | 0.60 |
| Urinary system diseases | | | |
| Infection of urinary tract | 0 | 2 | 0.36 |
| Ureteral calculi | 0 | 1 | 0.60 |
| Renal dysfunction | 0 | 1 | 0.60 |
| Nervous system events | | | |
| Dizzy | 5 | 1 | 0.00 |
| Insomnia | 0 | 2 | 0.36 |
| Headache | 0 | 1 | 0.60 |
| Numbness of limbs | 1 | 0 | 0.59 |
| Skin diseases | | | |
| Itchy skin | 0 | 1 | 0.60 |
| Allergic | 1 | 0 | 0.59 |
| Orthopedics disease | | | |
| Lumbago | 0 | 3 | 0.22 |
| Joint pain | 2 | 0 | 0.35 |
| Muscle soreness | 1 | 1 | 0.98 |
| Toe pain | 1 | 0 | 0.59 |
| Others | | | |
| Weight gain | 2 | 0 | 0.35 |
| Edema | 13 | 1 | 0.002 |
| Fatigue | 0 | 3 | 0.22 |
| Mouth ulcer | 0 | 1 | 0.60 |
| Periodontitis | 1 | 2 | 0.77 |
| Gout | 0 | 1 | 0.60 |
| Glossitis | 0 | 1 | 0.60 |
| Blurre vision | 1 | 0 | 0.59 |
| Menstrual disorders | 1 | 0 | 0.59 |
| Eject dysfunction | 0 | 1 | 0.60 |
| Hypoglycemia | 1 | 4 | 0.32 |
| SAE - number of patients | | | |
| Total SAE | 3 | 4 | 0.87 |
| The left ankle joint fracture of capitulum of fibula | 0 | 1 | 0.60 |
| Cerebral infarction | 0 | 1 | 0.60 |
| Acute appendicitis | 1 | 0 | 0.59 |

Table 4: Contd...

| Variables | Avandamet (n=198) | Metformin (n=200) | P |
|--|----------------------|----------------------|------|
| Coronary heart disease (angina pectoris) | 2 | 0 | 0.35 |
| IgA nephropathy | 0 | 1 | 0.60 |
| Perianal abscess | 0 | 1 | 0.60 |

AEs: Adverse events; SAE: Serious adverse event.

comparable with that of the previous published studies in Caucasians. Fonseca *et al.*^[4] reported in a study that after 26 weeks, compared with metformin-placebo treatment, rosiglitazone-metformin treatment led to a 1% in HbA1c decreased and 2.2 mmol/L in FPG decreased. Rosenstock *et al.*^[5] reported from a randomized open-label trial that after 24 weeks of Avandamet treatment, the average HbA1c decreased 4.0% ± 2.2% and the average FPG decreased 7.7 ± 4.4 mmol/L, as well as 33% patients reached the target of HbA1c ≤6.5%. In another randomized double-blinded trial,^[6] after 32 weeks of Avandamet treatment, the average HbA1c decreased 2.3% and the average FPG decreased 4.1 mmol/L with significance, and about 60% and 77% patients with Avandamet treatment reached the target of HbA1c ≤6.5% and HbA1c ≤7% respectively, which was higher than the proportion of patient receiving metformin treatment. Borges *et al.*^[7] in an 80-week randomized double-blinded trial reported that, the Avandamet treatment was superior to metformin treatment both in HbA1c and FPG.

In terms of fasting insulin, results from this study indicated that Avandamet treatment led to a decrease of fasting insulin more than metformin treatment, which was also in adherence with previous reports. Kahn *et al.*^[8] concluded from the results of ADOPT that compared with sulfonylurea, both rosiglitazone and metformin can decrease fasting insulin level, improving insulin sensitivity. Derosa *et al.* in a 1-year trial comparing metformin combined with rosiglitazone or pioglitazone showed that,^[9] except for glucose improving, metformin combined with rosiglitazone decreased fasting and postprandial insulin level significantly. A 6-month small study in Chinese^[10] also showed that metformin combination with rosiglitazone could decrease fasting and postprandial insulin level, which indicated that insulin resistance improving.

According to results from this study, compared with up titrated metformin treatment, Avandamet treatment was associated with less reduction in body weight as well as less decrease in lipid profile. Results were similar with those concluded from other studies. In Fonseca *et al.*'s study,^[4] total cholesterol, HDL-C and LDL-C were significantly higher in rosiglitazone-metformin treatment and body mass was increased compared with metformin-placebo control group. Reasons for the increasing of lipid profile may be associated with the mechanism of glucotoxicity improvement or different percentage of usage of lipid lowering therapy between groups, or other reasons we still no know. The

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weight gain in Avandamet group might be associated with fluid retention or increased appetite which was explained in other studies previously.^[4-6,11] The more reduction of CRP in Avandamet group might be associated with the efficacy in lowering free fatty acid or other inflammation factors.^[4,12]

There was no significant difference of the number of AEs and SAEs between the two groups. The hypoglycemic rate between groups was comparable. The incidence rate of diarrhea in patients with Avandamet treatment was significantly lower than that of patients in metformin group, while the incidence rate of edema with Avandamet treatment was significantly higher. The types of AEs as well as the incidence rate of total AEs of this trial were similar with those results of other clinical trials.^[3-6] In addition, no case of heart failure in either treatment group was reported during the 48-week of follow-up, but two occurrences of angina pectoris in Avandamet treated patients were reported. Both patients recovered and discharged from hospital soon, one continued the study drug while the other one discontinued. The incidence rate of angina pectoris between groups was comparable. Of course, longer duration and with the primary endpoint of study is needed to evaluate the cardiovascular outcome of Avandamet treatment in the future.

Although some of our study design was similar with that of previous studies carried out in Caucasians, there are some different points. First, this study was carried out in Chinese type 2 diabetes patients, which is a totally different ethnic population. Ethnicity difference might be associated with the incidence of type 2 diabetes as well as the treatment efficacy on glucose control or β -cell function or body weight changes,^[13,14] therefore, results from this study will give us the answer whether the superior efficacy of Avandamet treatment to metformin treatment alone could be shown in a Chinese population. Secondly, baseline characteristics of patients were different from previous studies in Caucasian population such as BMI, HbA1c, FPG, duration of diabetes and so on. Results from different kinds of patients may result in a different conclusion, therefore, we just want to see whether the efficacy of rosiglitazone combination with metformin treatment was superior to that of up titrated metformin treatment. Third, different dosage forms between our study and other studies. In most previous study, they prescribed patients with metformin plus placebo or metformin plus rosiglitazone. In our study, we prescribed patients only one tablet with Avandamet or metformin. What's more, study duration in this trial was 48-week, which is a longer duration for us to evaluate the efficacy of Avandamet treatment.

According to the result concluded from this study in Chinese type 2 diabetes patients, Avandamet treatment led to a higher proportion of patients achieving HbA1c < 7% compared with metformin although the superiority was not reached. Clinical significance for this result might indicate that for poorly controlled Chinese type 2 diabetes patients with metformin alone, Avandamet treatment instead of up titrated metformin may be a good choice for glycemic control and

insulin resistance improvement. Reasons for that might be the combination mechanisms of rosiglitazone and metformin, the possible better adherence of Avandamet treatment than up titrated metformin. Comparable results concluded from this study in Chinese type 2 diabetes patients also indicated that there may be no ethnicity difference in Avandamet treatment.

Of course, this study has some limitations. First, patients who lost follow-up in Avandamet group and metformin group were 23.23% and 24.00% respectively, the rate of which exceeded the expected loss rate (abscission rate up to not more than 15%), which may be the reasons for this study that failed to demonstrate the superiority of Avandamet treatment with respect to the higher dose of metformin monotherapy. But there was no significant difference in the abscission rate between groups with the *P* value of 0.9063, and the baseline characteristics of patients completed the trial as well as those of patients withdrawn did not show any significant difference between the Avandamet group and metformin group either (data was shown in supplement material), which might indicate that the higher loss rate was not resulted from different treatment group. Secondly, baseline characteristics of patients between Avandamet treatment group and metformin treatment group were comparable except that the average duration of diabetes in Avandamet group was significantly longer than that in metformin group (3.56 ± 3.49 years vs. 2.73 ± 3.10 years, *P* = 0.01). However, this difference at baseline did not seem to be associated with the efficacy difference between groups, just because patients in Avandamet group had a longer duration of diabetes which may indicate poorer insulin secretion and therefore poorer effect in hypoglycemic treatment. Controversely, at the end of the study, patients in Avandamet group had a higher decrease in HbA1c and a better control of glycemic treatment, which indicated that the baseline difference did not affect the final results.

In conclusion, results from this randomized, open label, parallel group study indicated that compared with up titrated metformin treatment, the efficacy of Avandamet treatment in patients uncontrolled with metformin alone was better, the proportion of patients who reached the target HbA1c was higher in Chinese type 2 diabetes patients.

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