Diabetes & Metabolic Syndrome: Clinical Research & Reviews 10 (2016) 137–142

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Effects of body mass index or dosage on gastrointestinal disorders associated with extended-release metformin in type 2 diabetes: Sub-analysis of a Phase IV open-label trial in Chinese patients

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ARTICLE INFO

Keywords:
Adverse drug event
Chinese
Diabetes mellitus
type 2
Glucophage
Gastrointestinal

ABSTRACT

Aim: To determine whether gastrointestinal (GI) tolerability of metformin monotherapy varies according to baseline BMI or at doses >1500 mg/day in patients newly diagnosed with type 2 diabetes.
Methods: We performed a sub-analysis of the safety population from a prospective, multicenter, Phase IV open-label study in which 371 Chinese patients with type 2 diabetes received extended-release metformin monotherapy for 16 weeks. The incidence, severity and duration of GI adverse events (AEs) were compared between normal-weight (BMI < 25 kg/m^2, n = 155) and overweight/obese (BMI ≥ 25 kg/m^2, n = 216) patients. The primary objective was to determine whether baseline BMI affect the incidence, severity and duration of GI AEs, using Fisher's exact test and Student's t-test. Secondary objectives were to compare these factors according to final metformin dose (≤1500 mg/day versus 2000 mg/day).
Results: The proportion of patients who reported ≥1 GI AE did not differ significantly between BMI groups (25.2% of the normal-weight group versus 21.3% of the overweight/obese group; p = 0.3840). Patients who reported GI AEs in the two BMI groups experienced similar GI AE severity (p = 0.5410), mean duration (p = 0.3572) and duration distribution (p = 0.1347). There was no significant difference in GI AE severity and duration between metformin dosage groups (≤1500 mg/day versus 2000 mg/day).
Conclusions: Newly-diagnosed Chinese type 2 diabetes patients of normal weight are no more likely than overweight/obese patients to suffer from increased incidence rates, severity or duration of GI AEs when treated with first-line extended-release metformin monotherapy. Doses of 2000 mg/day did not increase the severity or duration of GI AEs.

1. Introduction

Metformin is recommended as first-line antihyperglycemic treatment for type 2 diabetes in almost all international or national diabetes guidelines [1–6]. In the Chinese guidelines for type 2 diabetes treatment, metformin is the first choice in first-line therapies [1]. Gastrointestinal (GI) tolerance is a key factor in the success of metformin treatment for type 2 diabetes. GI disorders are the most commonly experienced adverse events (AEs) in both Western and Asian patients [2–4,7] and metformin-associated diarrhea and vomiting can affect treatment compliance [5]. A previous study in Japanese patients with type 2 diabetes, who received 500 mg or 750 mg metformin daily, showed that both body mass index (BMI) ≥25 mg/kg^2 and initial dose were risk factors for GI AEs associated with metformin. Currently, the majority of published clinical studies of metformin focus

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http://dx.doi.org/10.1016/j.dsx.2016.01.004
1871-4021/

on patients with BMI ≥25 kg/m^2, who are defined as 'overweight/obese' in guidelines where body weight is a factor affecting choices of first-line treatment [8,9]. However, a large proportion of Asian and Chinese type 2 diabetes patients are of normal weight (up to almost two-thirds in some regions) [9–12].

Previously we performed a multicenter, open-label study in 371 Chinese patients who were newly diagnosed with type 2 diabetes and received extended-release metformin monotherapy for 16 weeks, and demonstrated that baseline BMI had no impact on the efficacy of metformin monotherapy [13]. Patients of normal weight derived the same benefits in terms of glycemic control, fasting plasma glucose (FPG) reductions, improvements in plasma lipid profiles, and weight loss with first-line metformin at doses of 500–2000 mg/day as did overweight/obese patients [13]. Given recommendations for the first-line use of anti-hyperglycemic agents are often described in terms of the patient's BMI by other diabetes associations [13,14] and few data are available on metformin's GI tolerability in normal-weight patients, particularly in Asia, concerns may remain regarding the tolerability of metformin in normal-weight patients (BMI < 25 kg/m^2), especially if metformin is administered at higher doses. Therefore, we carried out a sub-analysis of the safety data from the abovementioned open-label study [13] so as to determine whether baseline BMI (<25 kg/m^2 versus ≥25 kg/m^2) or final metformin dose (≤1500 mg/day versus 2000 mg/day) affect the incidence, severity and duration of GI AEs.

2. Methods

2.1. Study design and treatment

The study design, patient eligibility criteria, assessment methods, and the process by which ethical approval was obtained for the study protocol have been previously described [13]. The study was performed in accordance with the Declaration of Helsinki.

Extended-release metformin (metformin XR [Glucophage® XR], Bristol Myers Squibb) was administered orally at an initial dose of 500 mg/day and up-titrated in 500 mg increments weekly until the maximum daily dose of 2000 mg/day was reached, unless intolerance or hypoglycemia were experienced.

2.2. Safety evaluation, analysis sets and objectives

Enrolled patients who had at least one dose of study medication were included in the safety population. According to the World Health Organization (WHO) definitions, normal weight is defined as BMI = 18.5–24.99 kg/m^2, overweight as BMI = 25–29.99 kg/m^2, and obese as BMI ≥ 30 kg/m^2 [9]. Therefore, for this sub-analysis of treatment-emergent GI AEs (defined as AEs that occurred during the treatment period), patients in the safety population were stratified into two groups according to baseline BMI: normal-weight (BMI < 25 kg/m^2) and overweight/obese (BMI ≥ 25 kg/m^2) [9].

To evaluate safety and tolerability, AEs were recorded at Day 1 (baseline) and at Weeks 4, 8, 12 and 16 as described previously [13].

The primary objective of this sub-analysis was to determine whether there is an association between baseline BMI and the incidence, severity and duration of GI AEs. The intensity of GI AEs was determined by the investigators and classified as "mild", "moderate", "severe" and "very severe" using the definitions described in the previous study [13]. The secondary objective was to investigate the relationship between GI AEs and the final metformin dosage. Patients in the safety population for whom dosage data were available were stratified into two dosage groups: those who received a maximum of 1500 mg/day, and those who received a maximum dose of 2000 mg/day.

2.3. Statistical analyses

Fisher's exact test was used to compare the incidence, severity and duration of GI AEs between the two baseline BMI groups (<25 kg/m^2 and ≥25 kg/m^2). The Student's *t*-test was used to compare the mean GI AE duration in weeks between BMI groups. In addition, GI AE severity and duration were compared based on final metformin daily dose (≤1500 mg/day and 2000 mg/day), with Fisher's exact test being used to assess differences in GI AE severity and the proportion of GI AEs in each duration category. Mean duration of GI AEs was compared between dosage groups using an ANCOVA model with BMI as the covariate. The relationship between BMI and dosage was analyzed in patients who reported ≥1 GI AE using the Fisher's exact test.

3. Results

The main clinical study (NCT00778622) was conducted at 20 hospitals in China between 19 November 2009 and 15 March 2011. This sub-analysis of the safety population was conducted between December 2012 and March 2014.

A total of 371 enrolled patients, who received at least one dose of study medication, were included in the safety analysis population; 155 patients with BMI <25 kg/m^2 were classified as normal-weight and 216 patients with BMI ≥25 kg/m^2 were classified as overweight/obese (Fig. 1). A similar proportion of patients in both BMI groups completed the study (87.1% of normal-weight and 88.0% of overweight/obese patients). The proportion of patients who discontinued from the study due to any AE was smaller in the normal-weight group (3.2%) than in the overweight/obese group (5.1%; Fig. 1). A smaller proportion of patients in the normal-weight group withdrew from the study because of GI AEs: 1.9% (3/155) of patients with BMI < 25 kg/m^2 versus 2.7% (6/216) of patients with BMI ≥25 kg/m^2.

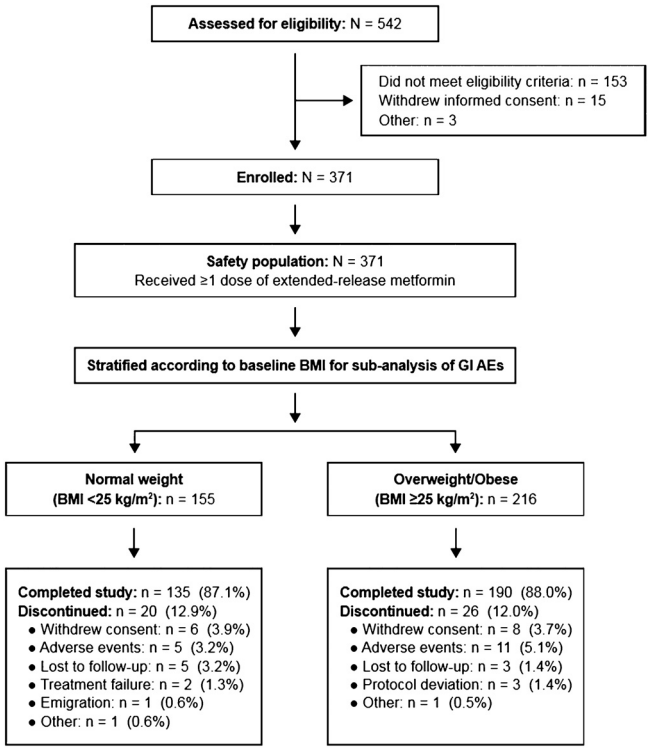

Fig. 1. Patient disposition. BMI, body mass index; GI AE, gastrointestinal adverse event.