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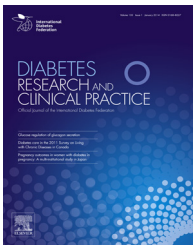

Efficacy and tolerability of exenatide twice daily and exenatide once weekly in Asian versus White patients with type 2 diabetes mellitus: A pooled analysis

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ABSTRACT

Aims: The efficacy and safety of exenatide twice daily (BID) and once weekly (QW) were assessed in Asian versus White patients with type 2 diabetes mellitus (T2DM).

Methods: This post-hoc pooled analysis evaluated patients receiving 10 μg exenatide BID for 12–30 weeks or 2 mg exenatide QW for 24–30 weeks in exenatide clinical development program trials. Race was self-identified.

Results: A total of 4625 patients were included (exenatide BID: Asian, $n = 787$; White, $n = 2223$; exenatide QW: Asian, $n = 511$; White, $n = 1104$). At study end, glycated hemoglobin (HbA1c), fasting glucose (FG), body weight, post-prandial glucose (PPG), and PPG excursions were significantly reduced (all $P < 0.0001$ vs baseline). For exenatide BID, HbA1c reduction was greater in Asians ($P < 0.0001$ vs Whites), whereas HbA1c reduction did not differ by race for exenatide QW. FG reduction did not differ by race for either exenatide formulation. Weight reduction was significantly greater in Whites ($P < 0.0001$ vs Asians), regardless of exenatide formulation. PPG reduction was greater in Asians ($P < 0.0001$ vs Whites) for exenatide BID but did not differ by race for exenatide QW. For exenatide BID, reductions in PPG excursions for all meals were significantly greater in Asians ($P < 0.0001$ vs Whites), whereas only post-breakfast and post-lunch excursions were significantly greater in Asians for exenatide QW ($P = 0.0009$ and $P = 0.0189$ vs Whites, respectively). Common adverse events included nausea, headache, and diarrhea.

Conclusions: Exenatide BID and QW improved glycemic control, including PPG, in Asian and White patients with T2DM. With exenatide BID, Asian patients exhibited significantly greater reductions in HbA1c and PPG than White patients. Both exenatide formulations were well tolerated in both groups.

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1. Introduction

In Western countries, type 2 diabetes mellitus (T2DM) is typically associated with obesity and advanced age [1]. In Asian countries, however, T2DM often occurs in patients with a lower body mass index (BMI) and in young and middle-aged adults [1]. Asian individuals often have higher levels of abdominal adiposity and lower muscle mass than their White counterparts, meaning a BMI in the "normal" range in the West (<25 kg/m^2) may be associated with a higher risk in Asian patients [1]. It has also been suggested that the development of T2DM in Asian patients is associated with impaired early-phase insulin secretion [2].

The characteristics of T2DM differ between Asian and White patients. Although both post-prandial glucose (PPG) and fasting glucose (FG) levels are important contributors to excess hyperglycemia, PPG levels are thought to be more influential in Asian patients, whereas FG levels appear more important in White patients [3]. The Asian diet comprises foods with high glycemic loads, such as rice and refined wheat [1]; however, excessive PPG excursions among Asian patients appear to be more than a function of diet. In response to identical meals, Asian patients exhibit greater PPG excursions than White patients [4]. Furthermore, the pattern of diabetes complications seen in Asian patients is different compared with White patients. For example, Asians are more prone to end-stage renal disease [1].

Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has multiple glucoregulatory effects including suppression of elevated post-prandial glucagon secretion, enhanced glucose-dependent insulin secretion, and slowing of gastric emptying [5]. Two formulations of exenatide are approved in the United States, European Union, Japan, China, and other countries for the treatment of adult patients with T2DM. The twice-daily (BID) formulation is given before the two major meals of the day. There is also an extended-release, once-weekly (QW) formulation, in which the active molecule is dispersed into biodegradable microspheres to allow extended diffusion following injection [6]. Exenatide BID and QW have been extensively evaluated in controlled clinical trials in multiple countries and races, including White and Asian patients. However, there is more limited information to inform if clinical practice should differ between ethnic groups. The current post-hoc analysis assessed the efficacy and safety of exenatide BID and exenatide QW in populations of Asian and White patients with T2DM who participated in selected studies from the exenatide clinical development program. These studies provided the majority of data leading to the regulatory approval of exenatide BID and exenatide QW for clinical use.

2. Patients, materials, and methods

2.1. Study and patient selection

This retrospective analysis employed pooled individual patient-level data derived from selected studies within the exenatide global integrated database. This database contains all exenatide BID and exenatide QW clinical studies comprising the exenatide clinical development program. Databases such as these are commonly required in order to respond effectively to analysis requests from regulatory authorities. For the purposes of the current analysis, clinical studies employing exenatide BID and exenatide QW were selected based on the following criteria:

I. Randomized and controlled.
II. 12 to 30 weeks for exenatide BID; 24 to 30 weeks for exenatide QW.
III. Primary objective was the safety and efficacy of exenatide BID or exenatide QW versus placebo or comparator in patients with T2DM already receiving treatment with diet and exercise with or without oral concomitant glucose-lowering therapy.
IV. Outcomes comprised glycated hemoglobin (HbA1c) level, FG, body weight, blood pressure, heart rate, lipid profile, immunogenicity, and safety data including hypoglycemia. Pre-prandial glucose and PPG excursions from self-monitored blood glucose (SMBG) assessments were evaluated when available.
V. Designed to maintain stable background glucose-lowering therapies. Studies that permitted reductions in background sulfonylurea (SFU) use due to hypoglycemia were included, but studies with continuous reductions in SFU doses were excluded. Studies using basal insulin as a background therapy were also excluded.

Any disputes regarding inclusion of studies were resolved through discussion by the authors until consensus was reached.

This retrospective pooled analysis included intention-to-treat (ITT) patients treated with either 10 μg exenatide BID (5 μg for 4 weeks and 10 μg thereafter) or 2 mg exenatide QW. Patients self-identified as a single race; Asian and White patients were selected for this analysis.

All studies included were conducted in accordance with the Declaration of Helsinki (1964), including the current Seoul revision (2008; when applicable), and were consistent with Good Clinical Practice and applicable laws and regulations. All patients provided written informed consent for the original clinical trials.

2.2. Statistical analysis

Changes from baseline at study end within each group for HbA1c, FG, body weight, blood pressure, heart rate, lipid parameters (ITT population), and SMBG responses (SMBG population; see below for definition) were assessed for statistical significance using paired student *t*-tests with missing data imputed using the last observation carried forward (LOCF) method. The proportion of patients with various anti-exenatide antibody titers (0, 25, 125, 625, 3125, and ≥15,625) at baseline and study end was also assessed in the ITT population.

Differences in HbA1c, FG, body weight, and SMBG responses between Asian and White patients were evaluated for exenatide BID and exenatide QW separately using independent