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Research Article
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Saxagliptin Responder Analysis: A Pooled Analysis of 5 Clinical Trials

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Abstract

Objective: To assess the treatment response of patients with T2DM to saxagliptin at 24 weeks based on their initial response to saxagliptin at 12 weeks.

Methods: Data were pooled from five 24-week, randomized, placebo-controlled trials of saxagliptin. Patients (N=1994) were categorized by change in glycated hemoglobin (HbA1c) after 12 weeks of saxagliptin treatment as responders (HbA1c decrease ≥ 0.5%; 61% of saxagliptin-treated patients), intermediate responders (HbA1c decrease ≥ 0.2% and <0.5%; 14% of patients), and nonresponders (HbA1c decrease <0.2%; 25% of patients).

Results: The adjusted mean change [95% CI] from baseline to week 24 in HbA1c with saxagliptin was greatest in responders (–1.05% [–1.11%, – 0.99%]) followed by intermediate responders (–0.32% [–0.43%, –0.22%]) and nonresponders (0.27% [0.18%, 0.36%]). The proportion of patients achieving HbA1c<7% after 24 weeks was greater in responders (48%) and intermediate responders (41%) versus nonresponders (22%, *P*<0.0001 for each). The adjusted mean increase from baseline to week 24 in HOMA-2%β was greatest in the responder group (16.9% [13.5%, 20.2%]) compared with the other groups (intermediate responders, 11.7% [5.9%, 17.5%]; nonresponders, 0.4% [–4.8%, 5.6%]). Baseline characteristics that were associated with glycemic response to saxagliptin included higher baseline HbA1c (*P*<0.0001), higher HOMA-2%β (*P*<0.0001), lower fasting insulin (*P*=0.0006), shorter T2DM duration (*P*=0.033), and male sex (*P*=0.031).

Conclusion: Responders, who comprised 61% of saxagliptin-treated patients analyzed, derived significant benefit from saxagliptin, with a ~1% decline in HbA1c and increased β-cell function at 24 weeks compared with nonresponders.

Keywords: Beta-cell; DPP-4 inhibitor; Glycated hemoglobin; Hyperglycemia; Saxagliptin; Treatment response; Type 2 diabetes

Introduction

Treatment of hyperglycemia in patients with type 2 diabetes mellitus (T2DM) is an important intervention that has been proven to reduce the risk of diabetes-related microvascular complications [1-5], and in the long term and as part of a multifactorial intervention targeting other risk factors, cardiovascular events and death [3,4]. However, management of hyperglycemia in T2DM is complex and involves both lifestyle changes and pharmacotherapy [6,7].

Pharmacologic treatment of T2DM should be individualized to maximize patient benefit and should consider efficacy, effects on body weight, potential side effects, hypoglycemia risk, cost, and patient preferences [6,7]. Although several classes of antidiabetes drugs are available, the response to a given pharmacologic treatment for T2DM may vary among individuals within a study population. Identification of characteristics associated with treatment response to different antidiabetes drugs may help in the management of T2DM.

Saxagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor that inhibits the rapid degradation of glucagon-like peptide-1, resulting in enhanced glucose-mediated insulin secretion and a reduction in glucagon secretion [8]. In phase 3 clinical trials, saxagliptin, when used as monotherapy [9,10] or as add-on therapy [11-14] in patients with T2DM, improves glycemic control and has a favorable safety and tolerability profile [15]. Saxagliptin also is weight neutral and has a low propensity for hypoglycemia, except when used with insulin or sulfonylureas [11,12]. Furthermore, data from the SAVOR cardiovascular outcomes study suggest that saxagliptin may reduce the usual decline in β-cell function in T2DM, thereby slowing diabetes progression [16]. In this study, we analyzed the 24-week treatment response to saxagliptin of patients with T2DM from 5 saxagliptin phase 3 clinical trials based on their initial response to saxagliptin at 12 weeks to determine which patient characteristics may be important in determining the response to saxagliptin.

Methods

This was a post hoc analysis of data pooled from five 24-week, randomized, placebo-controlled trials that evaluated saxagliptin at doses of 2.5, 5, and 10 mg/day; 2 trials of saxagliptin monotherapy in treatment naïve patients (NCT00121641 and NCT0031082) [9,10] and 1 each of add-on to metformin (NCT00121667) [13], add-on to pioglitazone (NCT00295633) [14], and add-on to glyburide versus uptitrated glyburide (NCT00313313) [12].

Inclusion and exclusion criteria for the 5 studies have been

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previously reported in detail [9,10,12-14]. In brief, eligible patients were aged 18 to 77 years with T2DM and inadequate glycemic control based on a glycated hemoglobin (HbA1c) level of 7%–10% [9,10,13], 7.5%–10% [12], or 7%–10.5% [14], a body mass index (BMI) ≤ 40 or ≤ 45 kg/m^2 (study dependent), and a fasting C-peptide concentration ≥ 1 ng/mL At study entry, patients were either treatment-naïve or were receiving a stable dose of metformin (1500–2550 mg/day) for ≥ 8 weeks prior, a stable dose of thiazolidinedione monotherapy for ≥ 12 weeks prior, or a submaximal dose of sulfonylurea for ≥ 8 weeks prior.

Exclusion criteria common to all 5 studies included current or symptoms of poorly controlled diabetes; a significant cardiovascular event within 6 months; New York Heart Association class III and IV heart failure or left ventricular ejection fraction ≤ 40%; significant history of kidney or hepatic disease; history of substance abuse in previous 1 year; immunocompromised state (eg, from having undergone organ transplantation or diagnosis of human immunodeficiency virus); and use of potent cytochrome P450 3A4 inhibitors or inducers.

Patients were classified by change in HbA1c after 12 weeks of saxagliptin treatment as nonresponders (HbA1c decrease <0.2%), intermediate responders (HbA1c decrease ≥ 0.2% and <0.5%), or responders (HbA1c decrease ≥ 0.5%). In an additional analysis, patients were classified by change in fasting plasma glucose (FPG) at 4 weeks as nonresponders (<4 mg/dL), intermediate responders (4–14 mg/dL), and responders (>14 mg/dL) Efficacy end points were change from baseline to week 24 in HbA1c, FPG, β-cell function by homeostatic model assessment (HOMA-2%β), and the proportion of patients achieving HbA1c<7%.

Statistical Analysis

The efficacy analyses for the change from baseline values, which included observations prior to rescue, were performed using a longitudinal repeated measures ANCOVA model with terms for baseline value, responder group, country, time, and the interaction of responder group and time. Fisher's exact test was applied for testing the proportion of patients achieving HbA1c<7% between responder groups. The association of baseline characteristics with the glycemic response to saxagliptin was assessed by multivariate logistic regression with clinically meaningful covariates (age, sex, race, duration of T2DM, baseline weight, baseline BMI, baseline HbA1c, baseline fasting insulin, and baseline HOMA-2%β).

Results

Of patients who were randomized and treated (N=1996), 495 (25%) were classified as nonresponders, 274 (14%) were intermediate responders, and 1227 (61%) were responders after 12 weeks of treatment with saxagliptin (Table 1). Across groups, similar proportions of patients had received prior antidiabetes medications.

Of the patients that were randomized and treated in these clinical trials, 452 (23%) patients discontinued from the studies. The proportion that discontinued was greatest in the nonresponder group (43%), followed by the intermediate responder (23%) and responder groups (14%). The main reason for discontinuing was lack of efficacy in 31% of nonresponders, 12% of intermediate responders, and 6% of responders. Discontinuations because of adverse events were infrequent and similar across groups (nonresponders, 2.8%; intermediate responders, 2.2%; responders 2.0%).

The adjusted mean change from baseline to 24 weeks in HbA1c was greatest in the responder group (–1.05%, P<0.0001 vs nonresponders), followed by the intermediate responder (–0.32%, P<0.0001 vs nonresponders) and nonresponder groups (0.27%) (Figure 1). The adjusted mean change from baseline to 24 weeks in FPG was greatest in the responder group (–21.1 mg/dL, P<0.0001 vs nonresponders), followed by the intermediate responder (–9.6 mg/dL, P<0.0001 vs nonresponders) and nonresponder groups (5.5 mg/dL) (Figure 2). The adjusted mean increase from baseline to week 24 in HOMA-2%β was greatest in the responder group (16.9%, P<0.0001 vs nonresponders) compared with intermediate responders (11.7%, P=0.0019 vs nonresponders) and nonresponders (0.4%) (Figure 3).The proportion of patients achieving HbA1c<7% after 24 weeks was significantly greater (P<0.0001) in the responder (48%) and intermediate groups (41%) compared with the nonresponder group (22%) (Figure 4). When patients with HbA1c<7% at baseline were excluded from the analysis, significantly more responders (45%) and intermediate responders (31%) still achieved HbA1c<7% at 24 weeks compared with nonresponders (14%). Difference [95% CI] compared with nonresponders was 31.4% [25.9%, 36.9%], P<0.0001, for responders and 17.0% [8.9%, 25.3%], P<0.0001 for intermediate responders.

By multivariate logistic regression, the baseline characteristics most closely associated with a glycemic response to saxagliptin included higher HbA1c (P<0.0001), higher HOMA-2%β (P<0.0001), lower fasting insulin (P=0.0006), shorter T2DM duration (P=0.033), and male sex (P=0.031) (Table 2).

Characteristic	Nonresponders: HbA1c Decrease <0.2% at 12 weeks	Intermediate Responders: HbA1c Decrease 0.2% to <0.5% at 12 weeks	Responders: HbA1c Decrease ≥ 0.5% at 12 weeks
n (%)	495 (25)	274 (14)	1227 (61)
Age, y	53 ± 10.2	55 ±10.1	55 ± 10.0
Women, n (%)	279 (56)	151 (55)	599 (49)
Race, n (%) White Asian Black/African American American Indian/ Alaska native Other	 353 (71) 76 (15) 26 (5) 12 (2) 28 (6)	 195 (71) 43 (16) 11 (4) 3 (1) 22 (8)	 844 (69) 194 (16) 54 (4) 20 (2) 115 (9)
BMI, kg/m^2	31 ± 5.1	31 ± 5.1	30 ± 4.9
BMI category, n (%) <30 kg/m^2 ≥30 kg/m^2	 234 (47) 261 (53)	 128 (47) 146 (53)	 628 (51) 599 (49)
Duration of T2DM, y	5.4 ± 5.1	4.9 ± 5.6	5.1 ± 5.2
HbA1c, %	8.1 ± 1.1	7.8 ± 0.9	8.3 ± 1.0
FPG, mg/dL	186 ± 49.7	160 ± 39.6	166 ± 43.0
120-min PPG, mg/dL	309 ± 89.3	282 ± 69.3	294 ± 75.0
HOMA-2%β, %	60 ± 36.4	74 ± 35.3	68 ± 37.9
Prior antidiabetes medications Metformin SU TZD Other	 177 (35.8) 158 (31.9) 83 (16.8) 8 (1.6)	 83 (30.5) 79 (29.0) 49 (18.0) 5 (1.8)	 426 (34.7) 367 (29.9) 269 (21.9) 16 (1.3)

Values are mean ± SD unless otherwise indicated. BMI= Body Mass Index; FPG = Fasting Plasma Glucose; HbA1c= Glycated Hemoglobin; HOMA-2%β=β-cell Function by Homeostatic Model Assessment; PPG= Postprandial Glucose; SU= Sulfonylurea; T2DM=Type 2 Diabetes Mellitus; TZD= Thiazolidinedione

Table 1: Demographics and Baseline Characteristics.

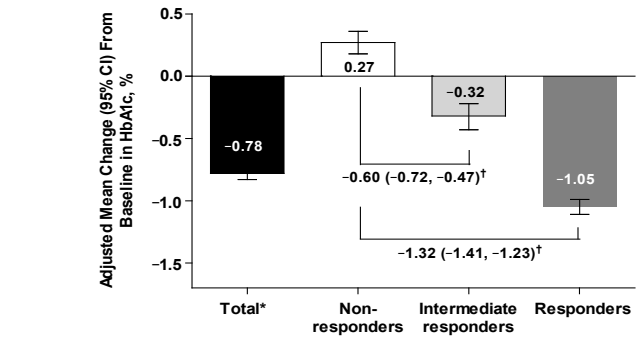

Figure 1: Change in HbA1c. Adjusted mean change from baseline to 24 weeks in glycated hemoglobin (HbA1c). *Mean change from baseline, observed values. †*P*<0.0001 versus nonresponders.

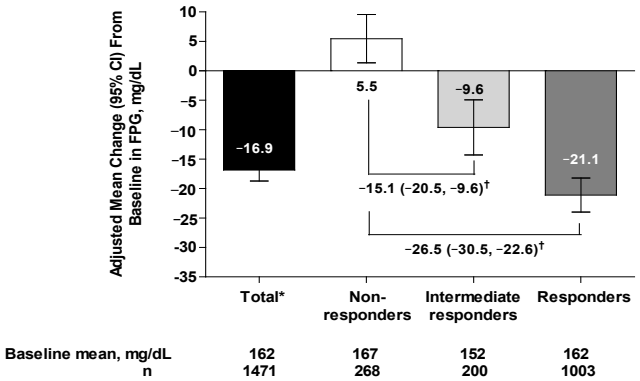

Figure 2: Change in FPG. Adjusted mean change from baseline to 24 weeks in fasting plasma glucose (FPG). *Mean change from baseline, observed values. †P<0.0001 versus nonresponders.

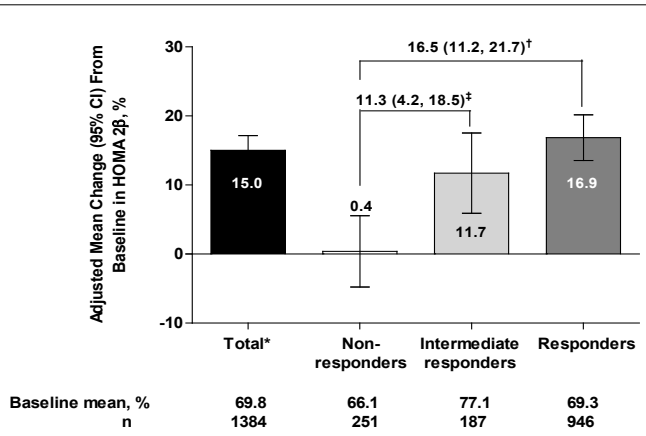

Figure 3: Change in HOMA-2%β. Adjusted mean change from baseline to 24 weeks in HOMA-2%β. *Mean change from baseline, observed values. †*P*<0.0001; ‡*P*=0.0019 versus nonresponders.

Classification of patients by change in FPG at 4 weeks rather than by A1C change at 12 weeks appeared to be less predictive of the response to saxagliptin at 24 weeks. For example, when patients were classified based on FPG change at 4 weeks, clinically meaningful reductions from baseline in A1C at 24 weeks of –0.36%, –0.66%, and –0.98% were noted for nonresponders, intermediate responders, and responders, respectively. In addition, using the FPG at 4 weeks classification, the proportions of patients achieving A1C<7% at week 24 (excluding those with A1C<7% at baseline) were 35%, 48%, and 38% for nonresponders, intermediate, and responders. Finally, the proportions of patients that discontinued from the study for lack of efficacy when based on the FPG change at 4 weeks were 17%, 8%, and 13% for nonresponders, intermediate, and responders, respectively. All these results suggest that the change in FPG at 4 weeks in response to saxagliptin was not predictive of the change in A1C at 24 weeks.

Discussion

Management of T2DM is complex, and choosing a pharmacotherapy that produces a clear, clinically meaningful benefit to patients can be challenging. Analysis of baseline characteristics that are associated with response to an antidiabetes medication may help in the selection of a disease management program for specific patients.

As a class, DPP-4 inhibitors are well tolerated with the added benefits of weight neutrality and a low risk of hypoglycemia [17,18].

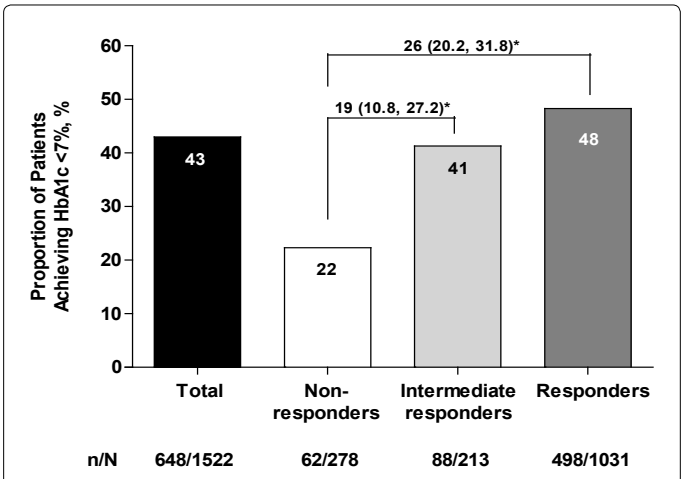

Figure 4: Proportion of Patients Achieving HbA1c <7% at 24 Weeks. **P*<0.0001 versus nonresponders.

Baseline Characteristic	Odds Ratio	Wald Chi-Square	*P* Value
HbA1c	1.702	76.962	<0.0001
HOMA-2%β	1.012	37.854	<0.0001
Fasting insulin	0.979	11.825	0.0006
Sex (male vs female)	1.336	4.678	0.031
Duration of T2DM	0.979	4.537	0.033
Age	1.008	2.621	0.105
Body mass index	0.974	1.500	0.221
Weight	1.002	0.154	0.695
Race (vs White)			
Black/African American	0.979	0.065	0.799
American Indian/Alaskan Native	0.981	0.030	0.863
Asian	0.874	1.305	0.253
Other	1.395	3.164	0.075

BMI= Body Mass Index; HbA1c=Glycated Hemoglobin; HOMA-2%β=β-cell function by Homeostatic Model Assessment; T2DM= Type 2 Diabetes Mellitus

Table 2: Multivariate Logistic Regression of Glycemic Response and Baseline Characteristics in the Responder Group.

Furthermore, patient adherence and persistence have been shown to be greater with DPP-4 inhibitors as initial pharmacotherapy compared with other classes of antidiabetes medications such as sulfonylureas and thiazolidinediones [19]. Clinical practice guidelines recommend DPP-4 inhibitors as an option for first-line therapy in individuals who are intolerant to metformin or in whom metformin is contraindicated [6,7]. In addition, DPP-4 inhibitors are recommended as an option for add-on therapy to metformin or as a component of triple therapy with metformin and other antidiabetes drugs [6,7].

Few studies have examined the association of baseline patient characteristics with the response to DPP-4 inhibitors. In a meta-analysis of 44 randomized clinical trials of DPP-4 inhibitors, baseline characteristics that were associated with greater reductions in HbA1c in response to DPP-4 inhibitors were older age, lower HbA1, and lower FPG [20]. In another meta-analysis of 78 randomized clinical trials involving 20,503 patients, the HbA1c response to DPP-4 inhibitors was mainly determined by baseline HbA1c and FPG, with a greater response occurring with higher baseline HbA1c and lower FPG [21]. Age, duration of T2DM, and previous therapy did not influence the HbA1c response. A retrospective observational cohort study of patients in a diabetes outpatient clinic receiving DPP-4 inhibitors for 6 months after failing other antidiabetes drugs found that positive responses to DPP-4 inhibitors after 6 months of therapy (HbA1c<7% or for those with baseline HbA1c>9%, HbA1c<8%) were associated with lower baseline HbA1c, shorter T2DM duration, higher BMI, more comorbidities, and male sex [22].

In clinical trials of saxagliptin, the average reduction in HbA1c ranged from 0.4% to 0.8% compared with placebo [23]. However, the data presented in this analysis indicates that a more pronounced reduction in HbA1c at 24 weeks can be expected in patients who have an initial good response (≥ 0.5% reduction in HbA1c) to saxagliptin at 12 weeks. In this 5-trial pooled analysis, we found that patients classified as responders at 12 weeks had the greatest reduction in HbA1c at 24 weeks (–1.05%), followed by those classified as intermediate responders (–0.32%) and nonresponders (0.27%). Moreover, significantly more patients in the intermediate responder and responder groups achieved HbA1c>7% at 24 weeks than those in the nonresponder group, even when patients with HbA1c<7% at baseline were excluded. Of note, even in the nonresponder group who had an HbA1c decrease <0.2% at 12 weeks, 14% of patients with HbA1c>7% at baseline were able to achieve HbA1c<7% at 24 weeks. Although this analysis was limited by its post hoc design, the baseline characteristics of patients that appeared to be associated with the glycemic response to saxagliptin included baseline HbA1c, HOMA-2%β, fasting plasma insulin, T2DM duration, and male sex. Baseline HbA1c was the characteristic most closely associated with a glycemic response to saxagliptin. This is consistent with findings that higher baseline HbA1c is associated with a greater reduction in HbA1c with DPP-4 inhibitors [21,24] and other oral antidiabetes medications [25]. HOMA-2%β values can be a functional result (insulin secretion stimulated pharmacologically) rather than a biological improvement in β-cell functionality. Therefore, the association of HOMA-2%β, fasting insulin, and duration of disease with the glycemic response to saxagliptin is consistent with the mechanism of action of saxagliptin which ultimately depends on incretin-mediated insulin release from functioning β-cells [8]. Progressive loss of β-cell function over time and an increase in insulin resistance are characteristics of T2DM [26], and patients with shorter disease duration, better β-cell function, and higher insulin sensitivity, as reflected in lower fasting insulin, would be expected to benefit most from DPP-4 inhibition. Of note, a recent study suggests that saxagliptin may reduce the usual decline in β-cell function in patients with T2DM, thereby slowing diabetes progression [16].

We also found that response to saxagliptin was more likely in men than in women. An association of men with a greater response to DPP-4 inhibitors has also been reported in analyses of DPP-4 inhibitors as a class [22,27]. Whether this is a chance finding or one of clinical significance is unclear. When analyzed in individual clinical trials of saxagliptin [12,13] or in a pooled analysis of 4 trials of saxagliptin monotherapy [28], no interaction between sex and the change in HbA1c has been observed. Moreover, sex does not appear to effect the pharmacokinetics of saxagliptin [29].

In this study, A1C was used as a predictive variable because it is a reflection of average blood glucose over time and is less affected by acute changes in blood glucose [7]. FPG measures blood glucose at a fixed point in time and can be more variable than A1C. Moreover, because of their mechanism of action, DPP-4 inhibitors are expected to affect postprandial glucose more than FPG. In this study, changes in FPG were found to be less predictive of glycemic response after 24 weeks of treatment than were changes in A1C. The use of other measures of glycemic control, such as postprandial glucose, may not be practical in routine clinical practice.

In conclusion, responders, who comprised 61% of saxagliptin-treated patients analyzed, derived significant benefit from saxagliptin treatment, with a ~1% reduction in HbA1c. Responders also had the greatest increase in β-cell function at 24 weeks, measured as HOMA-2%β, compared with nonresponders. Higher baseline HbA1c was the characteristic most closely associated with a glycemic response to saxagliptin. There remains a need for the identification of patient characteristics associated with robust responses to antidiabetes medications on which to base clinical decisions for selecting the pharmacotherapy most appropriate for a given patient.

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Author Disclosures

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Prior Publication

Some of the results of this study have been previously presented at the World Congress on Insulin Resistance, Diabetes and Cardiovascular Disease, November 20–22, 2014, Los Angeles, CA.

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