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Efficacy of vildagliptin versus sulfonylureas as add-on to metformin: comparison of results from randomized controlled and observational studies

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ABSTRACT

Aims/hypothesis: Randomized control trials (RCTs) do not always reflect real-life outcomes for glucose-lowering drugs. In this work we compared efficacy of the DPP-4 inhibitor vildagliptin or sulfonylureas added to metformin in RCTs with data from real life.

Methods: Data were pooled from five RCTs examining vildagliptin (n=2788) and sulfonylureas [(glimepiride (n=1259) or gliclazide (n=433)], added to metformin. For real-life conditions, data were extracted from an observational study examining vildagliptin (n=7002) or sulfonylurea (n=3702), added to metformin monotherapy. Linear regression analyses were performed between the baseline HbA_{1c} and the change in HbA_{1c} (Δ HbA_{1c}) after 24 weeks.

Results: Baseline HbA_{1c} correlated to Δ HbA_{1c} ($r^2 = 0.36$, slope = -0.54 [95% CI: -0.55, -0.53; $p<0.0001$]) for both treatments. With sulfonylureas, the slope of the correlation was steeper in the observational study than in RCTs (interaction coefficient = -0.327, $p<0.001$), whereas for vildagliptin, the slope was virtually identical in the observational study and the RCTs (interaction coefficient = 0.024, $p = 0.175$). For any given baseline HbA_{1c}, Δ HbA_{1c} with sulfonylureas was smaller in real life than in RCTs, whereas Δ HbA_{1c} with vildagliptin was the same.

Conclusions/interpretations: When comparing RCT to real-life data, the decrease in HbA_{1c} from baseline with sulfonylurea treatment is smaller in real life than in RCTs, whereas the reduction with vildagliptin is essentially the same, suggesting that the full power of treatment is retained in real life for vildagliptin but not for sulfonylureas, possibly due to fear of hypoglycaemia.

Keywords: DPP-4 inhibitor, GLP-1, interventional, observational, randomised controlled trial, sulfonylurea

Abbreviations:

ANOVA – analysis of variance

HbA_{1c} – haemoglobin A_{1c}

DPP-4 – dipeptidyl peptidase-IV

OAD – oral antihyperglycaemic drug

Δ HbA_{1c} – change from baseline in haemoglobin A_{1c}

INTRODUCTION

Many randomized, controlled, clinical trials (RCTs) have demonstrated efficacy and safety/tolerability of the DPP-4 inhibitor vildagliptin used as monotherapy and as add-on to oral antihyperglycaemic drugs (OADs) [1-4]. RCTs meet regulatory and scientific standards, but do not necessarily reflect what happens in real life, and thus do not always provide healthcare professionals with guidance regarding what to expect when prescribing a given drug. It is therefore important to complement the results from RCTs with those from observational trials [5;6]. In this work, RCTs of vildagliptin were compared with results of the EDGE trial, which was a non-interventional, non-randomized, (>45,000 participants) one-year observational study comparing vildagliptin to any other OAD added to prior OAD monotherapy in patients with type 2 diabetes and inadequate glycaemic control [7].

The vast majority of patients participating in EDGE were receiving metformin as their initial monotherapy, sulfonylureas were the most common comparator OAD, and many participants had an HbA_{1c} measurement after 24 weeks of treatment as part of their standard clinical care allowing this study to compare directly the performance of vildagliptin (87.5% of EDGE patients in the vildagliptin cohort) *versus* a sulfonylurea (72.8% of EDGE patients in the comparator cohort), both combined with metformin, under real-life conditions with those obtained from RCTs using the same treatment regimens. Thus, the present post-hoc analysis compared the contribution of vildagliptin and sulfonylureas added to metformin to the HbA_{1c} reduction at six months, in RCTs and real life. To account for differences in HbA_{1c} reductions due to baseline HbA_{1c} levels, HbA_{1c} reductions were analyzed relative to the baseline HbA_{1c} levels.

METHODS

Patients and study designs. For RCT population, data were pooled from the intention-to-treat (ITT) populations of five clinical trials [1-3;8;9] with 4480 patients with T2DM; 2788 patients received vildagliptin (50 [n=201] mg qd or 50 mg bid [n=2587]) plus metformin ≥1500 mg/day and 1692 patients received an SU (glimepiride up to 6 mg/day; n=1259 or gliclazide up to 320 mg/day; n=433) and metformin ≥1500 mg/day. For the observational population (studied under real-life conditions), data from 10,704 patients (7002 who received vildagliptin 50 mg bid added to metformin monotherapy and 3702 who received a sulfonylureas added to metformin monotherapy) were extracted and summarized from the EDGE study [7]. Dosage information was not collected in the EDGE trial. The RCTs were all randomized, double-blind, controlled clinical trials with a pre-specified Week 24 study visit; and in the observational study, oral antidiabetic dual therapy, clinic visits and HbA_{1c} monitoring were solely at the discretion of the physician.

Data analysis. Data describing baseline demographic and patient characteristics were summarized for the ITT populations participating in EDGE and RCTs. Baseline and Week 24 HbA_{1c} levels were measured in each study/population, and linear regression analyses were performed to identify the strongest "predictor" of treatment response (Δ HbA_{1c} at Week 24): baseline HbA_{1c}, age, body weight and sex were included in the linear regression model. Additionally, ANOVA was used to compare the change in HbA_{1c} (adjusted for baseline HbA_{1c}) between treatments and study conditions.

Ethics and Good Clinical Practice. All studies included were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization/Good Clinical

Practice guidelines. The study protocols were approved by an independent ethics committee/IRB at each site and all patients provided written informed consent.

RESULTS

Patient characteristics. In all participants the mean±SD age was 57.0±9.6 years in RCTs and 57.0 ±11.4 years in EDGE, the mean duration of diabetes was 5.1±4.9 years in RCTs and 5.4±5.4 years in EDGE and about 54% of patients were male, with little difference between treatment groups or study conditions. Mean baseline HbA_{1c} was higher in both treatment groups in the EDGE population (8.3±1.2% [67±13 mmol/mol] and 8.2±1.3% [66±14 mmol/mol] for vildagliptin, and sulfonylureas, respectively) than in the RCT population (7.9±1.0% [63±11 mmol/mol] and 7.6±0.9% [60±10 mmol/mol] for vildagliptin and sulfonylureas, respectively). Thus, in the RCT population, baseline HbA_{1c} in the vildagliptin group was somewhat higher than the sulfonylurea group.

Predictors of response. There was a strong correlation between baseline HbA_{1c} and the response to treatment (Δ HbA_{1c}). Assessing the entire data set (n=12001), 36% of the variability in Δ HbA_{1c} was attributable to baseline HbA_{1c} ($r^2 = 0.36$, slope= -0.54 [95% CI: -0.55, -0.53; $p<0.000$]). In contrast, age, and body weight were non-significantly correlated (slopes < -0.000) and there was very little correlation due to gender (slope = -0.03, $p<0.03$).

Figure 1 depicts the Δ HbA_{1c} as a function of baseline HbA_{1c} with sulfonylureas (a) or vildagliptin (b) as add-on to metformin. With sulfonylureas, the slope was -0.541 (95% CI: -0.56, -0.52; $p<0.001$) in RCTs, but was steeper under real-life conditions (in EDGE; interaction coefficient = -0.327, $p<0.001$). Thus for any given baseline HbA_{1c}, in RCTs the Δ HbA_{1c} with sulfonylurea treatment is greater than in real life. For example, in patients with mean baseline

HbA_{1c} of 8.5% (69 mmol/mol) the adjusted mean change from baseline (AMΔ) in A1C in the sulfonylurea treatment group was -0.9% (-10 mmol/mol) in EDGE *vs* -1.2% (-13 mmol/mol) in RCTs. Furthermore, the difference Δ HbA_{1c} reduction between real-life and RCTs increased as baseline HbA_{1c} approached normal levels, as illustrated by the shaded area in Figure 1. In contrast, the regression lines for vildagliptin were nearly superimposable in EDGE and the RCT populations where the slope of the regression line was -0.55 (95% CI: -0.56, -0.53; $p<0.001$) and there was no interaction with study conditions (RCT *vs* EDGE, coefficient = 0.024, $p = 0.175$). In patients with mean baseline HbA_{1c} of 8.5% (69 mmol/mol) the adjusted mean Δ HbA_{1c} in the vildagliptin treatment group was essentially the same in EDGE (-1.1%; -12 mmol/mol) and RCTs (-1.2%; -13 mmol/mol). In the RCTs body weight increased with sulfonylureas (1.0±0.1 Kg from 87.9±0.4 kg, n=1692) and decreased with vildagliptin (0.3±0.1kg from 89.2±0.4 kg, n=2787) (both P<0.001) and in EDGE, body weight reduced with both sulfonylurea (0.5±0.1 kg from 78.1±0.3 kg, n=2619) and vildagliptin (1.4±0.1 Kg from 81.7±0.2 kg, n=5045) (both P<0.001).

DISCUSSION

This post-hoc analysis was undertaken to compare the efficacy of sulfonylureas or vildagliptin used as add-on to metformin in patients with type 2 diabetes and inadequate glycaemic control with metformin monotherapy in RCTs *versus* in a real-life, observational, study. The present analysis confirms the expected relationship between baseline HbA_{1c} and the response to (essentially any) glucose-lowering therapy. While this is usually inferred from sub-group analysis (comparing change from baseline in patients with low *vs* high baseline HbA_{1c}), the correlation across a broad range of values is seldom, if ever reported. Furthermore, the

present work examines the relationships between baseline HbA_{1c} and Δ HbA_{1c} under the two study conditions with the two modes of treatment. The main finding of this work is that whereas the glycaemic response to vildagliptin in the observational study was entirely consistent with that seen in RCTs, the dependency of the response to sulfonylurea/metformin on baseline HbA_{1c} differed in RCTs and real-life conditions. Hence, the glycaemic response with sulfonylurea treatment was smaller in real life than in RCTs, whereas the glycaemic response with vildagliptin was essentially the same. While the magnitude of the response to sulfonylurea/metformin increased (the change becoming more negative) with increasing baseline HbA_{1c} under both conditions, the blunting of the response became amplified as baseline HbA_{1c} approached normal.

The cause of this blunting of the response in HbA_{1c} to sulfonylurea in real life is not clear. However, an important difference between vildagliptin and sulfonylureas is a higher risk for hypoglycaemia with sulfonylureas. Thus, it is tempting to speculate that this blunting is due to fear of the hypoglycaemia, that is commonly associated with sulfonylureas [10], and fear of weight gain associated with defensive eating, which may have reduced patient compliance with sulfonylurea therapy, and/or led to lack of aggressive dose up-titration, in observational studies in which no rigid protocol dictates dosing. In contrast, with vildagliptin, the risk for hypoglycaemia (and associated defensive eating) is markedly lower, thereby avoiding the fear of hypoglycaemia and allowing the same patient compliance in real life as in RCTs. The body weight data with sulfonylureas (a small decrease in EDGE and a significant increase in RCTs) is consistent with the above speculation. However, there is no clear explanation for the small differences in weight loss with vildagliptin under the two study conditions although it should be acknowledged that weight was more systematically determined in the RCTs than in EDGE. The

failure to collect dose information in the observational trial is also a limitation of the present comparison.

In summary, this work shows that the lowering of HbA_{1c} with sulfonylurea treatment was diminished in real life relative to RCTs, whereas for vildagliptin, the improvement in glycaemia was the same in RCTs and the observational trial. These data therefore show that the full power of treatment is retained in real life for vildagliptin whereas sulfonylureas are less efficacious in real life than in RCTs. We suggest that the reduced power of sulfonylureas in real life may be due to fear of hypoglycaemia and the associated weight gain.

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AUTHOR CONTRIBUTIONS AND POTENTIAL DUALITIES OF INTEREST

All authors had full access to all data and take responsibility for the integrity of the data and accuracy of analyses. All provided input to the analytical approach, interpretation of data,

preparation, revision and final approval of the manuscript. BA has received research support, honoraria for speaking engagements and served on advisory boards for Novartis and has received honoraria for lecturing or participation in advisory board also from AstraZeneca, GSK, Merck, Novo Nordisk, Sanofi and Takeda. CM has received honoraria for lectures and/or advisory work from Novo Nordisk, sanofi-aventis, MSD, Eli Lilly, Novartis, BMS, AstraZeneca, Pfizer, J&J, and Mankind; her institution has received research support from Novo Nordisk, sanofi-avenis, MSD, Eli Lilly, and Novartis. GB, AS and JEF are employees of Novartis; AS and JEF own shares in Novartis.

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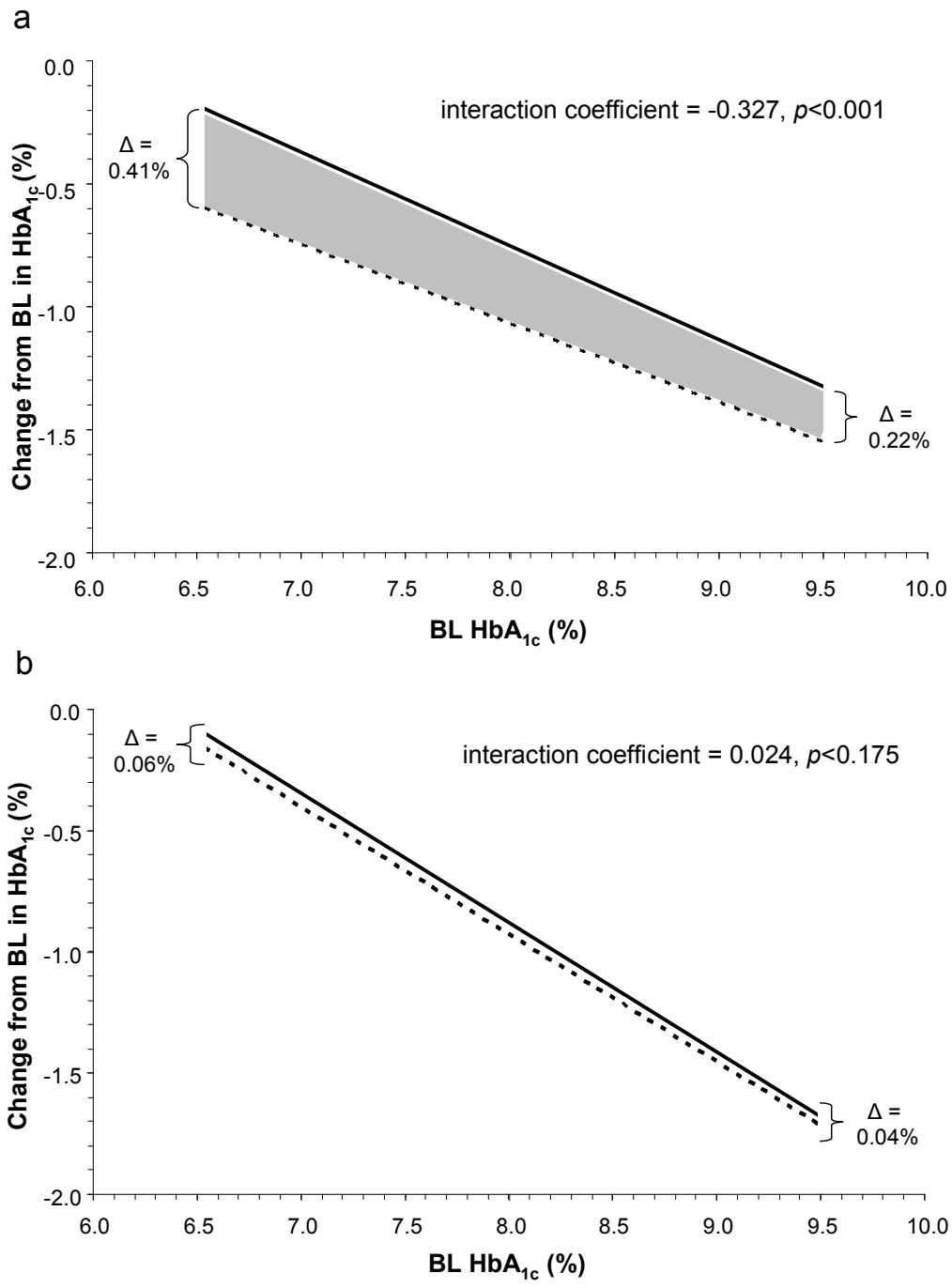

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Figure 1

FIGURE LEGEND

Figure 1: Change from baseline (baseline) in HbA_{1c} as a function of baseline HbA_{1c} in patients with T2DM after 12 month treatment with sulfonylurea (SU) and metformin (panel a) or vildagliptin and metformin (panel b) during an observational study (EDGE, solid line) or randomized, controlled trials (RCT, dashed line).