Vascular Health and Risk Management

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

A double-blind, randomized trial, including frequent patient–physician contacts and Ramadan-focused advice, assessing vildagliptin and gliclazide in patients with type 2 diabetes fasting during Ramadan: the STEADFAST study

This article was published in the following Dove Press journal:
Vascular Health and Risk Management
28 May 2014
Number of times this article has been viewed

Mohamed Hassanein[1]
Khalifa Abdallah[2]
Anja Schweizer[3]

[1]Betsi Cadwaladr University Health Board, Wales, United Kingdom; [2]Clinical Research Center, Alexandria University Hospital, Alexandria, Egypt; [3]Global Medical Affairs, Novartis Pharma AG, Basel, Switzerland

Background: Several observational studies were conducted with vildagliptin in patients with type 2 diabetes mellitus (T2DM) fasting during Ramadan, showing significantly lower incidences of hypoglycemia with vildagliptin versus sulfonylureas, including gliclazide. It was of interest to complement the existing real-life evidence with data from a randomized, double-blind, clinical trial.

Clinical Trials Identifier: NCT01758380.

Methods: This multiregional, double-blind study randomized 557 patients with T2DM (mean glycated hemoglobin [HbA_{1c}], 6.9%), previously treated with metformin and any sulfonylurea to receive either vildagliptin (50 mg twice daily) or gliclazide plus metformin. The study included four office visits (three pre-Ramadan) and multiple telephone contacts, as well as Ramadan-focused advice. Hypoglycemic events were assessed during Ramadan; HbA_{1c} and weight were analyzed before and after Ramadan.

Results: The proportion of patients reporting confirmed (<3.9 mmol/L and/or severe) hypoglycemic events during Ramadan was 3.0% with vildagliptin and 7.0% with gliclazide (P=0.039; one-sided test), and this was 6.0% and 8.7%, respectively, for any hypoglycemic events (P=0.173). The adjusted mean change pre- to post-Ramadan in HbA_{1c} was 0.05%±0.04% with vildagliptin and –0.03%±0.04% with gliclazide, from baselines of 6.84% and 6.79%, respectively (P=0.165). In both groups, the adjusted mean decrease in weight was –1.1±0.2 kg (P=0.987). Overall safety was similar between the treatments.

Conclusion: In line with the results from previous observational studies, vildagliptin was shown in this interventional study to be an effective, safe, and well-tolerated treatment in patients with T2DM fasting during Ramadan, with a consistently low incidence of hypoglycemia across studies, accompanied by good glycemic and weight control. In contrast, gliclazide showed a lower incidence of hypoglycemia in the present interventional than the previous observational studies. This is suggested to be linked to the specific circumstances of this study, including frequent patient–physician contacts, Ramadan-focused advice, a recent switch in treatment, and very well-controlled patients, which is different from what is often seen in real life.

Keywords: dipeptidyl peptidase 4, fasting, incretin, type 2 diabetes mellitus, hypoglycemia, Ramadan

Correspondence: Mohamed Hassanein
Betsi Cadwaladr University Health Board, Rhyl, N Wales, LL18 5UJ, United Kingdom
Tel +971 5566 76217
Email mhassanein148@hotmail.com

Introduction

The dipeptidyl peptidase 4 (DPP-4) inhibitor vildagliptin increases the sensitivity of the α and β cells to glucose, resulting in glucose-dependent secretion of insulin

and glucagon, which underlies its improvement of glucose control in patients with type 2 diabetes mellitus (T2DM), as well as its low risk of causing hypoglycemia.[1] Preservation of glucagon counter-regulation to hypoglycemia has been specifically shown for vildagliptin in patients with T2DM[2,3] and type 1 diabetes[4] and is likely a glucose-dependent insulinotropic polypeptide-mediated effect.[5] The corresponding clinical benefit is particularly promising for patients exposed to a higher risk for hypoglycemia, including elderly patients with T2DM[6] and patients with T2DM undergoing prolonged fasting, such as during the holy month of Ramadan.

Ramadan involves major changes in dietary habits, in particular, a complete abstinence from food and fluid intake from dawn to sunset. Decreased food intake or missed meals are well-established risk factors for hypoglycemia, which accordingly is a key concern in patients with T2DM fasting during Ramadan.[7] The population-based Epidemiology of Diabetes and Ramadan (EPIDIAR) study, for example, showed a 7.5 times increase in hypoglycemia (leading to hospitalization) during Ramadan versus during the preceding months,[8] and in an observational study, the incidence of symptomatic hypoglycemia was 20% during Ramadan in sulfonylurea (SU)-treated patients.[9] Although the American Diabetes Association recommends that SUs be used with caution and be individualized during Ramadan,[7] it also needs to be considered that the hypoglycemic potential of different SUs is not identical, with newer-generation secretagogues such as gliclazide often showing a lower incidence both in the general T2DM population[10,11] and when used during Ramadan.[7,9]

Several observational studies have been conducted with vildagliptin over the last years in patients with T2DM fasting during Ramadan, consistently showing a low incidence of hypoglycemia with the DPP-4 inhibitor.[12] The observational Ramadan study in the United Kingdom, VECTOR (Vildagliptin Experience Compared To gliclazide Observed during Ramadan; N=59), for example, reported that no patients in the vildagliptin plus metformin group versus 41.7% of patients in the gliclazide plus metformin group experienced hypoglycemia.[13] Vildagliptin also significantly lowered glycated hemoglobin (HbA_{1c}) (from 7.7% to 7.2%) versus gliclazide (from 7.2% to 7.3%) pre- to post-Ramadan. Furthermore, in the large (N>1300) observational Ramadan study, VIRTUE (VildagliptIn expeRience compared wiTh sulphonylUreas obsErved during Ramadan), conducted across 10 countries in the Middle East and Asia, significantly fewer patients reported hypoglycemic events (HEs) with vildagliptin compared with SUs (5.4% versus 19.8%).[14] The incidence of hypoglycemia was also lower with vildagliptin when compared with each individual SU, including gliclazide (19.2%). This was associated with good glycemic (HbA_{1c} change, −0.24% with vildagliptin versus +0.02% with SUs) and weight (−0.76 and −0.13 kg, respectively) control.

In contrast to the diverse experience available with vildagliptin in patients with T2DM fasting during Ramadan from observational, real-life studies, vildagliptin had not been studied during Ramadan in a randomized controlled, double-blind, clinical trial. Given that the two trial settings have different strengths and weaknesses, it was of interest to complement the existing evidence for vildagliptin with data from an interventional study. The present trial, STudy Evaluating vildAgliptin compareD to gliclazide in patients with type 2 diabetes FASTing during Ramadan (STEADFAST), was therefore undertaken across countries in the Middle East, Europe, and Asia and, to our knowledge, represents the first randomized, double-blind study with a DPP-4 inhibitor in patients with T2DM fasting during Ramadan. Beyond its randomized controlled, double-blind nature, the study had additional important design features, in that the protocol included multiple patient–physician contacts before and during the Ramadan fasting period, stipulated to provide Ramadan-focused advice, which plays an important role in the safe management of T2DM during Ramadan fasting,[15] and required patients to be switched from their previous dual SU and metformin therapy to the study treatments (vildagliptin or gliclazide plus metformin).

Methods

Study design and patient population

STEADFAST was a multicenter, double-blind, double-dummy, randomized, active-controlled, parallel-group interventional clinical trial conducted at 69 sites in 16 countries across the Middle East, Europe, and Asia.

The key inclusion criteria for this study included age 18 years or older, body mass index 22–45 kg/m^2, HbA_{1c} 8.5% or lower, T2DM treated with metformin (≥1,500 mg daily) plus any SU (for ≥12 weeks and, for SU, also ≤3 years) and the intention to fast during Ramadan 2013. Patients were excluded if they had an acute metabolic condition (such as ketoacidosis), a current diagnosis of congestive heart failure (New York Heart Association class III or IV), other significant cardiovascular history within 6 months, acute or chronic liver disease or abnormal liver tests (alanine transaminase or aspartate transaminase more than three times the upper limit of normal, or bilirubin [total] more than two times the upper limit of normal), or clinically significant renal dysfunction

(estimated glomerular filtration rate by Modification of Diet in Renal Disease, <60 mL/minute/1.73 m^2).

After an up-to-4-week screening period, eligible patients were randomized using interactive response technology in a 1:1 ratio to receive either vildagliptin or gliclazide in a double-blind, double-dummy fashion, in addition to continuing their open-label metformin therapy (at 1,500–2,500 mg daily). After the treatment switch from their previous SU therapy, vildagliptin was administered at 50 mg twice daily (bid), and gliclazide was to be given at an equivalent dose to previous SU in multiples of 80 mg, with the final dose decision being at the investigator's discretion.

In addition to the screening (V1) and randomization (V2) visits, the study required a pre-Ramadan visit (V3; within 4 weeks before the start of Ramadan, often occurring close to the start of Ramadan) and an end-of-study visit (V4; within 4 weeks after the end of Ramadan). In addition to the four office visits (3 before Ramadan and 1 after Ramadan), the study protocol required multiple telephone contacts (at least one between V2 and V3 and weekly starting from 1 week before Ramadan to the end of Ramadan). The protocol further stipulated that individualized Ramadan-focused advice was to be given to each patient at the pre-Ramadan visit (V3). This was to follow international and/or local guidelines in a personalized manner, rather than in a formal, standardized educational program; in this regard, the protocol specifically recommended inclusion of the importance of individualizing treatment/treatment adjustments, regularly monitoring blood glucose levels, and tailoring nutritional advice.

The overall treatment duration consisted of an 8-week or longer pre-Ramadan stabilization period, the 4-week Ramadan period, and a post-Ramadan period of 4 or fewer weeks.

Study assessments

The primary study objective was to assess the proportion of patients with at least one HE during the Ramadan fasting period in patients treated with vildagliptin or gliclazide plus metformin dual therapy. Each patient was provided with a diary, for recording hypoglycemia-related symptoms and blood glucose levels, as well as a home glucose monitor. Patients were educated regarding hypoglycemia symptoms and treatment and the use of the home glucose monitor.

Hypoglycemia was defined as reported symptoms of low blood glucose, with or without confirmatory self-monitored blood glucose (SMBG) measurement lower than 3.9 mmol/L plasma glucose equivalent, or any asymptomatic SMBG measurements lower than 3.9 mmol/L plasma glucose equivalent. In addition, confirmed hypoglycemia was assessed and included symptomatic and asymptomatic events with a SMBG measurement lower than 3.9 mmol/L plasma glucose equivalent and all severe episodes (ie, requiring assistance of another party, whether or not an SMBG measurement was available), which were also evaluated separately.

HbA_{1c} and weight were measured at all visits and assessed from pre-Ramadan (V3) to post-Ramadan/end of study and from randomization (V2) to post-Ramadan/end of study. In addition, the number of fasting days, treatment adherence, and study medication changes were recorded.

All adverse events (AEs) were recorded and assessed by the investigator for severity and possible relationship to study medication. Glomerular filtration rate was estimated by the Modification of Diet in Renal Disease method.

HbA_{1c} and routine biochemistry laboratory assessments were performed by a central laboratory (Eurofins, Breda, the Netherlands).

Statistical analyses

The Randomized set included all randomized patients. The Per Protocol set (PPS) included all randomized patients who received at least a single dose of study medication, who fasted and took study medication for at least 10 days during Ramadan, and who had no major other protocol deviations. The Safety set consisted of all randomized patients who received at least a single dose of study medication.

The proportion of patients reporting HEs (any, confirmed, severe) were analyzed using a one-sided Fisher's exact test performed on data from the PPS. Data were censored at the start of rescue medication. In addition, the relative risk ratio between the two treatment groups in the proportion of patients experiencing HEs (any, confirmed) during the Ramadan fasting period was analyzed in the PPS, using a Cochran–Mantel–Haenszel test stratified by pooled center.

The change in HbA_{1c} from pre- to post-Ramadan (ie, HbA_{1c} value at post-Ramadan/end point minus HbA_{1c} value at V3), as well as during the entire study duration (ie, HbA_{1c} value at post-Ramadan/end point minus HbA_{1c} value at V2 or the closest prior measurement if the V2 measurement was missing) was calculated in the PPS, using an analysis of covariance model with treatment and pooled center as the classification variables and baseline HbA_{1c} as the covariate. Post-Ramadan/end point was defined as the HbA_{1c} measurement obtained at V4 or the final available postbaseline HbA_{1c} measurement obtained at any visit during or after Ramadan if the V4 measurement was missing. Data were censored at the start of rescue medication. The changes in body weight

from pre- to post-Ramadan, as well as during the entire study duration, were analyzed using a similar model as for HbA_{1c}.

Other parameters such as number of fasting days in the Ramadan fasting period, treatment adherence during Ramadan, and study medication changes were summarized descriptively. Safety data were also summarized descriptively by treatment in the Safety set.

The values presented are means ± standard error unless specified otherwise.

Ethics and good clinical practice

The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000 and 2008, and the International Conference on Harmonization/Good Clinical Practice guidelines. The study protocol was approved by an independent ethics committee/institutional review board at each site, and all patients provided written informed consent.

Results

Patient disposition and patient demographic/clinical characteristics

A total of 557 patients were randomized: 279 patients to receiving vildagliptin (50 mg bid) plus metformin and 278 patients to receiving gliclazide (80–320 mg/day) plus metformin. In each treatment group, 239 patients (86%) completed the study, with the most common reasons for discontinuation being withdrawal of consent (vildagliptin, 5.0%; gliclazide, 4.7%) and AEs (vildagliptin, 2.9%; gliclazide, 3.6%).

Patients included in the study were recruited in the Middle East (>50%), Europe, and Asia. Contributing countries were Egypt (15.4% of patients), Lebanon (15.3%), Tunisia (10.2%), Russia (9.0%), Indonesia (6.8%), Germany (6.6%), Jordan (6.3%), Singapore (5.6%), United Kingdom (5.6%), Turkey (4.5%), Spain (4.3%), Malaysia (3.8%), Kuwait (2.3%), Saudi Arabia (2.3%), United Arabic Emirates (1.8%), and Denmark (0.2%).

Table 1 summarizes the demographic and clinical characteristics in the randomized population. Patients (47% men/53% women) had a mean age of 54.4 years, a mean body mass index of 30.9 kg/m^2, and a mean T2DM duration of 4.7 years. Patients' T2DM was well-controlled, with a mean HbA_{1c} of 6.9% (76% of patients with HbA_{1c} ≤7.5%) and mean fasting plasma glucose of 7.9 mmol/L. Before entering the study, patients were treated with metformin at a mean dose of 1,828 mg/day (mean duration, 44.7 months) combined with the following SUs (mean duration, 18.0 months): gliclazide (33% of patients; mean daily dose, 134.8 mg), glibenclamide (19% of patients; mean daily dose, 7.6 mg), glimepiride (42% of patients; mean daily dose, 2.4 mg), and glipizide (5% of patients; mean daily dose, 9.4 mg). More than 50% of patients had hypertension, more than 40% had dyslipidemia, approximately two-thirds of patients had normal renal function, and the remaining third had mild renal impairment (Table 1). These demographic and clinical characteristics were, overall, well-balanced between the two treatment groups.

Table 1 Patient demographic and clinical characteristics (randomized set)

Mean ± standard deviation or n (%)	Vildagliptin (50 mg twice a day)	Gliclazide (80–320 mg/day)
N	279	278
Age, years	54.6±9.3	54.3±9.1
Sex		
Men	132 (47.3)	128 (46.0)
Women	147 (52.7)	150 (54.0)
Race		
Caucasian	187 (67.0)	173 (62.2)
Asian	68 (24.4)	72 (25.9)
All other	24 (8.6)	33 (11.9)
HbA_{1c}, %	7.0±0.8	6.9±0.8
≤7.5%	205 (73.5)	218 (78.4)
>7.5%	74 (26.5)	60 (21.6)
Fasting plasma glucose, mmol/L	7.9±1.9	7.8±1.9
Body weight, kg	82.5±14.4	83.4±15.4
Body mass index, kg/m^2	30.7±5.0	31.1±5.2
Duration of type 2 diabetes mellitus, years	4.8±4.1	4.7±3.8
eGFR (MDRD)		
Normal, >80 mL/minute/1.73 m^2	189 (67.7)	180 (64.7)
Mild, ≥50 to ≤80 mL/minute/1.73 m^2	90 (32.3)	97 (34.9)
Cardiovascular history		
Hypertension	142 (50.9)	148 (53.2)
Dyslipidemia	115 (41.2)	127 (45.7)

Abbreviations: eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; MDRD, Modification of Diet in Renal Disease.

Patients fasted during Ramadan for a mean (standard deviation) of 28.3 (3.0) days in the vildagliptin group and 28.1 (3.8) days in the gliclazide group.

Treatment adherence and study medication changes

Treatment adherence during the Ramadan fasting period was high in both treatment groups, with only a small difference in the number of missed doses between vildagliptin plus metformin (7.3±1.4 doses) and gliclazide plus metformin (9.6±1.6 doses).

The metformin dose in both treatment groups (~1,800 mg/day), as well as the vildagliptin dose, remained nearly unchanged during the study (in accordance with the product information, dose adjustment of vildagliptin was not a given option in the study). The mean daily gliclazide doses were 122 mg at randomization (V2), 130 mg pre-Ramadan (as recommended by the investigator at V3), and 129 mg post-Ramadan. Data about timing/timing changes (including the morning versus evening split) for metformin and gliclazide were not collected in the study.

Hypoglycemia

The proportion of patients who reported any HE during the Ramadan fasting period was numerically lower in the vildagliptin 50 mg bid plus metformin group (6.0%) compared with the gliclazide plus metformin group (8.7%); however, the difference between treatments did not reach statistical significance (P=0.173; one-sided test). The numerical trend was more pronounced for the prespecified subcategory of confirmed HEs, with 3.0% of patients in the vildagliptin group versus 7.0% of patients in the gliclazide group reporting such an event (P=0.039; one-sided test). The corresponding relative risk (vildagliptin versus gliclazide) of patients with HEs during the Ramadan fasting period was 0.72 (95% confidence interval, 0.38–1.36; P=0.307) for any HEs and 0.46 (95% confidence interval, 0.20–1.06; P=0.059) for confirmed HEs. There were no severe HEs reported in either treatment group.

HbA_{1c} and body weight changes

Glycemic control from pre-Ramadan (V3) to post-Ramadan was stable in both treatment groups. The adjusted mean change in HbA_{1c} was 0.05%±0.04% (baseline =6.84%) in the vildagliptin 50 mg bid plus metformin group and −0.03%±0.04% (baseline, 6.79%) in the gliclazide plus metformin group (P=0.165 for between-group difference). Similar results were also seen during the entire study period. After the switch from their prior treatment with metformin and SU to the study treatments at randomization (V2), the adjusted mean changes in HbA_{1c} from identical baselines of 6.94% to post-Ramadan/end point were −0.01%±0.05% with vildagliptin and −0.13%±0.05% with gliclazide, respectively (P=0.100).

In both treatment groups, the adjusted mean decrease in body weight from pre-Ramadan to post-Ramadan was −1.1±0.2 kg (baseline, 82.2 kg [vildagliptin 50 mg bid] and 82.6 kg [gliclazide], respectively; P=0.987). Over the entire study duration, the adjusted mean decrease in body weight was −1.9±0.2 kg in the vildagliptin group and −1.7±0.2 kg in the gliclazide group (baseline, 83.0 kg and 83.2 kg, respectively; P=0.423).

Safety and tolerability

There were no important differences in the overall AE profiles between vildagliptin and gliclazide in combination with metformin. AEs were reported with a slightly lower frequency in patients receiving vildagliptin than in patients receiving gliclazide (34.4% versus 42.3%), driven partly by AEs in the system organ class of "infections and infestations" (4.0% with vildagliptin versus 7.7% with gliclazide). The incidence of serious AEs (2.2% versus 1.5%) and discontinuations because of AEs (2.9% versus 4.0%) was low and comparable in the two treatment groups. No patients died during the study. Other than hypoglycemia, the most commonly reported specific AEs in the study were dizziness (4.8% versus 5.1%) and diarrhea (4.0% versus 4.4%). Differences between treatment groups were small for specific AEs; a somewhat larger difference was reported for headache (1.8% with vildagliptin versus 5.8% with gliclazide).

Discussion

To our knowledge, STEADFAST is the first randomized controlled, double-blind study to date assessing the benefit of DPP-4 inhibitor treatment in Muslim patients with T2DM fasting during Ramadan.

The data from this interventional study showed that vildagliptin in combination with metformin is an effective and well-tolerated treatment option in patients with T2DM fasting during Ramadan, with a low incidence of hypoglycemia (6.0% for any HEs and 3.0% for confirmed HEs) and similar efficacy to the SU gliclazide in combination with metformin (HbA_{1c} +0.05% versus −0.03%). Vildagliptin was also associated with good treatment adherence, as well as a small decrease in body weight (−1.1 kg), and the study did not identify any safety signals or unforeseen risks in vildagliptin-treated patients with T2DM fasting during Ramadan. Importantly, the results from this randomized, double-blind study for vildagliptin are consistent with the findings from the previous observational studies and, thus, can predict the effectiveness observed under normal therapeutic conditions. For example, the large VIRTUE observational study reported that 5.4% of patients treated with vildagliptin experienced any HEs (with or without confirmation) and 2.7% reported confirmed (<3.9 mmol/L) hypoglycemia during the Ramadan fasting period,[14] which is very similar to the results of the present study.

Under the conditions of the present study, including multiple patient–physician contacts and protocol-stipulated Ramadan-focused advice, as further discussed here, gliclazide in combination with metformin also showed a low incidence of hypoglycemia. Although numerically still higher than with vildagliptin, in particular when assessing confirmed events, the difference between the two treatments did not reach statistical significance. Notably, in contrast to the findings with vildagliptin, gliclazide showed a markedly lower incidence of HEs in the present randomized, double-blind trial setting (8.7% for any HEs and 7.0% for confirmed HEs) than previously observed in several nonrandomized, observational studies comparing the two treatments.[13,14,16] For example, in the above-mentioned VIRTUE study, 19.8% of patients treated with any SU and 19.2% of patients treated with gliclazide reported HEs.[14] Of the events with SUs, 12.9% were confirmed.

Although it needs to be recognized that gliclazide is among the SUs with low rates of hypoglycemia and was used at an intermediate, rather than maximum, dose in the present study, the low hypoglycemia rate nevertheless merits comment, in particular, in view of the very low HbA_{1c} of the recruited patients (mean HbA_{1c} <7%, lower than in any of the previous studies). T2DM, as such, is associated with impaired glucagon counter-regulation,[17] and SUs have previously been shown to significantly impair this glucagon response in patients with T2DM.[18,19] At the same time, insulin secretion is stimulated in a glucose-independent way. Thus, hypoglycemia remains a considerable risk, especially at low levels of glycemia.

It is therefore of interest to further consider the effect of the interventional nature of the present study versus the naturalistic setting of the previous observational trials. First, special caution may have been applied in selecting patients enrolled in the present study, potentially favoring individuals who were very well-controlled and who have demonstrated that they can avoid HEs with an SU at their low level of glycemia. This may have played a more important role for physicians, given the randomized, double-blind nature of the study, which included treatment switches in both treatment group at randomization, compared with an observational study setting, in which the regular treatment of the patients is continued. Of note, the mean HbA_{1c} of the patients entering the present study (6.9%; 76% of patients with $HbA_{1c} \leq 7.5\%$) was considerably lower than that often seen in clinical practice in patients treated with an SU plus metformin, both when used in a population fasting during Ramadan[13,14] or in the general T2DM population.[20] Second, the switch in SU treatment to gliclazide a few weeks pre-Ramadan and the frequent contacts with the patients provided the physicians with the opportunity to prescribe and tailor the SU dose according to the patients' needs. It is important, in this regard, to keep in mind that in addition to the randomized, double-blind nature of the study, the STEADFAST trial had several important additional design features that may have contributed to the observed outcome.

The protocol required multiple patient–physician contacts, including three pre-Ramadan visits, with the third visit mostly being very close to Ramadan, as well as weekly telephone contacts starting 1 week before the start of Ramadan until the end of Ramadan. In addition, the patients in the study were distributed over a large number of sites/physicians. Finally, the protocol stipulated that individualized Ramadan-focused advice was to be given to each patient, in line with international and/or local guidelines. Thus, the interventional clinical trial setting, together with the specific protocol features, have created circumstances quite different from what is often seen in clinical practice or what has been reported in the previous observational Ramadan studies.[13,14,16] In particular, the study protocol requirements likely resulted in considerably more time spent between the physician/site personnel and the patient in the pre-Ramadan and Ramadan periods than would routinely occur under real-life conditions. This ensured an unusually well-controlled and educated population in which patients were properly advised regarding the risks and behaviors during Ramadan, as well as optimal management of gliclazide use. Of note, Ramadan-focused education has previously been shown to markedly reduce the risk of hypoglycemia in patients with T2DM treated mainly with gliclazide, either as monotherapy or combination therapy.[15] Bravis et al reported a nearly 50% reduction in the hypoglycemic event rate from pre-Ramadan to Ramadan, despite fasting, in a group participating in a Ramadan-focused diabetes education program, whereas the control group experienced a fourfold increase.[15] Of interest, lower incidences of hypoglycemia with gliclazide than seen in the observational Ramadan studies have also been observed in two randomized, open-label studies comparing sitagliptin and SUs, including gliclazide.[21,22] Thus, the particular attention and education provided within the interventional trial setting of the STEADFAST study, a situation rather different from what can often be achieved in clinical practice, may have significantly contributed to the observed low risk of hypoglycemia with gliclazide in the study. On the basis of its mechanism of action,[1] a similar difference between the trial situation and real life, as observed for gliclazide, would not be expected for vildagliptin and has not been seen.

Glycemic control, assessed as changes in HbA_{1c}, remained stable pre- to post-Ramadan with both treatments (0.05% with vildagliptin plus metformin versus −0.03% with gliclazide plus metformin), indicating that similar efficacy can be achieved during the Ramadan fasting period with vildagliptin and gliclazide. There was also no change in HbA_{1c} with vildagliptin, from randomization to the end of the study (−0.01%). Thus, patients in the vildagliptin group, who were all to be switched from an SU to vildagliptin at study entry, did not lose the glycemic control achieved with their previous SU treatment.

In both treatment groups, a small decrease in body weight from pre-Ramadan to post-Ramadan of 1.1 kg was observed. A similar decrease in body weight in patients with low (<7%) baseline HbA_{1c} has previously been reported for vildagliptin in a non-Ramadan setting.[23] Although gliclazide use is often associated with an increase in body weight,[24,25] it is of interest that in the previously discussed study by Bravis et al, patients mainly treated with gliclazide who were participating in a Ramadan-focused diabetes education program showed a small weight loss during Ramadan (−0.7 kg), similar to what has been seen in the present study; in contrast, the control group not participating in the program reported a weight increase of the same magnitude.[15]

Taken together, this randomized controlled, double-blind study with a DPP-4 inhibitor in Ramadan showed that patients with T2DM can safely and effectively fast during Ramadan. For vildagliptin, the low risk for hypoglycemia predicted from its mechanism of action was consistently seen between the present interventional and previous observational studies, with comparable efficacy to gliclazide. In contrast to previous observational studies, the reported difference in hypoglycemia between vildagliptin and gliclazide was smaller and did not reach statistical significance. The results suggest that the lower hypoglycemia rate for gliclazide seen in the present study may be linked to the special conditions of the STEADFAST study, in which the particular attention to each patient, Ramadan-focused advice, the recent switch in treatment, as well as the patients' very good glycemic control have created a setting that is often not reflected in real life, as seen, for example, from the results of the VIRTUE study.[14]

Acknowledgments

This study was funded by Novartis Pharma AG. The authors gratefully acknowledge all the investigators, staff, and patients at the participating sites and Sanchika Agarwal (Novartis Healthcare Pvt Ltd) for technical help.

The following investigators participated in the study and recruited patients: Denmark, Shabbir Ahmed; Egypt, Khalifa Abdallah, Aly Ahmed Abdel Rahim Mahmoud, Samir Assaad Khalil, Samir Assaad and Moghazy Mahmoud Mahgoub; Germany, Anwar Ansari, Katharina Balck, Fajr Bannout, Dietlein Michael, Iris Donati-Hirsch, Frank Franzmann, Uwe Gerbaulet, Mahmoud Sultan and Manuela Thinesse-Mallwitz; Indonesia, Djoko Soeatmadji, Soebagijo Adi Soelistijo, Dante Harbuwono, Roy Sibarani and Asman Manaf; Jordan, Mohamad Abu-Hijleh; Kuwait, Monira Al Arouj; Lebanon, Akram Salim Echtay, Rafic Kanaan, Sami Azar and Marie Merheb; Malaysia, Wan Mohd Izani Bin Wan Mohamed and Chia Yook Chin; Russia, Marina Sergeeva-Kondrachenko, Natalya Volkova, Liudmila Ivanova, Yury Khalimov, Ruslan Sardinov, Sergey Vorobyev, Yury Shvarts and Tatyana Morugova; Saudi Arabia, Abdul Mohsen Habib Al Elq and Saleh Jaser Al Jaser; Singapore, Wee Kien Han Andrew, How Choon How and Tang Wern Ee; Spain, Andreu Nubiola, Belen Benito, Joan Barrot, Manel Terns Riera, Francisco Tinahones Madueño, Enrique Crespillo and Guillermo Isasti; Tunisia, Slimane Hedia nee Houissa, Samira Blouza-Chabchoub, Faika Ben Mami Ep Ben Miled, Nejib Ben Abdallah, Zidi Borni, Larbi Chaieb, Khoctali Ines and Mohamed Abid; Turkey, Mehmet Buyukbese, Tuncay Delibasi, Yagiz Uresin, Zerrin Yigit and Ayhan Kilic; United Arab Emirates, Ghaidaa Kaddaha; United Kingdom, Mohamed Wasim Hanif, Rayez Malik, Anthony Barnett, Waqar Malik, Harnovdeep Singh Bharaj, Kamlesh Khunti and Iskander Idris.

Disclosure

AS is employed by Novartis and owns shares. MH received honoraria from Novartis, Novo Nordisk, Servier, Sanofi, and Eli Lilly. KA has received honoraria from Novartis, MSD, Novo Nordisk, Eli Lilly, Sanofi, Servier, AstraZeneca, and Merck Serono. The authors report no other conflicts of interest in this work.

References

1. Ahrén B, Schweizer A, Dejager S, Villhauer EB, Dunning BE, Foley JE. Mechanisms of action of the dipeptidyl peptidase-4 inhibitor vildagliptin in humans. *Diabetes Obes Metab*. 2011;13(9):775–783.
2. Ahrén B, Schweizer A, Dejager S, et al. Vildagliptin enhances islet responsiveness to both hyper- and hypoglycemia in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2009;94(4):1236–1243.
3. Farngren J, Persson M, Schweizer A, Foley JE, Ahrén B. Glucagon dynamics during hypoglycaemia and food-re-challenge following treatment with vildagliptin in insulin-treated patients with type 2 diabetes. *Diabetes Obes Metab*. Epub February 26, 2014.
4. Farngren J, Persson M, Schweizer A, Foley JE, Ahrén B. Vildagliptin reduces glucagon during hyperglycemia and sustains glucagon counterregulation during hypoglycemia in type 1 diabetes. *J Clin Endocrinol Metab*. 2012;97(10):3799–3806.

5. Christensen M, Vedtofte L, Holst JJ, Vilsbøll T, Knop FK. Glucose-dependent insulinotropic polypeptide: a bifunctional glucose-dependent regulator of glucagon and insulin secretion in humans. *Diabetes*. 2011;60(12):3103–3109.
6. Schweizer A, Dejager S, Foley JE, Shao Q, Kothny W. Clinical experience with vildagliptin in the management of type 2 diabetes in a patient population ≥75 years: a pooled analysis from a database of clinical trials. *Diabetes Obes Metab*. 2011;13(1):55–64.
7. Al-Arouj M, Assaad-Khalil S, Buse J, et al. Recommendations for management of diabetes during Ramadan: update 2010. *Diabetes Care*. 2010;33(8):1895–1902.
8. Salti I, Bénard E, Detournay B, et al; EPIDIAR study group. A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. *Diabetes Care*. 2004;27(10):2306–2311.
9. Aravind SR, Al Tayeb K, Ismail SB, et al; 2009 Ramadan Study Group. Hypoglycaemia in sulphonylurea-treated subjects with type 2 diabetes undergoing Ramadan fasting: a five-country observational study. *Curr Med Res Opin*. 2011;27(6):1237–1242.
10. Schernthaner G, Grimaldi A, Di Mario U, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. *Eur J Clin Invest*. 2004;34(8):535–542.
11. Tayek J. SUR receptor activity vs incidence of hypoglycaemia and cardiovascular mortality with sulphonylurea therapy for diabetics. *Diabetes Obes Metab*. 2008;10(11):1128–1129.
12. Schweizer A, Halimi S, Dejager S. Experience with DPP-4 inhibitors in the management of patients with type 2 diabetes fasting during Ramadan. *Vasc Health Risk Manag*. 2014;10:15–24.
13. Hassanein M, Hanif W, Malik W, et al. Comparison of the dipeptidyl peptidase-4 inhibitor vildagliptin and the sulphonylurea gliclazide in combination with metformin, in Muslim patients with type 2 diabetes mellitus fasting during Ramadan: results of the VECTOR study. *Curr Med Res Opin*. 2011;27(7):1367–1374.
14. Al-Arouj M, Hassoun AA, Medlej R, et al. The effect of vildagliptin relative to sulphonylureas in Muslim patients with type 2 diabetes fasting during Ramadan: the VIRTUE study. *Int J Clin Pract*. 2013;67(10):957–963.
15. Bravis V, Hui E, Salih S, Mehar S, Hassanein M, Devendra D. Ramadan Education and Awareness in Diabetes (READ) programme for Muslims with Type 2 diabetes who fast during Ramadan. *Diabet Med*. 2010;27(3):327–331.
16. Devendra D, Gohel B, Bravis V, et al. Vildagliptin therapy and hypoglycaemia in Muslim type 2 diabetes patients during Ramadan. *Int J Clin Pract*. 2009;63(10):1446–1450.
17. Bolli GB, Tsalikian E, Haymond MW, Cryer PE, Gerich JE. Defective glucose counterregulation after subcutaneous insulin in noninsulin-dependent diabetes mellitus. Paradoxical suppression of glucose utilization and lack of compensatory increase in glucose production, roles of insulin resistance, abnormal neuroendocrine responses, and islet paracrine interactions. *J Clin Invest*. 1984;73(6):1532–1541.
18. Landstedt-Hallin L, Adamson U, Lins PE. Oral glibenclamide suppresses glucagon secretion during insulin-induced hypoglycemia in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 1999;84(9):3140–3145.
19. Ahrén B, Foley JE, Ferrannini E, et al. Changes in prandial glucagon levels after a 2-year treatment with vildagliptin or glimepiride in patients with type 2 diabetes inadequately controlled with metformin monotherapy. *Diabetes Care*. 2010;33(4):730–732.
20. Lafeuille MH, Grittner AM, Gravel J, et al. Quality measure attainment in patients with type 2 diabetes mellitus. *Am J Manag Care*. 2014;20(Suppl 1):s5–s15.
21. Al Sifri S, Basiounny A, Echtay A, et al; 2010 Ramadan Study Group. The incidence of hypoglycaemia in Muslim patients with type 2 diabetes treated with sitagliptin or a sulphonylurea during Ramadan: a randomised trial. *Int J Clin Pract*. 2011;65(11):1132–1140.
22. Aravind SR, Ismail SB, Balamurugan R, et al. Hypoglycemia in patients with type 2 diabetes from India and Malaysia treated with sitagliptin or a sulfonylurea during Ramadan: a randomized, pragmatic study. *Curr Med Res Opin*. 2012;28(8):1289–1296.
23. Scherbaum WA, Schweizer A, Mari A, et al. Evidence that vildagliptin attenuates deterioration of glycaemic control during 2-year treatment of patients with type 2 diabetes and mild hyperglycaemia. *Diabetes Obes Metab*. 2008;10(11):1114–1124.
24. Matthews DR, Charbonnel BH, Hanefeld M, Brunetti P, Schernthaner G. Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study. *Diabetes Metab Res Rev*. 2005;21(2):167–174.
25. Filozof C, Gautier JF. A comparison of efficacy and safety of vildagliptin and gliclazide in combination with metformin in patients with Type 2 diabetes inadequately controlled with metformin alone: a 52-week, randomized study. *Diabet Med*. 2010;27(3):318–326.