Effectiveness and safety of fixed dose combination of acarbose/metformin in Indian Type 2 diabetes patients: Results from observational GLOBE Study

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**Refer to appendix for list of GLOBE investigators

ABSTRACT

Primary objective - evaluate effectiveness and safety of acarbose/metformin fixed dose FDC on glycemic control in Indian T2DM patients in real life clinical setting. Secondary objective - evaluate safety and satisfaction of treatment. Materials and Methods: Open-label, prospective, multicentre, single-arm, non-interventional study. Patients included were aged ≥18 years with T2DM on Acarbose (25/50 mg) and Metformin (500 mg) FDC. Glycemic parameters were recorded during observation. Results: Total 9364 patients were enrolled in the study (mean age, 50.7 years and 60.1% were male). Mean (SD) FBG and PPG was significantly reduced by 42.4 (32.6) mg/dl ($P < 0.0001$) and 80.2 (49.7) mg/dl ($P < 0.0001$) respectively at the end of observation. Mean (SD) HbA1c reduced by -1.0% (0.8) to 7.3% (0.7) at the last follow-up visit ($P < 0.0001$). Majority of patients (97.5%) and physicians (98.42%) were satisfied with acarbose/metformin FDC treatment. Also, significant reduction in body weight by -1.7 (2.2) kg was observed ($P < 0.0001$). Patients with known T2DM and newly diagnosed showed a similar glycemic control ($P < 0.0001$). Drug-related adverse events were reported by only 1.4% patients mostly gastrointestinal. Conclusions: Acarbose/metformin FDC was efficacious, safe well accepted in routine clinical practice. It was well-tolerated without significant risk of hypoglycemia and can be used in early T2DM management.

Key words: Acarbose, alpha glucosidase inhibitor, combination, HbA1c, India, metformin, postprandial glucose, Type 2 diabetes mellitus

INTRODUCTION

India is facing a huge burden of diabetes with 65.1 million adults diagnosed with the type 2 diabetes mellitus (T2DM) in 2013, and this figure is projected to increase to 109 million by 2035.[1] The major epidemiological studies support that maintaining glycosylated hemoglobin (HbA1c) levels as close to normal may achieve long-term beneficial effects on the risk of diabetes complications.[2] There is an increasing evidence of hyperglycemia being implicated in the development of both micro as well as macro-vascular diabetic complications. Thus, control of postprandial glucose (PPG), in addition to control of fasting blood glucose (FBG), might ensure overall glycemic control in diabetics.[3] Combining anti-hyperglycemic agents with complementary mechanisms of action has become a cornerstone of T2DM management these days. Sulfonylurea combinations seem to be associated with an increased risk of body weight gain and hypoglycemia.[4] Acarbose delays digestion of disaccharides and oligosaccharides by
competitive enzyme inhibition and delays the absorption of glucose from intestine. Acarbose decreases both postprandial hyperglycemia and hyperinsulinemia, and may improve insulin sensitivity and diminish the stress on pancreatic beta-cells. Metformin acts through different mechanisms of action and mainly reduces the hepatic output of glucose and increases the peripheral utilization of glucose. Acarbose and metformin have been shown to have many beneficial effects and can be combined with other antidiabetic medications.

With this background, the current GLOBE (GLucobay™-M: OBservation study for Efficacy and safety in treatment of type-2 diabetes patients) study was conducted to examine the effectiveness and safety of acarbose/metformin fixed dose combination (FDC) in Indian T2DM patients in real-life clinical setting.

**Materials and Methods**

This was an open, prospective, multicenter, single-arm, non-interventional study and was conducted at 271 investigational sites in India between October 2010 and January 2012. The ethics committee approval and patient written informed consent were obtained before the start of study. The study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki. The study was registered at Clinical trial.gov (NCT01219582) and at Clinical Trial Registry of India (CTR No: CTRI/2010/091/002911). Due to the non-interventional study design, there were no additional diagnostic or monitoring procedures and no allocation of patients to treatment was done. Patients of either sex were eligible for inclusion in the study if they were aged at least 18 years and had prescription of acarbose/metformin FDC before study inclusion. The decision to prescribe acarbose/metformin FDC treatment was made by the treating physician according to his/her normal medical practice, and patients were enrolled in the study only after the treatment decision had been made. Patients were excluded if acarbose/metformin FDC treatment was contraindicated.

Patients were assessed at an initial visit, when acarbose/metformin FDC was prescribed and at up to three follow-up visits by their treating physician at any time over a period of up to 12 weeks. The physician decided on the follow-up times for each patient. At least one documented initial visit and one follow-up visit needed to be available in order for a patient to be included in the efficacy population. The final visit was defined as the last visit recorded by the physician for that patient. The whole treatment, including anti-diabetic co-medication and appropriate dose of acarbose/metformin FDC, was decided by the physician and could be adjusted at follow-up visits, according to routine medical practice.

Outcome measures: The PPG, HbA1c, FBG and body weight were recorded at each visit according to the physician's normal clinical procedures. Physicians were also asked to provide the final assessment of acarbose/metformin FDC efficacy and tolerability in each patient on a four-point scale: “poor,” “fair,” “good” or “excellent.” No description of the categories was provided, and the ratings were based on the physicians’ assessment alone. In addition, physicians were asked to rate their own and the patient’s overall satisfaction with the treatment at the final visit, using a two-point scale: “satisfied” or “not satisfied.” Overall assessment of efficacy by patient and physician was done at the end of the observation period. Further, safety analysis was also performed. All adverse events (AEs) were assessed and recorded by the physician on the AE report form attached to the case report form.

**Statistical analysis**

By using incidence of adverse drug reaction incidence reported earlier,[4] a sample size of 10,000 was required to detect safety outcome at 99% confidence interval. All P-values were reported based on the two-sided significance test and all the statistical tests were interpreted at 5% level of significance. All patients who received at least one dose of study drug were included in the safety analysis. Full analysis set (FAS) included all enrolled patients who had taken at least one dose of study medication and had baseline and at least one post-baseline efficacy measurement.

**Results**

**Study population**

The demographic and baseline characteristics of the efficacy population are summarized in Table 1. A total of 9364 patients...
were enrolled, out of which 8609 patients (755 patients ineligible for analysis due to retrospective enrollment) were further evaluated for effectiveness and safety analysis. The safety and FAS population included 8599 (10 did not take study dose, and so were excluded from safety population) and 8415 patients, respectively [Figure 1]. Sixty percent of the patients were males. The mean (SD) age of patient was 50.7 (10.3) years. The mean (SD) body weight of the patient was 72.9 (11.7) kg. The mean (SD) duration of T2DM was 5.7 (4.8) years. Thirty-two percent and 16.4% patients reported concomitant hypertension and concomitant dyslipidemia, respectively. The most common prior anti-diabetic drugs taken by the patient were metformin (39.7%, n = 3413), sulphonylurea (18.5%, n = 1593), insulin (4.5%, n = 390), glitazones (3.5%, n = 299), dipeptidyl-peptidase-4 inhibitors (0.9%, n = 80), alpha glucosidase inhibitors (0.9%, n = 75), and glinides (0.1%, n = 7).

**Effectiveness of acarbose/metformin FDC treatment**

The mean glycemic parameters (FBG, PPG and HbA1c) decreased during the observation period. The mean (SD) FBG reduced from 158.4 (40.7) mg/dl to 115.9 (26.5) mg/dl at last follow-up visit. The mean (SD) FBG significantly reduced by –42.4 (32.6) mg/dl at the end of last follow-up visit at 13.1 (3.0) weeks (P < 0.0001) [Figure 2]. The mean (SD) PPG reduced from 248 (57.4) mg/dl at the initial visit to 167.9 (38.1) mg/dl at the last follow-up visit. The reduction in PPG was statistically significant (P < 0.0001). Mean (SD) change in PPG from initial visit to last follow-up visit was -80.2 (49.7) mg/dl [Figure 2].

The mean (SD) HbA1c reduced from 8.3% (1.1) at initial visit to 7.3% (0.7) at the last follow-up visit. The reduction in HbA1c was statistically significant (P < 0.0001). Mean change from initial visit to last follow-up visit was 1.0% (0.8). The body weight also showed a slight decrease during the mean observation period of 13.1 weeks. The mean (SD) body weight at 13.1 (3.0) weeks reduced from 72.8 (11.5) kg at the initial visit to 71.1 (11.2) kg at the last follow-up visit. The reduction in weight was statistically significant (P < 0.0001). Mean (SD) change from initial visit to last follow-up visit was –1.7 (2.2) kg (n = 7911).

The efficacy and tolerability was rated as “excellent” or “good” by 89.1% (n = 7503) by the physicians in their patients during observation period [Figure 3]. In addition, 97.5% patients (n = 8204) and 98.4% physicians (n = 8282) reported satisfaction with the acarbose/metformin FDC treatment.

In subgroup analysis, a significant reduction (P < 0.0001) was reported for FBG, PPG, HbA1c and body-weight in patients who were known cases of diabetes (n = 4509). Further, those who were newly diagnosed (n = 3514) also showed similar results (P < 0.0001) [Table 2]. In analysis by baseline HbA1c criteria, the reduction in HbA1c was more in patients with high baseline HbA1c (mean (SD) reduction, –0.35 (0.3); –0.65 (0.39); –0.94 (0.46); –1.38 (0.65) and –2.84 (1.33) in stratifications subgroups of < 7% (n = 287); 7 to < 8% (n = 2229); 8 to < 9% (n = 2147); 9 to <10% (n = 726) and ≥ 10% (n = 454), respectively).

**Safety analysis**

The physicians intended to continue the therapy with acarbose/metformin FDC in 89.2% (n = 8352) patient at the end of observation period. The discontinuation rate reported in study due to insufficient efficacy was 1.0% (n = 75) and due to AEs was 0.3% (n = 25). No
Table 2: Change in FBG (mg/dL), PPG (mg/dL), HbA1c (%) and body weight (kg) at each visit and change from initial visit to last follow-up visit in patients who were known diabetics or newly diagnosed with diabetes (FAS population)

| Glycemic parameters                      | Known diabetics* | Newley diagnosed with diabetes* |
|------------------------------------------|------------------|----------------------------------|
| Fasting blood glucose (mg/dl)            | n | Mean (SD) | n | Mean (SD) |
| Initial visit                            | 4509 | 163.1 (43.7) | 3514 | 152.4 (34.7) |
| First follow-up visit                    | 4509 | 135.9 (32.3) | 3514 | 127.9 (28.2) |
| Last follow-up visit                     | 4509 | 118.5 (28.4) | 3514 | 112.6 (22.8) |
| Change from initial visit to last follow-up visit | 4509 | −44.6 (34.9) | 3514 | −39.8 (28.5) |
| Post-prandial blood glucose (mg/dl)      | n | n | n | n |
| Initial visit                            | 4583 | 255.8 (60.7) | 3522 | 238.4 (50.6) |
| First follow-up visit                    | 4583 | 202.1 (47.2) | 3522 | 192.5 (42.4) |
| Last follow-up visit                     | 4583 | 170.4 (39.4) | 3522 | 164.4 (35.8) |
| Change from initial visit to last follow-up visit | 4583 | −85.4 (52.6) | 3522 | −74.0 (44.0) |
| Body weight (kg)                         | n | n | n | n |
| Initial visit                            | 4390 | 72.9 (11.8) | 3368 | 72.8 (11.2) |
| First follow-up visit                    | 4390 | 72.2 (11.5) | 3368 | 71.8 (11.0) |
| Last follow-up visit                     | 4390 | 71.4 (11.4) | 3368 | 70.9 (10.9) |
| Change from initial visit to last follow-up visit | 4390 | −1.5 (2.1) | 3368 | −2.4 (2.3) |
| HbA1c (%)                                | n | n | n | n |
| Initial visit                            | 3070 | 8.5 (1.2) | 2642 | 8.0 (0.9) |
| Last follow-up visit                     | 3070 | 7.4 (0.7) | 2642 | 7.2 (0.6) |
| Change from initial visit to last follow-up visit | 3070 | −1.1 (0.9) | 2642 | −0.9 (0.6) |

*As reported by treating physician due to non-interventional nature of study, there were no defined criteria. SD: Standard deviation, FBG: Fasting blood glucose, PPG: Postprandial glucose, FAS: Full analysis set.

Table 3: Incidence of treatment emergent adverse events-gastrointestinal disorders (safety population, n=8599)

| MedDRA system preferred term | Treatment emergent AEs, n (%) |
|------------------------------|--------------------------------|
| Any AE                       | 157 (1.8)                     |
| Flatulence                   | 71 (0.8)                      |
| Abdominal pain               | 37 (0.4)                      |
| Abdominal distension         | 28 (0.3)                      |
| Diarrhoea                    | 19 (0.2)                      |
| Abdominal discomfort         | 16 (0.2)                      |

AEs: Adverse events

**DISCUSSION**

Our observational study investigated the effectiveness, safety and tolerability of acarbose/metformin FDC in real-life clinical setting in Indian T2DM patients. The results demonstrated that acarbose/metformin FDC was effective in reducing all glycemic parameters measured.

The present study data shows that treatment with acarbose/metformin FDC in T2DM patients significantly reduced HbA1c, FBG, and PPG (−1.0%, −42.4 mg/dl, −80.2 mg/dl, respectively, all *P* < 0.0001). Further, majority of patients (97.5%) and physicians (98.4%) were satisfied with acarbose/metformin FDC treatment. Some anti-diabetic drugs are known for their weight-gaining effect. However, in this study the mean (SD) weight was reduced by −1.7 (2.2) kg from baseline to the final visit.

A comparative study by Jayaram, *et al.* evaluated the safety, tolerability and benefits of acarbose/metformin FDC versus...
metformin alone in T2DM patients from India. The mean reduction in FBG, PPG and HbA1c after treatment with acarbose/metformin FDC was 45.4 mg/dl, 91.4 mg/dl and 1.7%, respectively. The FDC associated improvement in glycemic control was superior as compared to metformin group. According to the physician’s global assessment, 91.8% of the patients showed excellent to good tolerance for acarbose/metformin FDC treatment and the tolerability were comparable to metformin monotherapy in the same study.

Another 16-week, randomized, double-blind, parallel-group, phase-3 study was conducted at 13 sites in Taiwan, to compare the efficacy and safety of acarbose plus metformin FDC versus acarbose monotherapy for T2DM. 233 were randomized (117 acarbose/metformin FDC: 116 acarbose) after a 4 week run-in with acarbose monotherapy (50 mg thrice-daily). These data show that in T2DM patients with unsatisfactory glycemic control, treatment with acarbose/metformin FDC for 16 weeks significantly reduced HbA1c, FBG, and 2-hour PPG (-0.75%, –25.7 mg/dL, –38.5 mg/dL, respectively, all P < 0.0001) with superior efficacy compared with acarbose monotherapy.

In accordance to these studies, our study show similar results on glycemic parameters (HbA1c, FBG, and PPG) in real life clinical settings.

In a study by Rosenstock et al. (1998),[9] it was observed that the addition of acarbose in patients with T2DM who are inadequately controlled with metformin and diet was safe and generally well tolerated and significantly lowered HbA1c, FBG, PPG and insulin levels. Further, a study by Phillips et al. (2003) suggested that addition of acarbose to metformin monotherapy provides an efficacious and safe alternative for glycemic improvement in overweight T2DM patients inadequately controlled by metformin alone.

A meta-analysis by McIntosh et al. (2011) assessed efficacy of all available classes of oral antidiabetic drugs (OAD) in patients with type 2 diabetes inadequately controlled by metformin monotherapy. The systematic review concluded that when combined with metformin, α-glucosidase inhibitors resulted in HbA1c reduction similar to other OAD classes; however, AGIs show modest benefits without increasing bodyweight or risk of hypoglycemia.[11]

In the present study, subgroup analysis for known cases and newly diagnosed cases of diabetes showed a significant reduction in FBG, PPG, HbA1c and body-weight (P < 0.0001) from baseline to last follow-up, concluding that acarbose/metformin FDC finds its usefulness in both newly diagnosed and known cases of T2DM. Studies of metformin plus acarbose, in either loose combinations or as FDC[6] have reported no synergistic increase in gastrointestinal AEs. Similarly, in the safety analysis of our study, it was reported that 89.2% patients continued the use of acarbose/metformin FDC and were well-tolerated overall. Physicians assessed the overall tolerability of acarbose/metformin FDC favorably and the efficacy and tolerability was rated “excellent” or “good” in 89.1% of patients.

Taken together, the anti-hyperglycemic efficacy of acarbose/metformin FDC coupled with beneficial effect on body weight, and low risk of hypoglycemia, suggest that this combination therapy has several attributes that are desirable in treating patients with T2DM.

Study limitations
Being observational in design, the current study does have certain limitations. The possibility of change in the patient’s behavior and selection of patients by study physicians, who are expected to be more suitable for the medication of interest, cannot be ruled out. AEs may be under-reported and co-medications may change over time. Since the study was planned as a post marketing surveillance study, it had the limitation of not being a placebo-controlled blinded study. Also, the study has been conducted in a real-world scenario where physician’s preferences, opinions and decisions vary. All such limitations might have a potential for confounding effects. Nevertheless, observational studies offer an opportunity to monitor the efficacy and tolerability of a medication in daily clinical practice, which may reflect the real-world experiences of patients and physicians more closely than can be achieved in the controlled conditions of a clinical trial. Thus, observational studies provide a valuable complement to randomized controlled trials.

Conclusion
Acarbose/metformin FDC was found to be efficacious, safe and well accepted by Indian T2DM patients in routine clinical practice. Also, acarbose/metformin FDC was well tolerated without causing significant risk of hypoglycemia. Acarbose/metformin FDC can be considered as convenient treatment option in a patient who is uncontrolled on monotherapy or who needs combination therapy at the time of diagnosis with high PPG.

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Rathod Rahul was involved in study concept; study design, data collection and analysis, manuscript writing, and reviewing. Saboo Banshi, Reddy Gundam Chandrasekhara, Juneja Subhashchander, Kedia Ashok Kumar, and Manjrekar Pravin were involved in data collection, analysis of data, and in writing and reviewing the manuscript.

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