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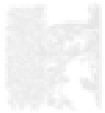
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SAFETY OF INSULIN DEGLUDEC/INSULIN ASPART IN PATIENTS WITH DIABETES MELLITUS OVER A PERIOD OF 1 YEAR DURING ROUTINE CLINICAL CARE IN INDIA: SMART (STUDY OF MANAGEMENT OF DIABETES WITH RYZODEG™ TREATMENT)

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Abstract. This post-authorization study was conducted to evaluate the safety of insulin degludec/insulin aspart (IDegAsp) in adult patients with diabetes mellitus (DM) during routine clinical care under a real-world setting in India. Eligible patients received IDegAsp for a minimum of 12 months during routine clinical management. Data were collected at 0, 3, 6, and 12 months. In total, 1029 adult patients with DM were included; 65.2% (n = 671) were men; mean age was 55.0 ± 12.2 years, and the mean duration of diabetes mellitus was 10.8 ± 7.4 years. Thirty adverse events were reported in 23 patients (2.2%) during the follow-up: two adverse events in two patients were serious with fatal outcomes, which were unrelated to IDegAsp use. At baseline, there were 176 confirmed hypoglycemic events in 67 (6.7%) patients while they were on their previous treatment options. At 12 months of treatment with IDegAsp, 11 confirmed hypoglycemic events were reported in 11 (1.1%) patients since the previous visit; there were no reported episodes of severe hypoglycemia. Mean glycosylated hemoglobin value reduced from 9.5% ± 1.8% at baseline to 7.7% ± 1.1% at 12 months. This study showed the safety of IDegAsp in patients with diabetes mellitus over a period of 1 year during routine clinical care.

Keywords: diabetes mellitus; glycemic control; IDegAsp; India; insulin therapy; safety

1. Introduction

The burden of diabetes mellitus (DM) is on the rise globally; at 77 million, India ranks second for the number of people with DM in the age group of 20–79 years, and by 2045, this number is estimated to rise to 134.2 million [1].

Insulin is the mainstay of therapy against type 1 DM (T1DM) and is also necessary for people with type 2 DM (T2DM) under certain circumstances at the diagnosis of T2DM, and particularly following the inability of oral anti-diabetic drugs (OADs) to maintain glycemic control [2,3]. The joint RSSDI-ESI (Research Society for the Study of Diabetes in India—Endocrine Society of India) clinical practice recommendations 2020 suggest that insulin initiation with once-daily co-formulation/premix or basal insulin should be considered if the glycosylated hemoglobin (HbA1c) value is not on target despite three OADs [4]. Basal insulins primarily control fasting plasma glucose (FPG), and overall HbA1c values might still exceed target value owing to uncontrolled post-prandial plasma glucose (PPG) excursions [5,6]. PPG excursion is of concern among people with DM in India, owing to relatively high dietary carbohydrate intake that can lead to relatively higher contribution of PPG to hyperglycemia [7,8]. Post-prandial hyperglycemia can be corrected by using prandial insulins [9]. However, introduction of an additional injection may reduce patient compliance [10]. IDegAsp is a co-formulation of 70% insulin degludec and 30% insulin aspart, offering total control of fasting and post-prandial glucose levels [11]. Phase 2 and 3 studies have demonstrated safety and efficacy of the IDegAsp compared with basal, basal-plus, basal-bolus, and analog premix insulin regimens [11,12,13,14,15,16]. This post-marketing surveillance (PMS) study of IDegAsp (Ryzodeg™), titled “Study of Management of diabetes with Ryzodeg™ Treatment (SMART)”, was conducted as part of a regulatory requirement. It aimed at assessing the safety of IDegAsp during routine clinical care under a real-world setting in India.

2. Materials and Methods

2.1. Participants

Men and women with DM aged >18 years who were scheduled to start treatment with IDegAsp based on the clinical judgement of the investigator during routine care were included in this study. Patients previously on IDegAsp therapy or those participating in another study were excluded. Patients with mental incapacity, unwillingness to participate, or language barriers precluding adequate understanding or cooperation were excluded. Women who were pregnant, were breast-feeding, or had the intention of becoming pregnant within 12 months were also excluded.

2.2. Study Design

This multicenter, prospective, single-arm, observational, PMS study (NCT02230618; CTRI/2015/12/006442) was conducted at 40 sites across India between November 2015 and June 2017. It was conducted as per the Declaration of Helsinki and International Conference on Harmonization-Good Clinical Practice guidelines. After obtaining approval from Institutional Review Board/Independent Ethics Committee of each participating center, the study was conducted in compliance with the protocol. All enrolled patients provided written informed consent.

At baseline (visit 1), data on demographics, medical history (DM history, prior DM treatment, history of hypoglycemia on previous treatment, and reason to start IDegAsp), concomitant medications, height, and weight were recorded. IDegAsp, marketed as Ryzodeg™ FlexTouch® prefilled pen injector (100 units/mL) and available in the market by prescription, was prescribed. The decision to initiate, titrate, and intensify with IDegAsp, its dose, its timings, and frequency were based on the investigator's discretion in line with approved Indian label. Safety data, including the hypoglycemic episodes since the last visit, were collected at 3 months ± 2 weeks (visit 2), 6 months ± 2 weeks (visit 3), and finally at 12 months ± 2 weeks (visit 4). Hypoglycemic events while on previous treatment were recorded based on patient recall of confirmed (blood glucose < 56 mg/dL) or severe hypoglycemic (requiring third-party assistance) events in the immediate 4-week period before starting IDegAsp. Because this was a non-interventional study, meticulously structured self-monitoring of blood glucose was not mandatory, and hypoglycemic events during the 12-month treatment with IDegAsp were recorded based on patient recall of confirmed or severe hypoglycemic events during follow-up visits.

2.3. Safety Assessments

During the 1-year study period, patients reported safety incidences were evaluated and categorized by physicians as follows: adverse events (AEs), serious adverse events (SAEs), adverse drug reactions (ADRs), serious ADRs, and confirmed or severe hypoglycemia. Additionally, causality (probable, possible, or unlikely), severity (mild, moderate, or severe), and outcome (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal, or unknown) of AEs/ADRs were recorded.

2.4. Assessment of the Change in HbA1c, FPG, and PPG

Endpoints included mean change in HbA1c, FPG, and PPG values from baseline at 3, 6, and 12 months in the overall population. The additional analysis included mean change in HbA1c, FPG, and PPG values from baseline to 3, 6, and 12 months, stratified by previous treatment (OADs or insulin). Given the non-interventional nature of this study, the most recent fasting and post-prandial glucose value was captured for assessment at different time points which could either be a lab or glucometer-based measurement.

2.5. Statistical Analyses

Assuming a 20% dropout rate, a sample size of 1000 patients was determined to provide a power of 80% to detect at least one AE that occurs with an incidence of 2 in 1000 patients, or approximately 6 events with an incidence of 1 in 100 patients. The descriptive statistics for continuous variables were

statistics were presented using counts and percentages. All the patients who received at least one dose of IDegAsp during the study were included in the safety analysis set (SAS), and patients who had at least one post-baseline measurement available for HbA1c, FPG, or confirmed hypoglycemic event were included in the efficacy analysis set (EAS). A paired two-sided t-test at a 5% significance level was used to evaluate the changes in HbA1c, FPG, PPG, and confirmed hypoglycemic events by the visit. Statistical analyses were performed using Statistical Analysis Software (Version 9.4).

3. Results

The mean (\pm SD) age of the study participants was 55.0 ± 12.2 years, and majority of them were male ($n = 671, 65.2\%$). The mean duration of DM was 10.8 ± 7.4 years. Based on EAS, before visit 1, 730 patients (72.8%) were on OAD(s) and 273 (27.2%) were on insulin therapy \pm OAD(s). Along with other concomitant drugs, OAD(s) in use at baseline included metformin ($n = 766, 74.4\%$), sulphonylureas ($n = 599, 58.2\%$), alpha-glucosidase inhibitors ($n = 203, 19.7\%$), meglitinides ($n = 2, 0.2\%$), thiazolidinediones ($n = 86, 8.4\%$), dipeptidyl peptidase-4 (DPP-4) inhibitors ($n = 363, 35.3\%$), and sodium-glucose co-transporter-2 (SGLT-2) inhibitors ($n = 16, 1.6\%$) apart from glucagon-like peptide-1 receptor agonists (GLP-1 RAs) ($n = 5, 0.5\%$). Treatment with IDegAsp and its continuation over a period of 12 months resulted in a change in use of OAD(s) such that at the last visit, OAD(s) in use were metformin ($n = 684, 66.5\%$), sulphonylureas ($n = 456, 44.3\%$), alpha-glucosidase inhibitors ($n = 159, 15.5\%$), meglitinides ($n = 6, 0.6\%$), thiazolidinediones ($n = 58, 5.6\%$), DPP-4 inhibitors ($n = 283, 27.5\%$), and SGLT-2 inhibitors ($n = 50, 4.9\%$) apart from GLP-1 RAs ($n = 5, 0.5\%$). Other concomitant medications in use reported in $\geq 5\%$ of patients are mentioned in **Table S1**. In terms of insulin therapy, at baseline, 124 patients (12.1%) were on basal insulins, 135 (13.1%) on premix insulins, and 95 (9.2%) on bolus insulins with or without basal/premix insulins before being enrolled in this study. Subsequently, 158 patients (15.4%) at visit 2 (at 3 months), 160 patients (15.5%) at visit 3 (at 6 months), and 162 patients (15.7%) at visit 4 (at 12 months) were on bolus insulin along with IDegAsp.

4. Discussion

IDegAsp (RyzodegTM) received its first regulatory approval by Japanese Ministry of Health in December 2012 [17]. United States Food and Drug Administration approved its use on 25 September 2015 [18]. It is available in the Indian market since January 2015 [19]. IDegAsp provides total (FPG + PPG) glycemic control with simplicity and convenience [11,16,20]. The basal insulin component in IDegAsp, i.e., insulin degludec has a long half-life and achieves a steady state within 2–3 days [21,22]. The efficacy and safety of IDegAsp had already been established based on the data obtained from earlier phase 2 and 3 studies [11,12,13,14,15]. However, to ensure its safety in the Indian population, Central Drugs Standard Control Organization (CDSCO) recommended a local post-marketing safety study. Hence, this multicenter, prospective, single-arm, observational study was conducted in patients who were scheduled to start treatment with IDegAsp as a part of standard routine clinical care. A one-year study duration was considered sufficient to determine any ADR associated with IDegAsp use.

5. Conclusions

This prospective, non-interventional study of IDegAsp confirms its long-term safety and tolerability with good improvements in glycemic control when used under routine clinical practice conditions.

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