Insulin degludec aspart: One-year real world experience

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ABSTRACT

Background: This retrospective analysis describes the use of insulin degludec aspart (IDegAsp) in India. Material and Methods: All subjects who had received IDegAsp for 52 weeks at two endocrine centers were included in this study. Results: Forty-eight subjects (40 men), with mean age of 54.33 ± 9.63 years and mean duration of diabetes of 6.33 ± 2.96 years, started IDegAsp as insulin of initiation (16), as an intensification regime (4), as de-escalation from basal-bolus therapy (16), or as switch from premixed insulin (12). The dose of IDegAsp fell from 43.17 ± 21.18 U/day or 0.56 ± 0.23 U/kg to 37.75 ± 17.13 U/day (0.51 ± 0.12 U/kg) at 24 weeks and 41.41 ± 15.33 U/day (0.56 ± 0.17 U/kg) at 52 weeks. Hemoglobin A1c (HbA1c), which was 9.52 ± 1.27% at the start of therapy, fell to 7.51 ± 0.46% at 26 weeks and to 7.48 ± 0.40% at 52 weeks. Fasting plasma glucose fell from 154.08 ± 33.30 mg% to 108.58 ± 22.26 mg% at 26 weeks and 102.17 ± 12.79 mg% at 52 weeks. Of the 48 subjects, 39 (81.25%) achieved a target of HbA1c <7.0% at both 26 and 52 weeks. No episode of hypoglycemia was reported in the 4 weeks preceding the analysis. Conclusion: This communication highlights the efficacy, safety, and tolerability, while providing insight into the usage patterns of IDegAsp.

Key words: Coformulation, degludec aspart, India, insulin, type 2 diabetes

INTRODUCTION

Insulin degludec aspart (IDegAsp) has been available in India for one year. IDegAsp is a dual action insulin, which provides both prandial and basal glycemic coverage without the need for multiple injections. While robust data from randomized controlled trials (RCTs) have been published, there is scarce data from observational trials or real world settings. This may be due to the fact that the co-formulation is available only in three countries so far: Mexico, India, and Bangladesh. This retrospective study shares data of 48 patients who have received IDegAsp for 12 months or more, at two endocrine centers in India.

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MATERIAL AND METHODS

All patients visiting the outdoor clinic of two endocrine centers in India from 15 December to 15 January 2015 were assessed for type of diabetes therapy. Patients who had been on IDegAsp therapy for 52 weeks or more were included in the study. Informed consent was obtained from all subjects for sharing of data. Details were collected regarding basic demographics, anthropometry, dosage and frequency of insulin, usage of oral glucose-lowering drugs, and glycemic control. Indications for the use of IDegAsp were recorded. Data at baseline, at 26 (±2) weeks, and at 52 (±2) weeks were used for analysis. Subjects were queried as to the frequency of hypoglycemia (major, minor, and nocturnal) during the past 4 weeks.

IDegAsp usage was classified as initiation (use in insulin-naïve patients), intensification or step-up (from...
basal insulin), de-escalation or step-down (from 4 to 5 dose basal bolus therapy), or interchange (switch) therapy (from premixed insulin). Data were analyzed using Microsoft Excel software.

**Results**

Forty-eight subjects met the inclusion criteria of having used IDegAsp for 52 weeks or more. These included 40 men and 8 women, with a mean age of 54.33 ± 9.63 years and a mean duration of diabetes of 6.33 ± 2.96 years. Of these, 16 subjects had started IDegAsp as insulin of initiation, 4 had used it as an intensification or step-up regime, from basal insulin, 16 had utilized it as a de-escalation regime or step-down from basal-bolus therapy (4–5 doses), while 12 had taken advantage of IDegAsp to switch from other dual action/premixed insulin. Eight subjects administered IDegAsp once daily (these included 4 who intensified from basal insulin and 4 who switched from once premixed insulin) whereas 36 received IDegAsp twice daily. Sixteen subjects had been de-escalated to a thrice daily IDegAsp basal regime (two doses of aspart and one of IDegAsp) [Table 1].

The choice of IDegAsp as an injectable therapy was based upon a process of informed, shared decision making, which took into account the pharmacokinetic and pharmacodynamic properties of IDegAsp, its potential advantages, and its cost. IDegAsp was used as a therapy of initiation in persons with oral hypoglycemic agent inadequacy, who needed safe glycemic control for elective surgery (2), control of concurrent dermatological or genital infection (3) management of diabetes foot (4), and resolution of osmotic symptoms/neuropathy (6). One person preferred IDegAsp as he wanted the “best” treatment to manage frozen shoulder associated with uncontrolled diabetes.

IDegAsp was chosen as step-up or intensification therapy by four persons with basal insulin inadequacy, all of whom wished to remain on once daily injection and have flexibility in injection timing. Two of these had concomitant depression and exhibited poor self-care ability. From basal bolus regime, de-escalation or step down to a three dose IDegAsp based regime was preferred by 16 subjects, all of whom wished to take advantage of the lower number of closer required with IDegAsp.

Reasons for switching to IDegAsp were more varied. These included high fasting glucose in 6 subjects, recurrent hypoglycemia in 2, marked glycemic variability in 2, poor response to management of concomitant foot infection in 1, and “lack of wellbeing” in 1 subject. The prevalence of concomitant infections and infestations in this cohort was significant. Infections documented at the onset of therapy with IDegAsp included diabetic foot (4), pruritus vulvae (2), acute or recurrent balanoposthitis (8), carbuncles (2), and pulmonary Koch’s (3). All these infections had resolved by 26 weeks of therapy.

The initial dose of IDegAsp was 43.17 ± 21.18 U/day or 0.56 ± 0.23 U/kg. The starting dose varied according to dosage frequency. While subjects on once daily IDegAsp were begun on 0.35 ± 0.21 U/kg, twice daily users started 0.60 ± 0.24 U/kg (P < 0.01), and those on a three dose regime (1Asp-1Asp-IDegAsp) began a total of 0.83 ± 0.12 U/kg of insulin. Twice daily users began morning and evening doses in a 50:50 ratio. At 24 weeks, the dose was 37.75 ± 17.13 U/day, (0.51 ± 0.12 U/kg) while at 52 weeks, it was 41.41 ± 15.33 U/day (0.56 ± 0.17 U/kg) [Table 2].

All eight subjects who received three doses at onset of therapy were still on three doses after 1 year. Of the 24 who began twice daily IDegAsp, 8 needed intensification to three dose regime at 24 weeks. Of these, 4 had reverted to twice daily dosage at 52 weeks. Of once daily users of IDegAsp, 3 had stepped up to twice daily IDegAsp at 24 weeks and another 3 required two doses by 52 weeks. Twice daily IDegAsp users reported morning–evening dose distribution in a ratio of 46:54, with the proportion of morning dose being 0.46 ± 0.046. The interchange therapy cohort had been on a mean dose of 64.0 ± 29.79 U/day (0.61 ± 0.26 U/kg) premixed insulin and were shifted to 53.17 ± 21.18 U/day (0.56 ± 0.23 U/kg) of IDegAsp. The cohort’s average dose at 26 weeks and 52 weeks was similar to that of the overall group.

### Table 1: Dose (U/kg) and frequency of insulin degludec aspart

|                      | Baseline | 24±2 weeks | 52±2 weeks |
|----------------------|----------|------------|------------|
| **Once daily**       | 0.35±0.21| 0.38±0.20  | 0.40±0.00  |
| (n=8)                |          | (n=5)      | (n=2)      |
| **Twice daily**      | 0.62±0.24| 0.61±0.23  | 0.59±0.19  |
| (50:50 ratio)        |          | (45:55 ratio) | (46:54 ratio) |
| (n=24)               |          | (n=19)    | (n=26)     |
| **Part of thrice daily** | 0.83±0.12 | 0.89±0.18  | 0.85±0.14  |
| (n=16)               |          | (n=24)    | (n=20)     |
| **Total**            | 0.56±0.23| 0.51±0.12  | 0.56±0.17  |
| (n=48)               |          |          |            |
| **HbA1c (%)**        | 9.52±1.27 | 7.5±0.46   | 7.48±0.40  |
| **FPG *(mg%)**       | 154.08±33.30 | 108.58±22.26 | 102.17±12.79 |
| **Weight (kg)**      | 71.43±18.16 | 74.43±14.43 | 74.01±17.60 |

*Fasting plasma glucose, HbA1c: Hemoglobin A1c

### Table 2: Regimes/frequency

|                      | Once daily | Twice daily | Part of thrice daily | Total |
|----------------------|------------|-------------|----------------------|-------|
| **Initiation**       | 0          | 16          | 0                    | 16    |
| **Intensification**  | 4          | 0           | 0                    | 4     |
| **De-escalation**    | 0          | 0           | 16                   | 16    |
| **Interchange**      | 4          | 8           | 0                    | 12    |
| **Total**            | 8          | 24          | 16                   | 48    |
Hemoglobin A1c (HbA1c), which was 9.52 ± 1.27% at the start of therapy, fell to 7.51 ± 0.46% at 26 weeks and to 7.48 ± 0.40%.

Fasting plasma glucose (FPG) fell from 154.08 ± 33.30 mg% to 108.58 ± 22.26 mg% at 26 weeks and 102.17 ± 12.79 mg% at 52 weeks. Of the 48 subjects, 39 (81.25%) achieved a target of HbA1c <7.0% at both 26 and 52 weeks.

Concomitant oral medication therapy was assessed at baseline, 26 weeks, and 52 weeks. Of the 48 subjects, 19 were on insulin monotherapy, 30 were on metformin, 10 on dipeptidyl peptidase-4 inhibitor + metformin, 3 on metformin + sulfonylurea, and 4 on metformin + acarbose therapy at baseline. No episode of hypoglycemia was reported by any subject during the preceding 4 weeks.

**DISCUSSION**

This is the first real world evidence of the use of IDegAsp over a 52-week long period. While this analysis is retrospective, not controlled, and is limited by the fact that drop outs were not studied, it does add value to existing literature. It must be noted that this study was performed in a nonreimbursed environment, where patients have to pay from pocket for insulin and other supplies.

The data reflect real world usage of IDegAsp, highlighting the various patterns and regimes it can be used in, its average dose requirements, and dose distribution according to meal times. The dose requirement of IDegAsp appears lower than that of other premixed insulin, and it allows basal bolus users to shift to a three injection regime. Relatively few persons use the flexibility of time of administration that IDegAsp allows (e.g., shifting from breakfast to lunch or dinner). The long-term tolerability and lack of major hypoglycemia are also noted.

Niskanen et al. in a 16-week long exploratory study found that IDegAsp was able to achieve target HbA1c <7.0%, without confirmed hypoglycemia in 67% subjects (who were poorly controlled on metformin). The daily dose requirement of IDegAsp was 0.57 ± 0.23 U/kg and was 13% lower than that of biphasic insulin aspart (BIAsp). Significantly lower FPG and confirmed hypoglycemia were noted.

In a 26-week long treat-to-target trial, Fulcher et al. included subjects with inadequate control on once daily or twice daily, premixed or self-mixed insulin. IDegAsp was able to achieve HbA1c targets that were noninferior to BIAsp, with superior FPG control, less weight gain, and a lower dose (1.08 U/kg). Lower rates of confirmed hypoglycemia (14 episodes per year [EPY]) and confirmed nocturnal hypoglycemia (2.5 EPY) week were noted.

A 26-week long Asian study observed lower dose requirement of once daily IDegAsp (0.79 U/kg), as compared to BIAsp, in controlling HbA1c, with lower FPG and similar (low) risk of severe hypoglycemia. Our study reveals lower dose requirements in comparison to previously used premixed insulin (in patients who switch therapy) and also in relation to those in RCTs. Safety and tolerability over a 1-year period mirrors the findings of RCTs. The lower dose requirement may reflect Indian clinical practice or may be due to sustained emphasis on (and adherence to) lifestyle modification.

Thus, the experience at our center supports the use of IDegAsp as a preferred injection of choice for initiation, intensification, de-escalation or step down from bolus therapy, and interchange from other premixed insulin.

**SUMMARY**

The one-year in-clinic experience at two endocrine centers in India reveals the efficacy, safety, tolerability, and versatility of IDegAsp as an insulin for initiation, intensification, de-escalation and interchange (switch) therapy, as monotherapy, or in combination with oral hypoglycemic agents.

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**Conflicts of interest**

There are no conflicts of interest.

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