Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a promising therapeutic class of glucose-lowering medications and include sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin. These inhibitors stimulate and increase the secretions of endogenous glucagon such as peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are hormones released in response to food intake. The enhancement of GLP-1 and GIP leads to insulin secretion by pancreatic β-cells, reduction in glucagon secretion, and reduction in liver glucose production.\(^{[1,2]}\) According to the recommendations from the American Association of Clinical Endocrinologists, DPP-4 inhibitors are recommended an option for first-line therapy in patients with an intolerance or contraindication to metformin such as renal or hepatic disease, gastrointestinal intolerance, or risk of lactic acidosis.\(^{[3,4]}\) DPP-4 inhibitors have also been recommended as part of combination therapy with two or three agents in patients with uncontrolled hyperglycemia.
Linagliptin is a competitive reversible DPP-4 inhibitor with a long terminal half-life. It has a high volume of distribution that leads to potent and long-lasting DPP-4 inhibitory effect in vivo.\(^\text{[3]}\) It has an elimination half-life of 131 h, and achieves steady-state concentrations after three doses of 5 mg once daily (OD).\(^\text{[6]}\) Daily doses of linagliptin 5 mg showed >80% inhibition of DPP-4 even after 24 h of administration. It has been demonstrated earlier that >80% DPP-4 inhibition did not result in additional glycemic efficacy\(^\text{[7]}\) and therefore, the trough DPP-4 inhibition of at least 80% is considered as a biomarker for the maximal glucose lowering capacity of these drugs. In a dose ranging study on Asian patients, inhibition of plasma DPP 4 at 24 h after 4 weeks therapy with linagliptin 0.5, 2.5, and 10 mg was 46%, 78%, and 90%, respectively.\(^\text{[8]}\) Both in vitro and ex vivo human and preclinical studies showed that linagliptin has higher potency and long duration of DPP-4 inhibition compared to other DPP-4 inhibitors.\(^\text{[9,10]}\) In fact, the maximum DPP-4 inhibition within one dosing interval at steady state was 92.3 and 93.7%, respectively for the 5 and 10 mg dose.\(^\text{[10]}\) A comparative study on the enzyme binding kinetics of the available gliptins indicates that linagliptin had a high affinity toward DPP-4 enzyme and had the slowest dissociation rate from the enzyme among the class. This is also the reason linagliptin can continue to inhibit the DPP-4 even after the free drug has been cleared from circulation.\(^\text{[10,11]}\) Pharmacokinetic (PK)-pharmacodynamic modeling and simulation studies with linagliptin assessed the impact of missing a dose and found that missing a dose could not adversely affect the DPP-4 inhibition, and it was maintained well above the required 80% inhibitory action.\(^\text{[10,11]}\) suggesting that linagliptin may be given on alternate days to achieve similar glycemic control as OD dosing. However, clinical evidence to support the hypothesis is lacking. With this background, we hypothesized that linagliptin retains its efficacy during alternate day dosing in type 2 diabetes patients when switched from OD dosing. This case series examined the hypothesis in a cohort of patients well controlled with 5 mg OD dosing of linagliptin, who were switched over to receive linagliptin 5 mg on alternate days.

**Materials and Methods**

**Study participants**

Eight cases of type 2 diabetes patients are described in this series. The patients were aged more than 18 years, well controlled on linagliptin for at least 6 weeks and with acceptable fasting plasma glucose (FPG), and postprandial glucose (PPG) levels, glycosylated hemoglobin (HbA1c) <7.0% (53 mmol/mol), and on stable antidiabetic treatment. No patient had any comorbid systemic ailment. All patients had documented stable hepatic and renal status. No patient received any concomitant medication which could have influenced linagliptin action.\(^\text{[12]}\)

**Method**

This hypothesis-generating study with cross-over design was conducted in compliance with good clinical practice and with ethical standards for human experimentation established by Declaration of Helsinki and in accordance with the applicable regulatory requirements. All subjects gave verbal informed consent before participation in the study. All the eligible patients receiving linagliptin 5 mg OD for at least 6 weeks along with other concomitant antidiabetic medication were switched over to the alternate day regimen, i.e. to receive linagliptin 5 mg alternate day, and were followed up for a median period of 21 weeks (range: 12–27 weeks). Subjects were followed up through telephonic calls at least twice a week and were reviewed in the outpatient clinic at least once in 6 weeks of therapy. During the last visit, they were evaluated for the efficacy and safety of linagliptin. Blood samples were collected for evaluation of FPG, PPG, and HbA1c at baseline and again on the last day of the follow-up period. Physical examinations, vital signs, 12-lead electrocardiographic, and safety laboratory measurements comprising hematology, clinical chemistry, and urinalysis were performed before and at the end of the study. Adverse events (AEs) were monitored throughout the study. Compliance was assessed by pill count method.

**Statistical analysis**

As the present study is a case series, descriptive statistics have been used to summarize the demographics.

**Results**

A total of 8 patients (7 male and 1 female) were enrolled and completed the study. The mean age, height, weight, and body mass index were 56.13 ± 15.78 years, 164.93 ± 7.41 cm, 73.25 ± 13.79 kg, and 26.57 ± 4 kg/m² respectively. The median duration of diabetes was 7 years (range: 0.75–16 years) [Table 1].

Before enrollment, all the patients were taking linagliptin 5 mg OD in combination with other antidiabetic medications (metformin in five patients, metformin and glimepiride, neutral protamine hagedorn (NPH) insulin, and premix insulin in one patient each) as part of the stable ongoing therapy for at least 6 weeks (range: 6–88 weeks). In one patient, NPH insulin was replaced with metformin 500 mg OD during alternate day therapy. The dose and frequency of concomitant medications in other patients were not altered.
At the end of 12 weeks or more of alternate dosing, the change in HbA1c compared to baseline was maintained [Table 2]. A further reduction in FPG was observed compared to baseline [Table 2]. However, a slight rise in PPG compared to baseline was observed [Table 2]. The HbA1c, FPG, and PPG change in the individual cases are depicted in Figures 1 and 2, respectively.

In one patient, variations in 24 h blood glucose levels were measured for 6 consecutive days during the linagliptin alternate day therapy using continuous glucose monitoring system device (CGMS iPro2; Medtronic Minimed, Northridge, CA, USA). No significant changes were observed in the 24-h blood glucose level profile during both day and night on the days of linagliptin administration and on days without linagliptin therapy, which suggested that linagliptin alternate day dosing was associated with stable and sustained glycemic control at all-time points [Figure 3]. Modest reduction in body weight was observed after minimum 6 weeks of therapy compared to baseline {70.50 kg (59–101) versus 67.25 kg (52–104.5)}. Linagliptin was well-tolerated in all the patients with no hypoglycemia reported during the study. All the patients showed good compliance with the medication regimen. No patient required alteration of dose of linagliptin or any other concomitant antidiabetic drug except in one where NPH insulin was replaced with metformin 500 mg OD during alternate day therapy.

**DISCUSSION**

The DPP-4 inhibitors are widely used in the treatment of type 2 diabetes mellitus. These include compounds, that efficiently lower fasting, and postprandial hyperglycemia and reduce HbA1c levels by 0.5–0.9% [11,13]. However, these compounds differ in terms of their potency to inhibit the DPP-4 enzyme, their duration of action, and their metabolism and elimination. The PKs of linagliptin, notably its long elimination half-life, suggests that alternate-day

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**Table 1: Baseline characteristics of the patients**

| Predose measurements |  |
|----------------------|--|
| Gender (n)           |  |
| Male                 | 7 |
| Female               | 1 |
| Age, years, and median (range) | 56 (34-75) |
| Duration of diabetes, years, and median (range) | 7 (0.75-16) |
| Duration of stable antidiabetic treatment, weeks, and median (range) | 39 (6-88) |
| Duration of follow-up, weeks, and median (range) | 21 (12-27) |

*Anti-diabetic treatment included tablet linagliptin 5 mg daily in addition to other agents for the said period*

**Table 2: Changes in glycemic parameters from baseline (on linagliptin 5 mg once daily) to the end of follow-up on alternate daily therapy (12 or more weeks)**

| Parameters | Baseline (linagliptin 5 mg once daily, median (range)) | End of therapy (linagliptin 5 mg on alternate days, median (range)) |
|------------|--------------------------------------------------------|------------------------------------------------------------------|
| HbA1c (%)  | 6.1 (5.8-6.9)                                          | 6.0 (5.1-7.1)                                                   |
| HbA1c (mmol/mol) | 43 (40-52)                                          | 42 (32-54)                                                    |
| FPG (mg/dL) | 117.50 (87-137)                                      | 103.0 (77-122)                                                 |
| PPG (mg/dL) | 122 (84-178)                                         | 135.5 (106-180)                                                |

HbA1c: Glycosylated hemoglobin, PPG: Postprandial glucose, FPG: Fasting plasma glucose

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**Figure 1:** Change in glycosylated hemoglobin while on alternate day dosing – patient level data (*linagliptin daily dosing; **linagliptin alternate day dosing*)

**Figure 2:** Change in fasting plasma glucose and postprandial plasma glucose (PPPG) while on alternate day dosing – patient level data (*linagliptin daily dosing; **linagliptin alternate day dosing*)

**Figure 3:** 24 h blood glucose levels obtained by continuous glucose monitoring system over 6 days period with linagliptin alternate day treatment in one patient.
dosing may be appropriate compared to the daily dosing. It also induces highly selective, potent, dose-dependent inhibition of DPP-4, with ≥ 80% inhibition of DPP-4 throughout the 24-h dosing interval. To our knowledge based on the available literature, the present case series is the first to investigate the effects of linagliptin 5 mg alternate day dosing on blood glucose levels in type 2 diabetes mellitus patients maintained on OD treatment. We are also not aware of any study using alternate daily dosing of any other DPP-4 inhibitor.

Several clinical trials have demonstrated that linagliptin causes significant reductions in HbA1c, FPG, and PPG, when administered as monotherapy,[12-15] initial combination therapy (with metformin or pioglitazone),[14-17] or add-on therapy to other oral antihyperglycemic agents (metformin and/or sulfonylurea) or basal insulin (with or without metformin and/or pioglitazone) in type 2 diabetes patients with AEs generally being mild or moderate in intensity. The present case series showed that efficacy of linagliptin 5 mg administered every other day for a median period of 21 weeks is similar to that of daily dosing in reducing glucose parameters in patients with diabetes mellitus. Linagliptin continued to inhibit the DPP-4 activity beyond 24 h after the last dose. Such prolonged DPP-4 inhibition may be sufficient to exert a meaningful clinical efficacy beyond 24 h. Based on the information, one can speculate, that linagliptin 5 mg alternate dosing would provide an equivalent effect to linagliptin 5 mg administered on a daily basis, however, further randomized studies in a large population are required to confirm this postulate. It is worth remembering that noncompliance is the major concern with alternate day dosing, which may affect the clinical outcome adversely. A major limitation of the study was a lack of randomized controlled arm although the crossover design (from OD dosing to alternate daily dosing) provided a template for comparison. We also could not perform serum linagliptin level estimation, or objective documentation of DPP-4 enzyme activity before and after the crossover, both of which could have been quite ideal for such a study.

**Conclusions**

Linagliptin 5 mg used alternate daily in patients who are well controlled with linagliptin 5 mg OD along with a stable background antidiabetic medication can maintain optimal glycemic control. Paradoxically, alternate-day dosing may affect compliance if the patient forgot when they took the last dose. Larger randomized clinical trials are warranted before the alternate-day administration is recommended for type 2 diabetes mellitus patients.

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**Conflicts of interest**

Manash P Baruah has received travel grants and speaker honoraria from Borheinger Ingelhem, Astra Zeneica, MSD, Novartis and USV in the past.

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