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BRIEF REPORT

Insulin Degludec in Clinical Practice: A Review of Japanese Real-World Data

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ABSTRACT

Introduction: In this literature review we evaluated the real-world clinical effectiveness of switching Japanese diabetic patients from their current insulin regimen to insulin degludec (IDeg).

Methods: Studies were identified from Japanese Diabetes Society (JDS) abstracts (2014–2015) and PubMed (2012 onwards). Inclusion criteria were: Japanese population, >15 participants, and studies switching patients from basal or basal–bolus insulin regimens to IDeg. Randomized controlled trials and case reports were excluded. Weighted mean changes in safety and effectiveness endpoints were calculated using the number of patients in each study.

Results: In total, 81 JDS abstracts and seven manuscripts met the search criteria, representing 4238 patients [1028 with type 1 diabetes (T1D), 602 with type 2 diabetes (T2D), 2608 with unspecified or mixed diabetes]. Glycated hemoglobin (HbA_{1c}) was reported in 93% of studies, with an improvement in 84% of these (51% significant, 33% numerical), no change in 12%, and worsening in 4% (3% numerical, 1% significant). Across all studies, the weighted mean absolute change in HbA_{1c} was −0.3% (−2.7 mmol/mol). Basal insulin dose was reported in 58% of studies and was lower in 60% of these (30% significant, 30% numerical), numerically unchanged in 26%, and higher in 14% (2% significant, 12% numerical). The weighted mean change in basal insulin dose was −4.8% and −3.0% for all studies and for studies with only significant results, respectively. The weighted mean change in basal dose based on all studies was −8.9, −5.5, and −2.9% for the T1D, T2D, and unspecified patient populations, respectively. Hypoglycemia was recorded in 31% of the studies. After switching treatment to IDeg, 55% of studies reported decreased hypoglycemia, 29% no change, and 16% an increase. Quality of life (QoL) was measured in 11% of studies, of which 82% reported improved QoL after switching, and 18% reported no change in QoL.

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Conclusion: Switching from a conventional basal insulin to IDeg has the potential to improve HbA_{1c} with a lower insulin dose. Switching to IDeg may also provide a reduced risk of hypoglycemia and improvement in QoL.
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Keywords: Degludec; Dose; Hypoglycemia; Insulin; Japan; Quality of life; Real-world

INTRODUCTION

Randomized controlled trials (RCTs) are the gold standard for comparing the safety and efficacy of new therapeutic agents against current practice; however, their external validity is limited by the study design, and inclusion and exclusion criteria [1]. For ethical, regulatory, and scientific reasons, the populations enrolled in phase 3 clinical trials differ from those of real clinical practice in terms of their clinical characteristics. Standardization of trial populations is required to reduce confounding and to allow statistical comparisons to be made regarding the safety and efficacy of the therapies being evaluated. Many clinical trials also include a run-in period, which further reduces heterogeneity [2]. As a result of these differences, there is a divergence between the narrowly defined patient profiles of RCTs and real-world prescribing decisions, leaving a knowledge gap between the evidence base of phase 3 trials and clinical practice.

Results from phase 3 trials have shown that insulin degludec provides a range of clinical benefits, including a reduction in insulin dose requirements, a lower risk of hypoglycemia, and improvements in quality of life (QoL), compared with conventional long-acting basal insulins [3–9]. The insulin degludec phase 3 trials used a treat-to-target methodology, as recommended by the European Medicines Agency [10] and U.S. Food and Drug Administration [11]. Treat-to-target trials with insulin evaluate both the benefits of glycemic control and the associated side effects, such as hypoglycemia, which allow risk–benefit assessments to be made. In treat-to-target studies, the insulin dose is adjusted for each individual patient, the aim of which is to achieve identical glycemic targets for both treatment arms. The main difference between insulin therapies evaluated using this methodology is observed in safety parameters (e.g., rates of hypoglycemia). In all of the phase 3 trials versus insulin glargine U100 carried out to date, insulin degludec resulted in non-inferior reductions in glycated hemoglobin (HbA_{1c}) [12–20].

Assessing the clinical effectiveness of insulin degludec in a real-world population could help to inform the decisions of healthcare practitioners and improve diabetes management by complementing data from the phase 3 program. Japan was one of the first countries in which insulin degludec was launched, and there is a growing body of literature reporting real-world clinical outcomes [21–24].

The aim of this literature review was to evaluate the real-world clinical effectiveness of switching Japanese diabetic patients to insulin degludec therapy.

METHODS

A literature search was conducted using the MEDLINE, I-Dis, and JDreamIII (2012 onwards) databases, and Japanese Diabetes Society (JDS) abstracts (2014–2015). Only studies in Japanese populations were included; however, searches included publications written in either the Japanese or English language. Japanese language publications were translated into English for the purpose of this review. Inclusion criteria were a minimum of 15 patients in each study, and only those studies in which patients switched from a conventional insulin regimen to insulin degludec (i.e., no insulin-naïve patients). RCTs and case reports were excluded. Two independent researchers assessed the abstracts for inclusion/exclusion criteria. The primary measures of clinical effectiveness were HbA_{1c} level, total daily basal insulin dose, and hypoglycemia. QoL was reported as a secondary measure of clinical effectiveness.

Changes in endpoints were classified as either an improvement (reduction in HbA_{1c}, basal insulin dose, or incidence of hypoglycemia; or an increase in QoL), unchanged, or worsening (increase in HbA_{1c}, basal insulin dose or incidence of hypoglycemia; or a decrease in QoL). When numerical changes were reported, results were stratified into two groups: (1) studies with significant changes only, and (2) all studies irrespective of significance. Using the sum of patients in each abstract, patient-weighted changes were calculated for studies in which only significant changes were observed, and for all studies irrespective of significance. That is, if a study reported a numerical but insignificant change in an endpoint, the patients in that study would be included in the significant patient-weighted calculation as patients with no change in the endpoint. In the alternative patient-weighted calculation, these patients would be included as per the numeric change.

Stratification of data by diabetes type was carried out where there were a sufficient number of observations to justify it. Results were reported as percentages for the numbers of studies reporting improvement, no change, or worsening in endpoints and as mean absolute percentage change and relative percentage change for HbA_{1c} and insulin dose, respectively.

This review is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

A total of 81 JDS abstracts and seven manuscripts met the search criteria [21 involving type 1 diabetes (T1D) patients, 17 involving type 2 diabetes (T2D) patients, and 50 involving patients whose diabetes type was not specified or was mixed], representing 4238 patients (T1D 1028, T2D 602, not specified 2608; Table 1 and Electronic Supplementary Material Tables S1–S3, Fig. S1).

HbA_{1c} was reported in 93% of studies ($n = 3873$ patients), of which an improvement in HbA_{1c} was observed in 84% (51% significant change, 33% numerical but not significant), no change was observed in 12% of studies, and a worsening of HbA_{1c} was observed in 4% (1% significant, 3% numerical; Fig. 1). Across all studies, the patient-weighted mean absolute change in HbA_{1c} was −0.3% (−2.7 mmol/mol) (Table 1).

Basal insulin dose was reported in 58% of studies ($n = 2573$ patients) and was lower (improved) in 60% of these (30% significant, 30% numerical), numerically unchanged in 26%, and higher in 14% (2% significant, 12% numerical; Fig. 1).

The weighted mean relative change in basal insulin dose was −4.8% and −3.0% for all studies and for studies with only significant results, respectively (Table 1). The weighted

Table 1 Participant characteristics and clinical outcomes for the total study population

Participant characteristic/clinical outcome	Value
Total study population, *n*	4238
Diabetes type, *n* (%)	
T1D	1028 (24%)
T2D	602 (14%)
Not specified	2608 (62%)
Change in HbA_{1c}, % (mmol/mol)	
Weighted mean absolute change from baseline in HbA_{1c}	−0.3% (−2.7 mmol/mol)
Change in basal insulin dose, %	
Weighted mean relative change from baseline in basal insulin dose (all studies)	−4.8%
Weighted mean relative change from baseline in basal insulin dose (only studies reporting a significant change)	−3.0%

Age, duration of diabetes, gender, hypoglycemia rates and quality-of-life scores were not listed by all abstracts and are therefore not included in the table

HbA_{1c} Glycated hemoglobin, *T1D* type 1 diabetes, *T2D* type 2 diabetes

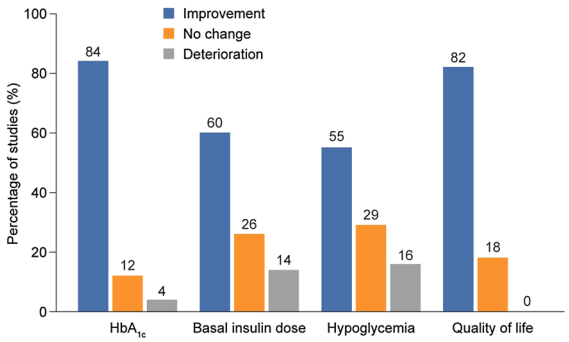

Fig. 1 Safety and effectiveness of insulin therapy in the reviewed studies. The percentage of studies reporting an improvement, no change, or deterioration (irrespective of significance) are shown. Percentages were calculated using the number of patients in all studies reporting each endpoint. *HbA_{1c}* Glycated hemoglobin

mean relative change in basal dose for all studies stratified by diabetes type was −8.9, −5.5, and −2.9% for T1D, T2D, and unspecified populations, respectively.

Hypoglycemia was recorded in 31% of the studies ($n = 1414$ patients). After the patient had been switched to insulin degludec therapy, 55% of these studies reported decreased hypoglycemia, 29% reported no change, and 16% reported an increase (Fig. 1).

QoL was measured in 11% of studies ($n = 747$ patients), of which 82% reported improved QoL after the switch to insulin degludec and 18% reported no change in QoL (Fig. 1).

DISCUSSION

This literature review reports the clinical impact of switching to insulin degludec from conventional basal or basal–bolus regimens in real-world Japanese populations. The collated evidence from clinical practice demonstrates that switching to insulin degludec is associated with improved glycemic control, a reduction in patients' basal insulin dose requirement, and a lower risk of hypoglycemia. Insulin degludec is also associated with an improvement in QoL.

The findings of this review concur with those of clinical trials in which similar improvements in clinical efficacy and patient-reported outcomes have been observed [3–7, 9]. In comparison with real-world studies, a recently published small-scale ($n = 51$), retrospective, single-center investigation reported similar improvements in HbA_{1c} after switching to insulin degludec, with reductions of 0.5 and 0.7% in patients with T1D and T2D, respectively [25]. In the same study, there was a significant >90% reduction in the rate of hypoglycemia despite an increase in insulin dose. However, it should be noted that one of the inclusion criteria for switching to insulin degludec was the experience of recurrent hypoglycemia [25]. Another real-world study in patients with T1D ($n = 357$) reported that after the switch to insulin degludec, patients' HbA_{1c} improved by 0.3% while the insulin dose was reduced by 12%. The switch to insulin degludec was also associated with a 20% reduction in the rate of overall hypoglycemia and a halving of the rate of nocturnal hypoglycemia [26].

The reasons for the reduction in insulin dose in the patients included in the present study are unclear, but they could be related to the long-acting and predictable pharmacodynamic profile of insulin degludec [27]. Further studies are needed to explore the relationship between insulin degludec and bolus insulin dose requirements, but there is evidence from both clinical practice and clinical trials demonstrating a reduction in total daily insulin requirements in patients treated with insulin degludec [28, 29]. A lower risk of hypoglycemia together with lower HbA_{1c} appears to be counter-intuitive; however, the reduced variability in blood glucose concentrations exhibited by insulin degludec, compared with insulin glargine U100, could be responsible for this observation [30]. The improvements in clinical outcomes and QoL may be associated. For example, reducing the incidence of nocturnal hypoglycemia might improve patients' general sense of well-being. Alternatively, the potential for flexible dose timing or the FlexTouch® pen device (Novo Nordisk, Bagsværd, Denmark) used for the delivery of insulin degludec could also have a positive effect on QoL. Notably, there were no reports of worsening in QoL. It is also possible that the clinical benefits observed in our review are the result of patients switching to a new

basal insulin and receiving closer clinical support or being motivated to adhere more strictly to their injection schedule and titration algorithm, rather than a direct pharmacological effect, but this should not be dismissed as insulin degludec provides an additional treatment option for clinicians. This study's findings may help to inform the decisions of both medical practitioners and healthcare payers in terms of considering treatment options for patients failing to reach blood glucose targets on conventional basal or basal–bolus insulin regimens.

This review is subject to limitations. Foremost, there is a possibility of overlap between the populations in the different abstracts. The decision to limit abstract selection to the largest Japanese diabetes congress (JDS) should have helped to reduce this risk as multiple submissions on the same study are discouraged. There is a greater possibility of overlap between the abstract and manuscript populations, but as the number of manuscripts included in the review was small, this should not have had a large effect on the observations. Furthermore, there is no suggestion that where overlap hypothetically exists, it would affect the direction of the results. Other limitations include the lack of a consistent definition for hypoglycemia across all studies and the absence of significance/non-significance being reported for the change in endpoints in some studies. The heterogeneity of populations included in the present analysis could introduce confounding or bias, which might influence the magnitude of reported outcomes. This is an inherent part of all real-world analyses, which sets them apart from highly controlled clinical trials. These limitations have an impact on the generalizability of the results. Large-scale observational studies, with greater uniformity in the recording of population characteristics and outcomes, are required to confirm the findings of our analysis.

CONCLUSION

Real-world evidence from Japanese clinical practice demonstrates that switching to insulin degludec has the potential to improve glycemic control and reduce insulin dose requirements. Switching to insulin degludec may also provide a reduced risk of hypoglycemia and the potential for improvement in QoL.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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