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Insulin degludec does not increase antibody formation versus insulin glargine: an evaluation of phase IIIa trials

We examined insulin antibody formation in patients with type 1 (T1D) or type 2 diabetes (T2D) treated with once-daily insulin degludec (IDeg) or insulin glargine (IGlar) to evaluate the impact of antibody formation on efficacy and safety. Insulin antibodies were measured using subtraction radioimmunoassays in six phase IIIa clinical trials using IDeg (n = 2250) and IGlar (n = 1184). Spearman's correlation coefficient was used to evaluate associations between cross-reacting antibodies and change from baseline glycated haemoglobin (HbA1c) and insulin dose. IDeg- and IGlar-specific antibodies remained low [<1% bound/total radioactivity (B/T)] and with low levels of antibodies cross-reacting with human insulin in patients with T1D (<20% B/T) and T2D (<6% B/T). Spearman's correlation coefficients between insulin antibody levels and change in HbA1c or insulin dose were low in both treatment groups. No clinically meaningful differences in adverse event (AE) rates were observed in patients with >10% B/T or without an absolute increase in antibodies cross-reacting with human insulin. IDeg treatment resulted in few immunogenic responses in patients with T1D and T2D; antibody formation was not associated with change in HbA1c, insulin dose or rates of AEs.
Keywords: insulin antibodies, insulin degludec, long-acting insulin, type 1 diabetes, type 2 diabetes

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RESEARCH LETTER

Introduction

Historically, patients receiving animal insulin preparations of low purity developed high levels of insulin antibodies, potentially affecting efficacy [1]. After the development of recombinant human insulin, and the rapid- and long-acting analogues, the number of patients developing high levels of insulin antibodies substantially decreased [2,3], with high levels of insulin antibodies rarely observed and with no apparent effects on efficacy [4–6]. Insulin degludec (IDeg) is a new basal insulin analogue with an ultra-long duration of action (>42 h) [7–9].

We measured insulin antibody levels in six randomized, controlled, open-label trials in patients with type 1 (T1D) or type 2 diabetes (T2D) who received IDeg (n = 2550) or insulin glargine (IGlar) (n = 1184) once daily (Table S1, Supporting Information) [10–15] to assess the impact of antibody formation on the change in HbA1c from baseline to end of trial (EOT), on insulin dose at EOT and on the incidence of specific adverse events (AEs).

Methods

Two trials [the BEGIN Basal–Bolus Type 1 Long (3583) [10] and the BEGIN Flex Type 1 (3770) [11]; treatment periods: 52 and 26 weeks, respectively] compared the efficacy and safety of IDeg with IGlar (both once daily at 100 U/ml) in patients with T1D also treated with insulin aspart [IAsp (100 U/ml)] in a basal-bolus regimen (initiated ≥12 months before the trial).

Three trials [the BEGIN Once Long (3579) [12], the BEGIN Once Asia (3586) [13] and the BEGIN Flex Type 2 (3668) [15]; treatment periods: 52, 26 and 26 weeks, respectively] in patients with T2D compared IDeg with IGlar (both once daily at 100 U/ml) ± oral antidiabetic drugs. The BEGIN Low Volume trial (3672) [14] compared IDeg (200 U/ml) with IGlar (100 U/ml) administered once daily for 26 weeks in combination with metformin ± a dipeptidyl peptidase-four inhibitor. Patients with T2D in trials 3579, 3672 and 3586 were insulin-naïve before the trial. Patients in trial 3668 were either insulin-naïve or receiving basal insulin ± oral antidiabetic drugs. Data were not collected from patients in the BEGIN Basal-Bolus Type 2 trial (3582), as insulin antibody levels were measured for insulin-treated patients with T2D in trial 3668.

Antibody measurements, from fasting serum samples, were carried out at baseline (week 0), weeks 12, 26, 40 and 52 (depending on treatment duration) and at end of follow-up (EOF), after a 1-week washout period (week 27 or week 53) while using NPH insulin. The washout was used to minimize interference of high EOT plasma concentrations of the recombinant insulin analogues (resulting from their longer half-lives [7,16]) with the antibody assays. Antibody levels were measured using a validated subtraction radioimmunoassay (File S1, Supporting Information). Antibody levels were expressed as % B/T, the percentage of bound radioactivity (B) relative to total radioactivity (T) added to the samples. Spearman's correlation coefficient was calculated to investigate the association between

Correspondence to: J. Vora, Royal Liverpool University Hospitals, Prescot Street, Liverpool L7 8XP, UK.
E-mail: jitenvora@btinternet.com

Table 1. Antibodies cross-reacting with human insulin (% B/T) at baseline and end of follow-up in phase IIIa trials comparing the safety and efficacy of insulin degludec with insulin glargine in patients with type 1 and type 2 diabetes.

Trial ID: study name (duration)	Dosing	IDeg-treated patients				IGlar-treated patients			
		Baseline		EOF		Baseline		EOF	
		n	% B/T Mean (s.d.) Median [range]	n	% B/T Mean (s.d.) Median [range]	n	% B/T Mean (s.d.) Median [range]	n	% B/T Mean (s.d.) Median [range]
Patients with T1D									
3583: BEGIN BB T1 Long (52 weeks) [10]	Once daily	471	13.5 (17.2) 6.0 [−1 to 81]	396	15.8 (18.0) 9.0 [0 to 84]	152	12.4 (15.4) 5.0 [0 to 69]	135	13.0 (16.9) 6.0 [0 to 76]
3770: BEGIN Flex T1 (26 weeks) [11]	Once daily	164	12.2 (14.7) 6.0 [−1 to 63]	145	19.3 (20.8) 10.0 [0 to 75]	160	11.5 (13.6) 5.0 [0 to 61]	154	14.3 (15.9) 9.0 [0 to 76]
	Once daily FF	162	11.2 (13.2) 6.0 [0 to 65]	141	17.7 (16.9) 12.0 [0 to 64]				
Patients with T2D									
3579: BEGIN Once Long (52 weeks) [12]	Once daily	763	0.4 (3.4) 0.0 [−2 to 59]	602	1.1 (5.5) 0.0 [−3 to 62]	255	0.2 (1.8) 0.0 [−1 to 26]	193	2.5 (7.8) 0.0 [−1 to 57]
3586: BEGIN Once Asia (26 weeks) [13]	Once daily	284	0.2 (1.2) 0.0 [−1 to 17]	269	0.5 (2.3) 0.0 [−1 to 22]	146	0.9 (6.7) 0.0 [−1 to 69]	138	6.0 (15.0) 0.0 [0 to 70]
3672: BEGIN Low Volume (26 weeks) [14]	Once daily	228	0.4 (5.1) 0.0 [−1 to 76]	214	0.6 (3.0) 0.0 [−1 to 35]	227	0.2 (1.3) 0.0 [−1 to 15]	208	2.4 (8.5) 0.0 [−1 to 67]
3668: BEGIN Flex T2 (26 weeks) [15]	Once daily	226	3.9 (10.9) 0.0 [−1 to 68]	210	5.1 (13.6) 0.0 [−1 to 71]	229	3.3 (9.5) 0.0 [−1 to 68]	210	5.0 (12.4) 0.0 [−1 to 70]
	Once daily FF	230	4.0 (12.4) 0.0 [−1 to 72]	209	4.5 (12.6) 0.0 [−1 to 72]				

% B/T, percentage bound of total radioactivity; BB, basal-bolus; EOF, end of follow-up; FF, forced flexible dosing; IDeg, insulin degludec; IGlar, insulin glargine; s.d., standard deviation; T1, type 1 diabetes; T2, type 2 diabetes.

cross-reacting antibodies at EOF and change in HbA1c from baseline to EOT, as well as total daily insulin dose at EOT.

Standardized Medical Dictionary for Regulatory Activities (MedDRA) queries were used to identify patients experiencing immunogenic or hypersensitivity reactions. For evaluation of AEs, patients who exhibited >10% B/T absolute increase in cross-reacting antibody level or >5% B/T absolute increase in IDeg- or IGlar-specific antibody level were considered to have increased levels of antibodies. These thresholds were arbitrary and based on the measurement of the antibody assay performance.

Results

Mean levels of IDeg- and IGlar-specific antibodies remained low for both treatment groups (Table S2, Supporting Information) at baseline and EOF, with little variation in IDeg-specific (0.0–0.1% B/T at baseline and 0.0–0.4% B/T at EOF) and IGlar-specific antibodies (−1.3 to 0.9% B/T at baseline and −1.1 to 1.1% B/T at EOF) across T1D and T2D studies.

Mean levels of antibodies cross-reacting with human insulin remained low for both IDeg and IGlar treatment groups (Table 1). In T1D the % B/T ranged from 11.2% B/T at baseline to 19.3% B/T at EOF (IDeg) and from 11.5% B/T to 14.3% B/T (IGlar). In T2D, cross-reacting antibody levels ranged from 0.2% BT at baseline to 5.1% B/T at EOF (IDeg) and from 0.2% B/T at baseline to 6.0% B/T at EOF (IGlar). Figure 1 shows levels of cross-reacting antibodies over time during the two 52-week trials in patients with T1D (Panel A: Trial 3583, n = 629) and T2D (Panel B: Trial 3579, n = 1030). The mean daily basal insulin (Table S1, Supporting Information) and bolus insulin doses (data not shown) were similar at baseline and EOT in the T1D trials of IDeg- and IGlar-treated patients; however, in the T2D trials, the mean daily basal insulin dose increased from baseline to EOT in both groups. In several trials, the basal insulin doses at EOT were lower in the IDeg group compared with the IGlar group [10,13,14]. Scatter plots showing levels of cross-reacting antibodies versus total daily insulin dose at EOT for patients in the 52-week trials [10,12] did not suggest that the level of cross-reacting antibodies had an influence on insulin dose or that dose influenced the level of cross-reacting antibody formation (Figure S1, Supporting Information).

To evaluate associations between insulin antibodies and efficacy, levels of cross-reacting antibodies at EOF versus change in HbA1c at EOT from all patients in the two 52-week trials [10,12] were plotted (Figure S2, Supporting Information). No patterns were observed in the change in HbA1c with respect to the level of cross-reacting antibodies for patients with T1D or T2D treated with either IDeg or IGlar.

Spearman's correlation coefficients evaluating the correlation between the levels of insulin antibodies at EOF and change in HbA1c from baseline to EOT, and between insulin antibody levels at EOF and basal insulin dose at EOT are shown in Table S3, Supporting Information. All correlation coefficients were low, suggesting there was no clinically relevant association between insulin antibodies and change in HbA1c or insulin dose.

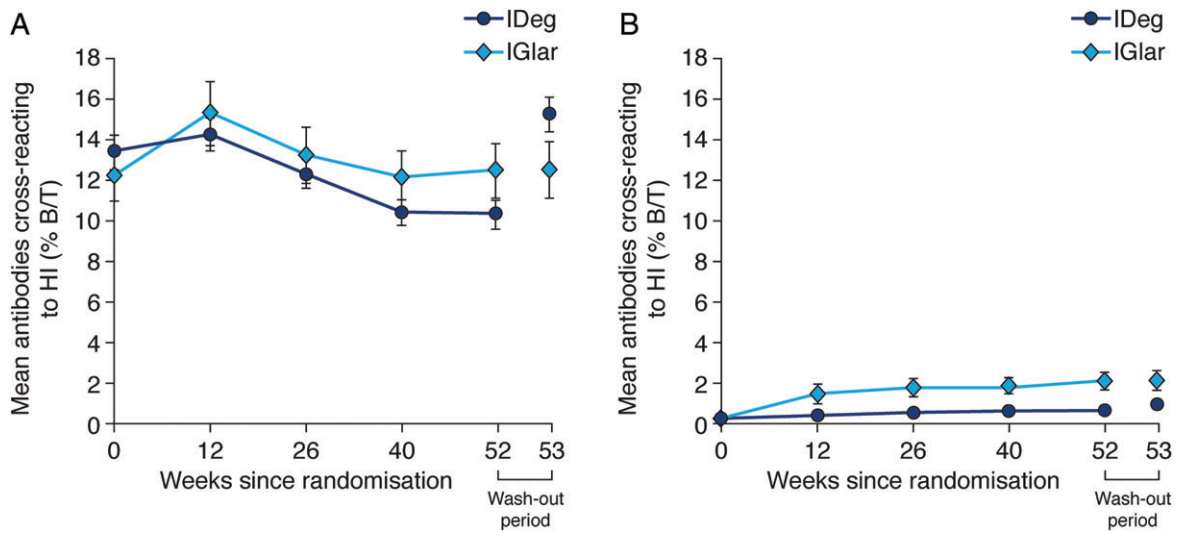

Figure 1. Cross-reacting antibody levels to human insulin (HI) over time in patients with (A) type 1 diabetes (BEGIN Basal-Bolus Type 1 Long [3583] [10]) and (B) type 2 diabetes (BEGIN Once Long [3579] [12]). Antibody levels were measured at week 0 (baseline), week 12, week 26, week 40, week 52 (end of trial, EOT) and week 53 (end of follow-up, EOF) after a 1-week washout period. Patients were treated with NPH insulin during the washout period to minimize interference of trial drugs with the antibody assay. Dark blue circles = insulin degludec (IDeg)-treated patients; light blue diamonds = insulin glargine (IGlar)-treated patients. Data are presented as mean ± standard error of the mean.

Rates of AEs associated with immunogenic reaction are shown in Table S4, Supporting Information. The AE rates (per 100 patient-years of exposure) in IDeg-treated patients with increased levels of cross-reacting antibodies (>10% B/T) were 15.4, 14.6 and 1.7 for injection site reactions, skin and subcutaneous tissue disorders and immune system disorders, respectively. In IGlar-treated patients these AE rates were 27.8, 14.8 and 9.3, respectively. The higher number of immune system disorders in IGlar-treated patients was driven by a higher rate of 'seasonal allergy' and 'multiple allergies', thus events unrelated to treatment with IGlar. In patients with no or ≤10% B/T absolute increase in cross-reacting antibodies, event rates were generally lower than those with >10% B/T. In IDeg-treated patients with ≤10% B/T absolute increase in cross-reacting antibodies, the AE rates (per 100 patient-years of exposure) were 13.0, 8.4 and 2.1 for skin and subcutaneous tissue disorders, injection site reactions and immune system disorders, respectively. Similarly, AE rates in IGlar-treated patients were 11.9, 9.7 and 2.7, respectively.

Two hypersensitivity reactions, both considered unlikely to be related to trial drug, were experienced by two patients in the IDeg group with >10% B/T absolute increase in cross-reacting antibodies. No reactions were reported in the IGlar group. In the population with no or ≤10% B/T absolute increase in cross-reacting antibodies, 19 patients experienced hypersensitivity reactions; the event rates in the IDeg and IGlar groups were 1.1 and 0.7 events per 100 patient-years of exposure, respectively. None of the patients with >5% B/T absolute increase in insulin-specific antibody levels (IDeg- or IGlar-specific antibodies) experienced hypersensitivity reactions.

There was no indication of a relationship between cross-reacting antibodies at EOF and the rate of confirmed hypoglycaemic episodes in either group (data not shown).

Discussion

Patients treated with IDeg for 26–52 weeks had low levels of both IDeg-specific antibodies and antibodies cross-reacting with human insulin at EOT. Cross-reacting antibody levels were similar in the IDeg-treated and IGlar-treated groups at EOF and, in general, were higher at EOF in trials with patients who were previously exposed to insulin. No association between change in HbA1c and insulin antibody levels was noted from scatter plots. Furthermore, Spearman's correlation coefficients evaluating the degree of association between insulin antibody levels and change in HbA1c from baseline were low. These results suggest that insulin antibody levels in IDeg-treated patients were not associated with the change in HbA1c in these trials.

The higher levels of cross-reacting antibodies reported from the BEGIN T1D trial (3583), compared with the T2D trial (3579), may be explained by differences in pretrial insulin exposure, i.e. those with T1D have previously been treated with insulin for many years and therefore have a higher antibody level at baseline when compared with those with T2D, who were insulin-naïve at randomization. The correlation coefficients between total daily insulin dose and insulin antibody levels were low, suggesting that neither the level of IDeg-specific antibodies, nor the level of antibodies cross-reacting with human insulin, were associated with the insulin dose.

No clinically meaningful differences were observed in AE types or rates between patients with or without an absolute increase of >10% B/T in cross-reacting antibody levels from baseline to EOF.

In conclusion, the immunogenic response to long-term treatment with IDeg was low in patients with T1D and T2D. The development of insulin antibodies to IDeg was not associated with change from baseline HbA1c or total daily

insulin dose at EOT, nor was it associated with higher rates of immunogenic reactions compared with IGlar.

J. Vora[1], J. Seufert[2], H. Solberg[3], O. Kinduryte[4], T. Johansen[5] & P. Hollander[6]

[1]Department of Diabetes and Endocrinology, Royal Liverpool University Hospitals, Liverpool, UK
[2]Division of Endocrinology and Diabetology, Department of Internal Medicine II, University Hospital of Freiburg, Freiburg, Germany
[3]Novo Nordisk A/S, Måløv, Denmark
[4]Novo Nordisk A/S, Bagsværd, Denmark
[5]Novo Nordisk A/S, Søborg, Denmark
[6]Baylor Endocrine Center, Dallas, TX, USA

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Conflict of Interest

J. V. has served on advisory boards for Novo Nordisk, Eli Lilly, Sanofi Aventis, MSD, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis and Abbott, has received research support from Novo Nordisk, MSD, Eli Lilly and Sanofi Aventis, and served on speakers' bureaux for Novo Nordisk, Eli Lilly, Sanofi Aventis, MSD, Novartis, Abbott and Boehringer Ingelheim. J. S. has attended advisory boards for Takeda, Bayer, Novartis, Merck Sharp Dohme, Astra Zeneca, Bristol-Myers Squibb, Novo Nordisk, Sanofi Aventis, Berlin Chemie, Lilly, Boehringer Ingelheim, Merck, Roche, Ipsen, Pfizer, Janssen and Lifescan, and has attended speakers bureaux for Takeda, Bayer, Novartis, Merck Sharp Dohme (MSD), Astra Zeneca, Bristol-Myers Squibb, Novo Nordisk, Sanofi Aventis, Berlin Chemie, Lilly, Boehringer Ingelheim, Roche, Ipsen, Pfizer, Janssen and Lifescan. H. S., O. K. and T. J. are employees of Novo Nordisk and have shares in the company. P. H. has served on advisory boards for Novo Nordisk, Merck and Sanofi.

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Some data have been previously presented in abstract form at the following meetings: 48th Annual Meeting of the European Association for the Study of Diabetes in 2012, 94th Annual Meeting of the Endocrine Society in 2012, 9th Western Pacific Region Congress of the International Diabetes Federation in 2012 and 56th Annual Meeting of the Japan Diabetes Society in 2013. The title of all the abstracts was 'Insulin degludec does not increase antibody formation compared to insulin glargine: an evaluation of phase 3a trials'.

J. V. acts as the guarantor for this manuscript and takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript. All authors (J. V., J. S., H. S., O. K., T. J. and P. H.) were involved in critical analysis and interpretation of the data, drafting/critically revising the article and shared in the final responsibility for the content of the manuscript and the decision to submit it for publication.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

File S1. Supplementary methods and supplementary references.

Table S1. Description of six phase IIIa clinical trials comparing the safety and efficacy of insulin degludec with insulin glargine.

Table S2. Insulin degludec (IDeg) and insulin glargine (IGlar)-specific antibodies (% B/T) at baseline and EOF in phase IIIa trials comparing the safety and efficacy of IDeg with IGlar in patients with type 1 and type 2 diabetes.

Table S3. Spearman's correlation coefficients for antibodies versus change in glycated haemoglobin level and antibodies versus total daily insulin dose.

Table S4. Rates of adverse events associated with immunogenic reaction by the absolute increase in cross-reacting antibody levels from baseline to end of follow-up.

Figure S1. Total daily insulin dose at end of trial versus cross-reacting antibody level at end of follow-up for patients in trials with a treatment duration of 52 weeks. (A) Data from patients with type 1 diabetes (BEGIN Basal-Bolus Type 1 Long [3583] [5]). (B) Data from patients with type 2 diabetes (BEGIN Once Long [3579] [7].

Figure S2. Change in glycated haemoglobin level from baseline to end of trial versus cross-reacting antibody level at end of follow up for patients in trials with a treatment duration of 52 weeks. (A) Data from patients with type 1 diabetes (BEGIN Basal-Bolus Type 1 Long [3583] [5]). (B) Data from patients with type 2 diabetes (BEGIN Once Long [3579] [7].

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