Switching from insulin glargine to insulin degludec reduced HbA1c, daily insulin doses and anti-insulin antibody in anti-insulin antibody-positive subjects with type 1 diabetes

Monnier et al. suggested that prior to phase-II or -III randomized clinical trials, better comprehension of the metabolism of the new basal insulin analogues would be invaluable [1]. Their excellent review article has been asking us what we see, know and are trying to comprehend [1]. There are controversial arguments over the safety and efficacy of a new long-acting basal insulin analogue, insulin degludec. The threonine amino-acid residue at B30 is deleted and a fatty acid (hexadecanedioic acid) is added to the lysine at B29 via a glutamic acid spacer [2]. Following subcutaneous injection, insulin degludec forms a depot of multihexamer chains, and these multihexamers gradually disassemble into active monomers that are slowly absorbed into the circulation [3,4]. The two-year results of a randomized clinical trial showed that long-term basal therapy using insulin degludec in type 1 diabetes required lower doses and was associated with a 25% lower risk of nocturnal hypoglycaemia than insulin glargine, suggesting that insulin degludec improves glycaemic control safely and effectively in subjects with type 1 diabetes compared with insulin glargine [5]. However, the underlying mechanisms of the insulin degludec-mediated reductions in daily insulin doses and risk of nocturnal hypoglycaemia remain largely unknown. Anti-insulin antibody induces an immunological insulin resistance that, in turn, induces an increase in daily insulin doses and unexpected hypoglycaemia.

We investigated the effects of switching basal insulin from insulin glargine to insulin degludec on HbA1c, daily insulin doses and anti-insulin immunoglobulin G antibody (IA) levels (normal reference level <0.4 U/mL) in 10 IA-positive subjects with type 1 diabetes treated with intensive insulin therapy. The means ± SD of age, height, weight, body mass index and duration of diabetes of these subjects (four men and six women) were 56.4 ± 18.0 years, 158.6 ± 6.8 cm, 57.8 ± 9.1 kg, 23.0 ± 3.7 kg/m² and 13.9 ± 12.2 years, respectively. In our IA measurement assay, IA levels significantly corresponded with 125I-insulin binding rate (r = 0.995, P < 0.001 by Pearson’s correlation). At 3 months after switching to insulin degludec, HbA1c tended to decrease from 8.9 ± 1.5% to 8.5 ± 1.4% (P = 0.058 by Wilcoxon signed-rank test). Daily insulin doses significantly decreased from 33.4 ± 10.6 units to 28.8 ± 8.2 units (P = 0.011), and IA levels significantly decreased from 4.0 ± 4.2 U/mL to 1.7 ± 1.3 U/mL (P = 0.017). At 6 months after the switch, although statistical significance was not reached, HbA1c (8.6 ± 0.8%) and daily insulin doses (30.9 ± 9.4 units) were still lower than those at baseline, and IA levels showed a further decrease to 1.2 ± 0.7 U/mL (P = 0.021). The reduction in IA levels at 6 months after the switch was significantly correlated with a decrease in HbA1c during the same time period (r = 0.75, P = 0.02).

The structural similarity between human insulin and insulin analogues may be an important determinant of the induction of IA, leading to immunological insulin resistance. Insulin degludec forms a depot of multihexamer chains after subcutaneous injection with an α-helix structure instead of a β sheet, and maintains the similar three-dimensional structure of human insulin [3], which may explain the decrease in HbA1c due to reduction in IA levels by switching to insulin degludec.

We have to mention the limitation of our present study. The number of subjects was small because the number of IA-positive subjects with type 1 diabetes was very limited. To elucidate our hypothesis, further studies with preferably larger numbers of subjects are needed.

In summary, switching basal insulin from insulin glargine to insulin degludec reduced HbA1c, daily insulin doses and IA levels in IA-positive subjects with type 1 diabetes.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


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