Management of type 1 diabetes

Insulins: Where are we now?

Adrian Scott
Consultant Physician in Diabetes and General Medicine, Northern General Hospital, Sheffield

After Leonard Thompson became the first person in the world to receive an injection of animal-derived insulin in 1922, pharmaceutical companies spent the following few decades trying first to purify extracted animal insulin and then to manufacture insulin that resembled human insulin. It soon became apparent that the relatively short action of these early insulins, necessitated multiple subcutaneous injections. The first successful attempts to prolong the action of insulin were with additives such as protamine (from fish sperm) and zinc. These insulins were far from perfect with unpredictable absorption patterns and unwanted peaks – so for the last 30 years or so, the efforts have focussed on modifying the molecular structure of insulin. This research resulted in both shorter- and longer-acting insulin "analogues" than the so-called "regular" (soluble) or intermediate-acting (isophane) human insulins. The hunt for the perfect peakless insulin has gone on, with insulin glargine (Lantus®), the first long-acting analogue, followed by insulin detemir (Levemir®) and more recently insulin degludec (Tresiba®).

> ***"...we approach the centenary of the discovery of insulin with some promising new additions to the insulin therapy arsenal."***

Coincidentally, with the end of the patent for insulin glargine, single-dose insulin glargine 300 U/mL (Toujeo®) has now been marketed with, seemingly, a more evenly distributed exposure and metabolic effect beyond 24 hours. Further studies are needed to see what difference this may make in practice, but, for individuals with large insulin requirements, such as insulin-resistant patients with type 2 diabetes, the smaller volumes may make injections more comfortable.

Any improvement in the performance and duration of these longer-acting insulins is welcome, and, as such, we approach the centenary of the discovery of insulin with some promising new additions. Whether we can afford these benefits remains to be seen. ■

Diabetes Obes Metab

Glycaemic control of insulin glargine 300 U/mL compared to 100 U/mL

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 The pharmacokinetic (PK) and pharmacodynamic profiles of new insulin glargine 300 U/mL (Gla-300) and insulin glargine 100 U/mL (Gla-100) in people with T1D were compared in two euglycaemic clamp studies taking place in Europe and Japan.

2 Eighteen Japanese adults and 24 European adults with HbA_{1c} ≤75 mmol/mol (≤9%) received single doses of Gla-300 0.4, 0.6 and 0.9 U/kg (0.9 U/kg in the European study only) and Gla-100 0.4 U/kg. Between each dose, there was a washout period of between 5 and 20 days.

3 Regardless of dose and ethnicity of the participant, Gla-100 and Gla-300 were found to have different PK profiles.

4 The authors observed that the serum insulin glargine concentration and glucose infusion rate developed more gradually into more constant and prolonged profiles with Gla-300 than with Gla-100.

5 In the Japanese study, blood glucose levels for both Gla-300 doses gradually increased up to approximately 6 h, and subsequently settled at the clamp level until 36 h. With Gla-100, blood glucose levels were maintained at the clamp level until approximately 24 h, and increased gradually thereafter.

6 Compared with Gla-100, Gla-300 maintained blood glucose control for up to 36 hours in euglycaemic clamp settings in Japanese and European participants with T1D.

Bolli GB, Riddle MC, Bergenstal RM et al (2015) New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). *Diabetes Obes Metab* **17**: 386–94

Type 1 diabetes

"To the authors' knowledge, this is the first study to show that the endogenous glucose production response to insulin-induced hypoglycaemia is normalised 6 months after islet transplantation."

Diabetes

Reduced hypoglycaemia after islet transplantation

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓✓

1 The authors sought to find out whether intrahepatic islet transplantation improves endogenous glucose production (EGP) in response to hypoglycaemia in people with long-standing T1D experiencing severe hypoglycaemia.

2 Twelve people who had T1D for approximately 30 years were monitored before and 6 months after intrahepatic islet transplantation using stepped hyperinsulinaemic-hypoglycaemic and paired hyperinsulinaemic-euglycaemic clamps. The results were compared to a control group of 8 people without diabetes.

3 After transplantation, HbA_{1c} normalised and there was essentially no time spent in hypoglycaemia (<3.9 mmol/L). Also, hypoglycaemia unawareness nearly disappeared completely for the transplantation group ($P<0.01$).

4 When hypoglycaemia was medically induced with insulin to measure the response after transplantation, C-peptide was suppressed, glucagon secretion was recovered and adrenaline secretion was improved.

5 To the authors' knowledge, this is the first study to show that the EGP response to insulin-induced hypoglycaemia is normalised 6 months after islet transplantation among those who had undergone the procedure.

Rickels MR, Fuller C, Dalton-Bakes C et al (2015) Restoration of glucose counterregulation by islet transplantation in long-standing type 1 diabetes. *Diabetes* **64**: 1713–8

Diabet Med

Is hypoglycaemia associated with mortality?

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓✓

1 The purpose of the study was to examine whether severe hypoglycaemia and impaired hypoglycaemia awareness are associated with all-cause mortality or cardiovascular mortality in people with T1D.

2 In two European cohorts, a Danish group (n=269) and a Dutch (n=482) group with 12 and 6.5 years follow-up respectively, hypoglycaemia awareness and severe hypoglycaemic episodes were measured, and medical reports and registries were used to calculate mortality.

3 All-cause mortality was 14% in the Danish cohort and 4% in the Dutch cohort.

4 In both cohorts, the frequency of severe hypoglycaemia and impaired hypoglycaemia awareness were not associated with increased mortality.

Sejling AS, Schouwenberg B, Faerch LH et al (2015) Association between hypoglycaemia and impaired hypoglycaemia awareness and mortality in people with type 1 diabetes mellitus. *Diabet Med* 20 May [Epub ahead of print]

Diabetes Technol Ther

CIPII versus SC insulin therapy

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 Continuous intraperitoneal insulin infusion (CIPII) is believed to have a more physiologic action of insulin than subcutaneous (SC) insulin administration, so the authors hypothesised that CIPII would result in less glycaemic variability than SC insulin therapy.

2 A 26-week, prospective, observational case–control study was carried out among 176 adults (37 used CIPII, and 139 used SC insulin therapy). Five-day blind continuous glucose monitoring was conducted at baseline and 26 weeks.

3 After adjustment for baseline differences, the coefficient of variation was 4.9% (95% confidence interval, 1.0–8.8) lower with CIPII- compared with SC-treated individuals, irrespective of the mode of SC delivery. There were no differences in other indices of glycaemic variation between groups.

van Dijk PR, Groenier KH, DeVries JH et al (2015) Continuous intraperitoneal insulin infusion versus subcutaneous insulin therapy in the treatment of type 1 diabetes: effects on glycemic variability. *Diabetes Technol Ther* **17**: 379–84

Diabetologia

Islet autoantibodies in childhood

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 Islet autoantibodies can be detected for a variable time before T1D onset.

2 As part of the TEDDY study, infants with *HLA-DR* high-risk genotypes received standardised autoantibody assessments quarterly throughout the first 4 years of life and then semi-annually.

3 Autoantibodies appeared in 549 children out of a total cohort of 8503 (6.5%).

4 In total, 43.7% of those who had autoantibodies had islet autoantibodies to insulin (IAA) only, and over a third had glutamic acid decarboxylase autoantibodies (GADA) only.

5 The incidence of IAA only peaked within the first year of life and declined over the following 5 years, but GADA only increased until the second year and remained relatively constant.

6 The findings suggest that islet autoantibodies can occur very early in life, but it is very rare.

Krischer JP, Lynch KF, Schatz DA et al (2015) The 6 year incidence of diabetes-associated autoantibodies in genetically at-risk children. *Diabetologia* **58**: 980–7