Studies of insulin glargine show no increased cancer risk

Daniel Flanagan, Consultant Physician, Derriford Hospital, Plymouth

Last summer the question of whether insulin glargine increased the risk of malignancy hit the headlines. Overall, the diabetes community has handled this debate in a reasoned and calm way. I would strongly recommend the article by Smith and Gale (2009) for a clear explanation of the issues. They point out that type 2 diabetes and obesity are themselves associated with increased cancer risk. Therapy with any insulin is associated with an increased cancer risk. There is also some evidence that therapies that reduce circulating insulin, such as metformin, reduce cancer risk.

> ***"It is worth reflecting that high circulating insulin concentrations, whether endogenous or administered by injection, appear to be associated with an increased risk of cancer."***

Insulin is itself a growth factor with complex interactions with the insulin-like growth factor axes. There are significant differences between human insulin and the insulin analogues in their interactions with growth axes (Hansen et al, 1996; Weinstein et al, 2009), and it would seem intuitively obvious that these differences would result in a different potential to cause tumour growth. The difficulty is to translate theory and laboratory-based experiments into clinical practice. There are theoretical mechanisms whereby insulin glargine may have a greater potential for tumour growth (Smith and Gale, 2009), but this is not the same as saying that the risk is clinically significant.

An important piece of information that has been missing until now is data from the manufacturer's own pharmacovigilance database; the article by Home and Lagarenne (2009; summarised alongside) presents these results. Thirty-one randomised controlled trials were included. The final conclusion of the article is that insulin glargine was not associated with an increased incidence of cancer. The result is important and reassuring for our patients on this therapy. The problem we have is that cancers take many years to develop and that many of the studies included were of short duration (some as short as 4 weeks) – only one study was of more than 12 months' duration. It is important to note that the manufacturers of insulin detemir have now published their own pharmacovigilance data and have come to the same conclusion (Dejgaard et al, 2009; summarised on page 78).

Insulin glargine has proven to be a useful clinical tool, and we must be cautious in changing practice on the information currently available. It is worth reflecting that high circulating insulin concentrations, whether endogenous or administered by injection, appear to be associated with an increased risk of cancer (Smith and Gale, 2009). This has not received much attention in the past as the risk was not felt to be modifiable. With the variety of modern treatments now available, this is perhaps something that should be given more thought.

Hansen BF, Danielsen GM, Drejer K et al (1996) Sustained signalling from the insulin receptor after stimulation with insulin analogues exhibiting increased mitogenic potency. *Biochem J* **315**: 271–9

Smith U, Gale EA (2009) Does diabetes therapy influence the risk of cancer? *Diabetologia* **52**: 1699–708

Weinstein D, Simon M, Yehezkel E et al (2009) Insulin analogues display IGF-I-like mitogenic and anti-apoptotic activities in cultured cancer cells. *Diabetes Metab Res Rev* **25**: 41–9

DIABETOLOGIA

Insulin glargine has no link to increased incidence of cancer

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Recent data have indicated that a relationship may exist between insulin glargine therapy and an increased incidence of cancer or breast cancer.

2 Whether such a relationship exists was investigated using randomised controlled trials of insulin glargine from the sanofi-aventis pharmacovigilance database.

3 The study comprised 31 trials (12 on type 1 diabetes; 19 on type 2 diabetes); 20 compared insulin glargine with neutral protamine Hagedorn (NPH) insulin and most (29) were parallel-group studies.

4 Participants comprised 5657 people randomised to insulin glargine and 5223 randomised to a comparator, with a total follow-up of 4711 and 4524 person-years, respectively.

5 There were no significant differences in the incidence of malignancies between insulin glargine and comparator treatments; 45 (0.8%) insulin glargine-treated people reported 52 cases of malignant cancer and 46 (0.9%) comparator-treated people reported 48 cases of malignant cancer.

6 The most frequently reported sites for malignancy (insulin glargine group vs comparator group) were skin (12 vs 6 people), colon and rectum (6 vs 10 people), breast (4 vs 6 people) and gastrointestinal tract (6 vs 4 people).

7 No association was found between insulin glargine therapy and increased incidence of any cancer compared with different comparators (mainly NPH insulin).

Home PD, Lagarenne P (2009) Combined randomised, controlled trial experience of malignancies in studies using insulin glargine. *Diabetologia* **52**: 2499–506

"Closed-loop insulin delivery can reduce nocturnal hypoglycaemia in young people with type 1 diabetes."

LANCET

Closed-loop delivery effective in reducing nocturnal hypoglycaemia

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓✓

1 Hypoglycaemia is a feared complication in children and adolescents with type 1 diabetes; technological developments in blood glucose monitoring and insulin delivery aim to reduce this risk.

2 Closed-loop systems have been developed, which enable insulin to be delivered according to real-time, continuous blood glucose measurements.

3 This study examined whether closed-loop insulin delivery would reduce nocturnal hypoglycaemia in 17 young people (aged 5–18 years) with type 1 diabetes.

4 Three randomised crossover studies compared continuous subcutaneous insulin infusion (standard therapy) with closed-loop delivery (n=13) and looked at the effect of a large evening meal on closed-loop delivery (n=7) and the effect of evening exercise on both treatments (n=10).

5 Time within the target range for blood glucose was longer for the closed-loop system compared with standard treatment, with fully effective delivery seen after midnight.

6 Frequency of hypoglycaemia was reduced with closed-loop delivery, with no plasma glucose measurements <3.0 mmol/L.

7 The authors concluded that closed-loop insulin delivery can reduce nocturnal hypoglycaemia in young people with type 1 diabetes.

Hovorka R, Allen JM, Elleri D et al (2010) Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. *Lancet* **375**: 743–51

DIABETES CARE

Diary improves QoL with good control

Readability	✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓

1 A diabetes interactive diary (DID) is a carbohydrate/insulin bolus calculator installed on a mobile phone.

2 This study compared the effectiveness of a DID with standard education in improving the metabolic control and quality of life (QoL) of people with type 1 diabetes; 67 people were randomised to the DID group and 63 people received standard education.

3 Body weight, HbA_{1c} and QoL were determined at 0, 3 and 6 months.

4 A significant reduction in HbA_{1c} was seen in both groups from 3 months, with the DID group reporting more favourably on some QoL factors.

5 It was concluded that the DID was as effective as standard education, gave better treatment satisfaction and required less time for education.

Rossi MCE, Nicolucci A, Bartolo PD et al (2010) Diabetes interactive diary: a new telemedicine system enabling flexible diet and insulin therapy while improving quality of life. *Diabetes Care* **33**: 109–15

DIABETIC MEDICINE

Elevated ALT linked with NAFLD-related risk factors

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 As type 2 diabetes is associated with non-alcoholic fatty liver disease (NAFLD), this study examined the prevalence of abnormal liver profiles in people with type 1 diabetes.

2 The prevalence of abnormal alanine transaminase (ALT) was determined at three cut-offs in 911 people with type 1 diabetes and in 963 people with type 2 diabetes.

3 The prevalence of elevated ALT using the three cut-off values of >30 IU/L in men and >19 IU/L in women, >50 IU/L and >63 IU/L were 34.5, 4.3 and 1.9% in the group with type 1 diabetes, and 51.4, 8.2 and 3.7% in the group with type 2 diabetes.

4 An elevated ALT was associated with NAFLD-related risk factors; an abnormal ALT in people with type 1 diabetes was linked with age >55 years, elevated triglycerides and an HbA_{1c} level >8.2% (66 mmol/mol).

5 The ALT cut-off value alters the prevalence of people at risk of liver disease. Assessment of elevated ALT is vital to enable disease intervention.

Leeds JS, Forman EM, Morley S et al (2009) Abnormal liver function tests in patients with type 1 diabetes mellitus. *Diabet Med* **26**: 1235–41

DIABETOLOGIA

Insulin detemir does not increase cancer risk

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓

1 This meta-analysis determined the risk of cancer in people with type 1 diabetes treated with insulin detemir.

2 The sample comprised 8693 people with type 1 or 2 diabetes involved in trials comparing insulin detemir, neutral protamine Hagedorn (NPH) insulin and insulin glargine.

3 The results showed a low number of cancer diagnoses, with no statistically significant pattern of events across the different treatment groups.

4 People treated with insulin detemir were found to have a lower or similar risk of cancer diagnosis than those treated with NPH insulin or insulin glargine, respectively.

Dejgaard A, Lynggaard H, Råstam J, Krogsgaard Thomsen M (2009) No evidence of increased risk of malignancies in patients with diabetes treated with insulin detemir: a meta-analysis. *Diabetologia* **52**: 2507–12