JrnlID 125_ArtID 1452_Proof# 1 - 07/07/2009

Diabetologia
DOI 10.1007/s00125-009-1452-2

LETTER

Similar risk of malignancy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: findings from a 5 year randomised, open-label study

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Received: 26 June 2009 / Accepted: 29 June 2009

Keywords Cancer · Insulin analogues · Insulin glargine · Insulin therapy · Malignancy · NPH insulin · Type 2 diabetes

Abbreviations
MedDRA Medical Dictionary for Regulatory Activities
NPH Neutral protamine Hagedorn

To the Editor: We have reported a randomised, long-term safety study comparing the effects of using the insulin analogue glargine (A21Gly,B31Arg,B32Arg human insulin) versus human neutral protamine Hagedorn (NPH) insulin for 5 years in the management of type 2 diabetes [1]. The study, in which 1017 patients were randomised and treated, was designed to assess ocular complications of diabetes: there was no excess of such effects with insulin glargine compared with NPH treatment and there was a similar slow progression of diabetic retinopathy with both types of insulin. Because of recent concerns about postulated neoplastic effects of insulins [2–5], we report here additional information from our study that bears on this question.

In total, the mean cumulative exposure in our study was more than 4 years (1,524 days in the insulin glargine group and 1,522 days in the NPH insulin group), with more than 70% of patients exposed to more than 4 years of treatment (76% and 71%, respectively) (Table 1).

The baseline demographics and diabetes status were similar between the two treatment groups (insulin glargine vs NPH insulin): diabetes duration (10.7 vs 10.8 years),

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JmlID 125_ArtID 1452_Proof# 1 - 07/07/2009

t1.1 **Table 1** Summary of extent of exposure (safety population)

Variable	Insulin glargine (n=514)	NPH insulin (n=503)	
Cumulative exposure (patient-years)	2144.0	2095.8	t1.3
Extent of exposure (days)			t1.4
Mean	1523.55±571.77	1521.82±562.14	t1.5
Median	1821.50	1823.00	t1.6

Data are mean±SD unless otherwise stated

BMI (34.5 vs 34.1 kg/m^2), oral hypoglycaemic agent duration (9.0 vs 8.9 years), prior insulin use (67% vs 70%), HbA_{1c} (8.4% vs 8.3%) and fasting plasma glucose (10.5 vs 10.0 mmol/l).

Although the study was not designed to investigate the frequency of tumour development, the long duration of the trial enables a comparative assessment of the occurrence of benign or malignant tumours with insulin glargine and NPH insulin during more than 4 years of exposure, captured as adverse events in the course of routine safety monitoring. The number of patients with treatment-emergent adverse events (defined as events that first occurred or worsened after randomisation) of neoplasm, summarised by System Organ Class and High-level Group Term levels using the standard Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary (version 10.0; Maintenance and Support Services Organization, Chantilly, VA, USA) [6], are shown in Table 2. Benign and malignant tumours reported by the investigators, along with those of unspecified pathology, are included. A more detailed listing of MedDRA-coded neoplasms is available [7].

The overall number of patients with neoplasms (using the standard MedDRA coding dictionary) occurring during the trial was similar in the two treatment groups: 57 patients (11.1%) in the insulin glargine group vs 62 patients (12.3%) in the NPH insulin group, with an RR for insulin glargine of 0.90 (95% CI 0.64–1.26). In addition, when only the number of patients with malignant neoplasms reported as serious

t2.1 **Table 2** Patients with neoplasms reported as treatment-emergent adverse events

All neoplasms[a]	Insulin glargine (n=514)	NPH insulin (n=503)
Any event	57 (11.1)	62 (12.3)
Breast neoplasms, malignant	3 (0.6)	5 (1.0)
Cutaneous neoplasms, benign	13 (2.5)	12 (2.4)
Endocrine neoplasms, malignant	5 (1.0)	7 (1.4)
Gastrointestinal neoplasms, malignant	6 (1.2)	9 (1.8)
Haematopoietic neoplasms	1 (0.2)	0
Hepatobiliary neoplasms, malignant	0	1 (0.2)
Lymphomas, non-Hodgkin's B cell	0	1 (0.2)
Metastases, unspecified neoplasm	0	1 (0.2)
Miscellaneous and site unspecified neoplasms, malignant	1 (0.2)	3 (0.6)
Nervous system neoplasms, benign	1 (0.2)	2 (0.4)
Ocular neoplasms, benign or malignant	3 (0.6)	2 (0.4)
Plasma cell neoplasms, benign or malignant	1 (0.2)	0
Renal and urinary tract neoplasms, malignant	2 (0.4)	1 (0.2)
Reproductive neoplasms female, benign	2 (0.4)	1 (0.2)
Reproductive neoplasms female, malignant	2 (0.4)	4 (0.8)
Reproductive neoplasms male, malignant	2 (0.4)	3 (0.6)
Respiratory and mediastinal neoplasms, malignant	6 (1.2)	2 (0.4)
Skin neoplasms, malignant	11 (2.1)	9 (1.8)
Soft tissue neoplasms, benign	3 (0.6)	4 (0.8)
Soft tissue sarcomas, benign or malignant	0	1 (0.2)

Data are n (%), in alphabetical order

All patients with neoplasm-coded adverse events (whether considered serious or non-serious) as reported by the investigator are included. Patients may have had more than one adverse event

[a] Includes MedDRA System Organ Class 'Neoplasm benign, malignant and unspecified (including cysts and polyps)' (version 10.0) [6]

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treatment-emergent events was captured, the rate was also similar in both treatment groups: 20 patients (3.9%) with 23 events in the insulin glargine group vs 31 patients (6.2%) with 32 events in the NPH insulin group, with an RR for insulin glargine of 0.63 (95% CI 0.36–1.09).

The number of patients with malignant breast tumours reported was also similar between the two treatment groups: three patients in the insulin glargine group (all reported as serious) compared with five patients (four reported as serious) in the NPH insulin group.

The RR estimate of all malignant breast tumour cases, including non-serious cases (three in the insulin glargine group vs five in the NPH insulin group) numerically favours insulin glargine (RR 0.59, 95% CI 0.14–2.44). Although the 95% CI includes 2, it must be noted that due to the small numbers of patients and the small number of cases, there was only a 22% power to reject a doubling in the risk (RR 2.0) of developing this tumour, should the true risks be equal.

Considering all neoplasms (RR 0.9) and all malignant neoplasms (RR 0.63), the results numerically favour insulin glargine with 95% upper CI limits of 1.26 and 1.09, respectively, indicating at most a 26% and 9% increase in risk.

In summary, this study is the longest controlled treatment comparison of insulin glargine versus NPH insulin in patients with type 2 diabetes mellitus. No new safety issues emerged for either insulin studied based on the data from this 5 year trial. Additional data reported here also confirm that there was no evidence of any difference in the rate of benign or malignant tumour development with insulin glargine compared with NPH insulin.

Duality of interest J. Rosenstock has received grants for research from and/or has been a consultant to Amylin, Boehringer-Ingelheim, Bristol-Myers Squibb, Centocor, Eli Lilly, Emisphere, GlaxoSmithKline, Johnson & Johnson, MannKind, Merck, Novartis, Novo Nordisk, Pfizer, Roche, Sankyo, sanofi-aventis and Takeda. V. Fonseca has received research support (to Tulane University) with grants from GlaxoSmithKline, Novartis, Novo Nordisk, Takeda, Astra-Zeneca, Pfizer, sanofi-aventis, Eli Lilly, Daiichi-Sankyo, Novartis, the National Institutes of Health (NIH) and the American Diabetes Association (ADA), and honoraria for consulting and lectures from GlaxoSmithKline, Novartis, Takeda, Pfizer, sanofi-aventis and Eli Lilly. J. McGill has received grant support (to Washington University) from sanofi-aventis, Pfizer, Eli Lilly, Novo Nordisk, Novartis, GlaxoSmithKline, Elixir, Tolerx, Biodel, Mannkind, Takeda; served on advisory boards and speakers' bureaus for sanofi-aventis and Novo Nordisk, and on speakers' bureaus for Eli Lilly, Merck, Novartis, Novo Nordisk, sanofi-aventis, Daiichi-Sankyo, Forest and GlaxoSmithKline; and has been a consultant/advisor for Merck, Novo Nordisk, Elixir, Mannkind, Amgen. I. Hramiak has received research grant support from Pfizer, sanofi-aventis, Novo Nordisk and Eli Lilly and has served on advisory boards for GlaxoSmithKline, Novo Nordisk, sanofi-aventis and Merck. J.-P. Hallé has received grants for research from and/or has been a consultant and/or on the speaker bureau of Bristol-Myers Squibb, ConjuChem, Bellus Health, Eli Lilly, GlaxoSmithKline, Merck Frosst, Novartis, Novo Nordisk, Pfizer, Roche, sanofi-aventis and Takeda. M. Riddle has received grants for research and/or honoraria for consulting or lectures from Amylin, Lilly, the Amylin-Lilly Alliance, Novo Nordisk, Pfizer, sanofi-aventis and Valeritas. P. Johnston is an employee of, and holds stock options from sanofi-aventis. M. Davis has received research support from sanofi-aventis.

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