The International Study of Insulin and Cancer

Studies have suggested the possibility of an association between use of insulin glargine and cancer, with conflicting results.[1–4] Among other issues under debate is the role of insulin itself in cancer development and the contribution of confounding factors or analytical methods to observations.[5] The International Study of Insulin and Cancer (ISICA) is an effort to address thoroughly the association of breast cancer with insulin use. ISICA has received an unrestricted grant from Sanofi-Aventis and has been reviewed by the European Medicines Agency.

Using case-control methods, the ISICA study aims mainly to assess the association of breast cancer with the use of individual insulins such as the analogues glargine, lispro, and aspart, and human insulin formulations such as isophane and regular human insulin, compared with non-insulin use in patients with diabetes. Analysis will account for mitigating or risk factors such as oral antidiabetes agents (specially metformin), type of diabetes, gestational diabetes, lifetime body-mass index, reproduction-related factors, oral contraceptives, hormone replacement therapy, cancer in first-degree relatives, socioeconomic status, and behavioural risk (alcohol, smoking), among others. Also, several biological variables will be assessed (eg, HER2, oestrogen, or progesterone receptors, and circulating insulin).

A registry of 12 500 patients with breast cancer, diagnosed with a first positive biopsy between January, 2008, and June, 2009 (ie, before the cited publications), will be identified through pathology records and medical charts by a network of at least 50 centres across the UK, France, and Canada that treat at least 100 breast cancer patients per year. Cases, defined as those who also have diabetes, will be identified. At least 1000 of such patients are expected to meet this criterion and 750 will be included. Eligible patients will be female, at least 18 years old, without previous history of breast cancer, and willing and able to participate. Controls will be patients with diabetes who fulfil the same eligibility criteria and who are free of cancer at the time of matching to cases. Controls will be independently recruited from general medical practices. An average of four controls will probably be matched to each case on type of diabetes, age, country, and region, totalling 3000 controls.

Exposure to insulin and other drugs will be collected from patients' general practitioners or pharmacy records. All patients will be interviewed for individual risk factors and blood samples will be collected and tested for biological markers. Data and blood samples will be available to various researchers. Descriptive analysis and multivariable modelling will be done for case-control comparisons. The study results are expected in mid-2012.

The ISICA group: M Blettner, Y Ohashi, J M Extra, L Mignot, F Penault-Llorca, D Rea, A Thompson, W Weller. LGB's institution (LA-SER) was paid by Sanofi-Aventis to independently conduct the study. MM has received consultancy fees from Sanofi-Aventis, Debiopharma, and Celgene; payment for development of educational presentations including service on speakers' bureaux from Roche and AstraZeneca; and reimbursement of travel or accommodation expenses from Sanofi-Aventis. MP has received consultancy fees or honoraria for work on ISICA from La-Ser and Sanofi-Aventis, and consultancy fees, grants, and travel expenses for other work from Novo Nordisk, Sanofi-Aventis, and Pfizer. DC received consulting fees and travel expenses during the design stage of ISICA from Sanofi-Aventis. MR has received honoraria for consulting and for chairing a consulting group regarding insulin glargine, as well as research grants, speakers' fees, and travel grants from Sanofi-Aventis. BC has received received fees for consultancy, advisory boards, speaking, travel, or accommodation from Takeda, GlaxoSmithKline, Merck Sharpe & Dohme, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Novo Nordisk, Roche, Sanofi-Aventis, and Novartis. AHB has received honoraria for advisory work and lectures unrelated to this work from Sanofi-Aventis, Eli Lilly, and NovoNordisk. PB's institution has received a grant for a study on glargine and cancer, and PB has received honoraria for advisory board meetings from Sanofi-Aventis. JFB has been a scientific advisory board member for Sanofi-Aventis and received reimbursement for travel to board meetings. ME has received grants and consultancy fees from Eli Lilly, Novo Nordisk, and Sanofi-Aventis. MR has received honoraria for advisory work and lectures unrelated to this work from Sanofi-Aventis, Eli Lilly, and NovoNordisk. JB has no conflicts of interest. LA's institution (LA-SER) received an unrestricted grant from Sanofi-Aventis for the ICISA study. LA is a stock owner and chairman of LA-SER and has received speakers' fees, payment for manuscript preparation, and has stock options in AstraZeneca, Boiron, Expanscience, Genevrier, GSK, Janssen-Cilag, Merck/Shering Plough, Negma/Wokhardt, Novartis, Pfizer, and several divisions of Sanofi. He was also a former Chief Medical Officer in France (1999–2003), and has taken decisions on almost all the drugs reimbursed during that period, including some studied during the ISICA study.

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1 Hemkens LG, Grouven U, Bender R, et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia* 2009; **52:** 1732–44.

2 Jonasson JM, Ljung R, Talback M, et al. Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden. *Diabetologia* 2009; **52:** 1745–54.

3 Colhoun HM; SDRN Epidemiology Group. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetologia* 2009; **52:** 1755–65.

4 Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia* 2009; **52:** 1766–77.

5 Pocock SJ, Smeeth L. Insulin glargine and malignancy: an unwarranted alarm. *Lancet* 2009; **374:** 511–13.