Insulin glargine and cancer: cause and effect unproven

The inference that insulin glargine may cause cancer[1-5] is the latest in a series of controversies to hit diabetes over the last few years, to include the alleged risk of rosiglitazone causing heart disease[6] and that intensive glycaemic control can kill.[7] Although careful analysis of the data, along with new information has since refuted these earlier allegations, their impact persists.[8-13]

In a recent issue of *Diabetologia,*[1] reference was made to a possible link between insulin glargine and cancer based on the analysis of four separate databases in Germany,[2] Sweden,[3] Scotland[4] and the UK.[5] The editors concluded that further investigation is now necessary. In a press release, as well as in 'information for patients', the EASD prematurely recommended that in the circumstances an alternative insulin preparation could be considered.[14]

In brief, the German cohort study from the Institute for Quality and Efficiency in Health Care (IQWiG)[2] involving 127,031 insulin treated subjects from a health insurance database concluded that there appeared to be an increased risk of malignancies in persons exposed only to a high dose of insulin glargine. The study employed unjustified and unconventional statistical analysis adjusting for insulin dosage while failing to adjust for body weight which is a key confounder when exploring the relationship between cancer and insulin. These critical limitations raise serious doubts about the validity of their findings and interpretation of the data. However, in the insulin glargine group, there was an overall decrease in the unadjusted hazard ratio (HR) for both cancer risk (HR 0.86, 95% CI 0.79-0.94) and all-cause mortality (HR 0.68, 95% CI 0.65-0.72) comparing insulin glargine alone with other insulins. In the Swedish study[3] however, which had access to 114,841 insulin treated persons with diabetes from their Prescribed Drug, Cancer and Causes of Death Registers, an increased risk of breast cancer in females using insulin glargine only was observed compared to the other insulins. This risk was not found when insulin glargine was used in combination with the other unspecified insulin preparations. Of note, as in the German study, there was no overall increase in malignancies with insulin glargine use (HR 1.07, 95% CI 0.91-1.27) and all-cause mortality was again reduced (HR 0.83, 95% CI 0.71-0.96). Similarly, the Scottish study[4] utilising 49,197 subjects from the Scottish National Diabetes and Cancer Registers revealed no overall increased risk of cancer when all insulin glargine users were included (HR 1.02, 95% CI 0.77-1.36). There was an increase in risk in the group of insulin glargine only users (n=447) where the majority of subjects (~97%) had type 2 diabetes, in contrast to 62% in the group on glargine in combination with other insulins (n=3512) who had type 1 diabetes and were younger and leaner. No increase in breast cancer with insulin glargine was seen in this study. Finally, the THIN study,[5] an analysis of 10,067 subjects from The Health Information Network, an UK general practice database, clearly re-affirmed that there was neither an increase in overall risk of cancer (HR 0.81, 95% 0.59-1.11) or breast cancer in subjects exposed to insulin glargine or to premixed insulin preparations.

The overriding concern regarding the relevance of these studies is the treatment selection bias due to the absence of randomisation between treatment types. There is almost complete lack of information about the other insulins used alone or together with insulin glargine. Neither is there any information about critical confounders such as adiposity, body weight or BMI, essential for assessing risk of cancer and determining a possible insulin dose response. The flawed methodology used to determine the dose-response relationship of insulin glargine with cancer in the German study makes the allegations groundless. The deficiency of information on major risk factors is evident through the inconsistencies seen in the results which clearly reflect important differences between the populations, both between and within the study groups being compared. The duration of follow-up between 1 to 3 years is also relatively short in relationship to the cancer question being addressed.

A smaller but randomised control trial conducted over 5 years to assess the risk of diabetic retinopathy in 1017 subjects with type 2 diabetes using insulin glargine once daily versus twice daily NPH insulin was published in the same issue of *Diabetologia.*[15] There was no excess risk of diabetic retinopathy with insulin glargine over NPH insulin[15] neither was there an increased risk for all neoplasms RR for insulin glargine (0.90, 95% CI 0.64-1.26) or breast cancer with insulin glargine.[16]

The theoretical basis for concern relating to insulin glargine has emerged from the findings of enhanced affinity for the IGF-1 receptors and mitogenic response in malignant cell lines.[17,18] Earlier studies involving a variety of cell lines have not shown significant differences between insulin glargine and human insulin in insulin and IGF-1 receptor binding, mitogenic response and growth promoting activity.[19-24] Affinity of insulin glargine for the IGF-1 receptor is 200-fold less than for endogenous circulating IGF-1.[21] It is only at very high concentration that insulin glargine is preferentially bound to IGF-1 receptors when compared with human insulin in cells from normal subjects and type 2 diabetes.[22] The carcinogenicity studies over two years in mice and rats (dose up to 12.5 IU per kg) revealed no increased incidence of malignancy,[24] in particular there was no proliferation of mammary tumours in these animals. It is also important to remember that a significant fraction of insulin glargine absorbed from the subcutaneous site of injection is metabolised within a short space of time. In the two active metabolites, two arginine amino acids (B31, B32) are removed from the C-terminus of the β chain of insulin glargine (M1 and M2). Both retain the equivalent glucose lowering potency of the parent compound whereas affinity for the IGF-1 receptor is markedly reduced. The extrapolation from *in vitro* studies

where equivalent molar concentrations of insulin glargine and human insulin are compared do not account for the metabolic processing.

Taking all this into consideration, the four observational studies mentioned above[2-5] have serious and widely acknowledged methodological limitations which question the validity of the findings and therefore do not allow any meaningful interpretation of the relationship between insulin glargine and cancer. The randomised control trial is reassuring,[15] however it involved a relatively small number of subjects over a longer but still relatively short period of time. Further epidemiological investigation of existing and more extensive databases is now warranted representing a true collaboration between academia and industry in an effort to resolve this dilemma.

Our commentary merely restates what has been more eloquently represented by others[25,26] including statements released by regulatory bodies like the FDA[27] and European Medicines Agency's (EMEA) Committee for Medicinal Products for Human Use[28] along with national diabetes associations such as the American Diabetes Association,[29] Diabetes UK,[30] and other associations like the American Association of Clinical Endocrinologists.[31] The consistent and emphatic message is that there is inconclusive evidence to associate insulin glargine with an excess risk of cancer and therefore there is no basis for denying subjects the known benefits of using insulin glargine as a basal insulin.

In hindsight a more measured response in respect to the recent publications would have prevented an 'unwarranted alarm' engendered in our patients and carers alike. A salutary lesson to be learnt!

Professor David R Owens, CBE, MD, Professor and Consultant Diabetologist, Diabetes Research Unit, University Hospital Llandough, Penarth, UK
Professor Julio Rosenstock, MD, Dallas Diabetes and Endocrine Center at Medical City, Texas, USA
Professor Geremia B Bolli, MD, Department of Internal Medicine, Endocrinology and Metabolism, University of Perugia, Perugia, Italy

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