Trials and tribulations of diabetes therapies: Insulin glargine

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The recent publications and debate arising from the suggestion of a cancer link with insulin glargine have thrown a sharp light on scientific and ethical issues that may influence clinical practice.

Following the publication in *Diabetologia* of four observational studies (Colhoun et al, 2009; Currie et al, 2009; Hemkens et al, 2009; Jonasson et al, 2009) and the accompanying editorial regarding insulin glargine (Smith and Gale, 2009), there was an atmosphere of concern for people with diabetes and their carers alike. These papers have now been dissected further by the research community with an emerging robust view that the original data were not clear due to deficiencies in the availability of confounding factors and other methodological quirks.

Diabetes drug trials have had a history of linking potential health hazards with effects of drug treatments. There are several examples of licensed drugs for which initial health scares were disproved by subsequent analysis. Four decades ago the University Group Diabetes Program data were published and raised a concern about sulphonylureas and myocardial infarction (Klimt et al, 1970). A decade later, re-analysis (Kilo et al, 1980) highlighted unequal case allocation between randomisation groups with regard to baseline vascular history – an issue that was overlooked in the original publication.

In the case of insulin glargine, important confounders were not available for some of the studies, and adjustment for them is crucial to the correct interpretation. The central tenet of the proposed link between high-dose glargine monotherapy and cancer cannot be substantiated at this stage due to the omission of key information in several of the studies, including obesity, smoking status and family history of cancer, which are well recognised as risk factors for cancer in their own right. Why basal insulin monotherapy, as opposed to insulin combination therapy, was linked with cancer, is indeed a conundrum. In our view the conclusions have created unnecessary alarm.

Two further examples are pertinent to the current debate. The original concerns around rosiglitazone with respect to adverse cardiovascular effects have been ameliorated to some extent following several re-analyses of the trial data (Home et al, 2009). Another example of a drug used in people with and without diabetes is ezetimibe, where a premature link with cancer was made. The concerns arose from one trial but, when analysed appropriately with other trial data, the association was not substantiated (Peto et al, 2008). As with the insulin glargine studies, the actual number of cancer cases was small and resulted in insufficient power to establish a link with specific cancers.

It is clearly important to monitor and report new side-effects of drugs to guide safe prescribing. Traditionally observational studies, as well as case reporting and newer randomised controlled trials, have been the mechanisms for achieving this. However, there are biases inherent in observational studies, and limitations due to selection criteria in randomised controlled trials that may limit the generalisability of findings. Thus, in the case of insulin glargine, strongly worded editorials were promptly published in both the *Lancet*, entitled "Insulin glargine and malignancy: an unwarranted alarm" (Pocock and Smeeth, 2009) and in *Diabetes, Technology & Therapeutics,* entitled "Insulin glargine and cancer – an unsubstantiated allegation" (Garg et al, 2009). Their analyses contrasted with the conclusions drawn from the original *Diabetologia* editorial and represent clarity in the correct interpretation of the available data.

We support the views of the European Medicines Agency (2009a) that the studies were found to be inconclusive and that the "relationship between insulin glargine and cancer cannot be confirmed or excluded". Their guidance (2009b) concluded that "changes to the prescribing advice [for insulin glargine] are therefore not necessary". ■

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