When “Flawed” Translates into “Flood”: The Unproven Association Between Cancer Incidence and Glargine Insulin Therapy

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A few months ago, a hot spot emerged in the area of diabetes and cancer epidemiology. Hemkens et al. [1], from the Institute for Quality and Efficiency in Health Care, published in Diabetologia a report of an observational cohort study based on a large health insurance database representing almost 18 million people from Germany. Their hypothesis was to test whether glargine, an insulin analog (Lantus®; sanofi-aventis, Bridgewater, NJ), was associated with a higher incidence of cancer than human insulin. Initial results not only rejected this hypothesis, but found a protective effect for glargine in the age-sex-adjusted analysis (for glargine and the risk for malignant neoplasm: hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.79–0.94), yet after a bias-introducing adjustment for the glargine insulin dose, the insulin analog seemed to confer a higher risk for neoplasm incidence (HR, 1.14; 95% CI, 1.05–1.24). Three other papers in the same issue did not find a convincing association [2–4].

In this issue of The Oncologist, Ehninger and Schmidt [5] review crucial methodological flaws in the Hemkens et al. [1] analysis. These include the highly distorting effects of “confounding by indication” or allocation bias (where patients with cancer risk factors may have been preferentially prescribed glargine), lack of control for other key confounders in the diabetes–cancer association (like smoking or obesity), lack of predetermined allocation to treatment groups (these are not randomized clinical trial data), and adjusting for glargine insulin doses in a way that overemphasized the importance of the small, very highest-dose group (thereby biasing the point estimate for the glargine term in the regression models). Moreover, a mean follow-up time for glargine patients of 1.3 years is too short an exposure time when looking for new cancer development and detection. Short follow-up introduces the problem of reverse confounding, in which clinical changes in people with latent cancers (that then occur soon into follow-up) may have caused patients to be prescribed glargine [6]. This is often handled in epidemiological analyses by dropping the first several years of follow-up after the baseline exposure period. The policy of Diabetologia was to accept the manuscript for publication after the peer-review process (during which some reviewers repeatedly recommended rejection), because “it was too important to ignore,” and at the same time, to look for the replication of the results in other co-
horts, “as it was too weak to be published in isolation” and “[r]eplication is the constructive alternative to rejection” [7]. In none of the replication cohorts, published in the same issue of *Diabetologia*, was an association between overall cancer incidence and glargine convincingly replicated [2-4]. Despite these issues, the authors stand by their procedures and conclusions [8].

The possibility that any drug, especially a drug with widespread use across the population and in many countries, could confer a higher risk for any potentially lethal adverse effect is an issue of major concern demanding prompt and rigorous investigation. Several recent precedents in type 2 diabetes care have shown that postcommercialization analyses were justified and, in some cases, led to drug withdrawal from the market [9, 10]. Thus, efforts to uncover potential secondary unexpected effects of drugs should always be welcome, and even more so if they are biologically plausible and supported by previous in vitro experiments [11-13]. We think first, do no harm. But doubtful information can also harm. When suggestions of deleterious effects are highly conflicting, caution must be exercised, especially when critical review suggests methodological problems in the research. Flawed papers may greet uncritical review in the lay press, “go viral” in the modern global world, and cause confusion in patients, doctors, and policy makers. These doubts may finally turn out to be unsupported on the scientific evidence, but with hard-to-reverse effects on patient perceptions, fears, and, potentially, diabetes control, as well as on the drug and the pharmaceutical company that holds the product. Often it is “guilty until proven innocent,” and the stain of guilt allegation spreads rapidly and is hard to remove. However, if data showing harm are convincing, then prompt action can be taken without confusion.

Clinical decisions are made based upon statistical results. When the study methodology is not appropriate and major flaws are not anticipated, statistical assumptions lead to the misinterpretation of the data and to the wrong conclusions. So, the editorial view in *Diabetologia* [7], “imperfect information is better than uninformed ignorance,” does not seem to acknowledge the complexities that statistics can introduce into analyses of outcomes studies. To cast doubt on a drug without at least more-likely-than-not certainty that the therapeutic agent does harm to the community does not seem to balance the benefit of drug harm detection with that of harms of doubtful data. Of course, in the media, the emphasis will be on the one positive study, with the lack of replication in three other (arguably better) studies given less attention. The argument stated by the editorialist, “we acknowledge the anxiety and distress that these reports might have generated, but we also believe that people have every right to be informed of possible danger” [7], might be more appropriate in other settings than in a medical journal, and especially on the basis of flawed and unreplicated analyses.

At this point, it is difficult to know if and when patients and doctors will recover their equilibrium about the safety of novel diabetes therapies. A trial to definitely rule out any possibility of a higher risk for cancer with the use of the analog than with human insulin would be prohibitively expensive and probably unethical. Hemkens et al.[1] calculated that a randomized, controlled trial would require about 7,500 patients, according to a crude sample size estimation based on the findings of their study (risk for malignant neoplasms of approximately 5% over 20 months, with a relative risk of 1.3 and a statistical power of 80%) [8]. It is possible that glargine insulin therapy does raise the risk for certain cancers. There is a plausible biologic mechanism via enhanced mitogenic insulin-like growth factor I pathway signaling [11]. Yet, mechanisms do not always translate into outcomes, and long-acting peakless basal insulin therapy is useful in many patients [14]. Therefore, it has been suggested by some epidemiology leaders that “we now need an informed scientific debate on what future evidence can realistically be obtained to further clarify this important public health issue” [6]. We agree; the question of a glargine–cancer association remains to be fully proven or disproven.

Now, expectations have been raised, and come what may, we think that one lesson to take away from this issue is that respected scientific journals have the power to balance the needs of patients and providers to know about possible harms of therapies, but also the responsibility to ensure that published data can stand up to fair methodological scrutiny. There are many reasons we have peer-reviewed science, and one is to prevent flawed (and perhaps sensational) data from flooding public perception as a hypothesis-tested fact. In addition to ensuring pharmaceutical public safety, we owe this scientific diligence to patients and the public.

**AUTHOR CONTRIBUTIONS**

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