Insulin therapy and cancer risk

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TO THE EDITOR: We read with interest the article by Ching Sun et al[1] on the relationship between diabetes therapy and cancer risk. We noted that there was no reference in the text to the long-acting insulins detemir and degludec, and we would like to add some relevant information.

With regard to detemir, a meta-analysis published in 2009 showed that patients treated with this insulin had a lower or similar rate of occurrence of a cancer compared with patients treated with neutral protamine Hagedorn insulin or insulin glargine.[2] In addition, in a cohort study, no difference in cancer risk between insulin detemir users and nonusers was reported.[3]

Insulin detemir has a lower binding affinity for human insulin receptor isoform A (IR-A) relative to human insulin, and a much lower affinity for isoform B (IR-B). The binding affinity ratio of insulinlike growth factor-1 (IGF-1) receptor to insulin receptor for detemir is less than or equal to 1 relative to human insulin and displays a dissociation pattern from the insulin receptor that is similar to or faster than that of human insulin. Consequently, the relative mitogenic potency of detemir in cell types predominantly expressing either the IGF-1 receptor or the insulin receptor is low and corresponds to its IGF-1 receptor and insulin receptor affinities.[4]

Regarding insulin degludec, its affinity for both IR-A and IR-B, as well as for the IGF-1 receptor, has been found to be lower than human insulin. Its mitogenic response, in the absence of albumin, was reported to range from 4% to 14% relative to human insulin.[5] Furthermore, in cellular assays, in which no albumin was added, the in vitro metabolic potency was determined to be in the range of 8% to 20%, resulting in a mitogenic-to-metabolic potency ratio of 1 or lower.[5]

It appears that insulins detemir and degludec have low mitogenic potential. However, additional studies are needed, especially with degludec, to further determine long-term safety.

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IN REPLY: Dr. Fountas et al highlight further data on insulin therapy and cancer risk, specifically in regard to insulin detemir and insulin degludec. Detemir first gained US Food and Drug Administration (FDA) approval in 2005 as a basal insulin, dosed once or twice daily.[1] Compared with regular human insulin, detemir has demonstrated proliferative and antiapoptotic activities in vitro in various cancer cell lines—eg, HCT-116 (colorectal cancer), PC-3 (prostate cancer), and MCF-7 (breast adenocarcinoma).[2] But clinically, detemir has

not demonstrated increased cancer risk compared with other basal insulins in randomized controlled trials or cohort studies.[3–5]

Degludec (U-200 insulin) is equal to twice the concentration of the usual U-100 insulin therapies presently available. In February 2013, the drug application for insulin degludec failed to obtain FDA approval, and the FDA requested additional data on cardiovascular safety. Thus, degludec is not currently available in the United States.[6]

Besides ameliorating nocturnal hypoglycemia,[7] U-200 insulin may mitigate potential mitogenic effects.[8] However, there are still very few data on degludec compared with the amount of data on insulin glargine. Insulin analogues with a decreased dissociation rate from the insulin receptor are associated with higher mitogenic potency than metabolic potency compared with human insulin.[9,10] Degludec, like detemir, has an elevated dissociation rate from the insulin receptor, a low affinity for IGF-1 receptors, and a low mitogenic activity in vitro.[8]

At this juncture, neither detemir nor degludec has been associated with higher cancer risk, but these therapies are relatively new. And as Dr. Fountas et al indicated, their safety, particularly in regard to cancer risk in diabetes patients, should continue to be assessed.

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