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Author names in bold designate shared co-first authorship

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REPLY:

We thank Dr. Ana Lleo and colleagues for having interest in our paper showing that long-term administration of denosumab safely increased bone mineral density in osteoporotic patients with primary biliary cholangitis (PBC) and autoimmune hepatitis.[1]

The beneficial effect of denosumab on bone metabolism is achieved by suppressing RANK signaling in osteoclastogenesis. The influence of inhibiting RANK-RANKL axis is now explored in other areas. A recent phase 3 trial demonstrated that adjuvant denosumab in postmenopausal patients with hormone receptor–positive breast cancer significantly improved disease-free survival compared with placebo (hazard ratio 0.82 [0.69-0.98]).[2] RANK and RANKL are expressed in immune cells and possibly in tumor and stroma cells, and these interactions in the tumor microenvironment could lead to immunosuppression.[3] Remarkable response was documented following concurrent treatment with denosumab and immune-checkpoint inhibitors in several case reports.[4] Therefore, denosumab might be used as an adjuvant in anticancer therapy.

In PBC, the RANK-RANKL axis might also have implications beyond osteoclastogenesis. A previous study demonstrated that the expression of RANK in cholangiocytes and RANKL in CD4, CD8, and CD19 cells around bile ducts was significantly greater in patients with PBC than those with other liver diseases,[5] suggesting the involvement of RANK-RANKL axis in the mechanism of bile duct injury in PBC. Therefore, denosumab might improve not only bone metabolism but also liver function in this intractable disease.

We analyzed the change in serum alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) levels in 6 patients with PBC who received 3-year denosumab therapy.[1] The ALP levels decreased, although it was largely attributable to the decline in bone-related isozyme. Serum GGT levels were not improved by denosumab therapy. As our patients had been receiving ursodeoxycholic acid for a long time when denosumab therapy initiated, there might be no room for further decrease in ALP and GGT. Nevertheless, a hypothesis that the RANK-RANKL axis plays a role in bile duct injury in PBC is worth further investigation. A prospective trial comparing the efficacy of denosumab with bisphosphonate in the treatment of osteoporotic patients with PBC is ongoing. Analysis from the viewpoint of improving bile duct injury might prove this hypothesis.

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Potential conflict of interest: Nothing to report.

Letter to the Editor: Hepatocellular Carcinoma Risk in Patients With Nonalcoholic Steatohepatitis Cirrhosis and Diabetes: Insufficient for Individual Management

TO THE EDITOR:

We read with interest the article by Yang et al.[1] The study demonstrated that diabetes is associated with an increased risk of hepatocellular carcinoma (HCC) in patients with nonalcoholic steatohepatitis (NASH) cirrhosis and validated their findings in an external cohort. However, several important issues might affect the study results or clinical significance, which are proposed as follows.

First, this study showed that there was no association between diabetic medications and HCC. According to the medication use recorded in Table 1 of Yang's study (note: belongs to Ref. 1), some diabetics had taken more than one kind of medication. This complex antidiabetic medication history, including medication changes or combinations, would affect subsequent risk analyses. Recent studies suggested that metformin was associated with a reduced risk of HCC in a dose-response pattern in type 2 diabetes.[2] Although without statistical significance, this study reported a hazard ratio of 1.93 (0.84-4.41) for HCC development in metformin users. From our perspective, the cumulative duration of metformin therapy might be heterogeneous in ever-users, which should be the major confounding factor resulting in the inconsistency. Also, hemoglobin A1c (HbA1c) of diabetics was reported as 7.6% ± 9.5%, varying over a wide range. HbA1c is an important indicator of long-term glycemic control and predictive for developing diabetes-related complications, even HCC.[3] However, the influence of glycemic control on HCC risk was not investigated. These issues undoubtedly affected clinical management of patients with NASH cirrhosis and diabetes (e.g., course of metformin therapy, HbA1c target). Therefore, the conclusions would be more meaningful if the researchers could provide more details about diabetes, including diabetes duration, duration of medication use, and glycemic control.

In addition, the Cox proportional hazard regression analysis, rather than competing risk analysis, was used to investigate the effect of diabetes on the risk of HCC. During the follow-up period, 57 patients received liver transplants and 123 patients died in the Mayo Clinic cohort. HCC development, transplantation, and death were three competing events, given that transplantation or death impeded HCC occurrence. The Cox proportional hazard model assumes that competing events are censored; therefore, it may overestimate HCC risk.[4] Propensity-score matching analysis could be used to adjust for the baseline imbalance between groups in both cohorts.

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