JACC: CARDIOONCOLOGY VOL. 2, NO. 3, 2020

EDITORIAL COMMENT

IMPROVE-IT

A Final Closure to Carcinogenicity of Ezetimibe?*

Eldrin F. Lewis, MD, MPH,[a] June-Wha Rhee, MD[a,b]

Low-density lipoprotein-cholesterol (LDL-C)-lowering strategies are the cornerstone of coronary heart disease prevention and treatment. Therapies to reduce LDL-C such as statins or ezetimibe have significantly improved cardiovascular outcomes; this benefit has been ascribed to pleiotropic effects beyond lowering LDL-C. However, such pleiotropic mechanisms have raised safety concerns about long-term use. A potential carcinogenic effect has been of particular concern as earlier studies suggested an association between baseline low LDL-C levels and incident cancer risk (1). Thus far, a wealth of outcome data on statin therapies has established no significant cancer risk of statins (2). The safety of other cholesterol-lowering therapies in regard to their cancer risk has not been well established. Moreover, the threshold for reporting safety analyses and the level of acceptable evidence, including exploratory analyses, are different than that of efficacy analyses.

In 2008, the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) investigators reported the initial results of their randomized trial investigating the effects of cholesterol-lowering therapies on cardiovascular outcomes among patients with aortic stenosis (AS) (3). Given the association between hyperlipidemia and AS, the study sought to examine potential beneficial effects of intensified cholesterol lowering with combined simvastatin/ezetimibe therapies in AS. Ezetimibe works differently from statins in that it inhibits the biliary and intestinal cholesterol absorption by binding to Niemann-Pick C1 Like 1. The study involved 1,873 patients with mild-to-moderate asymptomatic AS and the patients received either simvastatin/ezetimibe (40/10 mg) or placebo daily. Although the study did not find significant benefits from the intensive lipid-lowering therapy, it reported an incidental finding of increased cancer occurrence (105 vs. 70; $p = 0.01$) and cancer-associated death (39 vs. 23; hazard ratio [HR]: 1.67; $p = 0.05$) with simvastatin/ezetimibe compared to placebo. The cancer incidence did not cluster in particular organ sites. As prior studies have shown no significant link between statins and cancer risk, the results raised a concern that adding ezetimibe to statin therapy might increase the risk of cancer. This safety signal needed further investigation.

Subsequently, several studies have investigated the effects of combined ezetimibe and simvastatin therapy. First, the SHARP (Study of Heart and Renal Protection) trial investigated whether combination of simvastatin plus ezetimibe as compared to placebo would decrease major atherosclerotic events in 9,270 patients with chronic kidney disease (4). During a median follow-up of 4.9 years, the combination cholesterol-lowering therapy yielded a 17% risk reduction in major atherosclerotic events without increasing the risk of cancer (438 vs. 439; $p = 0.89$). Similarly, other retrospective analyses and meta-analyses (2) did not find a significant association between ezetimibe and increased risk of cancer. The U.S. Food and Drug Administration thus released an updated statement regarding the safety of the ezetimibe/simvastatin therapy and stated that it is unlikely that the drug would increase the risk of cancer or cancer-related death, although the existing data on

*Editorials published in *JACC: CardioOncology* reflect the views of the authors and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

From the [a]Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California; and the [b]Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford, California. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: CardioOncology* author instructions page.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2020.08.003

JACC: CARDIOONCOLOGY, VOL. 2, NO. 3, 2020
SEPTEMBER 2020:397–9

ezetimibe are "insufficient to definitely rule out a cancer risk" (5).

In this issue of *JACC: CardioOncology*, Giugliano et al. (6) report their systematic analysis of cancer incidences in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), a largest trial to date to investigate the cardiovascular effects of combined ezetimibe/simvastatin therapy (6). Here, 17,708 patients with recent acute coronary syndrome were randomized 1:1 to receive either simvastatin/ezetimibe (40/10 mg) or simvastatin (40 mg) plus matching placebo. To address a carcinogenic risk of the combined therapy, the IMPROVE-IT trial implemented: 1) an independent Oncology Clinical Endpoint Committee was formed to guide their study design and data adjudication; 2) training for investigators to report all suspected tumor cases, benign or malignant, during the trial period; and finally 3) independent adjudication of suspected tumors by oncologists unaware of treatment assignments or lipid levels. At the end of the trial with median follow-up of 6.0 years, 1,470 (8.3%) met the primary malignancy endpoint and no significant difference in cancer incidence was observed between the 2 treatment groups (744 in the ezetimibe arm and 726 in the placebo arm; HR: 1.03; $p = 0.56$). The rates of cancer-associated death were also similar (277 vs. 268; HR: 1.04; $p = 0.68$).

The IMPROVE-IT trial has several strengths over the SEAS trial in addressing the cancer risk of ezetimibe. First, the number of participants in IMPROVE-IT is approximately 10-fold more than in SEAS, improving the power to detect significant differences and lowering the chance to observe random events. Second, the trial was specifically designed to prospectively collect and analyze relevant tumor data, which were then independently adjudicated by oncologists. Third, the trial population is ethnically more diverse than SEAS (white race being 84% vs. 99%). Overall, the findings from this study (6) strengthen the accumulating data that the combined simvastatin/ezetimibe therapy does not increase cancer risk and suggest that the results from the SEAS trial may have been due to random imbalance of the cancer events. Similar observations were made previously in regard to the safety of statins. One trial reported an increased risk of breast cancer with pravastatin, an outcome which was not replicated in >20 other trials with the drug (7). As such, some imbalances may exist particularly when studies are not sufficiently powered and/or not specifically designed to see differences in the events of interest.

Although reassuring, it is worth highlighting several points. First, the event rates of each cancer type in IMPROVE-IT were low with lung cancer being the highest at 1.3% in the ezetimibe arm and 1.4% in the placebo arm. Therefore, despite the trial being the largest, it may not have been adequately powered to detect differences or interactions related to cancer subtype. Additionally, when evaluating breast cancer rates among female subjects who met the primary malignancy endpoints, there was a nonstatistically significant trend towards higher rates of breast cancer in the ezetimibe arm versus the placebo arm (26.4% vs. 18.9%; $p = 0.13$). The low representation of females in the trial (~25%) leaves a degree of uncertainty whether the observation is truly just an imbalance of the events. Finally, the 2 studies differ in that IMPROVE-IT specifically recruited patients with acute coronary syndrome whereas SEAS recruited patients with mild-to-moderate AS without a history of coronary artery disease. Despite this, it is reassuring that 21 additional months of registry follow-up of the original SEAS cohort demonstrated no increased risk of cancer or related mortality with combined treatment with ezetimibe and simvastatin as compared to placebo (8).

In summary, the IMPROVE-IT study appears to provide confirmatory reassurance that there is no link between ezetimibe and increased cancer risk. Although smaller concerns regarding unknown risk of cancer subtypes may exist, the available data provide no indication to dissuade clinicians from using ezetimibe clinically. Given that lipid-lowering therapy is generally a chronic medication for patients, continued surveillance of drug safety and cancer outcomes in this population is warranted. As new cardiovascular drugs are being introduced to clinics every day, the field of cardio-oncology faces additional challenges to address their oncologic risk beyond the traditional cardiovascular risk of cancer therapies. This is further challenged by difficulties to interpret and apply the results of exploratory safety analyses as they are inherently more prone for errors as seen in the case of SEAS, albeit critically important. Hence, multidisciplinary collaborations between cardiologists, oncologists, and population scientists will be essential to delineate potential cancer risks, optimize interventions to mitigate risk, and identify potential interactions between heart disease and malignancy to maximize survival and quality of life for patients and guidance for shared decisions.

ADDRESS FOR CORRESPONDENCE: Dr. Eldrin F. Lewis, Stanford University School of Medicine, 870 Quarry Road, Stanford, California 94305. E-mail: eflewis1@stanford.edu. Twitter: @EldrinL, @JuneWRhee.

REFERENCES

1. Benn M, Tybjærg-Hansen A, Stender S, Frikke-Schmidt R, Nordestgaard BG. Low-density lipoprotein cholesterol and the risk of cancer: a mendelian randomization study. J Natl Cancer Inst 2011;103:508–19.

2. Cholesterol Treatment Trialists' (CTT) Collaboration, Emberson JR, Kearney PM, et al. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. PLoS One 2012;7:e29849.

3. Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 2008; 359:1343–56.

4. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011;377:2181–92.

5. Center for Drug Evaluation, Research. Drug Safety Information for Healthcare Professionals - Follow-Up to the August 2008 Early Communication About an Ongoing Safety Review of Ezetimibe/Simvastatin (marketed as Vytorin), Simvastatin (marketed as Zocor) and Ezetimibe (marketed as Zetia) - FDA Investigates a Report from the SEAS Trial n.d. Available at: https://www.pbm.va.gov/PBM/vacenterformedicationsafety/nationalpbmcommunication/NationalPBMCommunicationEzetimibeandSimvastatin082608.pdf. Accessed July 30, 2020.

6. Robert GM, Baris Gencer M, Stephen D, Wiviott M, et al. Prospective evaluation of malignancy in 17,708 patients randomized to ezetimibe vs. placebo: a prespecified analysis from the IMPROVE-IT. J Am Coll Cardiol CardioOnc 2020;2:385–96.

7. Newman CB, Preiss D, Tobert JA, et al. Statin safety and associated adverse events: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol 2019;39:e38–81.

8. Green A, Ramey DR, Emneus M, et al. Incidence of cancer and mortality in patients from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial. Am J Cardiol 2014;114:1518–22.

KEY WORDS cancer, ezetimibe, hyperlipidemia, lipid-lowering therapy, malignancy, statins