Response to Letter by Lin et al Regarding Article, “Hepatitis C Virus Infection and Increased Risk of Cerebrovascular Disease”

Response:
In Taiwan, both hepatitis B virus and hepatitis C virus (HCV) are important for liver cirrhosis and hepatocellular carcinoma. The hepatitis B virus infection often occurs in early childhood and 15% to 20% may become carriers. In contrast, HCV infection can happen during the entire life and approximately 70% may become chronic infection. These 2 hepatitis viruses had different features in their virological properties. HCV infection is considered a systemic disease, which is associated with several extrahepatic manifestations, including diabetes, renal syndromes, lymphoproliferative disorders, and neuropathies.1 We found that HCV infection was associated with an increased risk of cerebrovascular death. However, based on the same cohort, hepatitis B virus infection was not found to be associated with various atherosclerosis-related diseases.2,3

The conventional risk factors could not completely explain the risk of developing atherosclerotic diseases; thus, infectious agents have been hypothesized to be the additional risk factors. Individuals with HCV infection had increased risk not only for stroke mortality, but also atherosclerosis-related and all cardiovascular mortality (Table).

Previous studies showed that HCV infection may impair insulin ability to lower plasma glucose levels and contribute to the development of diabetes.4 We collected diabetic history and insulin ability to lower plasma glucose levels and contribute to vascular mortality (Table). We found that diabetic history and insulin ability that participants with HCV infection had an increased risk of cerebrovascular death. However, based on the same cohort, hepatitis B virus infection was not found to be associated with various atherosclerosis-related diseases.2,3

As Lin et al suggested, there was a substantial proportion of anti-HCV-seropositives with liver cirrhosis. However, the findings cited by Lin et al that patients with nonalcoholic cirrhosis had a reduced risk of stroke with a crude hazard ratio of 0.55 are quite likely biased. Because many patients with decompensated liver cirrhosis have a high mortality rate from cirrhosis itself, they will not survive long enough to develop stroke at older ages. If patients with liver cirrhosis were less likely to experience stroke as Lin et al indicated, the risk of cerebrovascular death in patients with chronic HCV infection in our study would have been underestimated. In other words, the association between chronic HCV infection and stroke may even be stronger. The limitation of using mortality data is the difficulty to distinguish whether HCV infection increased the risk of cerebrovascular disease or worsened the prognosis of the disease. However, the dose–response relationships between serum HCV RNA levels and cerebrovascular deaths further strengthened the role of HCV infection. Because there is no evidence showing that viral infections had adverse effects on the treatment response of stroke, stroke mortality with or without HCV infection may not be different. Although we use the end point of stroke mortality, based on Hill’s criteria of causal inference,5 the temporality, the dose–response relationship, the strength, and the plausibility, we believed that the mortality data reflected cerebrovascular incidence substantially.

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<table>
<thead>
<tr>
<th>ICD-9 Code</th>
<th>Atherosclerosis-Related Deaths</th>
<th>Anti-HCV- Seronegative</th>
<th>Anti-HCV- Seropositive</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>430-438</td>
<td>Cerebrovascular disease</td>
<td>223</td>
<td>32</td>
<td>2.61 (1.80–3.78)</td>
</tr>
<tr>
<td>410-414, 429.2, 429.7</td>
<td>Ischemic heart disease</td>
<td>151</td>
<td>12</td>
<td>1.44 (0.80–2.59)</td>
</tr>
<tr>
<td>410-413, 414.0, 414.1, 424.1 429.2, 429.7, 430-438, 440, 443.9 445</td>
<td>Atherosclerotic disease</td>
<td>374</td>
<td>44</td>
<td>2.14 (1.56–2.92)</td>
</tr>
<tr>
<td>390-459</td>
<td>All cardiovascular disease</td>
<td>528</td>
<td>53</td>
<td>1.82 (1.37–2.41)</td>
</tr>
</tbody>
</table>

HCV indicates hepatitis C virus; ICD-9, International Classification of Diseases, 9th Revision.

*Per 100,000 person-years.
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