Reviewer's report

Title: Effects and Outcomes of Interferon Treatment in Japanese Hepatitis C Patients

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Reviewer: Hirofumi Uto

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This study examined the long-term prognosis of HCV-positive residents in an isolated Japanese island and investigated the effects of IFN treatment in comparison with the HCV-negative general population. This study is interesting because it elucidates the mortality in HCV-infected patients with IFN treatment is similar to that of general resident groups, although the mortality in HCV-infected patients without IFN treatment was higher than that of general resident groups. However, several points should be considered.

Specific Comments:

1. Authors stated that this study is prospective. However, gender- and age-matched general resident may be enrolled to this study after the follow-up period. If so, is this study prospective? Please indicate this point clearly.

2. Authors stated that the survival rate of members of the hepatitis C group who received IFN treatment was comparable to that of the general resident group irrespective of the effect of IFN treatment (Page 12, line 21-). However, these results should be due to the small number of patients. The survival rate in patients with Non-SVR seems to be lower compared to that with SVR (Figure 5C and D), even if there is no statistical difference. Authors should show the difference of survival rate between SVR group and non SVR group, and discuss this point clearly.

3. The effect of IFN treatment for improvement of survival rate though to be due to the reduction of liver-related death (Table 3). Please indicate the mortality associated with liver-related death in Group A1, Group A2 and Group B using the Kaplan-Meier method; these survival curves should be different. In addition, the other disease mortality in these Groups should be shown using Kaplan-Meier method; those survival curves would be similar. Furthermore, it was reported that patients with the risk factors of high age at HCV eradication and heavy alcohol intake might be at heightened risk for the development of HCC within 5 years after HCV eradication (J Gastroenterol. 2011; 46: 799-808). Because liver-related death had been occurred in IFN treatment group, the authors should discuss this point.

4. Previous reports (J Hepatol 2010; 53: 36-42) have already shown that chronic HCV infection is associated with a higher mortality and liver-related deaths. In addition, the percentage of cause of death in this study is similar to the previous reports (Hepatology 2009; 50:393-9). This study used gender- and age-matched
general resident as control and this comparison is interesting. However, authors should add the resident positive for HCV antibody and negative for HCV RNA as a control in addition to general resident in Figure 2, and discuss this point.

5. Residents older than 70 years were excluded in this study. IFN treatment may not be indicated for those residents, this exclusion seems not to be necessary.

6. Mortality or liver related death in HCV infected patients in hospital based study thought to be higher than those in cohort study (resident based study). This difference may be affected by patients’ characteristics. In this study, LC was observed in 177 patients with HCV infection, and these patients were excluded in figure 5. How are cumulative survival and liver related death in LC patients compared to Group B? In addition, ALT is important factor for HCC occurrence. Untreated group (Group B) included many patients with normal ALT compared to treated group (Group A). How is cumulative survival in patients with abnormal ALT (#40) compared to that with normal ALT (<40)?

7. Methods for diagnosis of HCC should be indicated.

8. The numbers of patients at risk in Group A in Figure 5C or 5D (15 years of follow up) seem to be mistake.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.