Author’s response to reviews

Title: Long-term outcomes and risk factors of thyroid dysfunction during pegylated interferon and ribavirin treatment in patients with chronic hepatitis C infection in Taiwan

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Author’s response to reviews:

The Editor,
BMC endocrine disorders

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Dear Editor:
Dear Editor:
RE: Chang et al. “The long-term outcomes and risk factors of thyroid dysfunction during pegylated interferon and ribavirin treatment in patients with chronic hepatitis C infection in Taiwan”

Thank you for the helpful review and the opportunity to improve our manuscript. We are enclosing the revised manuscript along with our responses to the reviewers’ comments. We hope that these revisions will be satisfactory and look forward to hearing from you.

Sincerely yours,

Kow-Tong Chen
Response to reviewer:

1. Among patients, 42.9% were diagnosed with hypothyroidism, 31.2% with hyperthyroidism, and 25.9% with thyroiditis. As known well, hyperlipidemia is closely associated with hypothyroidism. Conversely, hypothyroidism generally causes hypolipidemia. All patients with thyroid dysfunction were not always those with hypothyroidism; nevertheless, hyperlipidemia was one of the independent factors associated with thyroid disorders including hyperthyroidism. Did even patients who developed hyperthyroidism have hyperlipidemia at baseline? Would you please elucidate the association clearly?

Answer: Thank you for your comments. We added the description in discussion as “Lipid metabolism is an important liver function. Patients with HCV infection have lower lipid profiles [52]. Several studies have reported that HCV infection is associated with lower lipid profiles and progression to dyslipidemia, liver steatosis or advanced fibrosis [52,53]. A study in Taiwan showed that the clearance of HCV RNA is the main determinant for the increase in lipids after PEG-IFN/RBV treatment [54]. In addition, thyroid hormones are known to be the main regulators of total cholesterol (TC) and lipoprotein cholesterol metabolism [55]. Therefore, the impact of hypothyroidism is often linked to excess TC and low-density lipoprotein cholesterol (LDL-C) [56]. The roles of HCV and thyroid hormones on lipid metabolism needs to be further investigated in the future”. (discussion section, para 2, line 1, page 18).

2. Would you please clarify the definitions of hyper-/hypo-lipidemia and hyper-/hypo-thyroidism in the revised text?

Answer: We added the definition in method as “Hyperthyroidism, including subclinical hyperthyroidism, was defined as having a TSH level <0.4 mIU/mL. Hypothyroidism, including subclinical hypothyroidism, was defined as having a TSH level >4.1 mIU/mL [26,27]. Thyroiditis was diagnosed when sudden hyperthyroidism occurred, then, after several days/weeks, hypothyroidism developed, and during the following weeks and months, the thyroid gland resumed its normal function or hypothyroidism remained [28]”. (Method section, Line 1, par 5, Page 9).

3. Could you refer to the ratios of hypothyroidism, hyperthyroidism, and thyroiditis that were reported in previous studies in the revised Discussion section?

Answer: We added the description in discussion as “A previous study indicated that the most commonly recognized TDs among CHC patients treated with PEG-IFN/RBV were hyperthyroidism (45.5%), hypothyroidism (33.8%), thyroiditis (19.5%), and goiter (1.3%) [28]. Similar to the findings in the previous study [28], we found that the TDs identified among patients with HCV infection were hypothyroidism (42.9%), hypothyroidism (31.2%), and thyroiditis (25.9%)”. (Discussion section, para 1, Line 7, Page 14).

4. Although this is a long-term study, by when was the onset of thyroid dysfunction considered as being induced by interferon-based therapy? For instance, a patient developed thyroid dysfunction five years after the completion of treatment. Is this case related to interferon?

Answer: We added the description in discussion as “Compared to those reported previously, our study showed a lower incidence (4.5%) of IFN-induced TD in patients with CHC. The inconsistency may be due to the definition of TD, study population ethnicity, or regional differences in iodine status among the study subjects [44]. For example, if a patient developed TD several years after the completion of
treatment, should this case be classified as related to the treatment with interferon or not? In addition, the clinical characteristics of TD are often subclinical and masked by the effects of IFN therapy [13]”.
(Discussion section, para 2, line 3, page 16)

5. Thyroid dysfunction might be caused by HCV infection. If so, did not patients who achieved SVR with interferon-based therapy develop after treatment?

Answer: We added the description in context as “Although it has been found that some patients with CHC may have TD before treatment [45], it is believed that HCV itself may predispose patients to the development of TD. The most common hypothesis for the endocrine side effects of these IFN-α-based regimens, outside of the liver, is the production of autoantibodies that induce the development of TD [46-48]. However, we could not suggest this theory because our study did not collect data regarding sustained virologic response (SVR) among the studied patients.”. (Discussion section, para 3, line 1, page 16).

Response to Technique comment:

Please provide ‘competing interests’ under the ‘Declaration section’.

Answer: “competing interest” had been added in “Declaration section”. (Declaration section, line 1, page 21).