Letters to the Editor

is predominantly Caucasian, male (75%), younger (mean age 43), and has a higher proportion of current and former drug users (68%), than the Japanese cohort. We also had a lower prevalence of cirrhosis (11%). These differences meant that some parts of the decision tree were under populated. However, the tree was able to identify a subgroup of patients who achieved a RVR, with normal platelets and a low viral load, representing 17.5% of the cohort who had a 90% chance of achieving a SVR with standard care combination therapy. This level of SVR means it is much more cost-effective to treat such patients with standard peginterferon and ribavirin than to add a protease inhibitor as first line therapy. Equally there is currently no evidence that the protease inhibitors will improve the outcome in this patient group. We congratulate Kuroasaki and colleagues on an easy to use tool that helps patients and physicians make decisions on starting therapy and that with minor modifications may make the impact of the introduction of protease inhibitors much more cost effective.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Reply to: “Pre-treatment prediction of response to pegylated-interferon plus ribavirin for chronic hepatitis C using RVR”

Decision model incorporating IL28B genotype and ISDR could identify patients with high probability of SVR among patients who failed to achieve RVR

To the Editor:

We appreciate the interest of Dr. Wahed in our article recently published in the Journal of Hepatology [1]. We were impressed of their validation of our prediction model by substituting rapid virological response (RVR) for IL28B genotype (modified model) [2]. Wahed et al. showed that among patients with RVR, those with high platelet counts ($\geq 140 \times 10^9/L$), and low HCV RNA (<600,000 IU/ml)) had 90% chance of sustained virological response (SVR). Their results confirmed our finding that platelet count and pretreatment HCV RNA level are predictors of SVR, independently of early virological dynamics and showed that combination of these factors improved the prediction accuracy. However, according to their data, a modified model could not identify patients who have high chance of SVR among those who failed to achieve RVR.

In a study by Thompson et al. [3], RVR was correlated with the IL28B genotype and was a strong predictor of SVR regardless of IL28B genotype. On the other hand, the major IL28B genotype (CC at rs12979860) was associated with a higher rate of SVR (among Caucasians, 66% (IL28B major genotype) vs. 31% (IL28B minor hetero-genotype) and 24% (IL28B minor genotype)) among patients who failed to achieve RVR. There were similar findings in our cohort, where patients with RVR had a high rate of SVR independent of IL28B genotype (97% for IL28B major type vs. 100% for IL28B minor type) but among non-RVR patients, the IL28B major genotype was associated with significantly higher rate of SVR (45% for IL28B major genotype vs. 12% for IL28B minor genotype). Collectively, IL28B genotype has a significant predictive power even after virological response at week 4 of therapy was determined. This means that RVR is associated with IL28B genotype but RVR could not entirely replace IL28B genotype for the accurate prediction of SVR. In order to assess if our model still has the power to predict SVR after virological response at week 4 of therapy was determined, we modified our predictive model by adding RVR as a first splitting variable and applied the data of our cohort. As a result, among patients who failed to achieve RVR in our cohort, patients with IL28B major genotype who had (1) high platelet counts ($\geq 140 \times 10^9/L$), and low HCV RNA (<600,000 IU/ml) had 87% chance of SVR, (2) high platelet counts ($\geq 140 \times 10^9/L$), and high HCV RNA ($\geq 600,000$ IU/ml) had 60% chance of SVR, and (3) low platelet counts (<140 $\times 10^9/L$), and more than 2 mutations in interferon sensitivity determining region (ISDR) [4] had 69% chance of SVR (Fig. 1). Patients who fall into these three groups constitute 39% of non-RVR patients. Thus, our predictive model could determine patients with high probability of SVR even after virological response at week 4 of therapy was determined.

We fully agree with Dr. Wahed that it is important to identify the patients who would be cured with current standard of care combination therapy. This level of SVR means it is much more cost-effective to treat such patients with standard peginterferon and ribavirin than to add a protease inhibitor as first line therapy. Equally there is currently no evidence that the protease inhibitors will improve the outcome in this patient group. We congratulate Kuroasaki and colleagues on an easy to use tool that helps patients and physicians make decisions on starting therapy and that with minor modifications may make the impact of the introduction of protease inhibitors much more cost effective.

References


H. Jafferbhoy
M.H. Miller
Z. El Wahed
J.F. Dillon*

Gut Group, Biomedical Research Institute,
University of Dundee, Ninewells Hospital and Medical School,
Dundee DD1 9SY,
United Kingdom

Tel.: +44 (0) 1382 660 111.
E-mail address: j.f.dillon@dundee.ac.uk (J.F. Dillon).

*Corresponding author.
care to reduce the implementation costs of new drugs such as protease inhibitors and that RVR is the most reliable predictor of SVR. In addition, we believe that determination of IL28B and ISDR could further improve the prediction accuracy and that predictive model incorporating RVR, IL28B genotype and ISDR could be used not only for negative prediction but also for positive prediction.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References


NKT cells in liver fibrosis: Controversies or complexities

To the Editor:

We read with great interest a recent article in the Journal of Hepatology by Ishikawa et al. investigating the role of CD1d-restricted natural killer T (NKT) cells in thioacetamide (TAA)-induced liver fibrosis, by using CD1d knock out (KO) mice that are associated with NKT cell deficiency [1]. First, the authors observed that CD1d KO mice were resistant to TAA-induced liver inflammation, damage, and hepatocyte apoptosis. Second, the authors observed CD1d KO mice were resistant to TAA-induced liver fibrosis, indicating that NKT cells play an important role in promoting liver fibrogenesis in mice after chronic TAA treatment. The pro-fibrotic effects of NKT cells were also recently suggested by the data from a murine model of HBV transgenic mice [2], primary biliary cirrhosis [3], nonalcoholic steatohepatitis (NASH), and patients with NASH [4].

Recently, we identified the double sword face of invariant NKT (iNKT, type I NKT) cells in liver fibrogenesis in a model of CCl4-induced liver injury [5]. On the one hand, iNKT-deficient mice had increased liver injury and fibrosis, especially in the early stage of CCL4-induced liver injury, suggesting that natural activation of iNKT cells by endogenous lipid antigens plays a protective role in preventing CCL4-induced liver injury and fibrosis. On the other hand, strong activation of NKT cells by α-galactosylceramide (α-GalCer) accelerated CCL4-induced hepatocellular injury and subsequently enhanced fibrosis. Our findings clearly suggest a complex role of iNKT cells in liver fibrosis: inhibiting liver fibrosis via the suppression of HSC activation or indirectly promoting liver fibrosis via enhancing liver injury. We believe that the final effect of iNKT cells on liver fibrosis is determined by the balance between the inhibitory and stimulatory effects as we discussed above, but may also dependent on the real context of developing stage human liver diseases or animal models used. In addition to iNKT (type I NKT) cells, other subtypes of NKT cells including type II and possible type III NKT cells also exist [6]. These different subtypes of NKT cells exert many similar functions but may also exert some opposing functions, which further complicates the role of NKT cells in liver fibrogenesis [6,7].

In the study by Ishikawa et al. [1], it appears that CD1d restricted NKT cells play an important role in inducing liver injury, which may contribute to the pro-fibrotic effects of NKT cells observed in the TAA-induced liver injury model. In the supplementary material, Ishikawa et al. [1], reported that CD1d KO mice were also resistant to CCL4-induced acute liver injury; however, we found that CD1d KO mice had similar liver injury and fibrosis after chronic treatment with CCL4 (Park et al., unpublished data). Further studies are required to clarify the complex role of NKT cells in liver injury and fibrosis.

Conflict of interest

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References


Hua Wang*
Ogyi Park
Bin Gao

Laboratory of Liver Diseases, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD 20892, USA
*E-mail address: whua@mail.nih.gov (H. Wang)

Reply to: “NKT cells in liver fibrosis: Controversies or complexities”

To the Editor:

Emerging attention has been paid to the role of natural killer T (NKT) cells in a variety of liver diseases including nonalcoholic steatohepatitis (NASH) [1]. The role of NKT cells in hepatic fibrogenesis, however, has been controversial [2–4]. In our latest manuscript entitled “CD1d-restricted natural killer T cells contribute