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EDITORIAL

The prediction of immunological dysfunction during antiviral therapy for HCV after liver transplantation: can we improve outcomes?

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Much research has focused on the incidence and clinical characteristics of recurrent hepatitis C in liver transplantation (LT) patients during and after pegylated-interferon and ribavirin (PEG-IFN/RBV) therapy. These patients are generally characterized by a high prevalence of recurrent hepatitis C, a more aggressive rate of disease progression and low survival rates. Recurrent hepatitis C usually results from repeated therapy using corticosteroid and anti-lymphocyte antibodies [1]. Based on histological evidence, 50–90 % of patients who undergo LT develop recurrent HCV within 12 months, and 20–30 % of patients develop liver cirrhosis within 5 years [2, 3]. Patients with recurrent hepatitis C after LT have a 56.7 % of 5-year survival rate, which is significantly lower than that in HCV-negative patients [4, 5]. Furthermore, it is difficult to treat recipients with recurrent HCV recurrence [6]. The rate of sustained virological response (SVR) in these patients is frequently lower because of limited therapeutic options and potential immunological complications. Therefore, the treatment for post-LT patients with recurrent hepatitis C remains a significant clinical challenge.

Preemptive antiviral treatment and the treatment of established recurrent hepatitis C have been adopted in some clinical settings. Preemptive treatment refers to early antiviral therapy, which is given within days or weeks after LT in all patients, despite histological evidence of recurrence. However, 30 % of patients do not tolerate this treatment well, and half of the patients require drug dose reduction [7]. One randomized trial evaluated the efficacy of preemptive anti-HCV therapy and found that only 9 % of patients achieved SVR [8]. The treatment of established HCV recurrence can involve patients who are most likely to achieve the benefit from antiviral therapy, whereas patients without HCV recurrence can avoid the side effects. A recent study has established that the best treatment results for patients with established HCV recurrence were obtained from PEG-IFN/RBV treatment [9]. Patients who achieved SVR (20–30 %) showed slower disease progression and longer term graft survival compared to non-responders [10–12]. A higher proportion of genotype 1 disease, poor adherence to therapy or lower drug doses, and severe complications were responsible to lower SVR rates in these patients.

However, the efficacy of PEG-IFN/RBV treatment for post-LT patients with HCV recurrence is negatively affected by immunological dysfunction (ID), which includes acute cellular rejection (ACR), plasma cell/autoimmune hepatitis and chronic rejection [13–17]. ID usually occurs together with LT and recurrent hepatitis C during or after PEG-IFN/RBV therapy, and it is recognized as a unique clinical entity. Patients who develop ID are at risk of lower long-term survival rates, higher re-transplantation rates and fewer increases in the rate of SVR. In a multicenter case-controlled retrospective study, certain risk factors, including no prior PEG-IFN therapy before LT, therapy with PEG-IFN α-2a during PEG treatment and immune features (mainly plasma cell hepatitis) on liver biopsies before antiviral therapy, were associated with the development of ID [18]. However, PEG-IFN is the only anti-HCV drug used in patients with recurrent hepatitis C after LT, and there are no unified standards for liver pathologists to grade the biopsy, thereby limiting these risk factors as early predictors. Clinical factors that can predict ID are urgently required as, once ID develops, anti-HCV therapy may need to be terminated.

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To address these issues, Sharma et al. [19] designed a retrospective study in 74 deceased donor LT recipients with histological recurrence of hepatitis C treated with PEG-IFN/RBV. They defined ID as biopsy-proven rejection or moderate plasma cell hepatitis [20], and found that 12 patients (16 %) had ID and 8 (10.7 %) had cholestasis without ID during or after therapy. Furthermore, these data further confirmed the clinical significance of ID, as patients with ID had a trend toward a lower SVR rate and a higher rate of graft failure. In addition, two distinct forms of ID were observed during discrete time periods: early ID was seen during or within 6 weeks from the onset of PEG-IFN/RBV therapy, while late ID was observed $\geq$6 months from the onset of PEG-IFN/RBV therapy. Biopsy-proven ACR before treatment and the type of immunosuppressive agents administered during the initial treatment were shown to be independent prognostic factors in a multivariate analysis of the respective cohorts. Patients with acute rejection before the initiation of PEG-IFN/RBV treatment had a 4.8-fold higher risk of developing ID compared to those who did not have acute rejection. Additionally, patients treated with tacrolimus had a lower risk of ID compared to those treated with cyclosporine at the start of PEG-IFN/RBV therapy. Despite the fact that these findings were retrospectively collected from a single center and there were a limited number of cases that caused a potential bias in patient selection, the two factors are possibly practical because ACR is a precipitating event, and powerful immunosuppressive drugs are available in the clinical setting. Future studies based on a large prospective cohort should be used to validate the prognostic value of their findings.

Several concerns have been raised from these studies. Important prevalent features, the frequency of precipitating factors and the underlying pathogenic mechanisms of ID remain poorly understood. Current data regarding ID incidence have all been collected from Western countries and show a wide range from 3.2 to 16.3 %. In Asia, there are many patients with chronic hepatitis C who have undergone LT. Do these patients also frequently develop ID? Furthermore, the development of ID is a multistep progress that involves many types of immune cells; however, the immunological properties during ID development remain unknown, particularly for the differences between early and late ID. Indeed, immunological changes usually occur before histological grading. It is important to investigate whether earlier immunological changes could replace clinical factors for the prediction of ID or cholestasis and whether they could be used to guide earlier treatment approaches and lead to better outcomes.

In summary, it will be important in future studies to demonstrate the immunological properties of ID development and to identify immunological markers that can provide prognostic prediction. Meanwhile, to improve the management of post-LT patients with recurrent hepatitis C, it will be interesting to ascertain whether the SVR rate will be increased or the risk of ID will be minimized with direct-acting antiviral agent (DAA) therapies, such as triple therapy or advanced wave DAA therapy with or without PEG-IFN/RBV therapy. In addition, specific conditions, such as whether the IL-28B status can play a predictive role during the use of the above-mentioned therapies, the management of primary non-responders, patients with non-genotype 1 disease and the interactions between DAAs and immunosuppressive agents, require further investigation. In conclusion, we are still at the relatively early stage of discerning the optimal treatment for recurrent HCV infection in patients with LTs.

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Conflict of Interest None.

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