described as 'low risk'. Likewise, the management of OBI is an unsettled issue. ALT monitoring, HBV-DNA monitoring, vaccination or even pre-emptive nucleoside analogue prophylaxis were offered in recent consensus reports (2–4, 7). So, the knowledge about the drug(s), doses and absence or presence of cirrhosis would be very important to select a management choice in such a situation.

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Which level of immunosuppression is harmful for occult hepatitis B virus infection?: 'A million dollar' answer

To the Editor:

We thank Dr Ozaslan for his useful comments (1) concerning our paper (2). Fluctuating hepatitis B virus (HBV) viraemia during occult HBV infection in autoimmune hepatitis (AIH) patients under immunosuppressive therapy was seen (2). However, none of our patients with occult HBV had viral reactivation during immunosuppression. Specifically, in AIH patients ($n = 38$) with available serial samples during treatment, 33 (86.8%) tested seronegative for HBV-DNA before the initiation of treatment. All patients who tested HBV-DNA positive (5/38) before the initiation of immunosuppression became HBV-DNA negative during treatment. Serial sample testing also revealed that 2/33 HBV-DNA-negative patients before treatment became HBV-DNA positive during therapy. All the above patients received therapy, mainly with prednisolone alone or in combination with mycophenolate mofetil (MMF) according to a local protocol.

All seven AIH patients with occult HBV received initially 20–50 mg/day prednisolone with a gradual dose tapering down to a maintenance dose of 2.5–10 mg/day in combination with 1–2 g/day MMF. All but one patient is still on maintenance treatment (three patients on 2.5–10 mg/day prednisolone alone, one on 1.5 g/day MMF alone and two on a combination of 2.5–5 mg/day prednisolone with 2 g/day MMF or 125 mg/day cyclosporine). Only one patient was cirrhotic at the initial evaluation and the disease did not progress during this study. At present, all patients are in complete remission and no transaminase flare-ups have been recorded, including one out of seven patients who have had their treatment withdrawn 15 months ago.

Hepatitis B virus reactivation after cessation of immunosuppression is a well recognized and an important complication (3). Hepatic injury in these patients ranges from asymptomatic liver chemistry elevation to fatal fulminant hepatitis. Unopposed viral replication, followed by an exaggerated host immune response after withdrawal of immunosuppression, is the presumed pathogenetic mechanism. New immunosuppressives such as rituximab, alemtuzumab and infliximab have also been associated with HBV reactivation, likely resulting from the profound and long-lasting immunosuppression induced by these agents (4–6).

Therefore, investigation of occult HBV before immunosuppression and monitoring of reactivation is necessary in cases with serologic markers of past HBV infection particularly in HBV-endemic areas such as the Mediterranean region (7). We agree with Dr Ozaslan that investigation for occult HBV is important; however, the management of occult HBV in this setting remains unsettled and is much more difficult in AIH patients. Actually, the scientific community lacks a precise and

evidence-based answer to this question ('one million dollar answer'). For example, contrary to some previous suggestions (8), all our AIH patients with occult HBV received initially > 7.5 mg/day prednisolone as well as MMF, but so far no reactivation of HBV has been recorded.

In conclusion, we believe that in the absence of controlled prospective studies, a definite minimal level of immunosuppression below which HBV reactivation is no longer a risk cannot be safely defined at present. Therefore, pre-emptive therapy with nucleos(t)ide analogues should be offered to patients with occult HBV who will receive intensive immunosuppression or undergo any kind of transplantation. In other cases such as AIH patients, an individualized management is recommended (e.g. close follow-up and monitoring of transaminases and/or HBV-DNA or even pre-emptive therapy with antiviral agents). However, we definitely suggest pre-emptive therapy with one of the newer potent nucleos(t)ide analogues in patients with occult HBV and AIH-related cirrhosis, irrespective of the dose and the kind of immunosuppression, as in case of HBV reactivation, the risk of severe, fatal hepatic decompensation is high.

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