Optimising Hepatitis B Prophylaxis After Liver Transplantation: Combination Therapy and the HBV/HCC Connection

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Interview Summary

Chronic hepatitis B virus (HBV) affects nearly 300 million people worldwide and is a major cause of cirrhosis and hepatocellular carcinoma (HCC). Although nucleos(t)ide analogues (NUC) effectively suppress viral replication, they rarely achieve cure, leaving liver transplantation as the only definitive option for patients with end-stage disease. Historically, HBV was considered an indication of high risk for liver transplant because of high recurrence rates and poor survival. The introduction of combination prophylaxis with hepatitis B Ig (HBIG) and third-generation NUCs has transformed this outlook, reducing recurrence to below 10% and achieving survival rates comparable to those of non-HBV transplant recipients.

Recent studies have proposed to withdraw HBIG and maintain NUC monotherapy as a potential alternative to ongoing combination prophylaxis. However, uncertainty remains regarding risk stratification, particularly in the growing population transplanted with HCC. Evidence increasingly suggests a close relationship between HBV recurrence and HCC recurrence. Though the causal direction remains to be seen, Patrizia Burra, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Italy, argues that the association alone is strong enough to justify a precautionary approach, and advocates for lifelong combination prophylaxis in patients transplanted for HCC.

INTRODUCTION

Chronic HBV, which affects almost 300 million people globally, can lead to severe complications, including liver cirrhosis and HCC.[1] As such, it is a major cause of morbidity and mortality. While current NUC-based treatments can decrease viral load, they are curative in fewer than 5% of cases. Liver transplant is the only curative treatment for decompensated chronic HBV cirrhosis, with or without HCC.[1]

Historically, however, chronic HBV was a contraindication to liver transplant.[1] This was due to the high risk of infection recurrence, leading to recurrent cirrhosis, graft losses, and a 5-year survival rate of just 40%.[1,2] The introduction of prophylaxis regimens has transformed this picture. First, HBIG reduced the reinfection rate from around 80%[3] to between 19–35%.[4,5] Next, the introduction of NUCs and combination therapy further reduced the rate to approximately 10%.[2] As such, graft and patient survival rates are now comparable to those of patients who undergo liver transplant for aetiologies other than HBV.[5] HBV recurrence, defined by hepatitis B surface antigen (HBsAg) positivity in the serum, is less than 10%, and HBIG+NUC prophylaxis is recommended by most international liver societies.[1] As such, the 10-year survival rate for patients undergoing liver transplantation for chronic HBV infection in Europe is now up to 80%.[6]

Some studies have suggested that NUC monotherapy might be a safe and effective option for low-risk patients transplanted for HBV, with and without HCC.[1,7,8] However, these studies included mostly patients from Asia, with HBV and host-related factors for recurrence that may be different to those in Europe.[5] In addition, there has been a significant shift in indications for liver transplant: HCC cases have been increasing, while those of decompensated cirrhosis have been decreasing.[5] Understanding the optimal prophylaxis regimen for this group of patients is of paramount importance, according to Burra. “If you offer a treatment to a patient, it should be effective and safe in order to reduce the risk related to the reinfection of the graft. It should give them the possibility to survive with a good quality of life and avoid medical complications, such as recurrence of the original disease,” she said.

HIGH VERSUS LOW RISK AND THE ROLE OF HCC

The question of optimal prophylaxis regimes is particularly pertinent in high-risk patients. Yet, the distinction between high and low risk is “not exactly black and white,” explained Burra. "We are pretty sure about the low-risk patients, but the contrary is not always so clear," she said. She noted that low-risk patients are generally those with undetectable HBV DNA at the time of transplant and a good response to antiviral therapy. Whereas patients with ongoing viral activity at the time of transplant, as well as those with poor medication compliance, are considered at higher risk.[1,6] In addition, she went on, hepatitis D virus (HDV) coinfection increases the risk of advanced liver disease, HCC, and liver decompensation by two to three times, compared with HBV infection alone.[5,6]

What is still under discussion is the presence of HCC as an additional risk factor. Some centres, Burra explained, may withdraw combination prophylaxis in patients deemed to be at low risk.[6] In her opinion, this may not be the best course of action in those transplanted for HCC because, while the research is still unsure on whether the HBV recurrence triggers the HCC recurrence (or vice versa), the association is clear.

A 2008 retrospective study stratified 99 patients who were HBsAg positive according to transplantation for cirrhosis, either with or without HCC. It found that patients with HCC at the time of transplant were more likely to experience HCC recurrence than those who did not, and that HBV recurrence was more common in patients who experienced HCC recurrence.[9] There are two schools of thought on “which comes first,” explained Burra. One is, she went on, that residual HCC tumour cells contain HBV DNA, which can expand and replicate independently,

leading to both HBV and HCC recurrence, while the other is that residual HBV DNA or HBsAg cells produced by other non-tumour cells drive the reactivation of HBV, leading to HCC recurrence.[9,10]

"The best evidence we have so far demonstrates that, despite everything we do (combination prophylaxis), the presence of covalently closed circular DNA (cccDNA) in the liver means we still have the risk of recurrence," Burra went on.[1] "If we can avoid the recurrence of hepatitis, and possibly avoid the recurrence of HCC… why would we take the risk of lowering the power of the prophylaxis? My personal opinion is that it is safer to maintain the combination of immunoglobulins plus the NUCs, to avoid the recurrence of both HBV and HCC."

HBV AND HCC: FURTHERING THE EVIDENCE BASE

Burra's belief has been strengthened by the results of her latest study, which was published in March 2025.[5] The first nationwide retrospective study assessing results of liver transplant for patients with HBV in Italy, it assessed current practices for infection recurrence prophylaxis in the country, evaluating rates, risk factors, and the clinical impact of HBV and HCC recurrence. A total of 20 transplant centres took part, and 1,205 patients who underwent liver transplant following decompensation of cirrhosis (472 without HCC and 733 with HCC) between 2010–2021 were included. All were over the age of 18 years, and the median follow-up time post-transplant was 55 (27–93) months.[5]

In total, 99.8% of those without HCC and 99.7% of those with HCC received HBIG+NUC prophylaxis.[5] Of these, 83% of those without HCC and 84% of those with HCC were on long-life prophylaxis. Recurrence, which the study defined as HBsAg positivity and/or detectable HBV DNA in patients who previously achieved HBsAg negative status, was seen in 2.1% of those without HCC, and 3.1% of those with HCC. There was a "significantly lower rate of recurrence" in those receiving life-long HBIG+NUCs than those in which HBIGs were withdrawn, in those who received HBIGs only at transplantation, and in those who received NUCs alone (1.3% versus 8.6% versus 4.5% versus 5.9%, respectively; p=0.047), though Burra acknowledged that "few cases experienced withdrawal of immunoglobulins." Importantly, in those patients transplanted for decompensated cirrhosis without HCC, HBV recurrence was not associated with worse survival. In those transplanted with HCC, HBV recurrence was independently associated with HCC recurrence. "Therefore, 5-year survival was lower in this group than in those who did not experience HCC recurrence (32.5% versus 92.4%; p=<0.001),"[5] said Burra. "This is why I am still convinced that we have to avoid the recurrence of HBV: it is associated with the recurrence of HCC, which is associated with worse outcomes."

THE CHALLENGE OF IDENTIFYING LOW-RISK PATIENTS

Burra described the process of identifying which patients are truly at low risk of HBV recurrence after liver transplantation. "You need to identify the patient at low risk and then perform the follow-up in order to make sure all the estimations you made at the beginning are still the same," she said. Considerations include viral load and antiviral therapy before liver transplantation, as well as compliance with both HBV prophylaxis and immunosuppressive therapy post-surgery.[1,6] Another key concern is HDV, a documented risk factor that not all centres routinely screen for, said Burra.[5,6] While it may be less common in some regions, failure to test means clinicians lack an understanding of the risk profile. "If you don't think of it, you don't look for it," she said. Comorbidities can further complicate patient selection.[6] "It is very rare that you have the perfect patient. They may be overweight, obese, or have experience of metabolic syndrome, with diabetes or arterial hypertension." All these factors, she added, must be incorporated into the overall risk assessment.

While it is possible to personalise prophylactic regimens, Burra cautioned this was rarely feasible at the level of the

individual patient. As a result, she said she would "always stay in the safe part of management," meaning combination prophylaxis with HBIG+NUC, even in the face of perceived cost pressures. The introduction of alternatives to intravenous administration of HBIG, such as subcutaneous and intramuscular, have contributed to a reduction in costs, in part due to lower use of resources, including infusion clinics and dose reductions, she explained.[11,12] Burra went on to talk about how the data suggest that the cost impact of Igs is relatively modest. A 2024 Italian study, for example, reported that life-long HBIG prophylaxis was associated with a 6.6% increase in overall transplant costs,[13] which Burra described as "not too impressive." That said, the choice of administration route should be based on patient preference rather than price, Burra pointed out.

THE IMPORTANCE OF SPECIALIST FOLLOW-UP

Despite advances in prophylaxis, Burra emphasised that long-term outcomes depend on structured, expert follow-up. "The important thing is having a dedicated outpatient team to follow up these patients," she said, particularly highlighting those with HBV, HDV, and HCC. Burra noted that monitoring treatment and prophylaxis response, using anti-HBsAg levels, was essential to understanding disease activity and therapeutic efficacy. "You can have the best prophylaxis in the world but, if you release the patient who has that extra indication of HCC, they will experience recurrence and they will die, regardless of the recurrence of HBV."

CONCLUSION

HBIG+NUC combination prophylaxis has changed the landscape of HBV-related end-stage liver disease treatment.[1,2] However, debate continues over whether some patients could be safely managed with NUC monotherapy, either from the point of transplant or following post-transplant HBIG withdrawal. According to Burra, the close relationship between HBV recurrence and HCC recurrence adds complexity to this argument. While studies demonstrate a clear association exists, it remains uncertain which condition drives the other.[7] As such, she advocates for a precautionary approach, in which patients transplanted for HCC receive lifelong combination prophylaxis, rather than stepping down to monotherapy.

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