Management of hepatitis B virus

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Hepatitis B is a common problem worldwide with serious sequelae. Despite the explosion of new agents, management has grown even more complicated. The treatment paradigm is evolving from limited therapy to lifelong viral suppression in several populations. This shift has been a direct result of not only well-tolerated oral medications, but also the increasing recognition that active viral replication leads to untoward events such as cirrhosis, liver failure and hepatocellular carcinoma. However, therapy is not without risk, which includes side effects, cost and drug resistance. Controversy surrounds several clinical questions, including which patients are eligible for therapy, which treatment is optimal and at what point may therapy be discontinued. This commentary will discuss these questions as well as the limitations of the literature used to support our current treatment recommendations.

Keywords: HBV, therapy, treatment

Introduction

An estimated 400 million people worldwide are chronically infected with hepatitis B virus (HBV) with ~1.25 million hepatitis B carriers in the USA,1–3 of which 15% to 40% are at risk of developing serious sequelae including cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC).4 This risk is especially high in those with high levels of viral replication.5–7 The aim of chronic hepatitis B treatment is to prevent serious sequelae, which is best achieved through disease eradication. Unfortunately, because of extrahepatic reservoirs, integration of HBV-DNA into the host genome and protected intracellular, covalently closed circular DNA, hepatitis B cannot be cured.8

The next best alternative is sustained suppression of HBV replication. Currently, six therapeutic agents are approved to treat HBV in the USA: interferon-α (IFN-α), pegylated IFN-α 2a (PEG), lamivudine, adefovir dipivoxil, entecavir and telbivudine. Three additional agents (tenofovir, emtricitabine and clevudine) are in late stages of development with tenofovir’s approval expected this year. As these treatments do not eradicate hepatitis B, the clinical benefit is their ability to prevent disease progression and to sustain suppression of viral replication. All therapies have limitations and differ in duration, efficacy, side effects, resistance and cost.

Changes in treatment paradigm

In the past decade, the treatment paradigm has evolved from limited IFN treatment to term nucleos(t)ide analogue (NA) therapy to possible lifelong viral suppression. These changes are in part due to well-tolerated oral medications but also in recognition of the untoward effects of continued viral replication and data supporting a decreased risk of disease progression with viral suppression. The introduction of the oral nucleoside lamivudine revolutionized hepatitis B therapy. Its long-term use was found to decrease disease progression as well as the risk of developing HCC.9 Unfortunately, the enthusiasm for this agent was tempered by the recognition that drug-resistant mutations developed in >70% after 5 years of therapy and that these mutations diminish the beneficial effects of therapy.9,10 The realization that lamivudine resistance both conferred resistance and decreased the barrier to develop resistance to other NA therapy was most concerning.11–13

Since lamivudine, several NAs have become available for hepatitis B treatment. The rapidly growing body of literature involving both these agents as well as the natural history of hepatitis B challenges the current concepts surrounding patient selection for therapeutic intervention. This has resulted in the generation of multiple treatment guidelines that unfortunately lack consensus. Reading the literature can be daunting as each trial uses different enrolment criteria and definitions for therapeutic endpoints. Recently published guidelines have since standardized this terminology (Table 1).

Natural history

Hepatitis B is a highly unpredictable virus, known to flare and reactivate, despite years of inactivity. Chronic disease is most often a consequence of acquisition perinatally or in childhood.2 Despite this, several phases of chronic infection have been...
defined (Table 2). Immune tolerance is the initial phase where serum DNA is high but alanine aminotransferase (ALT) and histology are normal. Rarely is therapy considered during this time. HBeAg-positive chronic hepatitis is associated with attempts at immune clearance, high levels of DNA and ALT fluctuations. With loss of HBeAg, inactive carriers have minimal levels of replication, normal liver enzymes and no necroinflammation on liver biopsy. Those that continue to have HBV replication and HBeAg-negative chronic hepatitis tend to be older and may harbour viral mutations that prevent HBeAg production. The most important point is the understanding that no phase appears to be permanent.2

### Limitations of the literature

Early trials enrolled patients based on assumptions that only select HBV-infected populations had significant risk for disease progression. Historically, HBsAg-positive and HBeAg-negative patients with normal enzymes and minimal histological activity were coined ‘healthy carriers’. HBV-DNA was ‘undetectable’, but was measured by insensitive assays detecting virus only at levels >10^5 copies/mL.14–16 With time, it has been recognized that these patients are not exempt from liver disease. It was also erroneously assumed that HBV would only progress if HBeAg was positive, serum HBV-DNA was >10^5 copies/mL and serum ALT was elevated. Consequently, initial enrolment criteria were skewed and excluded some high-risk populations. These same assumptions were then carried over when determining trial endpoints; thus, treatment goals include histological improvement, normalization of liver enzymes, HBeAg loss and seroconversion, and HBV-DNA decline <10^5 copies/mL.

#### The role of HBeAg and HBeAb

Although a significant survival benefit after HBeAg clearance has been demonstrated, liver disease can progress after seroconversion (developing an HBeAb). Yuen et al.17 followed 3233 Chinese patients with HBV. The median age of seroconversion was 35 years, yet the median age for the development of complications was 57 years. Of patients with complications, 73.3% were anti-HBe-positive.17 In addition, HBeAg-negative patients may relapse after years of inactivity.18–20 HBeAg seroconversion has been found to be even less durable when achieved via therapeutic intervention.21

#### The role of viral load

Low-level viraemia does not ensure the cessation of disease progression. Two recent publications have assessed that ~25% to 44% of the patients with complications had HBV-DNA levels <10^5 copies/mL, suggesting that even low levels of viral replication may result in disease progression.17,22 Although most of these patients had lost HBeAg, this can only be partly explained by the recognition of pre-core and core promoter mutations as not every HBeAg-negative patient with chronic active hepatitis harbours these alterations. These mutations are HBV variants incapable of producing HbeAg, yet are still actively replicating.23 The risk of disease progression, despite low-level replication, is also supported by the REVEAL (Risk Evaluation of Viraemia Elevation and Associated Liver Disease) study. This was a large observational cohort that confirmed, despite minimal replication, patients with viraemia between 300 and 10^4 copies/mL remained at risk to progress to cirrhosis.6 This cohort also exposed the importance in baseline HBV-DNA which is likely to be more important than the level of replication at the time of disease development. A baseline HBV-DNA of 10 000 copies/mL or higher was highly associated with both progression to cirrhosis and development of HCC independent of eAg status.5,6 Those that have persistently high levels of replication are at highest risk for HCC.24

### Table 1. Category of response to antiviral therapy

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Virological (VR)</td>
<td>inability to detect serum HBV-DNA by sensitive PCR assays with loss of HBeAg in patients initially HBeAg-positive</td>
</tr>
<tr>
<td>Histological (HR)</td>
<td>decrease in histology activity index by at least 2 points and no worsening of fibrosis score</td>
</tr>
<tr>
<td>Complete (CR)</td>
<td>biochemical response, virological response and loss of HbsAg</td>
</tr>
<tr>
<td>Biochemical (BR)</td>
<td>normalization of serum ALT</td>
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### Table 2. Typical serologic patterns of chronic hepatitis

<table>
<thead>
<tr>
<th></th>
<th>Recovered HBV</th>
<th>Vaccination</th>
<th>Immune-tolerant</th>
<th>Chronic-inactive carrier state</th>
<th>Chronic-active</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>–</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HBsAb</td>
<td>+/−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Hbc-total</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HBV-DNA</td>
<td>−/L</td>
<td>−</td>
<td>H</td>
<td>L</td>
<td>H/L</td>
</tr>
<tr>
<td>HBeAg</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+/−</td>
</tr>
<tr>
<td>HBeAb</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+/−</td>
</tr>
<tr>
<td>HAI</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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</tbody>
</table>

HAI, histological activity index; +, detectable, −, not detectable, +/-, may be detectable; L, low-level viraemia, 10^5 copies/mL or <20 000 IU/mL (<2000 IU/mL in inactive HBV); H, high-level viraemia, ≥10^6 copies/mL or 20 000 IU/mL.
The role of HBsAg and HBsAb

Although prognosis improves in those that clear HBsAg, its loss does not denote cure. Low levels of HBV-DNA continue to be detectable in many that achieve this milestone. The examination of HBV biopsy specimens demonstrated detectable HBV-DNA in 100%, of which 44% were obtained from patients with HBsAb. Additionally, HBsAg seroclearance does not preclude complications. In a longitudinal observation of 298 HBsAg-negative patients, a small portion progressed to hepatic decompensation or liver cancer. Disease progression is much higher in those that have established cirrhosis. Despite these limitations, it remains an important milestone and favourable therapeutic endpoint.

The role of liver enzymes

Although an elevated ALT is frequently associated with hepatic fibrosis, inflammation and disease progression, normal enzyme levels do not correlate with disease risk. Serum aspartate aminotransferase or ALT on the high end of the acceptable range independent of aetiology has been shown to be associated with increased risk for liver disease and liver-related mortality. HBV-infected patients with an ALT level of 0.5–1 times the upper level of normal carried the same risk for hepatic complications as those with a serum ALT >6 times the upper level of normal. Yet, these patients are traditionally excluded from treatment studies. Interestingly, the highest risk for hepatic complications existed in those patients with ALT levels 1–2 times the upper limit of normal. In a cohort of HBV patients who underwent liver biopsy, 37% of the patients with persistently normal ALT and ongoing HBV viraemia have significant fibrosis and inflammation on liver biopsy. The majority of patients with advanced histology were older than 40 years of age and had a high normal ALT. The risk has been shown to increase significantly over time.

Controversies surrounding treatment recommendations

Several guidelines have been developed to help guide hepatitis B therapy. Although some disagreement between different publications exists, all consistently recommend therapy to chronic disease patients felt at the greatest risk of developing disease progression, i.e. those that have abnormal liver enzymes with high viral replication or abnormal histology. In the USA, the two most widely recognized guidelines are the AASLD practice guidelines and the Keefe treatment algorithm. Common to both is the emphasis on characterizing chronic hepatitis B as HBeAg-positive or -negative prior to initiating therapy as this differentiation offers vital insight into treatment efficacy and duration. Liver biopsy is strongly advocated to help distinguish those that may benefit from therapy but do not fall into a high-risk category. Significant inflammation or fibrosis on histology warrants consideration for medical treatment. Lamivudine is not recommended as a first-line therapy by either guideline, and serial monotherapy is also strongly advocated against as it has been shown to lead to multidrug-resistant HBV.

Certain aspects of treatment are not straightforward. One major issue has been in defining treatment endpoints. Long-term viral suppression has been proven to decrease disease progression; however, there is little data to ensure durable suppression and continued benefit after treatment discontinuation. Presumably, the best marker to predict durable response is HBsAg seroconversion. As HBsAg seroconversion is an uncommon event, most studies use the appearance of HBsAb to define a subgroup eligible to discontinue therapy. The HBsAb seroconversion rate after 1 year of therapy is ~30% with pegIFN-α and 12% to 22% with NA therapy. Six months after discontinuation, the rate of HBsAb seroconversion may continue to slightly increase in patients who have taken pegIFN-α, whereas the HBsAg may revert to positivity in 20% to 50% of the patients having discontinued NA therapy. However, rates of seroconversion have been shown to improve with longer treatment. According to the current guidelines, treatment with NAs should be continued until the patient has achieved HBsAb seroconversion and completed at least 6 months of additional treatment after the appearance of anti-HBe.

Patients that receive more than 6 months of consolidative treatment (drug exposure after the appearance of HBsAb) seem to be less likely to seroconvert or become viraemic in trials. This has led to the common recommendation that a minimum of 6 months of drug exposure should follow HBsAb seroconversion prior to stopping therapy. However, this rule may not be valid for those patients who gain HBsAb after years of treatment. In trials, it was only those that seroconvert early after drug exposure that received 6 months or more of study drug. In addition, most trials monitor patients for only 24 months after drug withdrawal to determine durable response. This is likely inadequate. During a 4 year follow-up of a cohort who had been recurrence-free 1 year after discontinuation of lamivudine, viraemia re-occurred in 44%.

Discontinuing therapy is even more controversial for HBeAg-negative patients with HBV. Although viral suppression is easily achieved, post-treatment relapse occurs after discontinuation in over 90% taking NAs and in ~80% taking pegIFN-α. According to the current guidelines, treatment with NAs should be continued until the patient has achieved HBsAg clearance. Some data exist that suggest some patients may indeed be able to stop medications. Hadziyannis et al. stopped adefovir in 33 patients after 4–5 years of therapy. All patients had undetectable virus at the time of treatment cessation. Although HBV-DNA became detectable in all patients, only 33% resumed therapy for persistent virus and increased ALT. In the remainder, the virus declined over time with 75% suppressing virus to <10 000 copies/mL after 2 years. Similar data exist for patients that received a year of pegIFN-α. Over 25% maintained HBV levels <10 000 copies/mL for 2 years post-treatment. Viral replication resumed nearly universally, albeit at a level presumed to be less likely to lead to clinical consequences. Again, there is no expert consensus involving NA discontinuation in HBeAg-negative patients. Several experts even advocate initiating combination nucleotide and nucleoside therapy in this subset as the anticipated drug resistance risk with lifelong NA treatment is high.

Resistance, combination therapy and monitoring

In attempts to achieve viral suppression, resistance can be a great hindrance. Resistance itself can be classified as genotypic,
virological or clinical (Table 3). Resistance may be related to prior HBV treatments, compliance, genetic barriers, pre-treatment HBV-DNA levels or rate and degree of viral suppression. Mutation selections may limit future treatment options by conferring cross-resistance. Combination therapy typically refers to the simultaneous use of two NAs, a nucleotide and a nucleoside, and is an effective strategy to both decrease the development of drug mutations and control the virus once mutations occur. However, its use, especially de novo, remains highly debated. Independent of initial drug choice, careful monitoring is paramount. If viral resistance is recognized early, at the stage of genotypic resistance, adding a complimentary agent easily re-suppresses the virus. However, if therapeutic manipulation is initiated at the time of clinical breakthrough, the virus is much more difficult to suppress. Sequential monotherapy with NAs is paramount. If viral resistance is recognized early, at the stage of genotypic resistance, adding a complimentary agent easily re-suppresses the virus. However, if therapeutic manipulation is initiated at the time of clinical breakthrough, the virus is much more difficult to suppress. Sequential monotherapy with NAs should be avoided as it has been shown to select for multidrug-resistant mutants.

Adequate monitoring is the only way to ensure adequate response and to avoid drug resistance. Although the cost of therapy is a common topic, the cost of monitoring is rarely discussed. Yet, lab costs can contribute significantly to the total expense. Integral to adequate monitoring is access to a sensitive accurate quantitative HBV-DNA assay. Following ALT alone is inadequate. Although each medication’s potency is different, DNA should be monitored at least every 3 months until the virus is fully suppressed. Frequent measurement of HBV-DNA offers insight into compliance as well as drug effectiveness. It allows early identification of patients at risk for a suboptimal therapeutic response, thus allowing early treatment modifications. If no response or viral rebound is seen, genotyping for drug resistance must be obtained. In patients with initial HBeAg positivity, the HBeAg and HBe antibody should be checked every 24 weeks during the treatment. If the patient remains HBeAg-negative with undetectable HBV-DNA, the HBsAg should be checked every 6–12 months. Some also advocate baseline genotyping. This is not standard, but allows identification of baseline drug mutations as well as those infected with genotype A and thus more likely to respond to IFN/PEG. It is important, independent of drug choice or response, that hepatitis B carriers, especially those that are African, Asian or have established cirrhosis, be monitored for the development of liver cancer.

### Table 3. Definitions of NA antiviral resistance

<table>
<thead>
<tr>
<th>Resistance type</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Genotypic</td>
<td>mutations within the HBV genome that are known to result in an eventual loss of drug susceptibility; without a change in management, genotypic resistance is typically followed by virological resistance</td>
</tr>
<tr>
<td>Virological</td>
<td>rebound in serum HBV-DNA levels following the development of genotypic resistance; rates of virological resistance are dependent on the sensitivity of the HBV-DNA assay used, as well as on the definition of virological rebound that is applied (generally 1 or 2 logs above nadir)</td>
</tr>
<tr>
<td>Clinical</td>
<td>a virological breakthrough accompanied by either elevations in ALT levels or worsening histology</td>
</tr>
</tbody>
</table>

### Conclusions

Considerable advances have been achieved in the management and treatment of hepatitis B in just the past few decades. Still, goals of viral suppression, not viral eradication, shape therapy to avoid major liver disease sequelae. Safety and resistance are increasingly important factors in our selection of therapy, as more patients are likely to receive lifelong medications. The paradigm shift of treating HBV infection to suppress virus over the long term will need to go hand in hand with careful monitoring and combination therapy to reduce the risk for resistance. As new information become available in the future, we may consider changing treatment candidacy from current parameters, which include age, ALT, histology and HBeAg status, to candidacy based upon disease risk derived simply from viral load and genotype.

### Transparency declarations


### References

12. Lampertico P, Viganò M, Manenti E et al. Low resistance to adefovir combined with lamivudine: a 3-year study of 145...


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