MINI REVIEW

HBV-carriers: When is monitoring and surveillance sufficient? (point of view)

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Summary  Medications currently available for the treatment of hepatitis B virus (HBV) infection are highly effective but not curative. The current paradigm is to recognize patients who require long-term treatment (with its inconveniences) among the majority of healthy carriers who do not need treatment. International guidelines have been established to identify patients requiring treatment but differences concerning the cut-off levels for viral load and transaminases, or need for liver biopsy, compromise their interpretation.

Immune tolerance phase: Patients with strictly defined typical forms (HBeAg-positive, normal transaminases level, very high viral load HBV-DNA more than $2 \times 10^6$ IU) have very limited liver injury and do not require treatment. Patients with atypical forms (low viral load HBV-DNA less than $2 \times 10^6$ IU) have a potential risk of more severe histological lesions, but the need for liver biopsy and treatment remains a matter of debate. Immune tolerant patients aged over 40 years should be treated because of the higher risk of hepatocellular carcinoma, even without cirrhosis.

Active phase HBeAg-positive or negative: Typical forms with elevated viral load and transaminases level should be treated. Mild hepatitis with moderately elevated transaminases levels (1–2 times upper limit of normal) can cause variable degrees of liver damage, and liver biopsy is necessary. HBeAg-positive hepatitis with very high transaminases levels have a very high rate of spontaneous HBe seroconversion. Hepatitis with high transaminases levels but low viral (HBV-DNA less than 2000 IU) is possible in HBe-negative patients but unusual in HBe-positive patients. Another cause of liver disease could be involved (hepatitis D, steatosis, alcohol).

Inactive phase: In the typical form, patients have a normal transaminases level and HBV-DNA less than 2000 IU; histological lesions are in general minimal. Treatment is not indicated. Atypical forms with normal transaminases levels but elevated HBV-DNA more than 2000 IU remain problematic. Forms with high-normal transaminases levels have a higher risk of complications. In the event of inactive cirrhosis, treatment is indicated if replication persists, even at a low level.

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Worldwide, chronic hepatitis B virus (HBV) infection causes millions of deaths each year. While treatments available are effective with demonstrated impact on mortality [1—4], the current issue is paradoxically whether certain patients can be spared treatment without compromising their outcome. This situation arises because a majority of infected people are “healthy” carriers, free of active liver disease, and also because treatments have certain drawbacks. Interferon or nucleos(t)ide (NUC)-based treatments only control disease, generally without curing it [5]. True HBsAg-negative “cure” is obtained in less than 10% of patients. In HBeAg-positive patients, HBe seroconversion with persistent inactivity despite treatment withdrawal is achieved in less than 20% of patients. Thus, a majority of patients will require long-term NUC therapy. This solution, which only suspends disease activity, carries several risks. The first is poor adherence, observed in slightly more than one-third of patients, with the subsequent risk of poor disease control. The second risk is virological escape, which is rare after 5 years with second-generation NUCs, but could become higher with prolonged use. The third risk is side effects which are now uncommon, although we have no way of knowing whether it will increase in the future with prolonged use over several decades [6]. Finally, all of these treatments have a very high cost, creating difficult problems in certain low-income high-endemic areas in Asia or Africa [7]. It is thus important to properly limit indications to patients actually in need of treatment. It is estimated that 20 to 30% of chronic HBV-carriers risk life-threatening disease progression. Schematically, patients in a phase of immune tolerance and those with inactive disease do not need treatment while HBeAg-positive and HBeAg-negative patients with active disease require treatment. The problem then becomes one of defining the limits for accurate classification of each patient into one of these four categories. Specific forms of the disease, difficult to classify into any of these four typical categories, must also be taken into consideration.

### Immune tolerance phase

#### Typical presentation

The typical presentation is a young HBeAg-positive patient with constantly normal ALT levels and a high replication rate. No HBeAg-negative patient should be considered as immunotolerant since clearance of HBeAg is a consequence of immune reaction. All guidelines agree that treatment is not required in the immune tolerance phase, and that a liver biopsy is not needed since the risk of histological injury is low. This phase of immune tolerance is observed in patients infected at birth by vertical transmission, commonly in Asian populations. In general, the situation remains unchanged during childhood and adolescence. After the age of 20 years, at 33 years on average, the tolerance is lost, and there is transition to the active phase of hepatitis, with elevated ALT levels and a concomitant fall in viral load. In two thirds of patients the active phase is short, lasting a few months before spontaneous transition to the inactive phase, with ALT levels returning to normal associated with HBe seroconversion and a fall in HBV-DNA below 2000 IU/mL [8]. Thus, the majority of patients never require treatment. The active phase persists in about only one-third of patients

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Cut-off levels for alanine transaminase and HBV-DNA levels used to determine the need for treatment as recommended by international societies.</th>
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<tr>
<td></td>
<td>HBeAg-positive</td>
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<tr>
<td>DNA (IU/mL)</td>
<td>ALT</td>
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<tr>
<td>APASL 2008 [2]</td>
<td>&gt; 20,000</td>
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<tr>
<td>AASLD 2009 [1]</td>
<td>&gt; 20,000</td>
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a ULN: men = 30, women = 19.
The HBV-carrier patient: who not to treat ?

who then require treatment. Initially, loss of tolerance can be intermittent, with phases of typical immune tolerance alternating with phases of transient activity (elevated ALT levels and HBeAg remaining positive). Monitoring among HBeAg-positive patients with normal ALT levels at a first test, who were initially considered as immune tolerant, showed that intermittent periods of elevated ALT levels were subsequently observed in 31% [9]. Therefore, as for patients with inactive disease, a normal ALT level, checked every 3 months for 1 year, is necessary before classifying these patients as truly immunotolerant.

Several studies have shown a link between high viral load and risk of death, cirrhosis or cancer [10—12]. This could raise the question of the appropriateness of treatment in immune tolerant patients who characteristically have very high viral loads. It must, however, be kept in mind that these studies did not involve typical immune tolerant patients since the majority of the included patients were HBeAg-negative and were aged over 30 years. Similarly, a link has been observed between high viral load and the severity of the histological lesions, but this appears true only in HBeAg-negative patients [13]. In HBeAg-positive patients, there is on the contrary an inverse correlation [14], which is logical considering the fact that HBV-DNA levels are lower in patients in the HBeAg-positive active phase (immune clearance phase) than those in the immune tolerance phase [15].

Special forms

Special forms occur because of uncertainties concerning the cut-off levels for viral load, ALT level or age:

- immune tolerant patients with moderate replication rates raise unsolved problems. Guidelines mention high replication rates yet fail to clearly define the HBV-DNA threshold to take into consideration. In two studies where patients were defined with the usual diagnostic criteria and with an arbitrary cut-off at HBV-DNA more than 2×10^6 IU/mL, liver biopsy showed minimal lesions, with a fibrosis score less or equal to F1 in all, without aggravation at the second biopsy when obtained during the follow-up [8,16]. A small proportion of HBeAg-positive patients with normal ALT levels have HBV-DNA levels below 2×10^6 IU/mL, probably corresponding to a certain form of immune reaction and raising the possible risk of histological lesions. In a study from India, which included immune tolerant patients irrespective of their HBV-DNA level (range 20—2×10^6 IU/mL), 13% presented more than F2 fibrosis [9]. Nevertheless, a more detailed analysis showed that the fibrosis scores were the same, irrespective of the viral load [17,18]. The discordance with earlier studies remains unclear. No specific guidelines have been put forward concerning immune tolerant patients with moderate replication. Further studies are needed to determine if they have a risk pattern different from usual immune tolerant patients or if a biopsy is necessary. Tighter surveillance to search for intermittent activity would be reasonable;
- immune tolerant patients with ALT levels near the upper limit of normal (ULN) would be classed in the active phase if the ULN are lowered, as discussed below [19]. However, currently available data about the presence of significant liver histological lesions in these patients are discordant [8,9,20], being absent in two studies and present in one. Further studies are needed to determine whether they should be considered as having weakly active disease, and if their evolution justify a treatment;
- immune tolerant patients over 40 years of age are exceptional. These patients have a high risk of cirrhosis and cancer [10—12,21]. Systematic treatment is to be recommended, even with only minimal histological lesions, because cancer can also develop on a non-cirrhotic liver if a high viral load persists.

HBeAg-positive or negative patients with active disease

Typical presentation

Typically, these patients are characterized by elevated ALT levels, high viral load and significant histological lesions. These patients have a high risk of progressing to cirrhosis and its complications [22,23]. Guidelines recommend treatment, but the ALT and HBV-DNA cut-offs and the requirement or not for liver biopsy vary between societies (Table 1). There is minimal agreement on treating all patients with clearly active disease characterized by ALT more than 2 ULN and HBV-DNA more than 20,000 IU/mL for HBeAg-positive patients and more than 2000 IU/mL for HBeAg-negative patients. In this situation, a liver biopsy is probably not indispensable since the clear ALT elevation is usually the sign of significant histological activity [24—26].

Special forms

- patients with moderately elevated ALT (less than 2 ULN) should not be misled because their risk of complications is as high or even greater as for patients with higher ALT levels [23,24], especially if they are over 40. In this minimally active phase liver lesions can be of all grades, and it is in this situation that liver biopsy is probably the most contributive. It shows the presence of significant histological lesions, implicating required treatment, in 30 to 75% of patients [14,27—31]. Inversely, surveillance is sufficient for patients with minimal histological lesions: many of these patients may remain in this situation indefinitely or become inactive; in the patients in whom later progression requiring treatment is observed, several years of treatment would have been spared. It would be interesting to have both liver biopsy data and non-invasive fibrosis results (elastometry, serum tests) to determine whether they are well correlated with the histological findings and would be potentially useful as markers for later surveillance;
- patients with very high ALT levels (more than 5 ULN) who are also positive for HBeAg raise a particularly difficult problem. On one hand, they are exposed to the risk of very severe liver disease, but on the other hand, the higher the ALT levels, the greater the probability of spontaneous HBe seroconversion. The two main factors predictive of hepatic decompensation are: presence of underlying cir-
rhosis and very high viral load with HBV-DNA more than 2×10^8 IU/mL [32]. If both of these factors are present, or if there are already signs of severe disease such as jaundice or high prothrombin time, treatment must be initiated immediately. Inversely, if these elements were absent, it would be reasonable to propose surveillance for a few months to wait for spontaneous HBe seroconversion, which occurs in 50% of patients with this type of ALT level [33]. If the patient is HBeAg-negative, even if the ALT level returns to normal spontaneously, there is no chance of moving to a definitive inactivity phase. The episodes of active disease will repeat, further worsening the fibrosis. These patients must thus be treated systematically;

- patients with moderately elevated HBV-DNA (less than 20,000 IU/mL for HBeAg-positive patients and less than 2000 IU/mL for HBeAg-negative patients), contrasting with their high ALT levels, must be explored in search of another cause of liver disease, for example co-infection with the hepatitis C or D viruses, a metabolic syndrome, or excessive alcohol intake. A liver biopsy could be particularly contributive in this situation to determine whether there is significant histological damage attributable to HBV warranting treatment. In one study, 62% of such patients had significant histological lesions with HBV as the sole cause [24].

### Inactive phase

#### Typical presentation

Typically, ALT levels are normal in these HBeAg-negative patients who have a very low or undetectable viral load (HBV-DNA less than 2000 IU/mL). They constitute the most frequent group of HBV-carriers. In general, it is recommended to not treat these patients [1–3] because the prognosis is excellent. Systematic liver biopsy is not recommended because histological lesions are considered minimal [34–36], sometimes with a variable amount of sequelar fibrosis, but no sign of activity [34,37]. A few more recent articles have questioned this notion [9,27] but their conclusions are limited by important inclusion biases [37]. Regular ALT tests (every 3 to 6 months) are recommended to detect reactivation, which occurs in 10 to 34% of patients, leading to consider a treatment [1–3]. The risk of reactivation is particularly high in the years following HBe seroconversion and decreases with time, but remains present even after several years of inactivity [38]. Initial determination of HBsAg titer less than 1000 IU/mL has been suggested as an efficient tool to discriminate true inactive carriers from active ones in transient remission, with 95% specificity, but it has to be confirmed by other studies before it can substitute for the traditional regular ALT testing [47]. HBs status must thus be monitored to detect spontaneous HBs seroconversion, which occurs at a rate of 0.5 to 1% per year, accelerating with age. The risk of cancer is higher than in the HBV-naïve population but remains low, around 0.06% per year [39], and systematic screening policy does not seem pertinent.

#### Special forms

Special forms occur because of uncertainties concerning the appropriate cut-off levels for viral load, or ALT level:

- inactive carriers with high-normal ALT levels raise the delicate issue of defining the normal ALT level. It has been demonstrated that inactive carriers with high-normal ALT levels from 0.5 to 1 ULN have a higher risk of disease progression [22], more severe histological lesions [14–27], higher viral load [26], and higher risk of reactivation [26] than those with an ALT level less than 0.5 ULN. Until recently, the ULN was different for each commercial test and variation resulted from the reference population considered normal, used to calibrate each test [40]. In the USA the median ULN is 63 for men and 52 for women for the tests currently in use [40]. In the last years, the ULN was more or less arbitrarily set at 40 IU/mL for men and 30 IU/mL for women by international guidelines. Recent attempts have been made to redefine more exactly the ULN, by excluding latent hepatic pathological conditions such as excessive alcohol intake, obesity or unrecognized viral infections in the reference population [19]. New normal cut-offs have thus been established for Asian and European populations respectively to 35 and 30 for men and 26 and 19 for women [19,41]. Since these new transaminases levels are lower than those retained earlier, patients with transaminases in the high-normal 0.5–1 ULN zone of the former normal range should thus be considered to have slightly elevated transaminases and being in a minimally active phase. The question remains open as to whether a liver biopsy should be ordered systematically to search for an indication for treatment. Indeed, it is not established if the situation is exactly the same than for patients with minimally active disease defined by elevated ALT less than 2 ULN, as discussed above;

- inactive carriers with high replication rates are HBeAg-negative patients with normal ALT levels but HBV-DNA in the 2000–20,000 IU/mL range. These patients constitute a specific group who often put clinicians in an uncomfortable position because of lack of clear guidelines. The highest acceptable level of HBV-DNA defining an inactive carrier has varied over time. Up through 2007, the cut-off was 20,000 IU/mL, which is approximately the detection limit of earlier tests performed without amplification. The 2000 IU/mL limit was set in 2007 by the AASLD [42], then retained in all of the international guideline publications. This threshold was initially established arbitrarily, based on two rather unconvinving arguments [43]. The first argument was that HBV-DNA more than 2000 IU/mL is rare in stable inactive carriers. In reality, studies have shown that 18 to 55% of inactive carriers are in this situation, even after 10 years of stability [44–45]. The second argument was that the 2000 IU/mL cut-off separates stable inactive carriers from HBeAg-negative chronic hepatitis with transiently normal ALT. Feld et al. [46] however, demonstrated that while the risk of reactivation is higher when the viral load is more than 2000 IU/mL (7% vs 37%), there is no HBV-DNA threshold indicating the absence of reactivation [46]. Liver biopsy data have shown that these patients have mild histological lesions comparable with those observed...
in classical inactive carriers [24–47]. The REVEAL study demonstrated that the risk of hepatocellular carcinoma is not different in patients with a stable HBV-DNA level, albeit below 2000 or 20,000 IU/mL [11]. For many practitioners, the 20,000 IU/mL cut-off remains thus a practical level which can be used to identify inactive carriers who do not need treatment but who should be followed more closely if their viral load is more than 2000 IU/mL;

- inactive carriers with a very high replication rate, characterized by a normal transaminases level, HBeAg-negative status and HBV-DNA more than 20,000 IU/mL, are rare. These patients have a very high risk of cancer, warranting systematic treatment [11,48]. These patients must not however be confounded with immune tolerant patients who are HBeAg-positive;

- inactive patients with cirrhosis account for less than 1% of inactive carriers when liver biopsy is obtained systematically [24–35]. Cirrhosis develops silently during the active phase of hepatitis, persisting as a sequel after spontaneous passage to the inactive phase. Despite normal transaminases and low viral load the cirrhosis expose to a persistent risk of cancer, and necessitate periodic screening by ultrasonography [49]. Systematic treatment with NUC is recommended in all cirrhosis to reduce this risk [1–3]. However, the benefit of this treatment has been demonstrated only among patients with a high viral load [4] but the benefit remains hypothetical for lower level of DNA. Screening for inactive cirrhosis must be systematic in inactive carriers, and has to date been based on routine clinical, biological or sonographic search for evidence. Elastometry or serum tests to assess fibrosis might provide a better method of detecting patients with suspected cirrhosis and needing confirmation by liver biopsy [50].

In conclusion, the majority of patients are inactive or immunotolerant patients, with a very low risk of complications and they do not necessitate treatment. Only patients with persistently active disease or high viral load should be treated. Easily obtained clinical and biological test results, provide sufficient evidence for most patients to be adequately classified, and enable the decision to treat or not. However, in some special forms there is a need to precisely evaluate the importance of fibrosis or activity in order to retain the indication of treatment. Liver biopsy remains the gold standard at this moment. When liver biopsy is not suitable or not accepted by the patient, decisions can be taken with the help of less invasive and more available methods such as elastometry and serum fibrosis tests [50]. In hepatitis C patients, it has been showed that, when concordant, the combination of these two tests provided adequate evaluation versus liver biopsy in 84% [51]. The same evaluation has to be performed in hepatitis B patients before these tests can be accepted as an alternative to liver biopsy for all cases. A decision not to treat should be reevaluated periodically depending on the progression of the patient’s status, and regular surveillance is necessary. All of the specific patient groups (co-infection, pregnancy, immunodepression) could not be examined in this short review.

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

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