Polish HBV Expert Group

THERAPEUTIC RECOMMENDATIONS FOR 2013: ANTIVIRAL TREATMENT FOR CHRONIC HEPATITIS B

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A typicalc feature of chronic HBV infection is its occurrence in phases, which are associated with variable relations between the immune system and the virus.

These phases do not always occur sequentially. They are as follows:

(a) The immunotolerance phase. In serum, in addition to HBsAg, is also present HBeAg and HBV DNA reaches high concentration values (above 10^6 IU/ml) in the absence or a small increase of ALT activity. Inflammatory and necrotic changes as well as fibrosis of the liver seen in biopsy specimen is small or nonexistent. In individuals infected in late childhood as well as in adults this highly infectious period, might last shortly.

(b) The immune reactive HBeAg-positive phase. As the reason for this phase to occur is considered change in expression of HBV antigens. The contents of HBV DNA in serum are variable but still smaller comparing to previous phase. The activity of ALT is periodically elevated. In liver tissue necrotic-inflamatory changes are moderate or intensified with more or less marked fibrosis (it could be increasing).This phase can last months or years and it might result in disappearance of HBeAg and occurrence of anti-HBe (2-15%). However, in about 1-4% of patients there is a possibility of HBeAg seroreversion. The more frequent are periods of exacerbations the more enhanced fibrosis of the liver.

(c) The inactive HBV carrier state. Anti- HBe are present and number of HBV DNA copies is low, usually below 2000 IU/ml; however sometimes it can be higher or HBV DNA might be undetectable. Activity of ALT remain normal. Histopathological changes depend on the magnitude of changes in the previous phase. Hence advancement of fibrosis and severity of inflammation are different. There is an increased risk of developing cirrhosis or hepatocellular carcinoma (HCC). Spontaneous disappearance of HBsAg and occurrence of anti-HBs is estimated at 1-3% per year after many years of presence of HBV DNA in serum. HBsAg levels (hereinafter: quantitative serum HBsAg level : qHBsAg) reaches value less than 1000 IU/ml, however this value also occurs in individuals with active infection.

(d) HBeAg - negative chronic hepatitis B. It corresponds with the concept of reactivation of infection. It occurs at maximum in 25% of individuals per year; in ca. 0.5% of individuals it can lead to liver failure. Antibodies anti-HBe are present and HBV DNA shows a variable concentration, which also concerns the activity of ALT as well as necroinflammatory liver changes. The most important feature of this phase of infection are periods of exacerbated inflammation which are interspersed with periods of remission.

(e) Occult infection (HBsAg negative). It most frequently has undetectable HBV DNA in the blood serum, but present in the liver. In the serum anti-HBc is present with or without anti - HBs. State of the immunosuppression might cause the recurrence of the replication of the virus, due to its episomal form of DNA, cccDNA HBV.

Goals of therapy in context of pathogenesis of infection and realistic possibilities of medical intervention.

The ultimate goal of antiviral therapy is eradication of HBV. At the current stage of our knowledge and therapeutic opportunities, it is not possible to achieve this aim due to the episomial DNA HBV form (covalently closed circular DNA, ccc DNA). The cccDNA structure is very resistant to antivirals. The persistence of this form of HBV DNA is responsible for recurrence of infection (1).

The concentration of HBsAg (qHBsAg) reflects the contents of active transcriptional cccDNA HBV in the liver more exactly than level of replication of HBV. Hence this test might be used for non-invasive assessment of viral DNA content in the liver. A gradual decrease of qHBsAg is a good indicator of effectiveness

of the therapy, as well as it allows preliminary assessment of the impact of treatment on cccDNA; which might be an important element in the process of HBV eradication and it might in the future change the final goal in antiviral therapy (1,2).

In the absence of possibility of eradication of HBV the main goal of therapy is now obtaining - permanent disappearance of HBV DNA in serum which is confirmed by highly sensitive PCR test (real time PCR), as well as obtaining the elimination of HBs antigen. Whereas seroconversion relays on production of anti-HBs and it is still a very rare phenomenon (see above) in connection with antiviral treatment, hence it should not be required as an ultimate target of the therapy, although it is very desirable. As it is put in recommendations of EASL 2012 "ideal" goal of treatment is permanent maintenance of nondetection of HBsAg with or without presence of anti-HBs (2,3). This applies to patients HBeAg positive and HBeAg negative. The disappearance or significant inhibition of HBV replication leads to:

(a) Suppressed progress of fibrosis of the liver or even partial reversal of this process.
(b) Normalization of biochemical indicators of liver inflammation. Suppressed HBV replication and relive of inflammation is usually accompanied with normalization of ALT and AST activity. In part of the cases it still might be elevated for reasons other than HBV e.g. non-alcoholic steatohepatitis, NASH.
(c) Reduced risk of developing liver cancer (HCC: hepathocellular carcinoma). A number of research reports indicate that replication of HBV, especially at a high level is one of the risk factors for developing HCC. Less frequent occurrence of HCC is reported in patients effectively treated with antiviral therapy.
(d) Extended survival rate in larger number of patients. Effective therapy and significant permanent reduction of the viral load (HBV DNA) in patients with advanced disease or cirrhosis slows the progression of fibrosis and increases the survival rate, as well as increases the period to development of the liver failure and eventual liver transplant.
(e) Prevention of reactivation of HBV infection in patients with liver transplant due to cirrhosis caused by HBV. The effectiveness of antiviral drugs in the survival of the transplant has been well documented.
(f) Improvement in the quality of life. Apart from general improvement and normalization of liver function which have a positive impact on the quality of life, in recent years it has been reported a convincing evidence of the impact that liver disease has on psychological and cognitive function in patients.
(g) Halting or remission of HBV related extrahepatic manifestations.
(h) Limited spread of HBV infection. Disappearance of HBV replication or its significant reduction lowers the infectivity of HBsAg positive person, which among others might be important for health professional performing invasive procedures.

Registered drugs

Drugs registered for treatment of HBV infection

- Interferon (IFN)
  - Natural,
  - Alfa 2a and alpha 2b (IFNα2a & IFNα2b),
  - Pegylated alfa2a (PegIFNα2a),
- Analogues (NAs)
  - Nucleoside: Lamivudine (LMV), Telbivudine (LdT), and Entecavir (ETV).
  - Nucleotide: Adefovir (ADV), Tenofovir (TDF).

Due to highest effectiveness, convenience and the dosing regimen (once a week), the PegIFNα2a among interferons should be used. Whereas among NAs drugs– recommended are ETV & TDF due to the strongest antiviral activity and the highest genetic barrier (1).

Qualification for the treatment of chronic Hepatitis B

Qualification for the treatment of patients both HBeAg- positive and HBeAg- negative requires fulfilling, at the same time, two out of three criteria listed below:

1) Value of HBV DNA larger than 2000 IU/ml
2) Activity of ALT exceeding the upper limit of norm
3) Features of inflammation or fibrosis of the liver with a value of at least 1° demonstrated histopathologically (liver biopsy) on scale of 5 degrees (from 0 to 4). To assess the severity of hepatic fibrosis non – invasive methods can be used, these include elastography and biomarkers, with confirmed diagnostic reliability. In an event where the results are obtained by several different methods, the final diagnosis should be based on liver biopsy and histopathological picture.

Patients who are in a immuno-tolerance phase of HBV infection (activity of ALT within norm, HBV DNA $>10^7$/ml), especially young ie. below 30 years of age, without clinical features of liver disease and family history of HCC do not require liver biopsy or non-invasive fibrosis evaluation and should not be treated. In this group of patients ALT activity should be checked every 3-6 months. Only in an instance where there is an increase of ALT activity antiviral treatment should be initiated. Persons with a strong family history of HCC or/and liver cirrhosis of unknown etiology, should be assessed for inflammation and fibrosis of the liver and in case of signs typical for hepatitis, they should be qualified for medical treatment.

Choice of the first line therapy

There is no evidence to justify different choice of the first line drug therapy in patients HBeAg positive and

HBeAg negative. So regardless of the patients status in this view, the first line therapy for patients with chronic HBV not previously treated should be medication with the highest proven efficacy and safety in a particular group. Among IFN – PegIFNα2a or from NAs ETV or TDF (1).

In accordance with the characteristics of medicinal product that has been approved by the *European Medicines Agency (EMA)*, treatment with LMV should only be considered when other antiviral medications with higher genetic resistance barrier are not available or could not be used (4). LMV should not be used as a drug of first choice because of high risk of selection of resistant variants, which after 5 years reaches 70% of treated patients. This narrows the possibilities of rescue therapy with use of other NA, and consequently reduces therapeutic possibility of HBV infection treatment. Furthermore the occurrence of resistance to LMV increases the risk of spread of HBV strain resistant to nucleoside analogues (1).

As it has been proven PeIFNα2a shows specific efficiency in chronic type B infections caused by genotype A which is dominant in Poland 77% (5). Apart from this PegIFNα 2a has a defined duration of treatment (6, 7). So, considering both of the arguments the optimum course would be the commencement of therapy with the above mentioned drug. This applies to all patients without any contraindications to 48 week interferon therapy (6, 7). In the case of ineffectiveness of thePegIFNα2a therapy during the course, or its ineffectiveness after the planned course, in patients who still fulfil treatment criteria, ETV or TDF therapy should be initiated. Though it should be remembered that PegIFNα2a, is contraindicated in decompensated cirrhosis of the liver, hence in this group of patients NAs should be used.

Monitoring of Interferon Therapy

Treatment with PegIFNα2a should be carried out for 48 weeks, unless during the course of therapy criteria specified below are fulfilled which indicate ineffectiveness of the therapy. The therapy should be checked by measuring of HBV DNA levels and qHBsAg in the 12^{th} and 24^{th} week of therapy.

Futility criteria leading to discontinuation of treatment with PegINFα2a:

a) In HBeAg positive patients (8)

- Infected with genotype A or D - if after 12 weeks of therapy there is no decrease of qHBsAg
- Infected with genotype B or C - if after 12 weeks of therapy qHBsAg has value exceed 20 000 IU/ml
- Regardless of genotype or if genotype is unknown - if after 12 weeks of therapy HBV DNA is not reduced by at least $2\log_{10}$, or if after 24 weeks qHbsAg is higher than 20,000 IU/ml

b) In patients HBeAg negative, regardless of the genotype (1,9)

- If after 12 weeks there is no reduction in concentration of qHBsAg

or

- If after 12 weeks there is no reduction in value of HBV DNA by at least 2 $\log_{10}$

In the above mentioned circumstances the PegIFNα2a therapy should be discontinued and as soon as possible highly active antiviral therapy NA (ETV or TDF) introduced, also in the case of normal levels of HBV DNA and ALT.

Due to probable long term effects of IFN therapy, lowering of the level of HBV DNA below 2000 IU/ml immediately after completion of the therapy should be taken as minimum goal of interferon therapy. If after the scheduled end of treatment the response was so definitive, the patient should be given every 6 months the following checks: activity of ALT, HBV DNA and HBsAg (qualitative method). Increase of ALT and/or HBV DNA above the values qualifying for treatment should be the basis for commencement of highly active antiviral therapy (ETV or TDF). There is no sufficient scientific support for IFN retreatment. In the case of disappearance of HBsAg patient should be tested for anti- HBs.

Monitoring and lenght of NA treatment (1)

The base for therapy to be recognised as successful, is suppression of HBV replication below the threshold of detection in blood serum (in accordance with modern standards it is assumed that the value of HBV DNA is below 15 IU/ml) . In the prevailing percentage of cases it is considered to be equivalent to remission of biochemical activity and histopathological improvement of disease process.

Throughout the therapy values of HBV DNA in blood serum and the activity of ALT should be systematically monitored (2-4 times a year). A criterion for effective therapy is demonstration of HBeAg seroconversion to anti-HBe, then HBsAg elimination, and most desirable is seroconversion to anti- HBs.

In a case of the use of NA there is no explicit end criteria to stop the therapy. In HBeAg positive patients it is commonly acknowledged that the disappearance of HBeAg and the emergence of anti- HBe which persists over the next 12 months in patients with normal ALT activity and viral load not exceeding 2000 IU/ml may be a reason to end the therapy.

After cessation of the therapy patient should be systematically tested (2-4 times/year) for HBV DNA, HBeAg/anti-HBe in the serum due to the risk of seroreversion.

HBsAg is tested every 12 months since the appearance of ani-HBe.

In HBeAg negative patients the only serological criteria for successful therapy is HBsAg loss and/or anti-HBs seroconversion. However this happens very rarely. Practically these patients are treated with oral medications continuously, similarly as in liver cirrhosis. They require HBV DNA checking for the purpose to change the therapy in the case of detectable viral load at the value of more than 15IU/ml, as well as HBsAg testing every 12 months to possibly end the therapy. In the case of elimination of HBsAg the therapy could be continued till the appearance of anti-HBs.

Drugs from NAs group are characterised by high safety for the patient which is related to relatively rare side effects. The most common side effect is renal function decline, especially in patients with reduced creatinine clearance. To medications with nephrotoxic potential mainly belong nucleotide analogues (ADV and TDF). During such a therapy it is necessary to test periodically kidney function by assessment of creatinine and phosphates concentration in the serum, as well as creatinine clearance. In the first year of the therapy such tests are done every 3 months, then twice a year. In the absence of virological response, the drug- resistance test for HBV is done (table 1).

Table I HBV variants and drug resistance (10)

HBV variants	Sensitivity level *(S – sensitive, I –decreased sensitivity, R – resistant)*				
	LMV	LdT	ETV	ADV	TDF
Wild type	S	S	S	S	S
M204V	R	S	I	I	S
M204I	R	R	I	I	S
L180M + M204V	R	R	I	I	S
A181T/V	I	S	S	R	S
N236T	S	S	S	R	I
L180M + M204V/I ± I169T ±V173L ± M250V	R	R	R	S	S
L180M + M204V/I ± T184G ± S202I/G	R	R	R	S	S

Types of virological response in the course of therapy (1)

- Effective therapeutic response – elimination of HBV viral load and HBsAg in the serum during the course of therapy (complete remission);
- Effective virological response- undetectable HBV viraemia in the course of therapy
- Partial virological response - reduction of HBV DNA of more than 1 $\log_{10}$ IU/ml initial values and persistence of it above the threshold of detection for duration of 6 months while taking the drug. In the case of drugs with a high genetic barrier treatment may be continued.
- Virological breakthrough – increase of HBV viral load by at least 1 $\log_{10}$ IU/ml in the course of earlier effective therapy, caused by selection of drug resistant HBV variants.
- Primary drug resistance - no reduction of viral load by at least 1 $\log_{10}$ IU/ml from the baseline during a 3 month period of taking the drug caused by infection with drug resistant HBV variants.

Both the primary drug resistance and partial response, or virological breakthrough could be mistakenly diagnosed in cases of non-compliance with therapeutic regime by the patient. This is especially true in patients treated with analogues of high genetic barrier .

Procedure at therapeutic failure and resistance to NAs

In patients treated with PegIFNα2, if after 24 weeks since the cessation of the therapy there is a lack of its efficiency, highly potent NA (ETV or TDF) should be implemented as soon as possible (1). Patients who are treated with one type of NA, in a case of primary drug resistance (most commonly observed in patients treated with ADV, 10-20%), should be checked for compliance to therapy. If the compliance is not a problem, tests to check for possible mutations should be carried out. The exception are patients who are treated with ADV, because of primary lack of its effectiveness in the majority of cases is due to low registered dose rather than existing mutations. In case of proven resistance to particular drug, this medication should be replaced by another more potent NA. This applies to all patients regardless of their status of HBeAg/anti-HBe.

Recommendations regarding procedures to switch NA:

- Instead of LMV - TDF
- Instead of ETV - TDF
- Instead of TDF or ADV – ETV (1)

In patients treated with one NA in the case of finding secondary drug resistance of partial virological response (as mentioned previously it concerns all patients independently on their HBeAg/anti-HBe status), it should be checked whether patient is adherent to the prescription. If so, actually applied NA is replaced with another, more potent NA. The following scheme of NA replacement is recommended:

- Instead of LMV - TDF
- Instead of ETV - TDF
- Instead of TDF – ETV
- Instead ADF – ETF or TDF (especially if patients previously received LMV), (1)

A second NA might be considered to be added to one that is already used in patients with partial virological response. This in particular concerns patients with high level of HBV DNA before treatment, and with confirmed significantly reduced levels of HBV DNA dur-

ring treatment. In order to avoid cross – resistance only nucleoside analogues with nucleotide analogs should be coadministered with each other e.g. LMV+ADV, ETV+TDF, (1, 11).

In patients treated with one NA who were diagnosed with primary or secondary drug resistance, or with partial virological response or with virological breakthrough (regardless of HBeAg/anti HBeAg status) treatment with PegIFNα2a should always be considered (1).

Treatment of liver cirrhosis and HCC associated with HBV infection.

Patients with compensated liver cirrhosis who in the past were not diagnosed with decompensation of the liver function e.g. ascites, encephalopathy, digestive tract bleeding, meet the criteria for inclusion to Child –Pugh category A and regardless of HBV DNA level or ALT activity should be treated with ETV at a dose 0.5mg or TDF. In such patients therapy with PegIFNα2a is possible as long as it is carefully monitored to detect early signs of liver decompensation or features indicating reaching Child-Pugh category B or C. In such case PegIFNα2a therapy should be replaced as soon as possible with ETV or TDF (1,12).

Patients before and after liver transplantation should be treated indefinitely with ETV at a dose of 1,0 mg or TDF. This requires a very careful biochemical monitoring for early diagnosis of possible metabolic complications.

Patients with decompensated liver function so in Child-Pugh category B or C , as well as with history of decompensate liver function and patients before and after liver transplant , qualify for indefinite ETV (at a dose of 1.0mg) or TDF treatment. This is regardless of HBV DNA level or ALT activity. In this group of patients PegIFNα2a should not be used (11,12).

Patients with HCC at each value of HBV DNA should be treated with ETV or TDF. It is also possible to treat patients with HCC with PegIFNα2a. It applies to both patients without liver cirrhosis and with cirrhosis as long as they meet Child-Pugh class A criteria (1, 12, 13).

Treatment of acute HBV infection with severe course.

There are no unequivocal results of controlled trials on the effectiveness of NA therapy in severe acute HBV infection including fulminant course of the disease. In these patients treatment with NA can only be considered with simultaneous assessment of the possibility of a liver transplantation (1).

Deciding on treatment with NA, patients should be started on drugs with high antiviral activity and high genetic barrier, as ETV or TDF (1). However, a liver transplantation should be an essential element in this process.

There may be difficulties in distinguishing between hyper-acute or fulminant hepatitis B and reactivation of chronic hepatitis B. In such cases it is also recommended to start NA therapy as soon as possible, even though it has little impact on reducing early mortality (14, 15).

Treatment of chronic viral hepatitis in children

In connection with the introduction in 1996 of mandatory vaccination against HBV on all newborns in Poland, in younger age groups up to the age of 14, there are only isolated cases of viral hepatitis B. However in a group of teenagers (15-19) in 2011 chronic hepatitis B was detected in 7.77 per 100,000 population and it significantly exceeded overall incidence in 2011 (4.11/100,000), (16).

The basic principles of treatment chronic hepatitis B in teenagers above the age of 14 is analogical to the treatment of adults. PegIFNα2a and ETV are currently under clinical trials, however own research indicates high effectiveness of these drugs in this group of patients. (17, 18). Clinical trials confirmed good tolerance and high efficiency of TDF in suppression of HBV viral load and normalization of ALT levels in teenagers aged 12-18, (19).

Procedures in chronic HBV in children below the age of 14 which is demonstrated in Figure1 should include:

- Testing of HBV DNA and qHBsAg levels for the purpose of identifying inactive carriers (1).
- Systematic monitoring (every six months) of ALT activity, HBV viral load and AFP concentration, as well as performing ultrasound for detection of early HCC. Increased ALT activity, concentration of AFP >10 ng/ml and HBV DNA >2000 IU/ml, presence of histopathological changes in the liver and family history of liver disease are determinative of eligibility for treatment (20).

Conditions requiring special consideration in decision to start treatment in a child infected with HBV.

- Worsening of liver function.
- Liver cirrhosis
- Glomerulonephritis of HBV etiology
- Prophylaxis of recurrence of HBV infection in liver transplant.
- Recipients of liver transplant from anti-HBc (+) donors.
- Immunosuppression/chemotherapy
- Co-infections: HBV/HIV, HBV/HCV, HBV/HDV
- Family history of HCC

Chronic HBV infection is not a contraindication for breastfeeding.

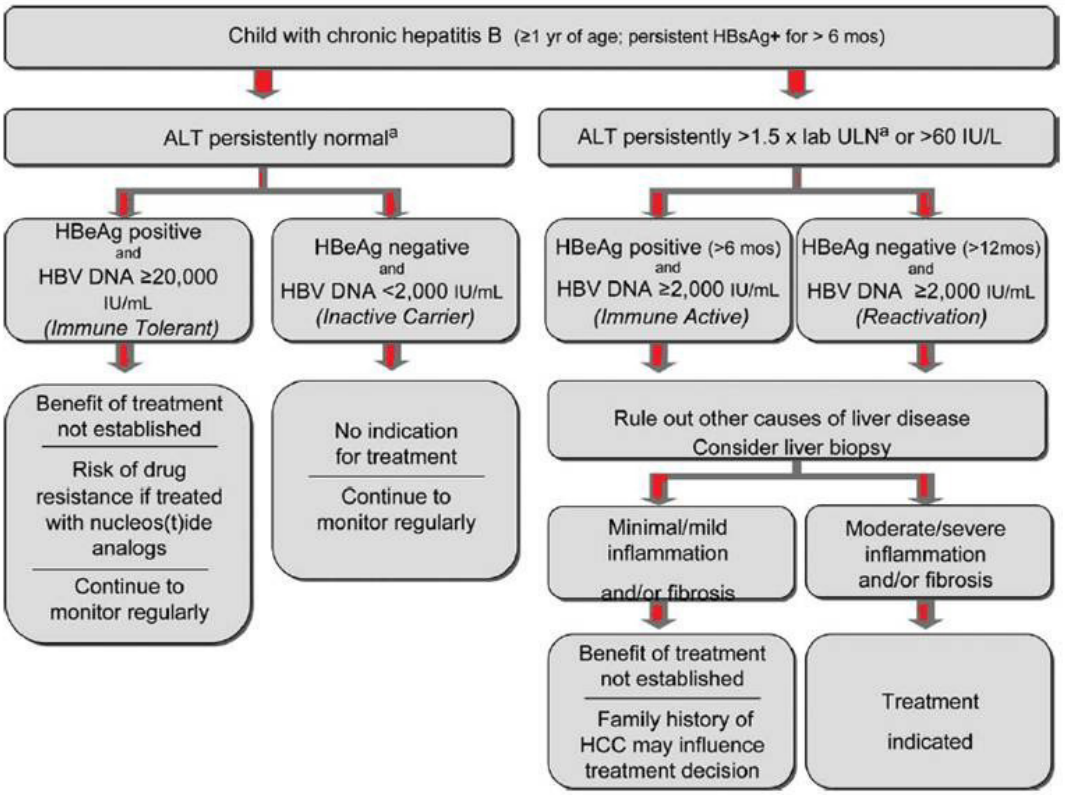

Fig.1. Algorithm for management of a child below 14yr old with HBV infection

Antiviral therapy for chronic hepatitis in women planning pregnancy.

A female who is planning pregnancy and who is infected with HBV should consult a specialist in infectious diseases. The consultation should include possible indication for antiviral treatment as well as safety of the therapy during the pregnancy.

Every pregnant woman should be tested for HBsAg. If the result of the test is negative, the test should be repeated in the third trimester of pregnancy. Decision to start anti-HBV treatment of women in reproductive age or during pregnancy requires consideration of following factors (21).

- In women under specialistic care who plan to get pregnant in the near future, and who have no advanced fibrosis of the liver, the most rational is to defer the treatment until the birth of the child.
- In women with advanced fibrosis of the liver who are planning pregnancy in the near future, the most appropriate treatment is PegIFNα2a until the pregnancy is confirmed. It is the physicians' responsibility to inform the patients about the need to use effective methods of contraception during the therapy. In case of contraindications to the treatment with PegIFNα2a, the patient should be treated with TDF or LdT (registered in Poland but not available).

Antiviral therapy for chronic hepatitis in pregnant women.

- PegIFNα2a, as well as IFN α2a and IFN α2b are contraindicated in pregnancy
- NAs: LMV, ETV, ADV belong to drugs on the FDA list category C; LdT and TDF – category B
- The risk of using ETV in pregnancy is unknown.
- The preferred drug is TDF because of better resistance profile and safety during the pregnancy.

If in the course of anti-HBV treatment woman gets pregnant, following procedures are recommended:

1) It is mandatory to cease PegIFNα2a or another IFN treatment.
2) If the patient was treated with NA, other than TDF treatment, TDF should be implemented.
3) Decision about possible continuation or modification of the therapy should depend on the stage of the liver disease. In advanced liver fibrosis (F3, F4) continuation of NA treatment. In fibrosis (F1, F2), indications for antiviral treatment should be re-examined.

Note: If a pregnant woman infected with HBV in view of low HBV viral load (HBV DNA <200 IU/ml) and/or with not advanced liver fibrosis is without anti-viral treatment or if therapy has been discontinued due to the pregnancy, then she should remain under the care of hepatologist due to the possibility of hepatic flares in particular after delivery (1, 22).

Prevention of mother-infant HBV transmission.

- A child born by a mother infected with HBV should be covered by active- passive preventative measures (specific anti-HBsAg serum and HBV vaccine) given in the first 24 hours of life.
- If a mother has been diagnosed with a high viraemia (HBV DNA>10^6IU/ml), then the risk of transmission increases by more than 10%, despite good active-passive preventative measures. In this situation chemoprophylactics such as LMV or TDF or LdT should be considered in the last trimester. The aim of this procedure is to protect the child from infection (23).
- If NA is administered only as a prevention, the therapy should be discontinued within 3 months after birth (21).

Preventative therapy of HBV-infected patients after a liver transplantation.

All patients before a liver transplantation within the qualification tests should be screened for HBsAg, anti-HBs and anti-HBc. Patients who are seronegative should be vaccinated against HBV before transplantation, and effectiveness of vaccination should be measured by anti-HBs level (24,25). In case of ineffectiveness of primary vaccination course, non-standard vaccination schedule should be considered. Each patient awaiting a liver transplant with any serological evidence of contact with HBV (also HBsAg negative) should be tested for HBV DNA (24, 25, 26). Each of the patients qualified for liver transplantation, with detectable HBV DNA, regardless of HBV viral load, should start NA therapy before transplantation and before the beginning of immunosuppressive therapy. Such procedure should be also applied in patients HBsAg negative, with detectable serum HBV DNA or anti- HBc. In patients previously untreated with low HBV DNA <2000 IU/ml, LMV could be considered (26). Patients with higher HBV DNA levels should be treated with ETV or TDF, and in the case of previous NA treatment drug resistance should be evaluated (25, 27, 28, 29).

Patients infected with HBV, who are HBsAg –negative and anti-HBc -positive with undetectable serum HBV DNA at the time of transplantation, regardless of anti-HBs status, should receive preventative LMV from the day of liver transplantation without time restriction (26, 29).

In patients with occult HBV infection at the time of transplantation, preventative measures against reactivation of HBV infection should include systematic administration of anti HBs (HBIG) serum and continuation of NA therapy. Intensity and route of HBIG administration should depend on initial HBV viral load, serological status and HBV drug resistance characteristics (26, 29, 30, and 31).

In case of recipients not infected with HBV, regardless of the anti-HBsAg , who received a liver transplant from anti-HBc positive donor, it is necessary to use HBIG and apply uninterrupted preventative measure with NA (30, 31).

Screening tests for early detection of HCC

HBV and HCV infections are currently considered to be the most important risk factors for HCC. This is why in patients infected with HBV and HCV, it is necessary to perform screening tests such as liver ultrasonography every six months. Analysis of recent studies demonstrated lack of sufficient sensitivity and specificity of alpha- fetoprotein in diagnosis of HCC (32, 33). However it does not change the fact of usefulness of AFP in qualification process for operative treatment or evaluation of its effectiveness.

If diagnosed focal change in the liver is smaller in diameter than 1cm, the ultrasound should be performed every 3 months, and in case of increasing size or changes in its character, the patient should be directed for 4-phase CT scan or MRI (32, 33). If the nodule in repeated tests is stable, the checks can be carried out every 6 months. If in ultrasound screening test the nodule is ≥1cm, above mentioned 4-phase CT should be carried out or dynamic contrast enhanced MRI (32, 33). Increased vascularity of the tumour shown in arterial phase following contrast washout in venous phase allows diagnosis of HCC. In case where the radiological image does not fulfil these criteria biopsy should be performed. Due to considerable difficulties in differentiating a dysplastic nodule from early HCC presentation, evaluation should carry out an experienced pathologist, always using molecular markers (glypican3, shock protein70, glutamine synthesis).

Prevention of HBV reactivation in patients with planned chemotherapy or started chemotherapy with other immunosuppressive drugs.

All candidates for the above mentioned treatment should be tested for HBsAg and anti-HBc. HBsAg positive individuals should be tested for HBV DNA and in case of positive result, regardless of the value, should receive NA throughout the whole treatment, and 12 month after the completion of the treatment. LMV is effective, but at the present time it is advisable to use ADV or TDF. Individuals tested HBsAg negative, and anti-HBc positive without detectable HBV DNA, regardless whether anti-HBs is present or not should be tested for HBV DNA as well as for ALT activity every 1-3 months. NA therapy is initiated after detection of HBV DNA. Some experts recommend the use of LMV in all HBsAg negative and anti-HBc positive patients. HBV seronegative patients should be vaccinated against hepatitis B (1).

Prevention of occupational HBV infections

In a case of HBsAg-positive healthcare workers (HCW) who is performing procedures during which there is a risk of HBV transmission to a patient, HCW should be tested for HBV DNA level and HBeAg/anti-HBe serological status If the results show HBeAg positive and the value of HBV DNA is above 10^4 copies/ml, such employees should not perform exposure-prone procedures where the patient may be exposed to their infected blood. HBeAg-positive healthcare workers should be tested for HBV DNA level every three months and HBeAg-negative HCWs -at least once a year. HBV infection should not be a reason for refusal of employment, and neither should it be a reason for his/her dismissal. Health professional may not give consent to undertake HBV test during the qualifying period for his/her job. Employee refusal to undertake such test cannot draw disciplinary measures. In case of the patient's exposure to blood or other biological material of the infected employee, it is necessary to immediately implement post HBV exposure procedures.

Pre-exposure prophylaxis

In addition to HCWs, students in both Medical Schools and Medical Universities, other professionals who due to their profession might be in danger of exposure to HBV should be immunised against HBV e.g. policemen, firemen, prison employees, deployed soldiers, municipal workers etc. Blood test to confirm anti-HBs response should be done within 1-2 months after the final vaccine dose. It is the responsibly of the employer to provide safe work environment in accordance with Employee Work Code.

Post-exposure prophylaxis

The kind of post-exposure prophylaxis depends on the immunity status of the exposed individual and the serological status exposure source. Within the HBV prophylaxis qualifying framework HBsAg marking should be performed on the exposure source (with prior approval), and the exposed individual- HBsAg or if they have been previously immunized, titre of anti-HBs. Vaccination should start as soon as possible, not later than 7 days after exposure. Anti-HBs immunoglobulin should be administered as specified on the product liflet, within 72 hours. In case of an individual sensitive to infected biological material transmitted from an individual with active HBV infection, or with unknown serological status, it is recommended to determine HBV infection markers (HBsAg, anti-HBc IgM) 6, 12 and 24 weeks post exposure (34).

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