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КРОВЬ

APASL
Single Topic Conference
Focus on the Virus Hepatitis B
Abstract Book

№ 2 (20) 2015

КРОВЬ НАУЧНО-ПРАКТИЧЕСКИЙ ЖУРНАЛ

2 (20) 2015

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CONTENT

Հարգելի գործընկերներ, տիկնայք և պարոնայք,

Հայաստանի Հանրապետության առողջապահության նախարարության և անձամբ իմ անունից սրտանց ողջունում եմ «Հեպատիտ B» միջազգային գիտաժողովի մասնակիցներին:

Վիրուսային հեպատիտը հիվանդությունների բազմաէթիոլոգիական խումբ է, որը պատասխանատու է տարեկան 1,5 միլիոն մահվան դեպքերի համար: Դրանց մեծ մասը կապված է հեպատիտ B-ի վարակի հետ: Շուրջ 600 միլիոն մարդ, կամ աշխարհի յուրաքանչյուր 11-րդ բնակիչ այժմ ապրում է HBV և HCV վարակով: Նրանք լյարդի ցիռոզի և լյարդաբջջային կարցինոմայի լուրջ ռիսկի են ենթարկվում: Այդ իսկ պատճառով վիրուսային հեպատիտը համարվում է համաշխարհային հանրային առողջապահական խնդիր:

Ուրախ եմ, որ Հայաստանի հեպատոլոգիական ֆորումի նախաձեռնությամբ կազմակերպված այս համաժողովը միավորել է ոչ միայն Հայաստանի և ԱՊՀ երկրների, այլև Եվրոպայի, Ասիայի և ԱՄՆ-ի առաջատար մասնագետներին, տարբեր բնագավառների բժիշկներին:

Բժշկության, ինչպես և յուրաքանչյուր այլ ոլորտում, անհնարին է առաջընթաց ապահովել առանց համագործակցության: Առավել ևս ժամանակակից բժշկությունն այսօր դժվար է պատկերացնել առանց ապացուցողական բժշկության վրա հիմնված միջազգային փորձի: Այս առումով մասնագետների, առաջատար բուժկենտրոնների, լաբորատորիաների և միջազգային ասոցիացիաների հետ համագործակցությունը կարող է լուրջ ներդրում ունենալ հեպատոլոգիայի արդիական խնդիրների լուծման ամենաարդյունավետ ուղղիները գտնելու գործում:

Կոնֆերանսի մասնակիցներին մաղթում եմ կառուցողական երկխոսություն և բեղմնավոր աշխատանք:

Արմեն Մուրադյան
Հայաստանի Հանրապետության
առողջապահության նախարար,
բ.գ.դ., պրոֆեսոր

Dear colleagues, ladies and gentlemen!

On behalf of the Ministry of Healthcare of the Republic of Armenia and me personally I cordially welcome the participants of the International Conference: ''Focus on the Hepatitis B''.

Viral Hepatitis is polyetiologic group of diseases, which is responsible for 1,5 million deaths each year. Most of them are associated with HBV-infection. Around 600 million people, or every 11-th person in the world, are currently living with HBV and HCV infection. They are at serious risk of developing the liver cirrhosis and hepatocellular carcinoma. That is why viral hepatitis is recognized as a global public healthcare problem in the world.

I am glad, that this Conference, organized on the initiative of Armenian Hepatological Forum, has unified the leading specialists and doctors of various fields not only from Armenia and CIS countries, but also from Europe, Asia and the USA.

In medicine, as in any other area it is impossible to achieve any progress without cooperation. Moreover, one can hardly imagine the modern medicine without the international experience in evidence-based medicine. In this context collaboration with specialists, advanced medical centers, laboratories and international associations could have a tangible contribution in finding the most efficient ways for the solution of the pressing issues of Hepatology.

I wish constructive dialogue and fruitful work to all the participants of the Conference.

Minister of Healthcare
Republic of Armenia,
MD, Professor
Armen Muradyan

Dear Colleagues,

On behalf of the Organizing Committee, it is a great honor and pleasure for me to invite you to the Asian Pacific Association for the Study of the Liver (APASL) Single Topic Conference (STC) on HBV in Armenia. The conference will be held in October 3-5, 2015, in Yerevan. This is the first time that an APASL event will take place in this new region.

The conference will focus on all aspects of the management of Hepatitis B Viral Infection and will include the important topics of epidemiology, virology and immunology of HBV Infection as well as optimal current and future treatment approaches for patients with HBV Infection. It will be one of the sequential APASL conferences on HBV with the aim to invite all experts in the field from the different regions of the world, to present the latest research and clinical data. The Scientific program of the conference is supported by a key international advisory group.

Yerevan is regenerated community based on the ancient city Erebuni which was founded by Urartian King Argishti I (r. ca. 785–753 BC) in 782 BC. It was built on the top of a hill called Arin Berd overlooking the Arax River. Yerevan is one of the world's oldest continuously inhabited cities. The city is a home to dozens of museums, art galleries, and libraries as well as to the largest Armenian Church in the world, the Cathedral of Saint Gregory the Illuminator, opened in 2001 when the entire Armenian nation had celebrated the 1700th anniversary of the establishment of the Armenian Church and the adoption of Christianity as a state religion in Armenia. Yerevan is as old as its traditions and culture.

Yerevan is also famous for its Brandy (Cognac) where there is a leading Brandy Company with its main brand name "Ararat".

Our guests will enjoy Armenian cuisine as well as the cuisine of other countries in the finest restaurants and cafes.

There is a large exhibition market next to the Republic Square where you can buy Armenian national souvenirs, handcrafts, clothes and accessories. October is the best season to visit Armenia. The weather is mild; it is warm and mostly sunny. It is called "gold" season with its beautiful autumn shades so called Saryan's colors. There are many Public Holidays in October. The main is Erebuni-Yerevan which is an event dedicated to the capital of Armenia.

We hope you will enjoy this conference as well as your stay in Armenia, the country with an extensive and rich history, culture and amazing traditions and hospitality.

We are looking forward to see you in Armenia.

With kindest regards

President of APASL STC 2015 in Armenia
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ACUTE ON CHRONIC LIVER FAILURE

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Liver failure can be presented as acute liver failure (ALF) (underlying healthy liver), acute-on-chronic liver failure (ACLF) (underlying chronic liver disease/ cirrhosis), or an acute worsening of the decompensated cirrhosis. There are two well established definitions of ACLF; the APASL, one defines it as “an acute hepatic insult manifesting as jaundice (serum bilirubin ≥ 5mg/ dl (85 micromol/l) and coagulopathy (INR ≥ 1.5 or prothrombin activity < 0%) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and is associated with a high 28 day mortality”. While liver failure is at the core of APASL definition, the definition by the Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) group emphasizes on the clinical outcomes based on the number of extrahepatic organ failures and sepsis. In a retrospective-prospective data collection of 1363 patients from 17 university hospitals across Asia-Pacific from October 2012 to December 2013, the overall 14 and 28 day mortality was 34,8% and 52,1%. The common hepatotropic acute insult was alcohol (563, 41,3%), viral infections (452, 33,1%), drug induced liver injury (93, 6,82%). The chronic etiologies included alcohol (645, 47,3%), viral (335, 24,6%), nonalcoholic fatty liver disease (NAFLD)/ cryptogenic (277, 20,2%) and others (106, 7,9%). The CLIF SOFA score was evaluated to assess organ failure in the Asian cohort. The proposed AARC grading of liver failure needs to be further validated.

The disease severity and outcome can be predicted by both hepatic and extra-hepatic organ failures. Detection of acute insult, stage of underlying chronic disease and presence of portal hypertension helps stratify patients. Liver pathology helps in diagnosis, treatment and early selection for transplantation. Specific therapies, such as nucleoside analogues for HBV reactivation, steroids for severe alcoholic hepatitis and possibly for severe autoimmune hepatitis are helpful. While liver transplantation is the definitive therapy, it is often not feasible. Artificial liver support systems such as MARS and Prometheus serve as a bridge therapy, especially in the presence of hepatorenal syndrome and/or hepatic encephalopathy. Cellular therapies, using bone marrow derived cells, and mesenchymal cells have shown some initial benefits. Alternatively, ameliorating on-going hepatic injury and augmenting spontaneous regeneration by using growth factors such as granulocyte colony stimulating factor (GCSF) have shown promise. This approach of in vivo BM stimulation is simple, readily usable and also helps prevent sepsis and organ failure. Use of other growth factors, such as erythropoietin in combination could help. New emerging therapies like modulation of gut flora and cellular therapies are of great interest in this rapidly evolving field.

HBV: TREATMENT INDICATIONS AND END POINTS

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The goal of therapy for CHB is to improve quality of life and survival of the infected person by preventing development of disease, progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death; and prevention of transmission of HBV to others.

The indications for treatment in hepatitis B are generally based on the combination of three criteria serum HBV DNA levels, serum ALT levels and severity of liver disease (assessed by clinical evaluation, liver biopsy or non-invasive methods). Indications for treatment should also take into account age, health status, family history of HCC or cirrhosis and extrahepatic manifestations Patients with decompensated cirrhosis and detectable HBV DNA require urgent antiviral treatment with NA(s), and while many may respond, these patients should also be considered for liver transplantation. Patients with compensated cirrhosis and HBV DNA >2,000 IU/mL should also be considered for treatment even if ALT levels are normal. Treatment may be started in pre-cirrhotic chronic HBV infected patients if they have persistently elevated ALT levels >2 times ULN and HBV DNA >20,000 IU/mL if HBeAg positive and >2,000 IU/mL if HBeAg-negative. A liver biopsy or non-invasive estimation of extent of fibrosis is useful. In patients with significant fibrosis with normal or minimally elevated ALT or HBV DNA levels below the defined limits, there is limited data. In the new proposed APASL guidelines, it was unanimously agreed that these patients do merit antiviral therapy, in order to prevent further progression of fibrosis and other complications of liver disease.

Patients with a rising trend in ALT or bilirubin may be developing an exacerbation, and even severe hepatitis or hepatic decompensation. They should be monitored for spontaneous HBeAg seroconversion. In patients with severe reactivation of chronic HBV infection with impending or overt hepatic decompensation treatment should be antiviral agents should be started immediately. Patients with persistently normal ALT or minimally raised ALT respond poorly, and hence should be followed till ALT>1,5 times ULN.

The ideal end-point in both HBeAg-positive and HBeAg-negative patients is sustained off-therapy HBsAg loss, with or without seroconversion to anti-HBs. Induction of sustained off-therapy virological response in both HBeAg positive (with sustained anti-HBe seroconversion) and HBeAg-negative patients is a satisfactory end-point. If sustained off-therapy response is not achievable, then a maintained virological remission (undetectable HBV DNA by a sensitive PCR assay) under long-term antiviral therapy in HBeAg-positive patients who do not achieve anti-HBe seroconversion and in HBeAg-negative patients, is the next most desirable end-point. Treatment naïve patients can be treated with Tenofovir 300mg daily, ETV 0,5 mg daily or telbuvidine 600 mg daily.

For HBeAg-positive patients without liver cirrhosis, the optimal duration of NA therapy is unknown. The therapy can be stopped after at least 1 year but preferably 3 years of additional therapy after HBeAg seroconversion with undetectable HBV DNA by PCR and persistently normal ALT levels. The optimal duration of NA therapy is unknown in patients with HBeAg-negative chronic hepatitis B. In patients without liver cirrhosis, the treatment can be withdrawn (1) after HBsAg loss following either anti-HBs seroconversion or at least 12 months of a post-HBsAg clearance consolidation period (B1) or (2) after treatment for at least 2 years with undetectable HBV DNA documented on three separate occasions 6 months apart. The NA therapy should usually be continued indefinitely in cirrhotic patients and patients with advanced fibrosis.

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RISK FACTORS FOR HEPATOCELLULAR CARCINOMA (HCC) DEVELOPMENT DURING NUCLEOTIDE ANALOGUE (NUC) TREATMENT FOR CHRONIC HEPATITIS B

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Hepatitis B virus (HBV) persistently infects approximately 350 million people worldwide and it is a major health problem especially in Asia-Pacific region. It is also one of the major risk factors for HCC. The persistence of serum hepatitis B e antigen (HBeAg) and high level of serum HBV DNA were reported to be risk factors for HCC. Liaw et al. reported that the lamivudine, a nucleotide analogue, reduced HCC development compared to control. Viral breakthrough by emergence of resistant mutation is one of the major problems diminishing the antiviral effect of the drug. However, despite the use of effective NUCs, HCC develops during the treatment; therefore we examined risk factors for HCC development in patients on NUC treatment.

We investigated the 225 chronic hepatitis B patients who received the NUCs (median age; 49 years, 58 (26%) with cirrhosis, 132 (60%) first administered with lamivudine, 93 (40%) first with entecavir). During the follow-up period (86±44 months), 16 (7%) developed HCC. Patients who developed HCC were elder (>50 years old), with lower platelet count (≤$10{,}0\times10^4$/mm^3), lower serum albumin level (≤3,5 g/dL) and first administered with lamivudine (14 (88%) vs. 117 (56%)). In univariate analysis for all 225 patients, older age, lower serum albumin level, HBeAg positivity at baseline, and cirrhosis were associated with subsequent HCC development. Of these variates, cirrhosis remained as significant predictive variate in multivariate analysis.

Generally, higher age, and advanced stage of hepatitis were thought to be the risk factors of HCC in treatment naïve patients. Our results indicate that these are the risk factors of HCC development under the treatment of NUCs.

In conclusion, there are certainly patients developing HCC even on NUC treatment such as elder age and advanced liver disease, and we should take care of these possibilities in clinical practice.

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MANAGEMENT OF CHRONIC HEPATITIS B IN RENAL FAILURE

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Hepatitis B virus (HBV) has significant impact in patients with chronic kidney disease (CKD). HBV per se is a risk factor for CKD, alters management and worsens prognosis of CKD. CKD patients with HBV have increased mortality and morbidity. Dialysis population has higher HBV prevalence than general population ranging from 1-10% in developed countries and 2-20% in developing countries. Also HBV behave differently in CKD patients. Chances of chronic infection are higher than usual due to low immunity. But contrast to common belief viral load is low. Serum aminotransferases levels are modestly elevated in CKD patients as baseline aminotransferases levels are low. Liver biopsy shows more fibrosis and less inflammation.

It is still debatable to whom to choose for antiviral therapy in CKD patients with HBV infection. Those patients with active replication (>2000 IU/ml HBV DNA) and increased transaminases should be started on therapy. In case of normal aminotransferases, liver biopsy or transient elastography should be done. Even if transaminases are normal and DNA>2000 IU/ml and liver biopsy /transient elastography shows moderate abnormality treatment should be given. Interferon alpha has been tried but have higher side effects and later higher renal graft rejection hence not recommended nowadays. Oral nucleoside (tide) analogues have better tolerance and outcome therefore nowadays used commonly. All nucleoside (tide) analogues are excreted by kidney hence need dose modifications according to GFR, above >50 ml/min e GFR no dose modifications are required. All nucleoside (tide) analogues are dialyzable but no additional doses are required after dialysis in view of intermittent nature of dialysis and high volume of distribution of NAs. In all patients with severe renal dysfunction <50 ml/min e GFR and naive to NAs entecavir can be used, in those with dialysis tenofovir can also be used. In patients with lamivudine resistance tenofovir is preferred irrespective of renal status with dose modifications. Telbivudine has been associated with improved renal functions but can be tried only with low viral load. Adefovir can be used but usually avoided as having highest nephrotoxicity reported. Lamivudine is used less frequently in view of high resistance development.

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CHANGING HEPATITIS B VIRUS EPIDEMIOLOGY IN ASIA

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Chronic hepatitis B virus (HBV) infection is a major global health problem especially in the Asia-Pacific region where more than 40 countries are encompassing a wide geographic area with a large population. It may cause progressive liver fibrosis leading to cirrhosis with end-stage liver disease, and a markedly increased risk of hepatocellular carcinoma (HCC). In many Asian countries, the prevalence of chronic hepatitis B (CHB) is highly endemic due to high occurrence of perinatal transmission and infection of HBV during early childhood.

An estimated 2 billion persons worldwide have been infected with HBV, and about 300 milion chronic HBV carriers live in Asia. Of these, 15-20% will eventually die of HBV-related end stage liver disease. During the past decade, a dramatic reduction in the prevalence of CHB has been demonstrated after implementation of infant immunization program in many Asian countries. However there is still large population of old adult patients who could not get the vaccination and are still at risk of end-stage liver disease or HCC.

CHB may present as either hepatitis B e antigen (HBeAg)-positive and (HBeAg)-negative disease. The prevalence of HBeAg-negative disease has been increasing over the past decade as a result of an ageing of patients with HBV infection. In addition, suboptimal response to antiviral treament may result in change from HBeAg-positive to HBeAg-negative CHB by achieving HBeAg loss/seroconversion but reappearance of HBV DNA in serum.

In spite of the success of unversal HBV vaccinaiton, great obstracles and challenges lie ahead for most of Asian countries. Mother-to-infant transmisison is still high and universal vaccination is not available in some countries. Around 10% of the infants born to HBeAg-positive CHB mothers still become chronically infected, especially when the maternal viral load is more than 7 $\log_{10}$ copies/mL. Migration from countries with high prevalence rate to countries with low HBV endemicity.

During the last few decades after introduction of HBV vaccination and excellent therapeutics, the global epidemiology of HBV infection has been and is still being changed in a good way. However, major challenges remain in Asia. Preventable transmission continues, the majority of infected individuals remain undiagnosed, and only a tiny minority currently receives treatment.

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HBV – GENOTYPES AND CORE/PRECORE MUTATIONS

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Hepatitis B virus (HBV) is a member of the Hepadnaviridae family and replicates via reverse transcription using an RNA intermediate. Because the viral polymerase lacks proofreading activity, mutations are very common accounting for the interesting genetic heterogeneity of HBV. The estimated mutation rate of the hepadnavirus genome is approximately 2 x 10(4) base substitutions/site/year, about 100 times higher than that of other DNA viruses that allows replication competent mutations to form. According to recent phylogenetic analyses, HBV can be classified into 10 genotypes (A to J) based upon an inter-group divergence of 8 percent or more In the past decade, there has emerged evidence supporting that HBV genotypes influence clinical outcomes such as cirrhosis and liver cancer, the presence of core and precore mutations, HBeAg loss and seroconversion rates, and response to antiviral therapy. The changes in the core and precore region are also of major interest today since these mutations drive the decrease and eventual "loss" of HBeAg (signifying that the eAg is present but lower than the limits of detection. These precore and core variant emerge early in the course of the disease and the HBV disease state must be looked at not as any one "pure" state but as a continuum of immune activity, and viral changes in response to immune pressure. The predominant mutation involves a G to A change at nucleotide 1896 (G1896A), which creates a premature stop codon (eW28X). This mutation prevents translation of the precore protein and can completely abolish the production of HBeAg in some patients who have a nearly pure infection with this variant. Nucleotide 1896 is engaged in the formation of a stem-loop structure, epsilon, which is required for the encapsidation of the pregenomic RNA into the nucleocapsid for completion of the viral replication cycle and may result in down regulation of HBV DNA and complete virion production.

Selection of the G1896A mutation is genotype-dependent and is more likely to occur when the nucleotide at the opposite position of the stem (nucleotide 1858) in the stem-loop structure of epsilon, the pregenome encapsidation signal, is T rather than C. This may explain why HBeAg-negative chronic hepatitis B and the common precore variant G1896A are less frequently encountered in the United States and Northern Europe where genotype A (which almost always has a C at nucleotide 1858) is more common. In contrast, in other parts of the world with a higher prevalence of precore mutants (such as Asia and the Mediterranean basin), HBV genotypes B, C, and D (which frequently have a T nucleotide at 1858) predominate. Highlighting how the genotype in a given patient and emergence of core and precore mutations can interact. The nationwide study in the United States found that precore variant was detected in 3, 46, 24, and 73 percent of patients with genotype A, B, C and D, respectively. The basal core promoter region (nucleotides 1742 to 1849) and the core upstream regulatory sequences (nucleotides 1643 to 1742) are located upstream of the precore region (nucleotides 1814 to 1901), and also have an important role in HBV replication and HBeAg production. Mutations in these regions down-regulate precore mRNA transcription and HBeAg synthesis. The most common core promoter variant involves a 2-nucleotide substitution: A to T at nucleotide 1762 and G to A at nucleotide 1764 (A1762T, G1764A). These changes were initially thought to be related to an "HBeAg-negative phenotype" but more recent studies showed that they can also be found

in HBeAg-positive patients, especially those with chronic hepatitis supporting the contention that HBV is viral continuum. The core promoter variant has been associated with more severe liver damage and HCC. The prevalence of the core promoter variant varies among different HBV genotypes. Several studies found that the core promoter variant is more often detected in patients with HBV genotypes that preclude the selection of the precore variant. Studies from Asia suggested that the dual core promoter variant (A1762T, G1764A) was more common in patients with genotype C than those with genotype B. The United States nationwide study reported that the prevalence of core promoter variant among patients with genotype A, B, C and D were 41, 27, 60, and 42 percent, respectively. When designing studies for HBV drug development, genotype and core and precore mutations need to be considered when allocating patients to different therapies.

IS CLEARANCE OF HBsAg AND cccDNA A REALISTIC TARGET?

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Chronic hepatitis B (CHB) is the world's most common serious liver infection and is a widespread global health issue that is under-diagnosed and under-treated. CHB will progress in about a third of untreated patients, causing liver damage, cirrhosis and hepatocellular carcinoma (HCC). Although hepatitis B virus (HBV) infection is not currently curable, it can be effectively controlled (defined by DNA undetectable and HBsAg clearance) using pegylated interferon-alpha (pegIFN-α) (17%) and/or nucleos(t)ide analog (NUC) antivirals (lamivudine, adefovir, entecavir, telbivudine or tenofovir) in sequence or combination or single therapy (10%) at 5 years. Determination of which therapy to use, and which combination includes careful consideration of duration of treatment, stopping rules, drug efficacy, use of quant(s)Ag, potential side effects, and potential for antiviral resistance with NUCs. PegIFN-α has the advantage of a fixed duration of therapy with the option of response-guided therapy based on HBsAg levels and can be an ideal option for some patients with high ALT and medium to low DNA noting that less than 20% of patients have a durable response defined by HBV DNA being undetectable and HBsAg clearance with combination therapy with Nucs at about 20% HBsAg loss at 2-3 years. Importantly, entecavir and tenofovir are able to maintain extended virologic control over several years, in compliant patients, resulting in histologic improvement over time and leading to a significantly reduced risk of cirrhosis, death, liver transplant and HCC are supported by moderate quality grade criteria. There is also some evidence that hepatic cccDNA levels can be decreased with NUC therapy. The success of long-term NUC treatment prompts new questions for future treatment strategies. Is it possible to permanently eliminate HBV infection with therapies that specifically target the cccDNA pathway or should we be aiming to achieve a "functional cure" using HBsAg elimination as an endpoint as the ultimate maker that we are changing outcomes? Many clinicians and scientist believe the answer is "yes", but the use of new technologies and anti-viral tools including iRNA, anti-sense, capsid inhibitors, and immune modulators including PDL1 antagonists, TLR7 agonists, tarmogen based vaccines, vaccines with adjuvants and extended preS1 epitopes as well as attacking the virus in the nucleus by changing histones in the cccDNA, and modifying acylation patterns that may allow lysis of the rcDNA as cccDNA unwinds. Ultimately we need to next clear sAg, then clear cccDNA, and finally clear all cells with HBV DNA integration and most importantly prevent integration from occurring in those patients with early phases of disease. The therapies need to target multiple sites in the HBV genome and /or the immune system. The major concept moving forward with HBV therapeutics is the use of new combination therapies, or new therapies in sequence. We need to further suppress virus, stop the regeneration of cccDNA and awaken the sleeping giant: the immune system that will ultimately have the final "word" in viral control and clearance. One-shot, single drug therapy is the "pie-in the-sky", realistically this next phase in the search for the grail of HBV therapeutics will require an integrated approach with pharma, clinicians and scientists. We now have the attention of the investment community that see HBV as the new "C". With all companies focusing on HBsAg loss at a minimum and cccDNA suppression or clearance as the world series. Will orange (HBV) really be the new black (HCV)?

HBV – WHAT WILL BE THE NEXT WAVE OF TREATMENTS?

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The host immune system plays an important role in chronic hepatitis B (CHB), both in viral clearance and hepatocellular damage. Advances in our understanding of the natural history of the disease have led to redefining the major phases of infection, with the “high replicative, low inflammatory” phase now replacing what was formerly termed the “immune tolerant” phase, and the “nonreplicative phase” replacing what was formerly termed the “inactive carrier” phase. As opposed to the earlier view that HBV establishes chronic infection by exploiting the immaturity of the neonate’s immune system, new findings on trained immunity show that the host is already somewhat “matured” following birth, and is actually very capable of responding immunologically, potentially altering future hepatitis B treatment strategies. While existing therapies are effective in reducing viral load and necroinflammation, often restoring the patient to near-normal health, they do not lead to a cure except in very rare cases, and viremia rebounds after cessation of treatment in many patients. Researchers are now challenged to devise therapies that will eliminate infection, in particular to eliminate the persistence of viral cccDNA in the nuclei of hepatocytes. In the context of chronic hepatitis B, new definitions of ‘cure’ are emerging, such as ‘functional’ and ‘virological’ cure, defined by stable off-therapy suppression of viremia and antigenemia, and the normalization of serum ALT and other liver related laboratory tests. Continued advances in the understanding of the complex biology of chronic hepatitis B have resulted in the development of new, experimental therapies targeting viral and host factors and pathways previously not accessible to therapy, which may lead to virological cures in the near term and functional cures upon long term follow-up and true cures in the more distant future.

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HEPATITIS B VIRUS INFECTION IN AMERICA

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Population-based surveys have estimated the prevalence of HBsAg seropositivity decreased from 0,38% in 1988-1994 to 0,27% in 1999-2006. Kowdley et al. estimated that 3,5% or 1,23-1,42 million of all foreign-born persons in the US have chronic hepatitis B. In the recent few decades, more than 60% of new immigrants to the US come from countries of high hepatitis B endemicity. In a report based on 2008 data, the age-adjusted mortality rate from HBV infection was 0,56 death per 100 000 persons per year (95% CI, 0,54 to 0,59), which has been gradually decreasing. In an analysis of liver transplant waiting list, the incidence of waitlist registration for end stage liver disease from HBV cirrhosis decreased significantly coincident with the introduction of effective oral antiviral agents. However, continue emphasis on screening, early diagnosis and treatment is needed to continue the trend.

HEPATITIS B AND HCC

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HBV infection is a major cause of HCC globally. Natural history studies in untreated patients have reported annual HCC rates of 0,3%–0,6% in noncirrhotic hepatitis B patients, and of 2,2%–3,7% in compensated cirrhotics, depending on geographic location. Several mechanisms may be involved in the pathogenesis of HBV-related HCC: (1) HBV DNA integrated into the host genome may down-regulate tumor suppressor genes, (2) The HBx protein modulates the activity of a wide range of cellular factors, thereby altering cell proliferation, apoptosis, and DNA damage response, and (3) Fibrosis and cirrhosis, resulting from persistent liver inflammation associated with chronic HBV infection, are well-established HCC risk factors, as they trigger a complex cascade of oxidative stress, hypoxia, necrosis, regeneration, and angiogenesis.

Epidemiological studies identify sustained viral replication and liver injury as key risk factors. Landmark studies have demonstrated that the degree of viral replication, as measured by serum HBV DNA concentrations, correlates directly with the future risk of HCC. Specific variations in the HBV DNA sequence may also affect the risk of HCC. In addition to these viral factors, older age, male gender, heavy alcohol consumption, exposure to carcinogens such as aflatoxin B, and a family history of HCC are established risk factors of HBV-related HCC. Other emerging risk factors include the metabolic syndrome associated with obesity and diabetes mellitus, whereas smoking remains controversial.

Antiviral treatment using agents approved for treatment of hepatitis B including interferon-alpha and nucleos(t)ide analogues (NAs) has been associated with reduced incidence of HCC risk (primary prevention) and with reduced risk of recurrence following resection (secondary prevention). Data in support of a causal association between antiviral treatment and HCC risk are stronger in patients with advanced fibrosis and cirrhosis and include a randomized clinical trial and multiple observational studies. Emerging data, however, also indicate that antiviral therapy confers beneficial effects on HCC in non-cirrhotics with the magnitude of risk reduction comparable to that observed in cirrhotic patients.

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CAN CIRRHOSIS BE REALLY REVERSED?

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The histological end point of all chronic liver diseases is cirrhosis which is associated with significant morbidity and mortality. Cirrhosis is characterized by annular fibrosis surrounding hepatocyte nodules. It is accompanied by vascular remodeling and regeneration with important functional and hemodynamic consequences that include development of portal hypertension and eventually decompensation and death. The dogma prevailing in the literature until recently was that fibrosis, and even cirrhosis, was irreversible and the best hope therapeutically would be to halt progression. Subsequent mounting evidence both in animal models and in humans have provided further support that liver fibrosis and even cirrhosis can regress or even completely revert to normal architecture on cessation of the cause of liver injury. Indeed, isolated reports have initially been published with biopsy-proven regression of cirrhosis of various origins. There are now well-documented studies analyzing large cohorts of patients with hepatitis C virus (HCV) or hepatitis B virus (HBV) cirrhosis effectively treated with antiviral regimens. In several of these studies, patients have been followed with serial liver biopsies performed with a sufficient time interval with as much as 75% of biopsies in hepatitis B or C having a decreased in their stage of fibrosis after viral eradications and whatever the initial score of fibrosis. Cirrhosis may also regress in a lower percentage although the return to a fully normal liver is rarely observed and difficult to prove. Interestingly, few studies have shown that histological regression of cirrhosis is clinically relevant since patients with cirrhosis regression have less liver-related events (decompensation, hemorrhage, transplantation) in their follow-up than those that did not regressed. Furthermore, in addition to a decrease of the amount of extracellular matrix, regression of fibrosis/cirrhosis is associated to a restauration of the lobular architecture and parenchymal specialized functions as shown by immunohistochemistry, which is an additional proof of reversal to a normal lobular architecture.

However, it is obvious that not all cirrhosis may revert, even after definite viral eradication or suppression. For fibrosis/cirrhosis regression to occur, several mechanisms need to be present. At first, the process of chronic inflammation must be stopped. Such is the case after viral eradication in viral hepatitis. The stopping of the chronic inflammatory reaction is a necessary event for liver regeneration to occur. However, even if this condition is reached, liver cell regeneration may not be possible such as in atrophic cirrhosis where the potential for hepatocyte to duplicate is exhausted due to major telomere attrition. In this case, reversion of cirrhosis is unlikely.

The vanishing of fibrous septa is another important issue. It is linked to enzymatic digestion of extracellular matrix that will allow the progressive return to a normal architecture. The activated hepatic stellate cells will either reverse to a quiescent phenotype or cells will dye by apoptosis. However, a high degree of collagen cross-linking or the presence of elastic fibers in abundance within extracellular matrix may limit fibrosis resorption.

Finally, cirrhosis reversion is associated to resurgence of portal tracts and restoration of a lobular vascularisation with a hepatic vein outflow. These portal tracts which usually emerge after fibrous septa resorption may be inefficient because of portal vein thrombosis which may impair the reshaping of portal tract and the regression of cirrhosis.

Finally, one major issue pertaining to the reversion of cirrhosis is the reliability of methods to measure changes in fibrosis longitudinally. Although assessment of liver fibrosis with liver biopsy remains the current reference standard for quantifying fibrosis, it is, as such, an imperfect gold standard. Another issue regarding evaluation of regression of cirrhosis pertains to most common fibrosis scoring systems have been developed before the idea of fibrosis regression gained importance and are not equipped for assessing this aspect, in which peculiar histologic features may be observed. The Laennec scoring system is a recent histological scoring system of cirrhosis which is divided in 3 substages (4A, 4B, 4C) according to thickness of fibrous septa and nodule size. Stage 4C with thick septa and small nodules is probably not accessible to regression while the other stages have more potential to regress. Nevertheless and based on the current limitation of liver biopsy, a key requirement for future diagnostics of cirrhosis regression assessment is the development of reliable and accurate noninvasive biomarkers of liver fibrosis. Although these approaches have progressively gained acceptance as an adjunct for diagnosing cirrhosis, these have not been fully validated for assessing the dynamics of liver fibrosis, especially longitudinal evaluation of fibrosis regression.

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ACUTE-ON CHRONIC LIVER FAILURE WITH HBV

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A proportion of patients hospitalized for an acute complication of cirrhosis (i.e., recent onset ascites, variceal hemorrhage, hepatic encephalopathy, bacterial infection, or any combination of these) are at high risk of short-term death. The term Acute-on-Chronic Liver Failure (ACLF) is used to characterize these patients. Until recently there was no evidence-based definition of ACLF. In 2013 a definition has been proposed based on results of a large prospective observational European study, called "European Association for the Study of the Liver (EASL)-Chronic Liver Failure (CLIF) Consortium Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC)" study. Results of this study led to propose new concepts about ACLF. First, ACLF is a syndrome that is distinct from mere decompensated cirrhosis. It was also shown that ACLF is a dynamic syndrome which can improve or conversely worsen. Patients who worsen die rapidly from multiorgan failures. The CANONIC study also found that identifiable precipitating events (e.g., bacterial infection, active alcoholism) are present in only 50% of cases of ACLF indicating that these events are dispensable for defining ACLF. In addition precipitating events may be initiators of ACLF but do not drive the outcome. An important concept derived from the CANONIC study is that ACLF is associated with systemic inflammation even in patients who do not have identifiable precipitating events. Finally it was found that ACLF may develop in patients without prior episodes of decompensation or in those with recent decompensation (<3 months). Moreover these patients with "early" ACLF were more severe than patients who developed ACLF after a long of history of decompensated cirrhosis. It is important to note that the CANONIC study was performed in Europe. Patients enrolled had cirrhosis due to excessive alcohol consumption or to HCV infection. In the CANONIC study, there were no patients with HBV-related cirrhosis. HBV reactivation is a very common cause of ACLF in Asia. Therefore diagnostic criteria for ACLF established in Europe should be validated in Asian patients.

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GLOBAL CONTROL OF HEPATITIS B WITH VACCIN

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Despite the availability of safe and effective hepatitis B virus (HBV) vaccines for over 30 years, strategies targeting risk groups failed to sufficiently control hepatitis B at population level; this is mainly due to difficulties in risk identification and in programme implementation. Hence, the global burden of disease of HBV still is substantial.

The World Health Organization recommends universal vaccination against hepatitis B to ultimately eliminate HBV; this recommendation had been increasingly followed in more than 190 countries by the end of 2013. However, hepatitis B immunization is currently becoming endangered of losing its place on the agendas of governments, agencies and international organizations, mainly due to the increasing success of these immunization programmes and to the interest in newer vaccines and the related programmes.

The benefits of universal HBV vaccination for newborns and infants are: higher impact on chronic carrier rate and transmission, established potential of high vaccine coverage in this age group, opportunities to combine HBV vaccination with existing universal vaccination programmes for newborns and infants and impact on perinatal transmission, if vaccination is started shortly after birth. Moreover, the safety, immunogenicity and long-term efficacy of newborn and infant HBV vaccination have been proven extensively.

Even if newborn and infant HBV vaccination programmes will have a delayed impact on sexual transmission of HBV, it should be considered the strategy with a tremendous effect, capable of providing important and sustained impact on global HBV incidence.

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WHO POLICY ON VIRAL HEPATITIS B

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Worldwide, there are an estimated 240–350 million people chronically infected with viral hepatitis B, particularly in low- and middle-income countries, and an estimated 650 000 people die of chronic hepatitis B complications each year. Hepatitis B mortality in the WHO European Region surpasses that of all other vaccine preventable diseases combined.

WHO response to viral hepatitis B has been increasing since the adoption of World Health Assembly on Viral Hepatitis in 2010 and 2014. It includes: raising awareness; formulating evidence-based policy and data for action; promoting prevention through vaccination, safe injection practices and blood safety; and promoting access to monitoring and screening, care and treatment for hepatitis B.

The first Global Health Sector Strategy on Viral Hepatitis 2016–2021 is currently being developed and will be considered for adoption by the World Health Assembly in 2016. It will identify priorities and set global targets for a coordinated global response within the vision of elimination of viral hepatitis as a public health issue of concern.

In March 2015, WHO launched its first *"Guidelines for the prevention, care and treatment of persons living with chronic hepatitis B infection"*. The recommendations:

- promote the use of simple, non-invasive diagnostic tests to assess the stage of liver disease and eligibility for treatment;
- prioritize treatment for those with most advanced liver disease and at greatest risk of mortality; and
- recommend the preferred use of the nucleoside analogues with a high barrier to drug resistance for first- and second-line treatment.

The WHO Regional Office for Europe is providing technical support to Member States in national planning and supporting regional partnerships. The European Vaccine Action Plan 2015-2020, endorsed by the Regional Committee in 2014, will be complemented by a document defining targets and proposing activities to achieve the goal of strengthening hepatitis B control through immunisation.

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OCCULT HEPATITIS B

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In essence Occult Hepatitis B (OBI) is the persistence of hepatitis B at very low levels, based on the presence of ccc HBV DNA in the nucleus of HBV exposed patients. The remnants of the viral genome remain replication competent, but the replication activity is highly suppressed due to various mutations and deletions in the genome.

The most concise definition of OBI is “the presence of the HBV genome in the liver tissue of patients, with detectable or undetectable serum HBV DNA, who test negative for HBsAg”. In practical terms however, due to non-availability of liver HBV DNA, it is the presence of serum HBV DNA in a patient who is negative for HBsAg. Anti-HBs and anti-HBc could be present (sero-positive OBI, 80% of cases) or absent (sero-negative OBI, 20% of cases). In either case, serum HBV DNA levels are generally very low (<200 IU/ml) and therefore a very sensitive (<10 IU/ml) PCR test is required to make the diagnosis. However, levels of up to 10^3 copies/ml can be found in some patients.

Although patients from countries that are highly endemic for HBV are more likely to develop OBI, this is a global issue and a significant number of both HCV and non-HCV chronic patients from Europe are also reported to have OBI. The prevalence of OBI is reported as highest in patients with chronic HCV or HIV infections, hepatocellular carcinoma (HCC) or cryptogenic cirrhosis.

There are two important aspects of the clinical significance of OBI: the risk of transmission and aggravation of underlying chronic liver disease. The only occasion, although very rare, that HBV transmission can happen through a blood transfusion, or at liver transplantation, in this age is when the donor has OBI. Moreover, there are some clinical situations where there is strong evidence for the adverse contribution of OBI, in particular in the development of HCC and cryptogenic cirrhosis. The effect of OBI on the natural history and treatment outcomes of HCV infection are less clear. However, reactivation of OBI to a full blown flare of HBV infection is clearly documented in patients with disease or treatment related immune-suppression.

OBI is therefore a real and interesting clinical entity that physicians practicing in high prevalence HBV countries should always be on the lookout for. Although precise treatment of this condition may not be possible currently, until we can eliminate cc DNA, transmission of HBV infection and flares of liver disease can be effectively prevented in given clinical situations.

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MANAGEMENT OF CHB PATIENTS WITH DECOMPENSATED CIRRHOSIS

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Around 25-40% of 350−400 million chronic hepatitis B (CHB) patients develop various life-threatening conditions and die of decompensation, cirrhosis or hepatocellular carcinoma (HCC). For patients with decompensated cirrhosis (DC), since interferon is contraindicated, antiviral agents, nucleos(t)ide analogues (NAs), are now considered as the most important medical management, in addition to liver transplantation.

The major goal of NAs therapy for CHB is to improve survival and quality of life by preventing progression of the disease to cirrhosis, DC, end-stage liver disease, HCC and death by suppression of the replication of HBV DNA and reduction in necro-inflammatory activity in liver. For patients with DC, they should be treated in specialized liver units for preparation of liver transplantation. HBV DNA level is a primary prognostic marker and risk factor for patients with hepatitis B DC. Nevertheless, NAs therapy is indicated irrespective of HBV DNA level and ALT level and should be initiated immediately in order to prevent hepatitis reactivation (ALT flares). NAs-treated patients may have improved Child-Turcotte-Pugh (CTP) and MELD scores significantly. Life-long treatment is particularly recommended in patients with DC who should be treated immediately, get clinical improvement and even avoid transplantation. Similar to the patients with compensated cirrhosis, long-term monitoring and surveillance for HCC is mandatory under effective NAs therapy.

In the setting of liver transplantation for HBsAg positive patients with HBV related end-stage liver disease, the addition of oral NAs will suppress the circulating viral load before transplantation with preventing early recurrence of HBV in the graft. In managing CHB patients with DC, renal function deterioration is one of the most important concerns in patients with DC. The concomitant use of calcineurin inhibitors in liver transplantation and long-term use of the NAs make it critical to consider the possible nephrotoxicity. In addition to monitoring renal function carefully, the impact of NAs on the estimated glomerular filtration rate has been discussed recently.

THE PREVALENCE OF HBV AND HCV AMONG TEENAGERS IN HBV AND HCV-ENDEMIC TOWNSHIPS IN SOUTHERN TAIWAN

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Background

Taiwan is an endemic area of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection with HCV infection reported previously not only in adults but in adolescents. This study aimed to assess the prevalence of HBV and HCV infection among teenagers in these townships.

Methods

A cross-sectional survey was conducted with 292 teenagers with documented HB vaccination records enrolled in the junior higher school located in Tzukuan Districts (TD) and aboriginal (Tauyuan and Moulin) Districts (AD) [172 teenagers (83 males) from TD and 120 teenagers (50 males) from AD born between 1999 and 2002]. They all received tests for serum liver enzyme, hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs) and antibodies to HCV (anti-HCV). Subjects were tested for serum HBeAge and HBV DNA if positive for HBsAg and tested for HCV RNA if positive for anti-HCV by real-time PCR assay.

Results

The overall seroprevalences of HBsAg, anti-HBs, and anti-HCV of 292 students were 0,68% (2, one female), 30,1% (88), and 1,37% (4, 3 females) respectively. The seroprevalences of HBsAg, anti-HBs, and anti-HCV in TD (172) and AD (120) students were 0%, 29,1% (50), and 0,58% (1) and 1,67% (2), 31,7% (38), and 2,5% (3) respectively. The frequency of abnormal ALT (49-258 IU/L) was 5,1%. Both of the 2 HBsAg carriers were negative for HBeAg and have negative HBV DNA (<20 IU/ML) and one has elevated alanine aminotransferase (ALT) level (1,25 times upper limit of normal). All the 4 students with positive anti-HCV have negative HCV RNA (<30 IU/mL) and normal ALT level.

Discussion

A low prevalence of HBsAg was noted in the HBV and HCV-endemic townships and only 30% of the non-carriers have positive anti-HBs. The prevalences of anti-HCV are lower than previous reports in TD, but high in AD students. Nevertheless, all subjects with positive HBsAg or anti-HCV are non-viremic. We concluded that infection of HBV and HCV happen in the students in HBV and HCV-endemic townships but viremia and active disease are rare.

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NUCLEOSIDE/NUCLEOTIDE AS A FIRST LINE TREATMENT FOR CHRONIC HEPATITIS B VIRUS

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HBV is a double-stranded DNA Hepadnaviridae virus. About 400 million people have chronic HBV around the world. Chronic HBV infection is a non-static process. The natural history of chronic HBV infection can be schematically divided into five phases, which are not necessarily sequential. Therapy must ensure a degree of virological suppression that lead to biochemical remission, histological improvement and prevention of complications. The current available treatment of CHBV include pegylated interferon-α, and oral nucleoside/nucleotide analogues (NAs) including lamivudine, adefovir, telbivudine, entecavir and tenofovir. NAs work by inhibiting hepatitis B virus (HBV) DNA polymerase activity and thus suppress HBV replication. Oral NAs have become the mainstay of CHB treatment, mainly due to their profound viral suppressive effects and the ease of single daily dosing with lack of significant side effects. One major drawback of NA therapy is the development of drug resistance. The usual markers of successful therapy are the loss of HBeAg, seroconversion to anti-HBe antibodies, and reduction of the circulating viral load. The loss of HBsAg is achieved infrequently in 2 to 5 percent of patients with current regimens. Future studies are needed to develop drug regimens that are even more effective in achieving clinical endpoints and to clarify the role of serum markers in the evaluation of prediction of therapeutic responses and treatment individualization.

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TREATMENT OF PATIENTS WITH CHB WITH PEGYLATED INTERFERON: CLINICAL SIGNIFICANCE OF HBV DNA AND HBsAg QUANTITATIVE TESTING

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The complete, sustained clearance of HBV among chronically infected patients, and the hope of eradicating HBV from our planet should be our dream and mission in the coming few years. In spite of long years of experience, long list of medications, and treatment protocols, the optimal treatment strategy for HBV is not yet clear and the accurate prediction of sustained virological response (SVR) to treatment is still a crucial problem needing profound investigation.

Antiviral therapy using nucleoside/nucleotide analogs such as lamivudine, entecavir, adefovir, or tenofovir is the mainstay of chronic hepatitis B treatment. While antiviral drugs can effectively suppress hepatitis B virus (HBV) replication for long-term during treatment, they usually do not lead to a cure, as indicated by HBsAg loss and HBs antibody seroconversion.

Studies to date indicate that starting treatment with nucleoside/nucleotide analogs plus pegylated interferon, adding interferon to suppressive nucleoside/nucleotide therapy, or switching from nucleosides/nucleotides to tenofovir may increase the likelihood of HBsAg loss. HBsAg clearance is considered to be the closest event to cure of HBV infection. Those who achieve HBsAg clearance have a more favourable prognosis regarding survival, decompensation, fibrosis and HCC. Definition of HBsAg loss: HbsAg loss on two analyses 6 months apart and persisting to the last visit. The cummulative HBsAg clearance rate is 8,1% at 10 years and 24,9% at 20 years and 44,7 % at 25 years follow-up. Viral and host factors associated with HBsAg loss are: older age, normal ALT, the presence of cirrhosis or fatty live, negative status for HBeAg or HBV DNA, genotypes A and B, adr HBsAg serotype. ***PEG-INF in HBeAg-positive****:* HBsAg loss is reached in 3-7% of patients. Viral response is defined as: HBeAg loss and HBV DNA, <10000 copies/ml at 6 months post treatment, is achieved in 25% of patients. Decline of HBsAg at weeks 12 and 24 during ttt can be used as a predictor of SVR. Low HBsAg levels or greater HBsAg decline earlier during treatment is associated with higher HBeAg seroconversion rates and HBV DNA suppression 6 months post treatment. **PEG-INF in HBeAg-negative:** HBsAg loss is 10%/year and is achieved in 44% in patients who maintained sustained HBV DNA suppression to undetectable levels 3 years after treatment. An HBsAg level <10 IU/ml at week 48 and on treatment decline of >1log10 IU/ml are significantly associated with sustained HBsAg clearance 3 years after treatment. The like hood of HBsAg loss in patients who achieve HBsAg levels <10 IU/ml at the end of treatment is 53% at 3 years. Viral response to PEG-INF therapy, defined as HBV DNA <2000 IU/ml and normal ALT 24 weeks post treatment is achieved in 25% of patients. A cut-off of 1 log 10 IU/ml decrease in serum HBsAg at week 24 of therapy has a 97% NPV of virological response. This criterion would allow physician to stop PEG-INF and switch to another antiviral therapy. As the structural protein forming the envelop of the mature virion, serum HBsAg is reported to reflect the level of intrahepatic HBV (cccDNA), the template of HBV replication. Because serum HBsAg seroclearance reflects nearly completely immunological control of HBV infection for most patients, HBsAg loss has become the ideal endpoint of therapy.

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DEVELOPMENT OF NOVEL THERAPEUTIC HEPATITIS B VACCINE

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Background

Hepatitis B virus (HBV) infections remain a major public health problem increasing the risk of liver diseases such as cirrhosis and hepatocellular carcinoma.

Current antiviral therapies fail to control viral replication in the long term in most patients and HBV persistence has been associated with a defect in the development of HBV-specific cellular immunity.

HBsAg-based vaccines, including prophylactic vaccines and formulations with novel adjuvants have been used as therapeutic approaches with unclear or negative results. The development of therapeutic vaccines against CHB requires proofing the capacity of the formulation to subvert a tolerated immune response.

Methods

Antigens: HBcAg protein was produced in E. coli and the HBsAg in Pichia pastoris.

Animals: Balb/c mice were obtained from CEMPALAB, Cuba.

Study population: Subjects were adults volunteers recruited into the study after obtaining written informed consent.

Serology: The immunological responses were evaluated using ELISAs, ELISPOT-IFN-g assay.

Virological response: Was measured by the HBV serum DNA quantification by real time PCR.

Results

The new generation vaccine candidate include the use of a novel immunization route (intranasal) and a novel antigen (HBcAg) in a combined formulation with HBsAg. The evaluation in mouse support the rationality of the therapeutic vaccine candidate targeting the stimulation of CD4(+) and CD8(+) T-cell responses and the induction of pro-inflammatory cytokines capable of controlling viral replication. The vaccine proved to be immunogenic in mouse models and then in phase I, II and III, randomized, double blinded and controlled clinical trials developed in healthy volunteers and CHB patients.

Summary

The use of the HBsAg and HBcAg produced as virus like particles, the intranasal immunization route and the incorporation of the HBcAg to the vaccine formulation mark the different with previous therapeutic immunization approaches and support the capacity of this novel vaccine candidate to disrupt tolerance and induce sustainable virological response.

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EPIDEMIOLOGY OF HBV INFECTION IN RUSSIA

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The Russian Federation belongs to the regions with intermediate prevalence of hepatitis B, where HBsAg is detected, on average, in 2% of adult population. The incidence of acute hepatitis B (AHB) has sharply decreased over the last 15 years from 39,9 in 2000 to 1,3 in 2014 per 100,000 population. The most pronounced decrease was observed among children under 17 years old. Only 25 cases of AHB have been reported in this age group in 2014, which amounted to 0,09 per 100,000 children. This favorable dynamics of the disease obviously is a result of broad vaccination programs, which have begun in late 90s. By 2014 more than 84 million people from 0 to 55 years old completed full course of hepatitis B vaccination. However, chronic HBV infection remains a significant public health problem in Russia. The incidence of inactive HBV carriage since year 2000 decreased from 95,7 to 16,0 per 100,000 population. Meanwhile decrease in incidence of chronic hepatitis B was much slower – from 14,2 to 11,3 during these years. In absolute terms, in 2014 more than 39,000 new cases of chronic HBV infection were reported. HBV is the second most important cause of liver cirrhosis after alcoholic liver disease in Russia. Most of chronically infected cases (84%) were found to be HBeAg negative. Among 3609 HBV strains 85% belonged to genotype D, 10,7% – to genotype A and 3,2% – to genotype C. All other genotypes were found in 1,1% of cases. HBV genotype distribution varied significantly among different regions. Genotype D was represented by subgenotypes D1, D2 and D3. A clear trend of increasing of subgenotype D3 proportion from the West to the East of Russia was found. Genotypes A and C were represented only by subgenotypes A2 and C1 respectively. According to serotype classification genotype D strains belonged to ayw2 or ayw3, genotype A to adw2 and genotype C to adr serotype. Hepatitis D coinfection rate was studied in some regions of Russia and could reach up to 40%. Among 152 HDV strains 76% belonged to genotype I and 24% – to genotype II. Genotype II strains were found almost exclusively in one region of Russia – Republic of Sakha (Yakutia).

In conclusion: Incidence of AHB dramatically decreased during the last 15 years. Chronic HBV infection is one of the major public health concerns and its incidences are persistently high. HBV genotypes and serotypes distribution has distinct characteristics in Russia and is unequal throughout the country. High rate of HDV coinfection in some regions of Russia may play an important role in liver-related morbidity.

MONITORING AND MANAGEMENT OF NUCLEOS(T)IDE ANALOGUE FAILURES

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Long-term treatment of chronic hepatitis B (CHB) with a nucleoside or nucleotide analogues (NAs) can lead to the development of drug resistance. The resistance is defined as a reduced susceptibility of a virus to the inhibitory effect of a drug due to the selection of viral variants possessing adaptive mutations. The risk of the resistance depends on a number of factors related to the virus, the patient, the disease or the drug characteristics. The major factors are potency and genetic barrier to resistance of the NA, baseline HBV DNA level, prior NAs treatment experience, duration of therapy and patient compliance. NAs with low genetic barrier to resistance or moderate potency (lamivudine – LMV, telbivudine – LdT, and adefovir – ADV) are no longer recommended as a first line therapy. Treatment of naïve CHB patients with entecavir (ETV) or tenofovir (TDF), NAs with high potency and high genetic barrier, related to very low chance of drug resistance. Patients under NAs therapy should be monitored for virological response by measuring of viral load every 3 to 6 month for low and high genetic barrier drugs respectively. The failure to achieve a 1 log decline in HBV DNA level at week 12 of treatment defines primary non-response. Detectable HBV DNA at week 24 for LMV and LdT or at week 48 for ETV and TDF is considered to be a partial response. At any time during treatment an increase in viral load by 1 log or more compared to the lowest value achieved earlier corresponds to a virological breakthrough. Virological breakthrough should be confirmed by the second viral load test approximately 1 month apart. Any type of suboptimal response in compliant patient may be related to the selection of viral variants carrying resistance mutations. Two types of mutations have been identified: primary, which are responsible for the drug resistance itself and secondary or compensatory, which restore the virus replication fitness. NAs resistance mutations are located in the reverse transcriptase domain of the polymerase gene. Each NA is characterized by a particular pattern of resistance mutations; however a cross-resistance phenomenon is well described. In case of suboptimal response to NA therapy testing for resistance mutations is recommended. Treatment optimization, preferably add-on strategy, should be based on the cross-resistance profile. Typical resistant variants of the virus and their cross-resistance profiles are shown in the table.

Table

Viral variant	LMV/LdT-resistant (L180M±M204V/I)	ADV-resistant (N236T)	ADV-resistant (A181T/V)	ETV-resistant
Sensitivity reduced	ETV, LdT	TDF	TDF, LMV	LMV, LdT
Sensitive	ADV, TDF	ETV, LMV, LdT	ETV	ADV, TDF

Close long-term monitoring of NAs treatment efficacy and optimization of treatment in timely manner according to cross-resistance profile is required to avoid the emergence of multidrug-resistance strains.

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A PROOF-OF-CONCEPT PHASE 2A CLINICAL TRIAL WITH MYRCLUDEX B

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Introduction

Current therapies for chronic hepatitis B rarely induce serological cure. Strategies targeting different steps of the HBV life-cycle may accomplish higher cure rates. Moreover, no effective treatment for the majority of hepatitis delta patients is currently available. Myrcludex B is an HBV-derived lipopeptide acting as a first-in-class HBV/HDV entry inhibitor by inactivation HBV receptor NTCP. We here present initial findings of the very first clinical trials of Myrcludex B in chronic hepatitis B and delta.

Aim: To evaluate safety and tolerability, as well as antiviral efficacy of Myrcludex B.

Methodology

Cohort A: 40 chronically HBV infected, HBeAg negative patients (all HBV DNA >2000 IU/ml median HBV DNA 4,7 $\log_{10}$ IU/ml; no cirrhosis) were treated for 12 weeks with once daily sc 0,5 mg, 1 mg, 2 mg, 5 mg or 10mg Myrcludex B for 12 weeks (8 patients per dose). Treatment was extended to 24 weeks in patients receiving 10mg. Cohort B: 24 patients with hepatitis delta (compensated liver disease; 12,5% cirrhosis) scheduled for 48 weeks of pegylated interferon alpha (PEG-IFNα) therapy. 8 hepatitis delta patients are currently receiving pre-treatment with 2mg Myrcludex B alone for 24 weeks (B1); Myrcludex B was added to (PEG-IFNα) for the first 24 weeks to another 8 patients (B2) while 8 patients are treated with PEG-IFNα alone (B3).

Results

Myrcludex B was very well tolerated, injection side dermatitis occurred in 3 patients receiving 10 mg of Myrcludex B, regressed on treatment. A psoriasis exacerbation occurred in one HDV patient (B2) leading to discontinuation. >1 $\log_{10}$ HBV DNA decline at week 12 was observed in 6/8 (75%) patients receiving 10 mg Myrcludex B while this occurred less often in the remaining dose groups (7/40; 17%). ALT normalized in 22/40 (55%) patients, median ALT values declined from 76 U/l before therapy to 36 U/l at week 12 ($p<0,001$). No significant changes in HBsAg levels occurred. In hepatitis delta, 6/7 and 7/7 of patients with data available experienced >1 $\log_{10}$ HDV RNA decline at week 24 during Myrcludex B monotherapy (B1) or combination therapy (B2) while this response was observed in 7/7 of B3 patients at week 12. HDV RNA became negative in 2 and 5 patients of groups B1 and B2. ALT values declined at week 24 in 6/7 (B1), 4/7 (B2) and 3/7 (B3, week 12) patients. One patient (B2) experienced 1 $\log_{10}$ HBsAg decline at week 24.

Conclusion

Myrcludex B is safe and well tolerated in HBsAg positive patients with or without HDV coinfection. HBV entry inhibition seems to be associated HBV DNA and HDV RNA declines and improvement of biochemical disease activity.

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THE ROLE OF NON-INVASIVE MARKERS AND IMAGING IN STAGING IN CHRONIC HBV INFECTION

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The role of liver biopsy in detection and staging the fibrosis of chronic hepatitis B is well established. The usefulness of noninvasive evaluation for predicting liver fibrosis remains to be fully evaluated in chronic hepatitis B. Hepatic fibrosis, regardless of the underlying etiology, is a consequence of the accumulation of extracellular matrix components in the liver. This process is caused by persistent liver damage and consequent wound healing reaction and can progress to cirrhosis, portal hypertension, and hepatocellular carcinoma (HCC), leading to increased morbidity and mortality. An accurate diagnosis of liver fibrosis is thus essential for the management of chronic liver diseases. Though liver biopsy is the “gold standard for staging of fibrosis in chronic hepatitis B, however, sampling error, can lead to underestimation of the degree of liver fibrosis. On the contrary, the noninvasive markers are suitable for repeated evaluations, clinical staging, predicting complications of cirrhosis and treatment response monitoring. We reviewed in one of our recent studies, the correlation between liver elasticity measured by Transient Elastography (Fibroscan) and liver fibrosis assessed by histology in patients with chronic hepatitis B, which rendered TE (Fibroscan) as an accurate and reliable non-invasive marker for significant hepatic fibrosis.

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MANAGEMENT OF CHB IN CHILDREN

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In APASL countries, transmission of HBV is predominantly from mother to child. Most children infected at birth are immune-tolerant and spontaneous seroconversion is rare, occurring in 2% per year in children below 3 years and in 4-5% children older than 3 years of age. 32 per 100,000 person-year children with chronic HBV infection develop HCC during childhood. Treatment decision is based on elevated ALT, HBeAg positivity, high HBV DNA levels, assessment of severity of liver disease, family history of HCC and co-existing liver diseases. In presence of high ALT, assessment of HBV DNA is important, as high HBV DNA warrants anti-viral treatment. As response to antivirals in children is partial, histologic assessment of degree of inflammation and stage of fibrosis is recommended before considering treatment. Response to both interferon (IFN)-α and nucleos(t)ide analogues (NA) is more likely, when at least moderate hepatic necroinflammation and/or fibrosis is present. Family history of HCC warrants treatment in children even with mild histological changes, as they are at increased risk of developing HCC. Non-invasive methods to assess hepatic fibrosis like FibroScan, may prove useful to avoid liver biopsy, especially during follow-ups. IFN-α, lamivudine, adefovir, entecavir and tenofovir can be used in children. IFN-α can be given to children older than 12 months, lamivudine starting at 3 years, adefovir and tenofovir in children aged 12 years and older and entecavir starting from 16 years. IFN-α results in virological response in 26% children, however, long-term follow-up studies suggest that untreated children may have similar rates of HBeAg seroconversion. Compared to NA, IFN-α has the advantages of lasting response and no risk of mutations. Major disadvantages include high cost, frequent side-effects and the need for thrice-weekly injections. The later can however be reduced by pegylated IFN-α. Entecavir is more effective than lamivudine and adefovir. Finite-duration IFN-α therapy remains the treatment strategy of choice for children. Ttenofovir and entecavir, which have high genotypic barrier, are the first-line NAs for treatment of children. The principles of management of treatment failure and antiviral resistance remain the same in children as for adults.

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NATURAL HISTORY OF CHRONIC HEPATITIS B AND PREDICTORS OF DISEASE PROGRESSION (VIRAL AND HOST)

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It is estimated that 240 million people are chronically infected with hepatitis B (defined as hepatitis B surface antigen positive for at least 6 months) by the WHO. And more than 780 000 people die every year due to complications of hepatitis B, including cirrhosis and liver cancer. Hepatitis B prevalence is highest in sub-Saharan Africa and East Asia, where between 5–10% of the adult population is chronically infected. CHB is usually acquired perinatally or in childhood in Asia and Africa. Chronic hepatitis B has a variable and dynamic course. The host immune system plays an important role in chronic hepatitis B (CHB), both in viral clearance and hepatocellular damage.

Early during Hepatitis B infection (positive HBsAg), HBeAg and HBV DNA are usually present in high titers, with mild to moderate elevations in serum aminotransferase levels. This is known as the “immune tolerance phase”. However, individuals infected perinatally goes through a prolonged period with normal or low serum alanine aminotransferase (ALT) levels, positive sera for hepatitis B e antigen (HBeAg), high serum HBV DNA levels, yet with a minimal or no liver inflammation and lower production of IL-10 and pro-inflammatory cytokines (IL-6, IL-8 and TNF-a) and no or slow progression of fibrosis Infected persons may remain in this “high replicative, low inflammatory” phase (previously termed “immune tolerant”) for many years without disease progression. Despite this seemingly silent disease, it is during this period that DNA integration into the liver cell genome probably occurs, with its subsequent effect on oncogenicity, although such integration is not required for productive HBV replication. In this phase the immune system is “trained” and “conditioned” to be activated by changes or maturation of subsets of the immune response.

A phase of “immune clearance”, characterized phase of HBeAg positive CHB, shown initially by initially intermittent or persistent elevation to normal ALT (<30 IU/mL for men and <19 IU/mL for women) of ALT levels and widely fluctuating HBV DNA levels, although not as high as in the immune tolerant phase, then decreasing from high to low or undetectable DNA. The ALT fluctuations represent acute changes in inflammation or intermittent episodes of hepatitis, eventually leading to loss of HBeAg in wild type infection. This is a period of immune mediated liver damage as evidenced by necroinflammation on liver biopsy and varying degrees of fibrosis. A typical feature of this phase is the occurrence of spontaneous flares which represent an intensification of the immune response to HBV. Although the cause remains obscure, these flares are often preceded by increased levels of replicating wild type virus shown by an increase in the HBV DNA level. Factors predicting HBeAg seroconversion following a flare include alpha fetoprotein (AFP) greater than 100 ng/mL, presence of bridging necrosis on liver biopsy and also the degree of ALT elevation.

A “non-replicative” or phase of “immune control” (previously known as “inactive carrier”) characterized as loss of HBeAg, development of HBeAb, normalization of ALT and reduction of HBV DNA levels to undetectable or very low levels signifies clinical remission of CHB. It is important that a patient should be shown to have normal ALT levels and 2-3 HBV DNA

levels in the appropriate range (ideally <2000 IU/mL) over the course of at least 1 year prior to classification into this phase of disease, since HBeAg negative CHB may run a unpredictable course. Although transition to HBeAg negative CHB can occur in approximately one third of patients, this risk decreases with time. The prognosis for patients in the inactive carrier state remains stable.

In attempts in which immune clearance is ineffective, a state of active liver disease associated with HBeAg negativity due to the presence of mutations in the precore and/or basal core promotor region of HBV is evident. This is characterized by persistent necroinflammation when HBV DNA levels are moderate to high (although 1–2 logs lower than in patients in the immune clearance phase), exhibiting progressive liver disease. Patients in the HBeAg negative CHB phase are older and therefore have higher rates of fibrosis than HBeAg positive patients. The importance of HBV DNA concentration in this phase has been shown in the REVEAL-HBV studies in which 85% of the cohort were HBeAg negative and in whom the risk of cirrhosis and HCC were strongly correlated with HBVDNA positivity. Moreover, patients with older age at onset of cirrhosis and persistent HBeAg seropositivity following the onset of cirrhosis were independent factors for the disease progression in the first 10-year after the development of cirrhosis in patients with chronic hepatitis B.

Lastly, the highest degree of immune control is HBsAg seroclearance with anti-HBs positivity which maybe the closest clinical endpoint to functional cure. This “HBsAg loss/occult phase”, in which despite a loss of HBsAg, there is an intrahepatic persistence of entire, episomal, replication-competent HBV genomes such as HBV cccDNA chromatinized episomes. Although HBV DNA is often not detectable in the blood of HBsAg-negative individuals and reactivation does not occur in immunocompetent individuals, a risk of reactivation exists at the time of immunosuppression synthesis.

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HEPATITIS B THERAPY: BEYOND THE GUIDELINES

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Several Clinical practice Guidelines [including the APASL 2015 guidelines to be published soon] have been developed to assist physicians in recognition, diagnosis and optimal management of patients with hepatitis B virus infection. Current guidelines recommend the use of antiviral treatment in only a distinct subset of the total HBV chronically infected population, which may be only 25-50% of the total infected population. The subset of chronically HBV-infected individuals for whom the treatment has been demonstrated to produce desirable outcomes are those with abnormal liver enzymes and a viral load above a defined threshold, presumably identifying those at highest risk for development of cirrhosis and hepatocellular carcinoma. However, some individuals whose clinical features place them outside these guidelines, for whom treatment is not recommended, are also at significant risk for liver disease complications and liver-related death. The studies have shown that age-specific 10-year risks of liver-related mortality in individuals for whom treatments are not recommended in current guidelines, range from 0,3-4% in the West to 0,3-20% in Asia. Some of the issues include patients with normal ALT, definition of normal ALT, use of noninvasive markers of fibrosis in guiding treatment decisions, treating significant viremia with minimal fibrosis and age <30 years, patients with low viremia and significant fibrosis, use of IFN therapy [when to start, what cut off of ALT or viremia], role of HBsAg in monitoring of efficacy of therapy, stopping rules for NAs in HBeAg negative group.

Guidelines only suggest preferred approaches and physicians are expected to exercise clinical judgment to determine the most appropriate management based on the circumstances of the individual patient. Physicians should try to engage patients in decision making process.

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EPIDEMIOLOGY OF HBV AND HDV IN MONGOLIA

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Mongolia is a developing country, which is located in Central Asia. The people of Mongolia as of July 2014 are estimated at around just 3 million people, ranking the 138th in the world in-terms population. HBV and HDV are one of the major causes of liver cirrhosis and HCC in Mongolia.

Mongolia is an area where viral hepatitis B and D are highly prevalent. The seroprevalence of HBV is 11,8% in the unvaccinated population (meta-analysis of 8 studies) and that of HDV is 16% in the apparently healthy population. Although, there is no accurate reason for such a high prevalence of HBV and HDV in Mongolia, it is well known that improper sterilization and disinfection of medical or dental equipment might contribute to the spread of HBV. Prevalence of HBV and HDV were 17% and 32% among the patients with acute hepatitis in Mongolia. Mongolia is one of the nations with highest incidence of HCC worldwide; it occurs in 54,1 cases per 100000 people each year and is attributable to a high prevalence of chronic viral hepatitis. Prevalence of HBV is 35% and prevalence of co-infections HBV and HCV were 14% among the patients with HCC in Mongolia. Although universal vaccination of HBV has been implemented and sterilization of medical devices is being improved, the prevalence of chronic hepatitis B and D is still high. Previous epidemiological study in Mongolia demonstrated that a history of dental work and surgery was a significant and dependent predictor for HBsAg seropositivity. Fortunately, the reuse of needles for phlebotomy or injection has been prohibited recently and disposable single-use needles have been introduced in Mongolia. Many traditional remedies including tattooing are still being practiced in Mongolia.

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CHARACTERISTICS OF CHRONIC HEPATITIS D IN KAZAKHSTAN

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Background/Aim

Despite the low prevalence of HBsAg carriage in Kazakhstan (less than 2% in blood donors and pregnant women), HDV is still an important cause of chronic hepatitis (CH) and liver cirrhosis (LC). The purpose of this study was to reveal clinical peculiarities of chronic HDV infection in patients admitted to our Institute.

Methods

297 cases of viral LC were analyzed by etiology. 104 HBV and HDV-infected patients were armed into 4 groups: (1) CHD, n=17, (2) CHB, n=20, (3) LCD, n=35 and (4) LCB, n=32. 11 patients with CH/LCD were given Peg-Interferon alfa 2a, 180 mcg weekly for 48 weeks. Standard examination was performed.

Results

HDV etiology was revealed in 30% cases of viral LC. The patients with CHD were 10-50 years younger (36,45±5,28) compared to CHB (46,9±2,81; p=0,045). The same difference (8.66 years) was noticed between LCD and LCB (40,68±2,33 and 49,34±2,07 respectively, p=0,005). Frequency of portal hypertension and hepatic encephalopathy was higher in LCD than in LCB (OR 0,21, CI 0,05; 0,85 and OR 0,27, CI 0,09; 0,87, respectively). Platelet count was significantly low in CHD (152,4±9,1x10^9/l) compared to CHB (210,6±17,6x10^9/l; p=0,003) and in LCD (114,8±10,5x10^9/l) compared to LCB (169,9±11,6x10^9/l; p=0,001). PI was statistically low (p=0,003) in LCD (62,6±1,3%) compared to LCB (69,2±1,7%). APRI turned to be as many as 3 times raised in LCD (1,35±0,37) than in LCB (0,40±0,10; p=0,001). End-of-treatment virologic response estimated as HDV-RNA negativity, was noticed in 4 of 11 (36,4%) and maintained negative after 6 months FUp in 3 patients (27,3%) and after 12 months FUp – in 2 patients (18%).

Conclusion

HDV causes as many as 30% of viral LC amongst the patients admitted to our Institute and characterized by rapid liver disease progression in younger age, more frequent complications and low efficacy of therapy.

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EPIDEMIOLOGY OF HBV IN BELARUS

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HBV-infection is actual medical problem in Belarus. Statistical registration of chronic hepatitis was initiated at 1996. More than 22000 cases were diagnosed during 19 years. Because of the National Vaccination Program the annual number of acute Hepatitis B decreased in 20 times since 1993. Fulminant hepatitis B was extremely rare during last years. But Chronic Hepatitis B is the real clinical problem now. The estimated number of HBsAg-positive persons is significantly higher and can involve about 0,5-1% of population. Contingents of especial risk are patients with immunosuppression. First of all, it is hematological, oncologic, transplant and hemodialysis patients. HBV-infection is significantly lower than HCV-infection among HIV-infected group, even among drug users.

Modern principals of treatment are implemented in clinical practice. The main task of present period is wide involving of all HBsAg-positive contingents at the process of effective ambulance management and treatment.

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VIRAL HEPATITIS B IN UKRAINE

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The prevalence of hepatitis B in Ukraine in the general population is 1,3%. Total number of infected people is about 514,200 (WHO 2013). The incidence of acute hepatitis B in 2013 decreased by 1,0% and the rate of chronic hepatitis B increased to 10,6% compared to 2012, and amounts 4,0 and 3,8 per 100,000 population, respectively. Among children up to 17 years, the incidence of acute hepatitis B increased to 13,5% (1,48 per 100,000). The frequency of deaths is 0,4%. For the implementation of the decision of the 63rd World Health Assembly (May 21, 2010) on March 9, 2011 the Cabinet of Ministers of Ukraine approved the Concept of the State Target Program of prevention, diagnosis and treatment of viral hepatitis in the period up to 2016. In April 2013, it was developed and approved the State target social program of treatment, diagnosis and prevention of hepatitis B and C for the period until 2016, and it was designed the clinical guideline to provide medical care for patients with hepatitis B. At this point in the country are represented all classes of drugs to treat hepatitis C - pegylated interferon, nucleoside reverse transcriptase inhibitors. It is widely used the latest generation of drugs, namely tenofovir.

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CHRONIC HEPATITIS AND LIVER CIRRHOSIS HBV ETIOLOGY IN MOLDOVA

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Background

Chronic diffuse liver diseases (CDLD), especially chronic hepatitis (CH) and liver cirrhosis (LC), are a major problem of contemporary hepatology. Numerous epidemiological studies evaluated in different areas of the world showed a high prevalence of CH HBV. About 2 billion of the world population have suffered a history of HBV virus infection, of whom 240-350 million people are chronic HBsAg carriers. Carriage of HBsAg spread in different geographical areas is uneven: from 19% (Africa), 16% (Philippines) to 2,4 to 4,7% (India) and 0,2-0,5% (USA).

Results

In Moldova survey of patients with viral hepatitis began in 1966 (registration CH HBV). At that time CH HBV prevalence constituted 34,3 cases/100 000 population. Frequency of CH HBV gradually increased in our country in 1985, having already high indices.

Closer to present the data have changed. The prevalence of CH HBV increased from 328,9 (2005) to 454,5 (2009); 588,2 (2012); 654,0 (2013); 709,6 (2014) cases per 100 000 population, and the incidence – from 41,9 (2005) to 57,3 (2009); 65, (2012); 60,2 (2013); 61,3 (2014) per 100 000 population.

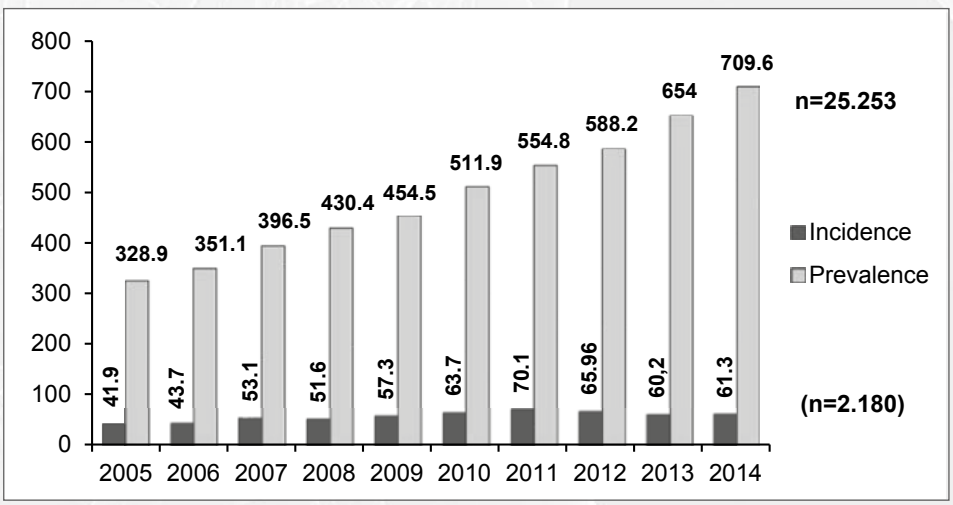

Fig. 1. The incidence and prevalence dymanics of chronic hepatitis HBV in Modova (100 000 population)

Compared to chronic hepatitis, LC of viral etiology in Republic of Moldova until 2004 was confirmed less and the rate of viral LC in the total liver cirrhosis does not exceed 20%. In recent years there is a tendency for more frequent diagnosis of viral infections in patients with LC, reaching 44,95% in 2014.

The LC HBV prevalence increased respectively as well from 30,5 (2005) to 50,1 (2009); 58,5 (2012); 59,6 (2013); 61,5 (2014) per 100,000 population. The incidence of HBV LC has the same increasing trend from 7,4 (2005), 10,8 (2009) to 10,3 (2012) and 8,6 to 9,5 (2013-2014) cases per 100 000 population.

The above mentioned official statistical data don't reflect the real frequency of CH and LC of HBV etiology in moldavian adult population.

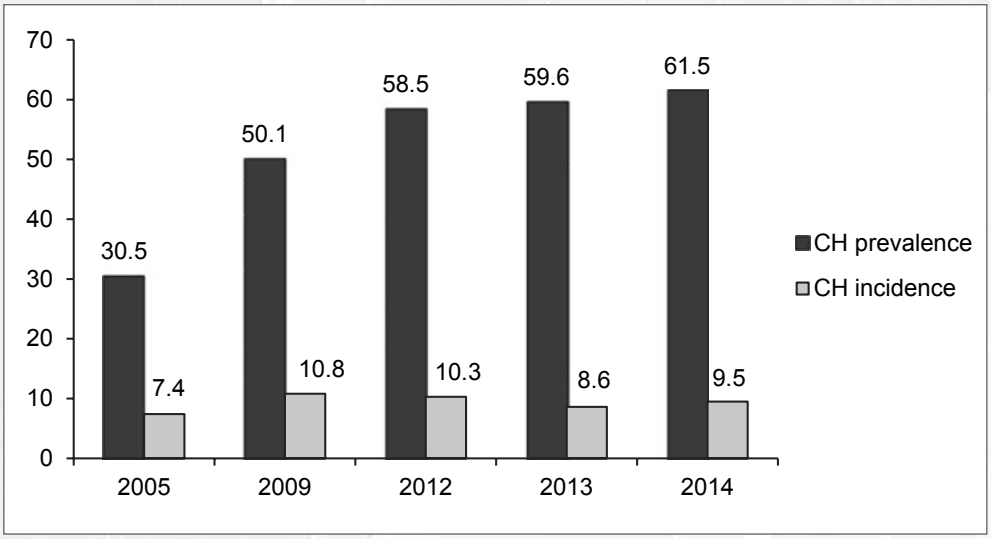

Fig. 2. The incidence and prevalence dymanics of liver cirrhosis HBV in Modova

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HBV INFECTION IN GEORGIA

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Total population of Georgia is about 4,5 million; territory is about 70 thousand square kilometers.

On the latest CDC maps showing the geographic distribution of HBV infection all over the world, Georgia is mentioned as a high intermediate HBV prevalence region, estimated 5-7%. It is also mentioned that the data of most countries are incomplete and/or inaccurate. NCDC/Georgia in collaboration with CDC/USA is in the process of evaluating the prevalence of HBV among general population of Georgia. We hope to have a preliminary data of this survey by the time of our presentation.

According to the data from NCDC Georgia, incidence rate of HBV infection per 100 000 population was growing from 2000 to 2008, started decreasing afterwards, and reached the incidence rate of about 22,7 in 2012. The prevalence of acute HBV infection in in 2012 among newly diagnosed HBV was about 15.9%.

Vast majority of HBV infected patients in Georgia have HBV genotype D.

An estimated 80% of patients with chronic active HBV infection are HBeAg negatives.

Estimated prevalence of anti-HBc in general population is unknown.

National prenatal screening program, which includes HIV, Syphilis and Hepatitis B, was introduced in Georgia in 2008. In 2013, HBV screening was done to 41714 women, which is about 85% of total number of pregnant women. The results of the screening were as follows: 2,53% of pregnant women were HBsAg (+).

Transmission mode in vast majority of chronic HBV cases was unknown. However, taking into consideration the fact that most of these patients had one or more surgeries, and many dental or other invasive procedures, it can be concluded that unsterile procedures seem to increase the risk of HBV transmission in chronic cases.

Preventive measures have been gradually introduced (1997 – blood screening, 2003 – child vaccination, 2007 – HBIg, 2008 – pregnant women's screening), however, more commitment is needed in order to apply these measures to a wider population.

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HEPATITIS B AND PREGNANCY

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It is estimated that 350 million to 400 million or 1 in 20 people worldwide are chronically infected with the hepatitis B virus (HBV). In high endemic regions the prevalence of HBV Infection among women of child-bearing age is 10-20% (China − 10%, India − 1-9%, Thailand − 8%, Middle East − 2-20%).

In regions with high prevalence, HBV infection is most commonly acquired through either perinatal or horizontal transmission. However, perinatal transmission of HBV is predominant route in areas of high endemicity (e.g. South-East Asia, China, Sub-Saharan Africa). Hepatitis B during pregnancy is presented with unique management issues for both the mother and fetus, including the effects of HBV on maternal and fetal health, the effects of pregnancy on the course of HBV infection, treatment of HBV during pregnancy and prevention of perinatal transmission.

There are different effects of HB on pregnancy outcome. Acute HBV is the most common cause of jaundice in pregnancy. Acute HBV infection during pregnancy is usually not severe and not associated with increased mortality or teratogenic effects and there is no indication of termination of pregnancy. However, the increased incidence of low birth weight and prematurity has been reported in infants born to mothers with acute HBV. Acute HBV occurring early in the pregnancy has been associated with a 10% perinatal transmission rate, whereas HBV infection at or near delivery with rates reported as high as 60%.

Impact of chronic HBV on pregnancy associated with gestational diabetes, low Abgar scores, higher risk of prematurity.

Pregnancy is a physiological condition, which suppresses immunity. Immunosuppression occurs to insure the mother`s immune system does not recognize the fetus as foreign. HBV liver diseases have demonstrated a period of remission during pregnancy, but they tend to hepatic flare after delivery.

Almost 30% of these women increase liver inflammation in the postpartum period usually asymptomatic and resolve spontaneously.

So, there is no worsening of liver disease in majority of HBV infected women during pregnancy. Liver enzymes frequently normalize. However, case reports of fulminant hepatic failures in HBsAg-positive pregnant women, but in untreated women close monitoring after delivery is necessary because of the risk of hepatic flares.

The other more important issue of HBV in pregnancy is associated with HBV mother to child transmission.

Perinatal transmission of HBV is the predominant route in areas of high endemicity. Different risk factors have been identified, that increase the risk of hepatitis B virus transmission. HBeAg status and the degree of maternal HB viremia are significant factors increasing rates of HBV vertical transmission. Transplacental (intrauterine) transmission is very rare and associated with HBeAg positivity and high HBV-DNA levels. Perinatal transmission of HBV at or near birth is 85% and 31% in HBeAg-positive and HBeAg-negative mothers respectively. Higher HBV viral load (VL) confers increased risk of transmission compared to lower HBV-DNA titers.

Although cesarean delivery has been proposed as a means of reducing mother-to-child transmission (MCT) of HBV the mode of delivery does not appear to have a significant effect on the interruption of HBV maternal-baby transmission by immune-prophylaxis. Delivery by cesarean section for the purpose of

reducing MCT is not presently recommended. HBsAg can be detected in breast milk of HBV infected mothers. However, breast feeding is not associated with transmission and is not considered a contraindication in HBsAg-positive women.

All decisions concerning initiating, continuing or stopping the antiviral treatment of HBV infection during pregnancy must include an analysis of the risks and benefits for mother and fetus. There are two principal indications of antiviral treatment: treatment of chronic HBV for the mother and prevention of perinatal HBV transmission to the child.

The trimester of the pregnancy and the stage of the mother`s liver disease are important factors.

The following seven therapies have been licensed for the treatment of hepatitis B, including interferon (both standard and pegylated), lamivudine, adefovir, entacavir, telbivudine and tenofovir. Factors, that influence treatment choice in women of childbearing age, include safety in pregnancy and breastfeeding, efficacy of the agent, its barrier to resistance and the proposed length of therapy. For women who require antiviral therapy the issue of pregnancy must be discussed before starting treatment. A “planned pregnancy” is preferable and may influence the choice and limiting of therapy, or potentially the timing of pregnancy. In pregnant women with chronic HBV infection who need antiviral therapy, the liver disease stage of the mother and potential benefit of treatment must be weighed against the risk to the fetus. IFN-based treatment is contraindicated because of its anti-proliferative effect: the only choice is nucleos(t) ide analogues with small risk to the fetus. Treatment with tenofovir is an ideal choice, given its efficacy, high barrier to resistance and safety profile in pregnancy. 8% of infants who receive prophylaxis become infected, which is associated with high maternal HBV-DNA and HBeAg positivity. Antiviral therapy administered in late pregnancy may reduce the risk of HBV infection from highly viremic mothers, as compared to passive active immunization alone.

VIRAL HEPATITIS IN ARMENIA

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Viral Hepatitis is global public health problem in the world as well as in Armenia.

Development of durable dynamics of viral hepatitis A (HAV) disclosed trend with cyclical places without expressed, distinct periodicity in previous years. There was a significant reduction (average >30 times) in the incidence of a 20-year period from 100,4 (1993) to 3,2 (2012): rate per 100 thousand, especially among children (50- fold).

Antibodies of viral hepatitis E (HEV) were defined in 2.5% of adults during serological screening in 2006, the indicator of possible HEV circulation in the country, which probably associated with migration of population.

According to geographical distribution Armenia is the country with intermediate endemicity of hepatitis C virus (HCV) ranged 4-5%.

The predominant genotype of HCV is genotype 1 (G1). However the number of HCV infected patients is increasing in Armenia as well as in the world.

Seroprevalence of hepatitis B virus (HBV) in Armenian general population is ranging from 2-3%. Predominant genotype of HBV is genotype D (96%). During a 20-year period almost 60-fold reduction in morbidity is noted among children and 6-fold among adults. Several factors are contributing dynamic changes in HBV epidemiology, including HBV vaccination, improvement in blood screening, education on prevention of parenteral transmission by unsafe sex, illicit drug use, iatrogenic routes.

Due to immunization (1999) of infants in Armenia there are recorded isolated cases of acute HBV among children under 14 in recent years.

Recent serological screening showed the activity of circulation of HBV and HCV among risk groups and played main role in maintaining intensity of epidemic process of both viruses in Armenia.

Identified seroepidemiological patterns of parenteral hepatitis are important for improving the system of regular epidemiological control of these infections which are the main reasons of almost all liver damages in Armenia.

ABSTRACTS

THE PREVALENCE OF HEPATITIS B AND C VIRUS INFECTION IN ONCO/ONCOHEMATOLOGICAL PATIENTS

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Background

Hepatitis B and C viruses (HBV, HCV) are oncogenic viruses. Chronic infections with HBV or HCV are associated with the development of hepatocellular carcinoma (HBV or HCV infections account for 78% of cases worldwide). Other cancers are as common in patients with HBV or HCV as they are in the general population. And the prevalence of HCV and HBV make them an important public health concern.

The aim: To evaluate hepatitis B and C virus prevalence in patients with malignancies in Armenia.

Material and Methods

We studied 12427 (11427 solid tumor and 1000 oncohematological) patients for 3 years. Prevalence testing included serological (HBsAg, AntiHCV, AntiHBc), virological (qualitative or quantitative HBV DNA, HCV RNA).

Results

Markers of hepatitis B and C viruses were found in 687 (5, 5%) (587 – solid tumors, 100 – oncohematological) patients from 12427. Hepatitis virus prevalence distribution by malignancies: in solid tumor patients – HBV 222 (1,9%), HCV 359 (3,1%), in oncohematological patients – HBV 37 (3,7%), HCV 63 (6,3%), co-infection in 6 (0,9%). Of 687 patients 33 % (229) – female, 67 % (458) – male, the mean age was 40 (3-77). 587 solid tumor patients consisted of 103 (18%) – breast, 58(9,9%) – lung, 57(9,7%) – gastrointestinal, 33 (5,6%) – urological, 60 (10%) – gynecological, 20 (3,4%) – brain, 53 (9%) – soft tissue, 203 (34%) – other cancers. 100 oncohematological patients consisted of 53 (53%) – leukemia, 30 (30%) – lymphoma (83% lymphoproliferative diseases), 17 (17%) – others.

Conclusion

Hepatitis B and C virus prevalence is 3,8% and 6,1% accordingly in oncohematological patients, which is higher, than in solid tumor patients (1,9% and 3,1%). Hepatitis B and C virus prevalence in solid tumor patients is the same, as in general population.

Hepatitis B and C virus high prevalence in oncohematological patients, its association with nosology is suggested with possible role of hepatitis viruses in the pathogenesis of lymphoproliferative diseases and with necessity of multiple transfusions in these patients.

Table

Patient	Total N A.N.		NBV/HCV		HBV		HCV	
			P±m	A.N.	P±m	A.N.	P±m	
Solid Tumor patients	11427	587	3	0.03±0.02	222	1.9±0.12*	359	3.1±0.2*
Onco-haemotological patients	1000	100	3	0.3±0.2	37	3.7±0.4*	63	6.3±0.8*
Total N	12427	687	6	0.9±0.3	259	2.1±0.1*	422	3.4±0.2*

P<0.001

HEPATITIS B REACTIVATION IN CANCER PATIENTS UNDERGOING CHEMOTHERAPY

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Background

Reactivation of hepatitis B virus is a serious complication of chemo/immunosuppressive therapy and a serious cause of liver-related morbidity and mortality**.**

The **aims** are to determine:

The incidence of liver injure associated with HBV reactivation in cancer patients with chemotherapy.

The optimal strategy for antiviral prophylaxis.

Patients and methods

Solid or hematologic cancer patients with positive hepatitis B surface antigen (HBsAg) who underwent cytotoxic chemotherapy were included for 4 years. Prophylactic lamivudine was started with the initiation of chemotherapy, continued for the whole period of chemotherapy, discontinued between 1to 6 month after completion of chemotherapy. All eligible patients were regularly followed up.

Results

Out of 50 patients, 30 (60%) were with oncohematological, 20 (40%) with solid tumors, 28 (56%) were men; mean age of patients was 40 years (3-77).

Median duration of regularly follow up was 18,5 month (1-36).

Out of total 39 (78%) were HBsAg inactive carriers, 11(22%) with chronic hepatitis B. Prophylactic lamivudine with the initiation of chemotherapy was started in 10 patients and in 3 patients after reactivation of HBV.

In 12 (24±5,9%) of 50 patients hepatitis developed due to viral reactivation, among whom 4 (33,3%) were with solid tumors, 8 (66,7 %) oncohematology, 9 (75%) HBeAg negative. Viral reactivation cases share in patients with solid tumors and oncohematology distribution was 20% and 26,7%, respectively.

The degrees of liver damage were 3 (25%) of 12 with icteric, 3 (25%) fulminant hepatitis, 6 (50%) asymptomatic hepatitis with elevation of aminotransferases (10-20 folder).

There was not reported any liver damage and HBV reactivation in 10 patients (RR=0,4) with lamivudine prophylaxis with the initiation of chemotherapy.

Our data underscored the type of underlying malignancies and HBeAg negative status were significantly independent risk factors for HBV reactivation.

Conclusions

- HBV reactivation is common cause of liver injure in cancer patients undergoing chemotherapy.
- Hematology malignancies and HBeAg negative status are significantly risk factors for HBV reactivation.
- Lamivudine prophylaxis reduced HBV reactivation and interruption or modification of chemotherapy in those patients.

HEPATITIS B AND C VIRUS INFECTION AND RISK OF HEPATOCELLULAR CARCINOMA IN CIRRHOTIC PATIENTS

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Background

Many etiological factors have been realized with hepatocellular carcinoma (HCC) development, such as cirrhosis, hepatitis viruses and alcohol cirrhosis. Chronic HBV and HCV infections often result in cirrhosis and enhance the probability of developing HCC.

Aim: To evaluate the risk factors for development of HCC in cirrhotic patients.

Material and Methods

Our study included 300 patients with cirrhosis. Data from clinical, biochemical, virological and instrumental studies were analyzed.

Results

HCC were diagnosed in 48 (16%) patients from the total 300 with cirrhosis. Mean age of patients with HCC was 61±1,1 year (ranged 45-77). Distribution by sex was men 35 (73%).

30 (62,6%) of the total 48 patients were positive for HCV antibodies and HCV RNA 12 (25%) patients were positive for any HBV marker including 7 (14,5%) of HBsAg positivity, 2 (4%) for HBsAg negativity and antibody positivity. HBsAg, anti-delta (co-infection) positive, previous alcohol abuse, a cryptogenic cirrhosis were present in 3(6,25%) respectively.

Significantly increased risk of HCC was in cirrhotic patients with HCV antibody and HCV RNA positivity. According to our data age older than 60 years with anti-HCV and HCV RNA positivity appeared to be associated with HCC. By multivariate analyses age, male sex, longer duration of cirrhosis and HCV RNA positivity were strongly and independently factors for HCC.

Conclusion

HCV is the major risk factor for development of HCC.

HCV RNA positivity in male with age older than 61 years significantly increased the risk of HCC among cirrhotic patients.

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EPIDEMIOLOGY OF HBV INFECTION IN ARMENIA

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Background

Hepatitis B virus (HBV) infection occupies one of the most significant places among health protection issues worldwide.

Aims: To evaluate the morbidity of acute HBV infection and to determine the distribution of HBV genotypes in Armenia.

Methods

According to registered cases of acute hepatitis B a retrospective epidemiological analysis of long-term morbidity was done. HBV genotypes were determined using real-time polymerase chain reaction.

Results and discussion

In multi-year (1995-2014) dynamics of the morbidity of acute HBV infection in general population a significant, strong trend of decline (9,7-1,9‰) was observed. During 2001-2014 period this trend was more expressed among young age groups, for instance, among persons older than 14 years the incidence decreased on average 1.8 folder (4,1-2,3‰), whereas among children – 15 folder (3,1-0,2‰). This situation results from immunoprophylaxis of hepatitis B in Armenia since 1999 (routine vaccination programme among children, including vaccination of newborns). Among the cases of acute hepatitis B there has been a clear reduction in the proportion of children under 14 years (23,7-1,8%). A total of 81 patients with acute and chronic HBV infection were investigated on HBV genotypes. Genotypes D and A distribution was 78 (96,3% ±2,1%, $p<0,001$) and 3 (3,7%) patients respectively.

Conclusion

During the recent years a significant increase of share of parenteral hepatitis in the etiological structure of acute viral hepatitis was determined. Vaccination against HBV effectively prevents transmission of HBV infection. Genotype D is the predominant type found among patients with different clinical forms of HBV infection in Armenia.

SEROLOGIC MONITORING OF HBV AND HCV IN ARMENIA

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Background

Seroprevalence of HBV and HCV in the general population and various groups worldwide are regularly updated. Data obtained from serological surveys are very important to assess the epidemiological status of parenteral viral hepatitis.

Aim: To evaluate the prevalence of HBsAg and anti-HCV in the general population and high risk groups of parenteral hepatitis in Armenia.

Material and methods

These studies were performed among conditionally healthy persons, sexual transmitted infection (STI), tuberculosis, hemodialysis patients, injecting drug users. A total of 4500 persons were involved in serological screening. HBsAg and anti-HCV were determined in using IFA methods.

Results and discussion

In conditionally healthy population groups HBsAg or anti-HCV were determined in 1,8±0,2%, 3,6±0,3% ($p<0,05$) respectively. On the other hand, data obtained among STI, tuberculosis, hemodialysis patients and injecting drug users were much higher than the corresponding figures in conditionally healthy population (with exceptions HBsAg in tuberculosis patients). In these groups the level of prevalence of HBsAg in 16,4±1,7%, 2,0±0,6%, 8,2±1,7%, 8,8±1,8% ($p<0,05$) were revealed. Anti-HCV were found in 10,2±1,7%, 9,0±1,3%, 29,4±2,9%, 64,0±3,0 ($p<0,05$) respectively.

Conclusion

The results obtained from these studies indicate, that risk groups of HBV and HCV infections have contributed and still are contributing to maintaining the intensity of epidemic process of parenteral hepatitis in Armenia.

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HEPATITIS B IMMUNOPROPHYLAXIS IN ARMENIA

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Background and aims

Hepatitis B virus (HBV), a DNA virus with a human-only reservoir, is a worldwide public health problem. More than a third of the world's population has been infected with HBV, more than 350 million are chronic carriers, almost one million people of whom die annually of HBV-related liver disease and 15-40% are at risk for developing HBV-associated liver diseases, including cirrhosis and hepatocellular carcinoma. Hepatitis B is a serious health challenge in many countries including Armenia. Safe and effective HBV vaccines have been available since 1982. The implementation of effective vaccination programs have resulted in a significant decrease in the incidence of chronic hepatitis B infection. Nevertheless, hepatitis B remains an important cause of morbidity and mortality among the chronic carriers worldwide. To describe the effectiveness of Hepatitis B universal vaccination and trends of incidence of acute Hepatitis B among children under 14 years old in Armenia during 2000-2014 monthly and annual reporting forms on vaccination coverage and disease, as well as epidemiological investigation cards of cases were summarized and studied.

Methods

Monthly and annual reporting forms on vaccination coverage and disease, as well as epidemiological investigation cards were summarized during the study.

Results

In Armenia, coverage of infant vaccination and three doses of Hepatitis B universal vaccination is increasing gradually. As a result, incidence of acute cases of Hepatitis B has been dramatically decreased among the children under 14 y.o. since introduction year in 1999 (0,18 in 2014 vs. 9,7 in 1999/per 100,000 children <14 y.o. accordingly). Basically, during the period of 2008 to 2014 only single cases of acute Hepatitis B were recorded.

Conclusion

Taking into account the high vaccination coverage in Armenia and decreasing trends of incidence of acute Hepatitis B among children <14 y.o., high effectiveness of universal vaccination allows government to expand vaccination strategy among the risk groups as a cost effective preventive measure to control Hepatitis B in the country.

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THE HOST – PATHOGEN INTERACTION DURING HBV INFECTION

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Hepatitis B virus (HBV) infection is one of the major causes of liver diseases affecting more than 350 million people worldwide and more than one million deaths annually from liver cirrhosis and hepatocellular carcinoma. HBV is non-cytopathic, and both viral control and liver pathology are mediated by the host immune system. The crucial role of adaptive immune responses in controlling HBV infection is well accepted, but the potential contribution of the innate system is now an important area of controversy. Unanswered questions include whether and when HBV can trigger components of innate immunity, and whether HBV can actively suppress the induction of innate immunity. In the first part of this presentation I will discuss the data available from different models addressing the role of innate immunity. In the second part, I will address the immunopathogenesis of the inflammatory events that characterize chronic hepatitis B. The mechanisms thought to be responsible for liver inflammation, namely the intrahepatic recruitment of inflammatory cells, which is orchestrated by chemokines. Finally, I will discuss new and innovative therapeutic approaches for patients with chronic HBV (CHB) infection. Immune therapy has emerged as an alternate therapeutic approach for CHB patients because studies have shown that host immunity is either impaired or derailed or distorted or diminished in CHB patients compared to patients with acute resolved hepatitis B who contain the HBV replication and control liver damages. The concept of immune therapy for treating CHB patients seems to be rationale and scientific, however, concerns remain about suitable designs of immune therapy for CHB patients.

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MANAGEMENT OF CHB IN CO-INFECTED PATIENTS HBV/HCV AND HBV/HIV

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Background

HBV-infected patients with concurrent HCV, HDV or HIV infections tend to have a higher incidence of cirrhosis, HCC and mortality. It is generally agreed that the dominant virus should be identified before designing therapeutic strategy. If HBV is dominant, treatment should be aimed toward this virus.

HBV/HCV co-infected patients

In HBV-infected patients HCV co-infection accelerates liver disease progression and increases the risk of HCC. In HBV/HCV co-infected patients HBV DNA level is often low or undetectable. In the same time HCV is responsible for the activity of chronic hepatitis in most patients, probably due to indirect mechanisms mediatedby innate and/or adaptive host immune responses. Antiviral treatment should be initiated for HCV, therefore HBV DNA monitoring is necessary. There is potential risk of HBV reactivation during treatment or after clearance of HCV. Any HBV reactivation must then be treated with NA(s). Sustained virological response rates for HCV are broadly comparable with HCV mono-infected patients.

HBV/HIV co-infected patients

It is well known that HIV-infected patients are often affected by viral hepatitis, i.e. about one-third is co-infected with either HBV or hepatitis C virus HCV. Numerous studies have shown that HIV/HBV co-infection is associated with a higher risk of chronic carrier state, lower rate of spontaneous loss of HBeAg/HBsAg, lower seroconversion to anti-HBe/anti-HBs, higher rate of viral reactivation and HBV replication and a higher rate of occult HBV.

We consider it is necessary to mention the fact of important benefits of HAART presence in HIV/HBV co-infected patients which are as follows:

- Decreases in HBV replication,
- Spontaneous anti-HBe or anti-HBs seroconversion
- Decreases in HBV-associated liver disease, and;
- Increases in hepatic flares (eg, ALT elevations).

Goals of HIV/HBV Co-infection Therapy

The goals of HBV therapy in patients with HIV/HBV co-infection do not differ from those in patients with HBV mono infection, which are to achieve sustained suppression of HBV replication and hepatic disease and prevent cirrhosis, hepatic failure, and hepatocellular carcinoma.

All HBsAg-positive patients should be screened for HIV before these drugs are used in the treatment of HBV infection. Lamivudine, Entecavir and Tenofovir have activity against both HIV and HBV and are contra-indicated as single agents for hepatitis B in co-infected patients because of the risk of HIV resistance. If any of these two NAs with a low barrier to resistance does not reach the goal of undetectable HBV DNA after 12 months of therapy, treatment of HIV infection should be envisaged.

HBV Treatment Options in HIV/HBV Co-infected Patients

- In HIV/HBV co-infected patients for whom both HIV and HBV require treatment, a tenofovir-based regimen is preferred because it is active against both HBV and HIV. It may be used in combination with either emtricitabine or lamivudine in HBV treatment-naïve patients and with emtricitabine or entecavir in patients with lamivudine-resistant HBV.
- Peginterferon alfa-2a or adefovir plus entecavir are preferred HBV regimens when HBV only needs to be treated.

Report of HIV coinfected in Armenia

2070 HIV-infected patients (69% male) were including in the study. Vast majority of the patients (64%) were from 18 to 40 years old (n=1334). AIDS stage diagnosed in 1078 patients (52,1%). The study was done in Armenicum Clinical Center and AIDS National Center from 2005 to 2015. Sexual transmission was the major way – 66,4% (n=1375); intravenous drug users (IVDUs) – 27,15% (n=562); mother-to-child – 1,35% (n=28); blood-burn – 0,2% (n=4); in 4,9% (n=101) way of transmission remains unclear. All patients were checked on HBV and HCV. HIV/HBV-coinfected patients received ARV regimens with Lamivudine or Tenofovir/Emtricitabine.

Majority of international studies and cases show that the following patients should be taken into consideration when starting HIV treatment in HBV co-infected patients:

All patients with a history of an AIDS-defining illness or with CD4 count <350 cells/mm^3, patients (regardless of CD4 count) with the following conditions: pregnancy, HIV-associated nephropathy, and hepatitis B virus (HBV) co-infection when treatment of HBV is indicated and patients with CD4 counts between 350 and 500 cells/mm^3 (March 2012 DHHS Panel and 2012 IAS-USA guidelines, 2012 APASL Guideline).

Results of the Report

Among all 2070 HIV-infected antiretroviral therapy received 38,6% of patients (n=800), 20,9% (n=167) of them were HIV/HCV co-infected, 3,25% HIV/HBV co-infected (n=26) and HIV/HCV/HBV co-infected 1,25% (n=10). Lethal outcome documented in 21,7% (n=449), mainly in AIDS stage 79,5% (n=357). 81% of patients receiving scheme with Lamivudine had not markers of HBV replication. In all patients with ARV including Tenofovir/Emtricitabine HBV DNA was undetectable. Lethal outcome documented in 21,7% (n=449) from 2070 HIV-patients under diagnosis of AIDS National Center. According to AIDS National Center mortality in Viral Hepatitis coinfection HIV patients was 32 (8,6%) among them:

- HIV/HCV - 18 patients
- HIV/HCV cirrhosis - 8 patients
- HIV/HBV - 5 patients

The abovementioned treatment has been adopted and implemented according to 2012 IAS-USA guidelines and 2012 APASL guidelines.

Summary

Among HIV-infected patients in Armenia HCV- and HBV co-infection diagnosed in 13,8%. In Armenia co-infection with viral hepatitis is high in IVDU: HIV/HCV – 29,5%, HIV/HBV – 2,8%, HIV/HCV/HBV – 1,6%. Tenfovir/Emtricitabine containing ARV regimens effectively suppressed HBV replication.

Hence, general international guidelines show that:

1. HBV co-infection complicates disease course and management of HIV patients
2. HBV co-infection does not substantially affect the course of HIV infection
3. HIV co-infection significantly alters the course of HBV disease.

According to these guidelines all patients with active HBV infection should be treated with ART containing emtricitabine/tenofovir DF. Entecavir may be useful in patients with active replication despite tenofovir DF or in persons with contraindications to tenofovir DF in both infections.

IMMUNOLOGICAL INDICATORS IN HIV POSITIVE PATIENTS WITH VIRAL HEPATITIS B

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Background

It is known that in chronic active forms of viral hepatitis (VH) the concentration of soluble receptor of interleukin 2 (RIL-2), tumor necrosis factor a (TNF-a), soluble receptors of TNF-a-p55 and p75 considerably increases, which corresponds to the intensity of morphological process. In their turn, immunological changes in HIV infection reflect on the duration of VH. The aim is the investigation of immunological indicators (Ii) and their interactions in relation to VH.

Methods

The majority (80%) of 149 patients are Caucasians in different stage of HIV infection. Age of patients is from 21 to 40 years old, 79% are male. Number of population with AIDS is 109 (27%). In HIV infected patients (n=149) persons with chronic VH – 76% (n=114), from them HBV – 30% (n=34), HCV-70% (n=80) and herpetic infection (HI) – 24% (n=35) are prevalent. HIV infection accompanied with VH and HI, were detected in 25 patients (17%). Ii were analyzed in relation to accompanied diseases and their combination.

Results

Data comparison of patients with HIV/HBV revealed that in patient with medial or high level of ALAT (2 times higher than Norma) the concentration of following indicators were increased: CD8+ cells (682±82 against 588±33; pw>0,05), RIL-2p (83,0±10 pM against 65,4±6 pM; pw=0,05), B2MG (6,91±1,1 mg/ml against 4,4±0.3 mg/ml; pt=0,05, pw=0,039,pu=0,003). Thus, soluble markers of immune activation were considerably expressed in patients with relatively deep hepatocellular damage by HBV. The concentration of B2MG was higher in group of patients with VH or HI in contrast with HIV infected patients with VH and HI (pw=0,037).

Summary

Some immunological indicators are reliably different in patients with HIV infection and chronic HBV.

There are expressed deviations in system of regulation of humoral immune response in patients with accompanied VHB.

These deviations are connected to chronic hepatitis and mixed with HIV associated disorders of cellular immune response.

PREVALENCE OF CHRONIC HEPATITIS B AND C IN HIV-INFECTED PATIENTS IN ARMENIA

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Background

According to the WHO in 2014, 36,9 people were living with HIV in the world. HIV-infected patients are often affected by viral hepatitis – about one-third are co-infected with either hepatitis B virus (HBV) or hepatitis C virus (HCV). In addition, persons who are co-infected with HIV and HBV can have serious medical complications, including an increased risk for liver-related morbidity and mortality.

The aim of this study is the investigation of chronic HBV- and HCV-infection prevalence in HIV-infected patients in Armenia.

Methods

2070 HIV-infected patients (69% male) were including in the study. Vast majority of the patients (64%) were from 18 to 40 years old (n=1334). AIDS stage was diagnosed in 1078 patients (52,1%). The study was done in Armenicum Clinical Center and AIDS National Center from 2002 to 2015. Sexual transmission was the major way – 66,4% (n=1375); intravenous drug users (IVDUs) – 27,15% (n=562); mother-to-child – 1,35% (n=28); blood-burn – 0,2% (n=4); in 4,9% (n=101) way of transmission remains unclear. All patients were checked on HBV and HCV.

Results

Among all HIV-infected persons in 285 (13,8%) viral hepatitis B or/and C were revealed. Chronic HCV-infection was diagnosed in 234 patients (82,1%), among them 19 (8.1%) in cirrhosis stage. In 38 patients (13,3%) we observed chronic HBV-infection, with 1 cirrhotic patient (2,6%). Mixed hepatitis B+C diagnosed in 13 HIV-infected (4,6%) with cirrhosis formation in 2 cases (15,4%), mixed hepatitis B+C+D – in 1 patient. AIDS stage was enrolled in 76,5% of co-infected (n=218) patients. Among all 2070 HIV-infected patients the antiretroviral therapy received 38,6% of patients (n=800), 20,9% (n=167) of them were HIV/HCV co-infected, 3,25% HIV/HBV co-infected (n=26) and HIV/HCV/HBV co-infected 1,25% (n=10). Lethal outcome was documented in 21,7% (n=449), mainly in AIDS stage 79,5% (n=357).

Summary

1. Among HIV-infected patients in Armenia HCV and HBV co-infection was diagnosed in 13,8%.

2. In Armenia co-infection with viral hepatitis is high in IVDU: HIV/HCV – 29,5%, HIVHBV – 2,8%, HIV/HCV/HBV – 1,6%.

COMPOSITION OF ERYTHROCYTES MEMBRANE PHOSPHOLIPIDS IN PATIENTS WITH ACUTE HEPATITIS B PLUS NON-ALCOHOLIC FATTY LIVER DISEASE

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Background

Basic role of membrane phospholipids (PhL) is in a structural function. Stability of membranes depends on balance between destruction and synthesis of separate fruitions of PhL. Disbalance of erythrocytes membrane (EM) composition as a consequence influences on membranes fluid plasticity.

The aim of the study is evaluation of PhL of EM in patients with acute hepatitis B (AHB) and in patients with acute hepatitis B plus non-alcoholic fatty liver disease (NAFLD).

Methods

112 patients were included in the study: 88 with AHB and 24 with AHB+NAFLD. We checked relative level of the following PhL in EM: *Acidic Phospholipids – Monoinositidphosphatides (MIPh), Phosphatidylserine (PhS) and Cardiolipins (CL);* N*eutral Phospholipids – Lysophosphatidylcholines (LPhC), Phosphatidylcholines (PhCh), Phosphatidylethanolamines* (*PhEA*) *and Sphingomyelins (SphM).*

Results

In patients with AHB+NAFLD high level of *Acidic Phospholipids* in EM was enrolled during the height stage of hepatitis up to discharge from hospital. MIPh was significantly higher in the height of disease in patients with AHB+NAFLD 13,8±0,16% from all PhL, *vs.* patients with AHB – 12,9±0,06% (p<0,01). In dynamic activity of monoinositidphosphatids (MIPh) gradually decreased, but still remain higher normal range (8,51±0,18%). On the sixth week of jaundice MIPh was correspondingly 9,2±0,11% in AHB and 10,3±0,20% in AHB+NAFLD (p<0,05). The same dynamics was observed for CL and PhS. Proportion between fractions in n*eutral phospholipids* spectrum is expressed with LPhC increasing in 2 times. In the height stage of hepatitis LPhC in AHB+NAFLD was – 21,3 ±0,19% *vs*. AHB – 20,6±0,09% (p<0,001). Level of SphM AHB was 14,8±0,13%, *vs.* significant lower 13,6±0,21% in AHB+NAFLD.

Summary

Changes in phospholipids component of erythrocytes membrane by decreasing of Sphingomyelins, Phosphatidylcholines, Phosphatidylethanolamines with the same time increasing of Phosphatidylserine, Cardiolipins, Monoinositidphosphatides and Lysophosphatidylcholines are especially expressed in patients with acute hepatitis B plus non-alcoholic fatty liver disease.

ABSTRACTS

PARAMETERS OF LIPID PEROXIDATION IN PATIENTS WITH ACUTE VIRAL HEPATITIS B IN COMBINATION WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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Background

It was found that the unique mechanism of damage of cell membranes is associated with increased peroxidation of lipids (LPO), in particular because of the shortage of antioxidants. The **aim** of this study is the comparative evaluation of the level of LPO of erythrocyte membranes (EM) in acute hepatitis B (AHB) and acute hepatitis B in combination with non-alcoholic fatty liver disease (NAFLD).

Methods

The study included 88 patients: with AHB (n=64), and AHB in combination with NAFLD (AHB+NAFLD) (n=24) at the age of 18 to 70 years old. The concentrations of hydroperoxidation in ascorbate-induced and NADPH-dependent peroxidation, the activity of superoxide dismutase (SOD) were detected in the EM.

Results

The studies reviled the high concentration of hydroperoxidation defined in ascorbate (LPOa) and NADPH-dependent (LPOn) peroxidation in EM. The indicators of LPOa were significantly higher in patients with AHB+NAFLD – 20,0±0,60 E/mg. In the period of recovery indicators are still significantly higher than the normal value: in the 6th week on 10% in AHB and on 22% in AHB with NAFLD. Our observations confirm the shortage of antioxidant SOD in EM both in patients with AHB and AHB+NAFLD with a high correlation with the level of LPOn and LPOa throughout the period of observation. Thus, the higher the restraining effect of SOD on lipid peroxidation and free radical processes, the less intense the accumulation of intermediate products of lipid peroxidation, in particular hydro peroxides. SOD parameters in case of moderate duration of AHB and AHB with NAFLD were correspondingly 15,9±0,23 ua/mg and 14,0±0,63 ua/mg

Summary

Lack of key enzymes of antiradical protection – superoxide dismutase and the accumulation of peroxidation products are naturally linked, reflect the depth of damage to the membrane, and are more pronounced in case of AHB combined with NAFLD compared to AHB.

Table

SOD Activity in Patients with AHB and AHB-NAFLD

Time of checking (weeks)	SOD activity (ua/mg protein)	
	AHB (n=64)	AHB + NAFLD (n=24)
I	15,9±0,23	14,0±0,63*
II	19,6±0,26	17,3±0,73*
III	25,0±0,27	22,9±0,5*
IV	28,3±0,27	25,5±0,56*
V	30,6±0,35	29,5±0,54*
VI	36,0±0,32	33,6±0,61*

** - differences are significant (p≤0,05) between groups AHB and AHB+NAFLD.*

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MANAGEMENT OF CHB IN THE IMMUNOSUPPRESSED PATIENTS

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In hepatitis B virus (HBV) infection in contrast to HCV, immunosuppression due to treatment with immunosuppressive drug more often may lead to HBV reactivation. Screening for HBV followed by antiviral prophylaxis started before or at the time of initiation of cancer chemotherapy. There are 4 major guidelines (the Centers for Disease Control and Prevention, 2008; the American Association for the Study of Liver Diseases, 2009; the Asian Pacific Association for the Study of the Liver, 2012; and the European Association for the Study of the Liver, 2012), which vary in the types of recommended screening tests and the indications for prophylactic antiviral therapy, but each endorses HBsAg and anti-HBc screening as a critical first step for reducing the risk of HBV reactivation. Baseline risk and disease outcomes could be most clearly assessed in 3 types of malignancy: lymphoma, breast cancer, and hepatocellular carcinoma. The risk of reactivation is especially high associated with rituximab – tumor necrosis factor (TNF) inhibitor, which are used in patients with leukemias, non-Hodgkin lymphoma, cryoglobulinemia, rheumatoid arthritis, and idiopathic thrombocytopenic purpura.

HBV reactivation characterized by a sudden increase in serum HBV viral load and increasing alanine aminotransferase (ALT) level mostly associated with a hepatitis flare several weeks later. HBsAg positive patients are 5-8 times more likely to develop HBV reactivation than HBsAg-negative/anti-HBc-positive patients. In HBsAg carriers, reactivation is defined by de novo detection of HBV DNA or a 10-fold (1 log10) increase in HBV DNA level and 2-3 fold elevation in ALT. In HBsAg-negative/anti-HBc-positive patients reactivation has been considered to occur with demonstration of reverse seroconversion to HBsAg-positive status.

HBsAg-positive patients who are candidates for receiving chemotherapy or immunosuppressive therapy should be tested for HBV DNA levels and should receive pre-emptive nucleos(t)ide analogues (NA) administration during therapy, regardless of HBV DNA levels. HBsAg-negative, anti-HBc positive patients with detectable serum HBV DNA should be treated similarly to HBsAg positive patients. The frequency of ALT and HBV DNA level monitoring can range from 1 to 3 months depending on the type of immunosuppressive therapy and comorbidities.

RESULTS OF SHORT QUESTIONARY CONCERNING GUIDELINES ON MANAGEMENT OF HBV-INFECTION AMONG ARMENIAN PHYSIACIANS

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Background

Chronic hepatitis B virus (HBV) infection is a common cause of liver related morbidity/mortality including cirrhosis and hepatocellular carcinoma (HCC). Armenia characterized with intermediate prevalence of HBV-infection. Despite updates and improvements in Clinical Practice Guidelines by major Hepatological Societies during the past decade, greater patient and physician education is still needed. The aim of study is assess applicability of the main Hepatological Societies Clinical Practice Guidelines for Management of chronic hepatitis B (APASL, EASL, AASALD) by Armenian Physicians.

Methods

18 physicians (8 Infectionists and 10 Gastroenterologists) were included in the study. Questionnaire includes 25 items and consisted of two parts: eight – information regarding the physician personal data (specialty, stage, scientific degree, lecturing in Medical University, participation in international conference during last 3 years, number of publications on Hepatology in international/local journals during last 3 years, using of Clinical Practice Guidelines in daily practice) and seventeen – on natural course, screening, treatment of HBV-infection and HCC.

Results

In average physicians knowledge was better depend on longer practical stage in gastroenterology/ infectious diseases and teaching experience. Completely correct answers on questions concerning natural course of HBV-infection (characteristics of occult HBV-infection, distinguish between HBeAg-negative chronic hepatitis B and inactive HBV carrier state) only of 4 physicians. Results of antiviral therapy connected questions: higher percentage on treatment monitoring, less – on criteria's of initiation, preferable scheme and effectiveness of therapy. Better result enrolled on HBV-infected pregnant women prophylaxis, but less satisfied on HCW prophylaxis. The lowest results enrolled in knowledge of HCC: risk groups, screening, diagnosis, BCLC classification and management. Vast majority select as the most important investigation in HCC screening AFP, only one physician choose abdominal ultrasound.

Summary

Result of short questionnaire on HBV-infection management among Armenian physicians involved in field of Hepatology suggests necessity of more careful approach to current Clinical Practice Guidelines.

The risk of HCC development is 100-200-fold higher in HBV-infected patients as compared to non-infected individuals.

According to current conception about the natural history and immunopathogenesis of HBV infection

68%, 48% considered the HCV genotype as risk factor for HCC development ($p<0,05$). 90% of physicians specialized in tropical medicine, internal medicine or gastroenterology and 67% of physicians in other specialties advise patients to undergo screening for HCV and HBV infection as well as liver cirrhosis ($p<0,05$). 72% of doctors with an MD degree, 55% of doctors with a master degree or a diploma, hospital doctors consider ($p<0,05$). 65% of physicians in tropical medicine, internal medicine or gastroenterology and 37% of physicians in other specialties recommend as HCC screening interval of 3 months ($p<0,05$). 71% of doctors, 50% and 60% follow the same recommendation

(EASL Clinical Practice Guidelines: Management of chronic hepatitis B, 2012) HBeAg positivity in the *"immune tolerant"* phase continuing in the *"immune reactive HBeAg-positive phase"*, end of which characterized with seroconversion to anti-HBe. It may follows by *"inactive HBV carrier state"* (HBV DNA below 2000 IU/ml, persistently normal level of ALT at least every 3-4 months within 1 year, low risk of cirrhosis or HCC with spontaneously HBsAg loss and seroconversion to anti-HBs antibody in 1–3% of cases per year) or "*HBeAg-negative chronic hepatitis B".*

MANAGEMENT OF CHRONIC HEPATITIS B: KNOWLEDGE AND PRACTICES OF PHYSICIANS IN PAKISTAN

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Background

In Pakistan, approximately 4,5 million people are afflicted with CHB. The compliance with HBV management guideline is still unknown. This is the first study from Pakistan in which the knowledge and the current practices of treating physicians is compared with the three standardized guidelines (APASL 2012 / EASL 2012 /AASLD 2009).

Method

A cross-sectional study was conducted during 2014-2015 at four tertiary care teaching hospitals in Karachi. The study participants were internists, gastroenterologist and senior medicine residents who were involved in the management of CHB patients. A survey questionnaire was developed which evaluate compliance with international HBV consensus guidelines.

Results

A total of 179 physicians (103 residents, 76 consultants) participated and 69,3% were male. The mean age of participant was 35±9,3 years. Most of the participants followed AASLD (27,3%) and EASL (24,0 %) guidelines. Pegylated interferon or Entecavir was considered as first line therapy by 47% & 43% respectively, 17,9% preferred Entecavir in combination with tenofovir for rescue therapy, 25,7% and 23,5% preferred Tenofovir or Entecavir as both first line and rescue therapy. Serum HBV DNA and ALT level were used to monitor therapy by 83,8% and 68,4%. 67% followed APASL recommendations for withdrawal of treatment in HBeAg–negative patients after 2 years of treatment with HBVDNA loss. HCC screening was considered for all HBV cases by 51,4%, cirrhotic only by 31,3 % using US (55,3%) and AFP (52,5%). Overall 68,2% have good knowledge about consideration of liver biopsy, treatment and antiviral prophylaxis. There was a significant difference between mean knowledge of gastroenterology and internal medicine specialty with a mean difference of 1,99, 95% CI 1,32-2,67, p= <0,001.

Conclusion

Overall the knowledge and compliance of clinical practices with guidelines was good. However, some areas of practices and knowledge need to be improved.

Table 1

Consideration for liver biopsy, treatment and antiviral prophylaxis in HBeAg +ve and HBeAg –ve patient

Case Scenarios			
Do you consider liver biopsy for following cases?	Yes (%)	No (%)	May Be (%)
a. HBeAg-ve, ALT > 2 x ULN, age > 40 yrs, HBV DNA > 2000 IU/ml	26,3	54,7	18,4
b. HBeAg+ve, ALT > 2 x ULN, age > 40 yrs, HBV DNA > 20,000 IU/ml	24,6	64,8	9,5
c. HBeAg-ve, Normal ALT, age > 40 yrs, HBV DNA >20,000 IU/ml	50,3	29,1	19,6
Would you start treatment for CHB in following cases?			
a. HBeAg-ve, normal ALT, age > 40 yrs, HBV DNA > 2000 IU/ml	24,0	51,4	23,5
b. HBeAg-ve, normal ALT, age < 40 yrs, HBV DNA > 2000 IU/ml	22,9	54,7	20,1
c. HBeAg-ve, ALT > 2 x ULN , age <40 yrs, HBV DNA > 2000 IU/ml	69,8	11,7	17,9
d. HBeAg+ve, normal ALT, age > 40 yrs, no cirrhosis, DNA > 20,000 IU/ml	59,2	21,8	19,0
e. HBeAg+ve, ALT > 2 x ULN , age < 40 yrs, HBV DNA > 20,000 IU/ml	92,2	2,5	5,0
f. HBeAg+ve, normal ALT, age > 40 yrs, moderate to severe cirrhosis, DNA > 20,000 IU/ml	66,5	18,4	14,0
Do you consider antiviral prophylaxis for following patients undergoing immunosuppression or chemotherapy?			
a.HBsAg+ve, HBV DNA< 4log	43,6	39,7	15,1
b.HBsAg+ve, HBV DNA >4log	73,2	15,1	10,6
c.HBsAg-ve, antiHBc+ve, HBV DNA undetectable	24,0	60,3	14,5
d.HBsAg-ve, antiHBc+ve,HBV DNA detectable	54,2	27,4	16,8

Table 2

Treatment management for suspected antiviral resistance

	Gastroenterology Consultant (n=41)	Internal Medicine Consultant (n= 35)	Gastroenterology Resident (n=17)	Internal Medicine Resident (n=86)
On LAM				
Switch to ADV	4,9	29	--	10,5
Switch to ETV	26,8	25,7	29.4	37,2
Switch to TDF	46,3	22,9	41.2	7,0
Add on ADV	17,1	25,7	5.9	10,5
Add on ETV	7,3	5,7	29,4	19,8
Add on TDF	9,8	2,9	11.8	1,2
Not sure what to do	2,4	37,1	11,8	27,9
On ADV				
Switch to ETV	36,6	31,4	35,3	26,7
Switch to LAM	--	--	--	9,3
Switch to Interferon	2,4	14,3	5,9	2,3
Switch to TDF	41,5	5,7	23,5	4,7
Add on LAM	7,3	8,6	5,9	9,3
Add on ETV	22,0	22,9	17,6	12,8
Not sure what to do	4,9	40,0	17,6	46,5
On ETV				
Switch to ADV	--	--	11,8	5,8
Switch to LAM	2,4	2,9	--	10,5
Switch to Interferon	2,4	22,9	5,9	17,4
Switch to TDF	65,9	31,4	47,1	11,6
Add on ADV	4,9	2,9	5,9	8,1
Add on TDF	24,4	25,7	23,5	8,1
Add on LAM	2,4	2,9	--	3,5
Not sure what to do	7,3	37,1	11,8	46,5
Multidrug Resistant (LAM+ADV OR ADV+ETV)				
Switch to TDF	46,3	8,6	23,5	5,8
Switch to TDF+ETV combination	34,1	28,6	41,2	25,6
Not sure what to do	17,1	62,9	35,3	68,6

Values given are in percentages
LAM lamivudine, ADV adefovir, TDF tenofovir and ETV entecavir

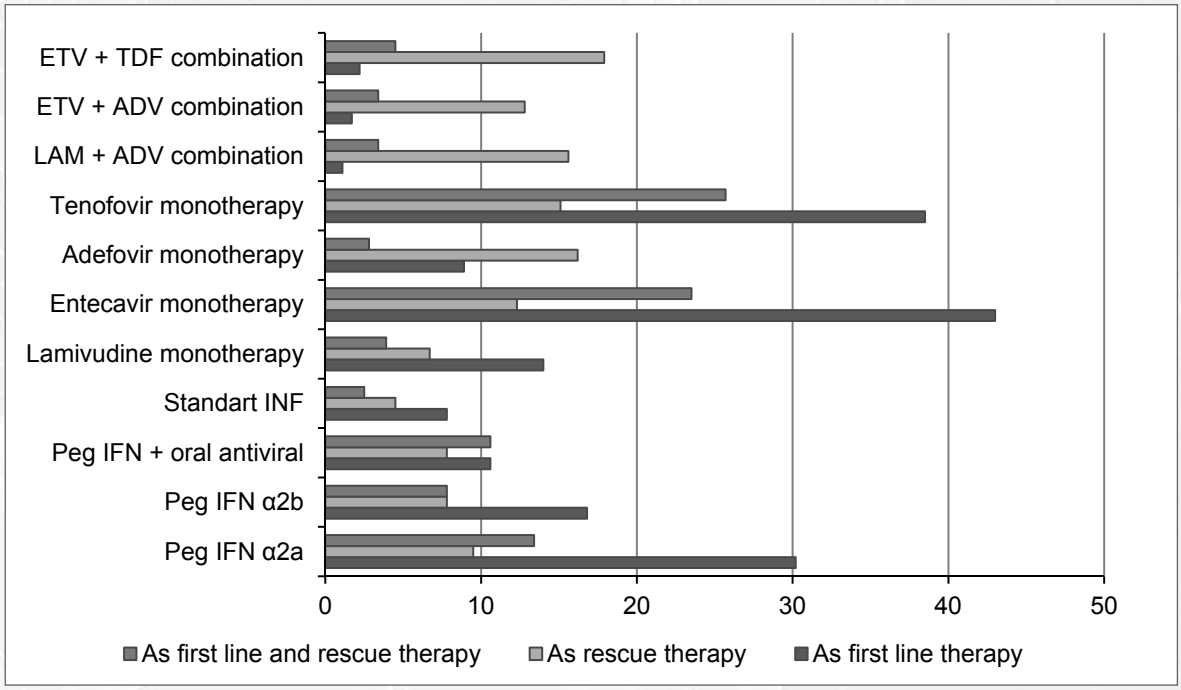

Fig. 1. Preferences for CHB therapy

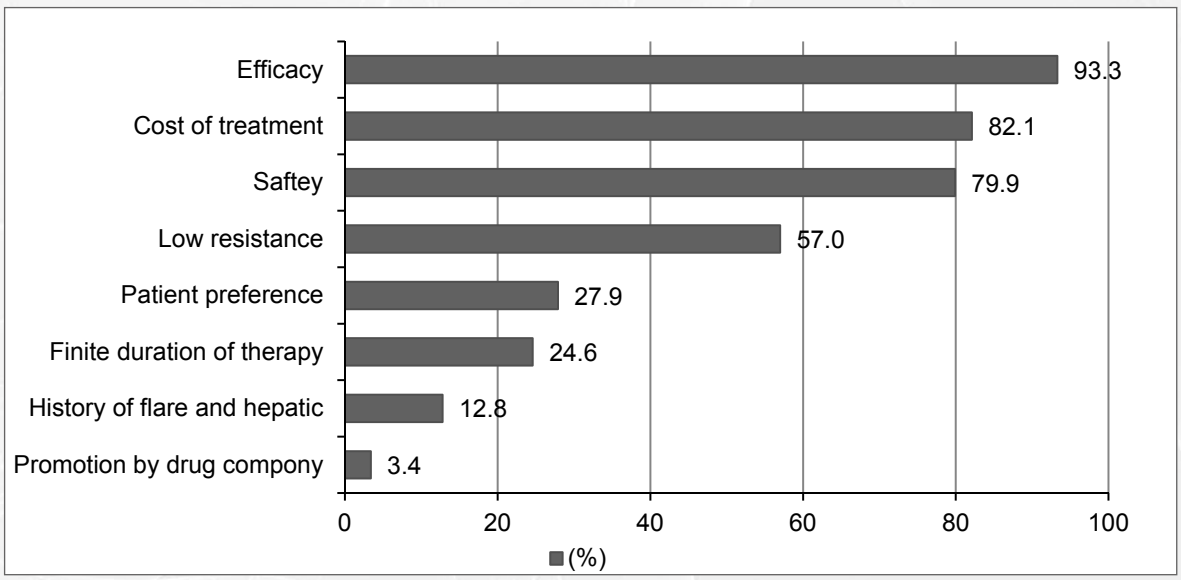

Fig. 2. Which factors would you consider for choosing the treatment for CHB? (Rank top four only)

LOSARTAN USE IN PATIENTS WITH CHRONIC VIRUS HEPATITIS B

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Background

The studies have shown that Losartan is effective at slowing down, halting or reversing liver fibrosis in patients with non-alcoholic steatohepatitis and chronic viral hepatitis C.

Objective

To study the antifibrotic action of losartan in patients with chronic virus hepatitis B *(*HBV).

Methods

A total of 44 patients with chronic HBV and 25 healthy controls were studied. Patients were divided into two groups. The first group (11 patients) received antiviral therapy according to conventional protocols. The second group included 13 patients who received antiviral therapy and antifibrotic treatment (Losartan) in a dose of 50 mg daily. Controlled treatment period was 24 weeks. The effectiveness of the treatment was monitored by the dynamics of the clinical syndromes and laboratory parameters. Laboratory parameters including TNF-α and IL-6 were determined at baseline and after 24 weeks.

Percutaneous needle liver biopsy and 13C-methacetin breath test (13C-MBT) was performed all patients. Liver fibrosis measured by METAVIR scoring system. 13C breath test data were expressed as means with standard deviation.

Results and discussion

According to 13C-MBT the hepatocytes mass in F3 METAVIR patients increased by 32% after the use of losartan, in compare with the results in first group. For F2 METAVIR this difference was 13%.

Conclusions

Long-term Losartan use (for 6 months) in a daily dose of 50 mg in treatment of patients with chronic HBV followed by improvements in 13C-MBT, indicating an increase *functioning hepatocyte mass*.

SERUM CYTOKINES ASSOCIATED WITH LIVER DYSFUNCTION DEGREE IN CHRONIC HBV PATIENTS

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Background

It is known that the proinflammatory cytokines as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) play important role in the development of liver disease. Clinical studies have demonstrated the role of these cytokines in the pathogenesis of chronic virus hepatitis B (HBV).

Objective

To identify the correlation of proinflammatory cytokines (TNF-α and IL-6) with the ^{13}C-MBT results in chronic HBV patients.

Methods

A total of 44 patients with chronic HBV and 25 healthy controls were studied. Special laboratory tests included the determination of serum levels of TNF-α and IL-6 by enzyme-linked immunosorbent assay.

Percutaneous needle liver biopsy and ^{13}C-methacetin breath test was performed all patients. Liver fibrosis measured by METAVIR scoring *system.*

Results and discussion

The data indicate that for chronic HBV including outcome in liver fibrosis accompanied by an increased concentration of TNF-α, IL-6 in serum (P <0,01 compared with control group).

In patients with normal liver function (*functioning hepatocyte mass* (FHM) = 100%) of the ^{13}C-MBT results, serum concentrations of cytokines exceeded 1,7 (for TNF-α) and 1,2 (for IL-6) times to control. The level of TNF-α and IL-6 was in patients with abnormal liver function (FHM less than 100%) of the ^{13}C-MBT results exceeded 5,1 (for TNF -α) and 3,9 (for IL-6) times to control.

Conclusions

Serum TNF-α and IL-6 is associated with hepatocytes mass and liver dysfunction degree, as evidenced by the differences in studied cytokines levels in subgroups of patients with normal and decreased liver function according to ^{13}C-MBT, as well as an inverse correlation between $^{13}CO_2$ cumulative dose and serum TNF-α (r = -0,75; P = 0,012) and serum IL-6 (r = -0,58; P = 0,016).

HBV/HDV IN ARMENIA

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Introduction

350-400 million people are HBV infected and 15-20 million have also been exposed to HDV. The prevalence HBV infection in Armenia is 2,0-3,0%. HBV vaccination program launched in Armenia in 1996 year.

Aim: To research the prevalence of HDV in patients of acute and chronic HBV and assessment clinical and serological features of HBV and HDV.

Methods

During 2010-2014, 373 patients with acute and chronic HBV infection were studied. These patients tested to HBV, HAV, HCV, HDV, HIV serological markers and underwent a study in liver function tests, complete blood count and ultrasound. Patients were 1,5–77 years old. There were only two children among them – 1,5 and 8 years old.

Results

96 of 373 patients had acute HBV, 165 – chronic HBV, 66 – liver cirrhosis and 46 – HBsAg carriers. Among patients with acute HBV 70% were of the 20-40 age group. The previously risk factor of transmission was medical procedures.

302 patient`s blood tested for anti-delta, 27 (8,9%) of them had HDV positive markers, from which 5 patients were with acute hepatitis HBV/HDV, 7 – with chronic hepatitis HBV/HDV, 2 – with HBV/HDV/HCV and 13 – with liver cirrhosis.

HDV infection detected in 4,4% (5/113) of acute HBV, 7,1% (9/127) of chronic, 21,0% (13/62) of cirrhosis. 5 patients with co-infection HBV/HDV had severe forms of disease. In 2 patients with triple coinfection HBV/HDV/HCV inhibition of genomes HBV and HCV has been observed.

More than half patients with cirrhosis had complications: ascites and liver encephalopathy. One patient had transformation from cirrhosis to primary liver cancer.

C**onclusion**

Armenia is an intermediate endemic region of HBV. The age of acute HBV patients shifted to older age group. The prevalence of HDV infection was 8,9%. More than 1/5 of patients with HBV cirrhosis had revealed positive markers of HDV.

THE AFFECTION OF THE MUCOUS MEMBRANE OF CHEEKS AND TONGUE IN VIRAL HEPATITIS B

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Background

The changes of the oral mucous membrane and the tissue of the parodont in acute and chronic infections affection of the liver, particularly in viral hepatitis B (VHB), attracted the attention of researches comparatively recently.

The objective of the present paper is the study and avaluation of the condition of buccal mucous membrane and the tongue in patients with VHB.

Materials and methods

50 patients from 20 to 57 have been treated at “Nork” Clinical Hospital of Infectious Diseases in Yerevan in 2014-201, 356 patients were men, 15 – women. The method of treatment was the objective examination of the oral cavity of the patients with VHB

Results and discussion

As a result of the objective examination of the buccal mucous membrane and the tongue, some changes of colour of the mucous membrane, hyperemia and cyanosis have been discovered. 17,4% of the patients had a coating of the tongue. The changes of the gums were accompanied by hyperemia, cyanosis, oedema, painful condition, and bleeding. Purulent discharges from pathological gingival pockets have been observed – the condition of the parodont reminds of hypertrophical gingivitis and parodontitis of the II–III degree depending on the form and severity of VHB.

Thus, the changes of the mucous membrane of the oral cavity and parodont in hepatitis B are characterized with various manifestations which are evident not only by functional, but also morphological breaches.

The obtained data show that we may suppose that the mucous membrane of the oral cavity and parodont are, in some degree, involved in the reciprocal reaction of the organism under the influence of hepatitis B virus.

ALLERGIC MANIFESTATIONS IN CHILDREN WITH CHRONIC HEPATITIS B AND LIVER CIRRHOSIS

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Backgraund

Chronic viral liver disease is still rather common in children. According to clinical observations children with chronic hepatitis B and liver cirrhosis developed also different allergic manifestations.

Aim: To study the frequency and clinical features of allergic manifestations in children with chronic hepatitis B and liver cirrhosis

Methods

128 patients with chronic hepatitis B and liver cirrhosis were investigated (aged 3-15 years). Allergic examination included medical history, prick skin tests with food and respiratory allergens in children with allergic history, as well as determining the total IgE in the blood by Eliza method.

Results and discussion

Allergic manifestations were observed in 56,2% of patients. Children with chronic viral hepatitis B developed more frequently food allergy (58,8%), then drug and respiratory allergy symptoms (respectively in 47,0% and 43,1% of cases). In patients with cirrhosis the frequency of drug allergy was higher (29,8%) in compare with manifestations of food (19,4%) and respiratory allergy (3,9%). Combined allergic reactions occurred in 52,9% of patients with chronic hepatitis B and in 14,2% - with liver cirrhosis. Elevated levels of total Ig E in the blood were detected in 74,3% of patients. They were 2 times higher in children with positive allergy history and correlated with disease activity.

Conclusions

In patients with chronic hepatitis B and liver cirrhosis HBV infection has sensitizing influence and contributing to the development of allergic manifestations. They were more often as a food and/or drug allergy manifestations, rare as a respiratory symptoms. Exacerbation of chronic viral liver disease accompanied by increased frequency of allergic manifestations, as well as by elevated levels of the total Ig E in the blood, which correlated with activity of the disease.

HEPATITIS B REACTIVATION AFTER PEGYLATED INTERFERON PLUS RIBAVIRIN IN CHRONIC HBV/HCV-COINFECTED TAIWANESE PATIENT

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Introduction

Pegylated interferon (PegIFN)/ribavirin combination therapy remains the standard of care for chronic hepatitis C (CHC) in areas where new direct antiviral agents (DAAs) are not available, such as Taiwan. PegIFN and nucleos(t)ides analogues (NAs) has been advocated as a first-line therapy in patients with chronic hepatitis B (CHB). Patients with chronic hepatitis C virus (HCV) and B virus (HBV) coinfection can be treated with PegIFN/ribavirin for CHC. Serum HBV DNA may appear in patients with undetectable pretreatment levels of HBV DNA before treatment. Since reactivation of hepatitis B in patient with inactive CHB, either spontaneously or under some clinical condition such as with immunosuppressive therapy or organ transplantation, can occur after the increase in serum HBV level. The hepatitis B reactivation has been considered as a condition which needs to be cared.

Case Presentation

A 53 year-old female patient visited our OPD due to seeking for therapy for her chronic hepatitis B and C diagnosed for years. She was an active CHC patient with positive serum HCV RNA as well as an inactive CHB carrier with negative serum HBV DNA. After PegIFN/ribavirin therapy for 24 weeks with the reimbursement of national health insurance, she got rapid, early and end-of-treatment virological response. The serum HBV DNA levels and HBeAg are negative during the period of PegIFN/ribavirin therapy. After cessation of anti-HCV therapy with follow-up, she suffered from reactivation of HBV at 1st month and flare of ALT (2116 IU/L) and jaundice (bilirubin: 2,54 mg/dL) at 3rd month and got admission thereafter. Telbivudine (600mg/day) was given with the peak INR up to 1,18 (on 5th day) and peak bilirubin up to 3,56 mg/dL (on 8th day) than became normal at 1st month after telbivudine therapy. The ALT and bilirubin levels remained within normal range with continuing therapy for more than 5 years NA therapy till now, with switching of telbivudine to lamivudine (100 mg/day) since18 months ago.

Laboratory findings:

Baseline positive HBs Ag, anti-HBe, anti-HCV and HCV RNA (PCR) and negative HBeAg and HBV DNA (PCR) were noted. HCV genotype: 1b. HCV RNA level: 690,312 IU/mL. Total bilirubin: 1,5 mg/dL and AST/ALT:35/45 IU/L. Abdominal sonography: chronic liver disease without cirrhosis. IL28B 8099917 genotype: TT (favorable).

During PegIFN/ribavirin therapy: negative for HCV RNA, HBeAg and HBV DNA.

After cessation PegIFN/ribavirin therapy: HBV DNA: 67,790 IU/mL at Month 1 and at 11,732,832 IU/mL at Month 3 with ALT: 2116 IU/L and Bilirubin: 2,54 mg/dL. Then telbivudine was given.

After telbivudine Therapy: persisted negative for HBV DNA, HBeAg and HCV RNA as well as normal ALT and bilirubin.

Conclusion

In the patients with inactive HBV-coinfection:

PegIFN/ribavirin combination therapy is effective for clearance of HCV.

Hepatitis B reactivation can occur severely (with jaundice) early and after cessation of PegIFN/ribavirin combination therapy. Closed monitoring is mandatory.

NA therapy is effective for reactivation of hepatitis B after PegIFN/ribavirin therapy and seems to have no impact on cleared HCV.

A CASE OF HBV RELATED CHRONIC LIVER DISEASE PRESENTING AS ACUTE HEPATITIS

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A 32-year-old gentleman presented with short history of jaundice, preceded by prodrome. He was disoriented at presentation. On examination, he was deeply icteric, had flapping tremor and ascites. Investigations revealed, serum bilirubin 9 mg/dl, ALT 3400 U/L, serum albumin 19 gm/L, INR 2,4, serum creatinine 2,1 mg/dl and total WBC count 17,400 cells/cmm. He had coarse liver and ascites on abdominal ultrasound. He underwent trans-jugular liver biopsy, which revealed HAI-NI 7 and HAI-F 3. He was HBsAg positive, HBeAg positive and anti HEV IgM positive and his HBV DNA was $2,3x10^5$ IU/ml.

CHEMOTHERAPY-INDUCCED FULMINAMT LIVER FAILURE IN ONCOHEMATOLOGICAL PATIENTS WITH HEPATITIS B VIRUS INFECTION (HBV)

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Introduction

HBV reactivation is a well described complication in chronic HBV infection for oncohematological patients receiving chemo/immunosupressive therapy. Reactivation of hepatitis B refers to the abrupt increase in HBV replication in a patient with inactive or resolved hepatitis B. Reactivation can occur spontaneously, but more typically is triggered by immunosuppressive therapy of cancer, autoimmune disease, or organ transplantation. Reactivation can be transient and clinically silent, but often causes a flare of disease that can be severe resulting in life-treating complications such as acute hepatic failure.

The liver-related mortality in patient with HBV reactivation varies from 4-60%.

Case Presentation

Male patient, 53 years old was hospitalized with severe jaundice and intoxication with hepatomegaly as well as ecchymosis of skin. He was HBsAg inactive carrier for 3 years, before starting chemotherapy with the diagnosis of chronic leukemia. The duration of chemotherapy was 3 moths (3course). Baseline transaminases were normal and HBV-DNA was negative.

Laboratory findings:

Baseline positive HBs Ag and negative HBV DNA, total bilirubin and AST, ALT were normal.

Laboratory results after 3 course of chemotherapy, positive HBsAg andHBV DNA, negative HBe Ag and Anti HBcor IgM, HBV DNA quantitative >100 000 000copies/ml, TB 368,3, direct-bil 241,7, ALT 4860 U/L, AST 3340 U/l, Albumin 25,0 PT 42%, WBC 42 k/ul, PLT 184 k/ul.

During 7 day of hospitalization despite of receiving pathogenetic, antiviral lamivudine and even artificial liver did not prevented progression of liver insufficiency to fulminant failure. The patient died due to hepatic encephalopathy and hepatorenal syndrome.

Conclusions

All onco/oncohematological patients should be checked for HBV before chemotherapy.

Prophylactic antiviral treatment with starting of chemotherapy significantly reduced the likelihood of HBV reactivation.

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UNUSUAL CASE OF HIGHLY REPLICATIVE HEPATITIS B VIRUS INFECTION WITH EXTRAHEPATIC MANIFESTATIONS

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Introduction

The two major extrahepatic complications of chronic HBV polyarteritis nodosa (PAN) and glomerular disease occur in 10-20%. In 1990 American College of Rheumatology established criteria's to differentiate PAN from other forms of vasculitis and selected 10 disease features: at least 3 of the 10 should be present for diagnosis. Antiviral therapy is the essential component in the treatment of HBV-related vasculitis, because it would be effective not only against possible aggravations of hepatitis due to enhanced viral replication after immunosuppressive therapy, but also for managing HBV-related vasculitis itself.

Case report

Patient, 44 years old male with insidious onset of disease – fatigue, arthralgia, asthenia. Epidemiological anamnesis: non-protected sexual contact 2 months before manifestation of disease. After 3-4 months – persistent high fever, weight loss 10kg, impotentia with subsequent Mononeuritis Multiplex N.Peroneus, N.Tibialis, cough, urticaria. First time was checked on HBV after 4 months from the start of disease: high viral load – 756.690.511 IU/ML, Abbott Real Time PCR; high quantity of HBsAg >124,25 IU/ML, Architech, Abbott; HBeAg positive. On 6 months of disease adds depression symptoms and high blood pressure with following laboratory findings: minimal aminotransferase activity, lymphopenia, anemia, ESR 99mm/hour, elevated glucose, creatinine, decreased creatinine clearance, CRP 19,12mg/dL, Anti-HDV, HIVCombo, RF, ANA and other autoimmune markers – negative. Liver elastography by FibroScan–F0. Diagnosis: acute progredient HBV-infection? HBV-associated vaculities/PAN, Mononeuritis multiplex N.Peroneus, N.Tibialis, rash, nephropathy. Because of very high replicative activity of HBV, which can progress to acute liver failure, and absence of life-threatening symptoms of vasculitis, monotherapy with Entecavir was started. Immunosuppressive therapy adds on 10 day of nucleotide analogue. 2 months later HBV-DNA quantification – 2358 IU/ML, with improvement of vasculitis symptoms.

Conclusion

Patients with vasculitis, especially PAN, should be checked on HBV-infection with opportunity of etiotropic treatment for complex disease and prevention of acute liver failure and chronisation.

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TREATMENT OF CHRONIC HEPATITIS B IN BELARUS: TENOFOVIR VS LAMIVUDINE

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Background: Chronic hepatitis B is a global problem affecting more than 350 million people. Prevalence of CHB in Eastern Europe is considered to be intermediate (2,4%). Hepatitis B virus has 10 genotypes, with clinical features and treatment options varying in different genotypes.

Methods: 51 adult CHB (HBsAg-positive) Belarus patients were included. HBV genotype was identified in part of patients. Phylogenetic analysis was performed. Treatment effectiveness was accessed at 6 month and 24 month.

Results: HBV genotype/subtype was identified in 29/59 (56,9) patients. 26 patients had D genotype of HBV, and others 3 had A genotype. Study subgroups were defined according to treatment regimen. Treatment efficiency (virologic, biochemical response) was compared between Lamivudine and Tenofovir groups. There was no significant difference in probability of ALT normalization at 6 months of therapy between Lamivudine subgroup and Tenofovir subgroup (hazard ratio, 0,55; 95% CI 0,24 – 1,3; P=0,0721). Significant difference was found in probability of aviremia at 24 months of therapy (hazard ratio, 2,46; 95% CI 1,05 – 5,79; P = 0,0484).

Conclusion: Genotype D was found to be the most common in Belarus. Tenofovir was superior to Lamivudine.

Keywords: *chronic hepatitis B, genotype, treatment, Lamivudine, Tenofovir*

More than 2 billion people globally are estimated to have been infected with hepatitis B virus, and more than 240 million (WHO 2015) people have chronic hepatitis B currently. Geographic disparities in disease prevalence (1% - 20%) are observed worldwide [1].

In areas of intermediate prevalence of chronic hepatitis B (3-5%), including Eastern Europe (2,4%), sexual and percutaneous transmission and perinatal transmission are consider to be main transmission routes [2].

Hepatitis B virus has 10 distinct genotypes (A to J) and several subtypes, genotypes A2 and D are the most common in Europe.

Different genotypes affect natural history of HBV infection. Acute infection with genotypes A1 and D results in higher rates of chronicity than genotypes A2, B and C. Patients infected with genotypes C and D, HBV tends to have HBe antigen seroconversion less frequently than patients with genotypes A2 and B. Genotypes C and D are associated with higher rates of the most dangerous sequelae, cirrhosis, and HCC. Genotype A2 and B patients have better responses to interferon-based therapy than genotypes C and D, but there are few consistent differences for direct HBV antivirals [3].

Chronic hepatitis B results in more than half a million deaths annually worldwide due to its complications of liver decompensation and/or hepatocellular carcinoma [4]. Prognosis of decompensated HBV cirrhosis without antiviral therapy is usually poor with a 5-year survival rate 14-35% [5].

The goal of therapy for CHB is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC, liver transplant and death. This goal can be achieved if HBV replication can be suppressed in a sustained manner [6].

There are two broad therapeutic options available for antiviral treatment of chronic hepatitis B infection, injectables (pegylated interferon alpha (PegIFN)) and oral therapies including nucleos(t)ide analogues (NAs). The advantages of PegIFN include a finite course of treatment, the absence of drug resistance, and an opportunity to obtain a durable post-treatment response to therapy in 13-17% of patients. However, PegIFN carries numerous side effects and the treatment is often discontinued prematurely. The advantages of NAs are excellent tolerance and potent antiviral activity associated with high rates of on-treatment response to therapy defined by ALT normalization and DNA suppression to less than LOQ. New oral NAs such as entecavir and tenofovir are the

ARTICLE

first line medications for HBV and effectively suppress hepatitis B virus (HBV) with minimal risk of drug resistance. Treating patients with chronic hepatitis B, >90% of adherent patients will become HBV-DNA undetectable within the first one to two years of treatment with these drugs [7].

Approximately 0,5 % patients spontaneously seroconvert annually from having the hepatitis B surface antigen (HBsAg) to having the hepatitis B surface antibody (anti-HBs) [8]. In HBsAg-positive patients treated with PegIFN and tenofovir during 48 weeks HBsAg loss rate was 7,5%, and 5,7% seroconverted from HBsAg to anti HBs [9]. Long-term studies with TDF has shown HBsAg loss to be over 10%.

Material and Methods

We have performed a study of an antiviral therapy of 51 adult CHB (HBsAg-positive) patients who were on dispensary observation between 1995 and 2014 at Center of Viral Hepatitis (Minsk City Hospital of Infectious Diseases).

HBV DNA was isolated using the "RIBO-prep 100" commercial kit. Nested PCR carried out on Veriti Thermal Cycler, AB, USA , in final volume 25µl: 1st round: 2,5µl 10x PCR Buffer, 1,5µl 25mM $MgCl_2$, 0,5µl 10mM dNTPs, 0,2µl 5U/µl TaqPol, 16,9µl H2O, 0,2µl 10pM primers p1, pR5, 3µl HBV DNA.

2nd round PCR: Buffer x10 2.5 µl; 25 mM MgCl2, 1,5µl; 10mM dNTPs 0.5µl; 0,2µl primer p4 10pM; 0,2µl primer pr2 10pM; 0.2CTaqPol 5U/µ; H_2O -16,9µl; DNA - 3µl. Both PCR rounds carried out in the following regime:

95°C – 3 min;
95°C – 30sec;
55°C – 30 sec:
72°C – 1.5min;
72°C – 5 min;
100°C - store
} 35 cycles

PCR products purification was performed by using Thermo Scientific GeneJet PCR purification Kit.

Electrophoresis of DNA fragments cleaned after PCR was conducted at the genetic Analyzer ABI PRISM 3100-Avant, Applied Biosystems, USA.

HBV drug resistance, HBsAg escape mutations identification and sequence analysis software products "Sequencing Analysis" v.5.1.1, BioEdit, SeqScape, "HBV Drug Resistance Database" Stanford University, HBV-Grade 12/2008 and Gen02phenov3 were used.

Double-stranded sequencing was performed with the BigDye terminator sequencing kit (Applied Biosystems v.3.1, Foster City, CA). Phylogenetic analysis using MEGA4.1 software with the neighbor-joining and Kimura two-parameter method was performed.

All statistical analysis and construction of graphic images were performed using MedCalc for Windows version 12.7 (MedCalc Software, Ostend, Belgium).

Categorical variables (i.e. presence or absence of attribute) were described in form of proportions using %), continuous variables with normal distribution were described in form of a mean ± standard error of the mean (±SEM) or in the form of a median with interquartile range in case of non-normal distribution. Values of the variables were presented with 95% confidence intervals [95% CI]. Follow-up time was defined from treatment initiation to date of last medical examination. Categorical variables were assessed with the Chi-squared test; continuous variables were assessed with the Student's t-test (necessity of Welch correction for unequal variances was estimated with preceding F-test) if normally distributed and with nonparametric methods (the Mann-Whitney test for independent samples) if not. Normality of variables was evaluated with one-sample Kolmogorov-Smirnov test. Kaplan-Meier survival analysis was performed to estimate probabilities of aviremia (reduction of viral DNA to undetectable level tested with PCR) and ALT normalization. Next log-rank test was used to compare survival functions describing these variables. For all statistical tests a two-tailed P value less than 0,05 was considered significant.

Results

We included 51 eligible patients, 34 males and 17 females (M/F ratio = 2/1). Mean age at baseline was 43,8±1,9 years (min 22, max 83). At the end of follow-up 24% patients (12/51) completed a course of antiviral therapy. Mean duration time of therapy before termination was 16,8±2,3 months [95% CI 11,7-21,9 months]. 92% patients (47/51) were tested for HBe antigen at the initiation of antiviral therapy. There was 38% (18/47) HBeAg-positive patients and 62% (29/47) HBeAg-negative patients. 12% (6/51) patients had clinical signs of cirrhosis of the liver.

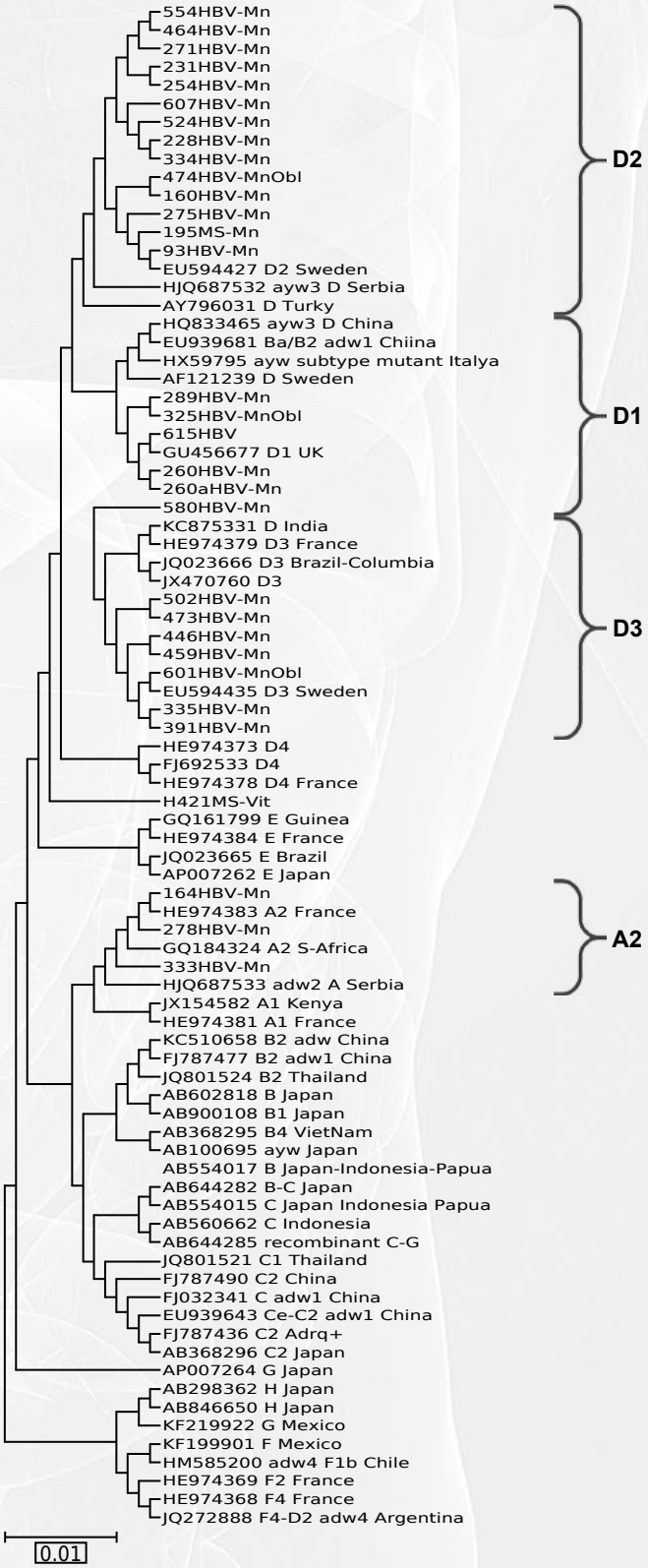

Fig. 1. Phylogenetic analysis of HBV DNA from Belarus

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Of 51 taken blood plasma samples in 29 (56,9%) HBV genotypes/subtypes were defined. 26 isolates belonged to D genotype and 3 to A. From 26 samples of D genotype, 14 (53,8%) were defined as D2a subtype, 8 (30,8%) – D3 and 4 (15,4%) – D1. All isolates of A genotype belonged to A2 subtype (Fig. 1). In 11 DNA samples D2 subtype were revealed so-called Vaccine-escape mutation P127T and in two specimens (subtype D2 and D3) mutations 180M, 204V resulting in virus drug resistance to lamivudine, telbivudine, (Tyzeka, Sebivo), and also resulting in partial resistance to entecavir (Baraclude) is found.

Following subgroups of study were defined according to drugs being applied.

- **Lamivudine (41%; 21/51)**
- **Tenofovir (41%; 21/51)**
- **Other variants** (18%; 9/51) including **Telbividine** (56%; 5/9) and combination of **Lamivudine and Tenofovir** (44%; 4/9).

Pretreatment characteristics of CHB patients of Lamivudine subgroup (n=21)

Mean age of patients of given group was 48,9±11,3 years. Male to female ratio was 1,33/1.

Blood serum of 91% patients (19/21) was tested for HBe antigen. There was 21% (4/19) HBeAg-positive patients and 79% (15/19) HBeAg-negative patients. 71% patients (15/21) were also tested for anti-HBcore IgM at the initiation of antiviral therapy. Anti-HBcore IgM was found in 60% (9/15) patients, in 40% (6/16) patients anti-HBcore IgM were absent.

Median baseline ALT level was 1,87 times above the upper limit of normal [95% CI 1,01 – 2,92] (interquartile range from 0,91 [95% CI 0,60 – 1,54] to 3,86 [95% CI 2,15 – 12,82]). Baseline ALT level exceeded the upper limit of normal in 57% (12/21) patients.

Median viral load level (DNA HBV) was 29,5x106 copies/ml [95% CI 1,46x106 – 100x106 copies/ml].

Mean follow-up time equaled 21,3±3,0 months [95% CI 15,3-27,5 months].

Characteristics of antiviral therapy effectiveness in Lamivudine subgroup (n=21)

Biochemical response was evaluated with Kaplan-Meier survival analysis among 12 patients with initially increased ALT level (Fig. 2).

Normalization of ALT serum level occurred in 33% (4/12) patients at the end of the first month of

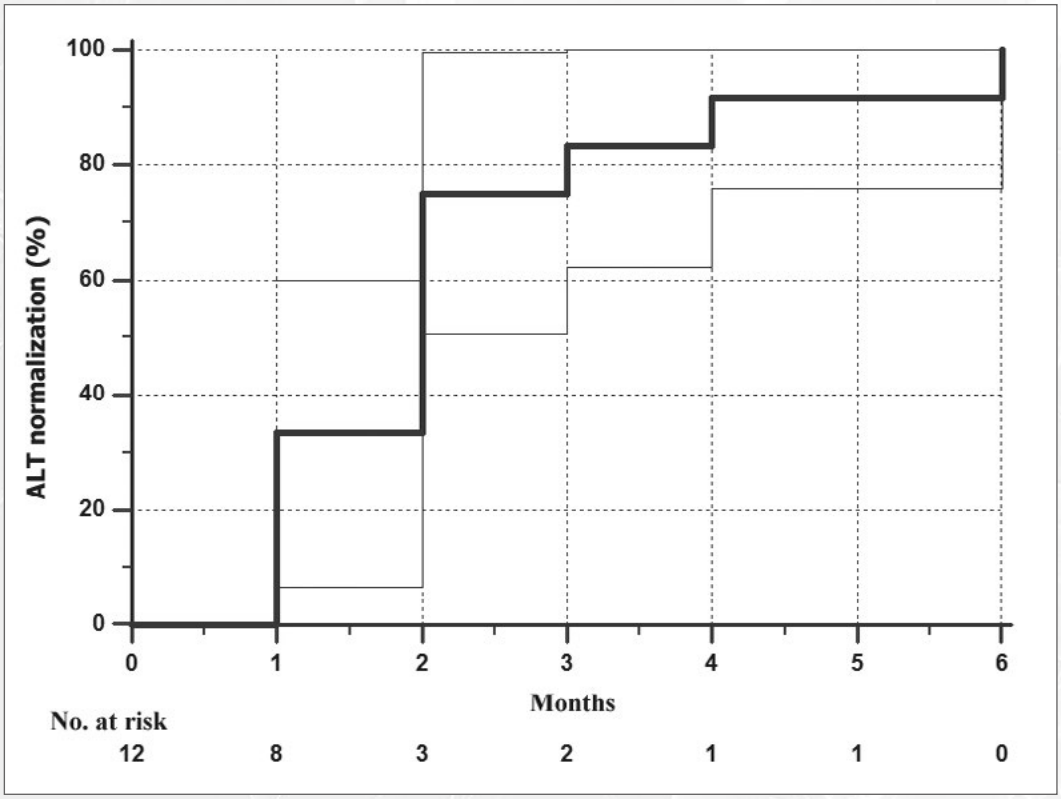

Fig. 2. Biochemical response to antiviral therapy in Lamivudine subgroup (n=12)

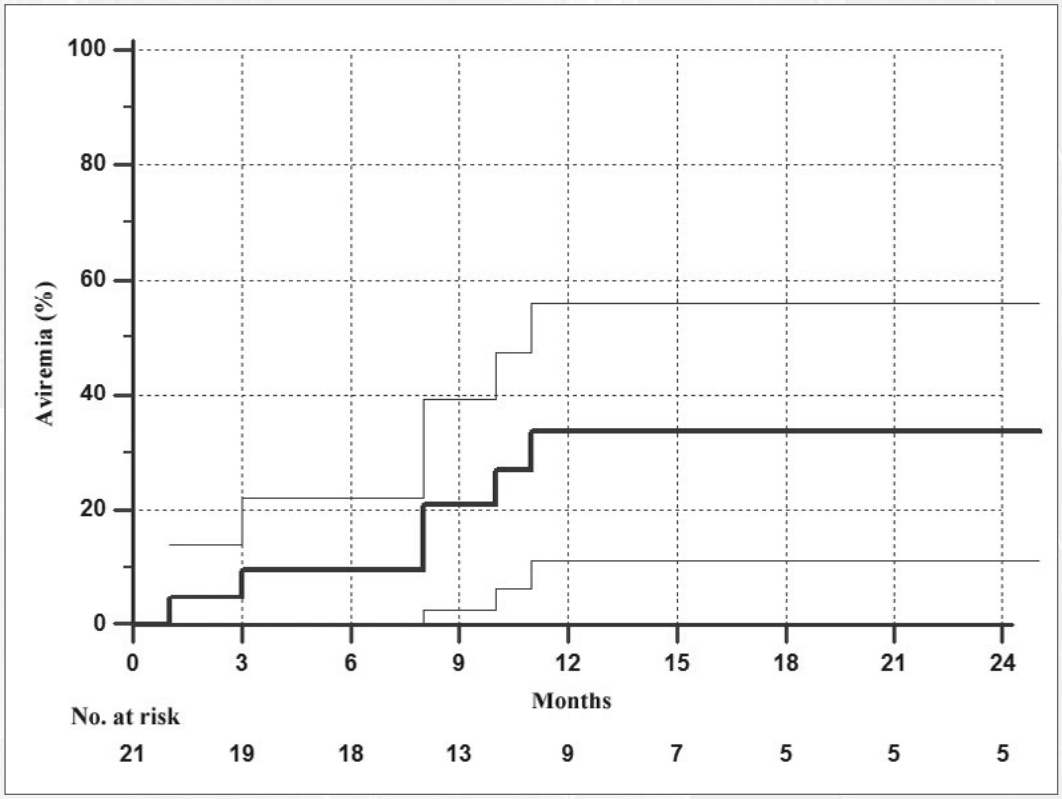

Fig. 3. Virological response to antiviral therapy in Lamivudine subgroup (n=21)

antiviral therapy, in 75% (9/12) patients at the end of the second month, in 92% (11/12) patients at the fourth month, and in 100% patients (12/12) at the sixth month.

HBeAg seroconversion appeared in 1 of 4 initially HBeAg-positive patients.

As the result of two-year (24 month) antiviral therapy in lamivudine subgroup aviremia was observed in 29% (6/21) patients. On average, aviremia was reached after 6,8±1,6 months [95% CI 2,6-11,0 months], including minimum of 1 month and maximum of 11 months.

Virological response (i.e. aviremia or complete HBV suppression) was estimated with Kaplan-Meier survival analysis, the derived data was rendered at survival curve (Fig. 3). In given subgroup (Lamivudine, n=21) aviremia frequency comprised 9,5% [95% CI 0-22,0%] at 3 months of therapy, 20,7% [95% CI 2,6-38,9%] at 9 months and 33,5% [95% CI 11,3-56%] at 12 months.

Partial virological response (defined as a decrease in HBV DNA of more than 1 log10 copies/ml but detectable HBV DNA after 6 months of therapy [9]) was observed in 71% (15/21) patients.

Virological breakthrough (defined as an increase in HBV DNA level of more than 1 log10 copies/ml compared to lowest value HBV DNA level on therapy [9]) was observed in 48% (10/21) patients during two-year follow-up, including 40% (4/10) patients with preceding aviremia on current therapy. Mean treatment time in given subgroup (Lamivudine, n=21) before signs of virological breakthrough appeared was 10,5±2,1 months [95% CI 5,8 – 15,2 months], including minimum of 2 months and maximum of 24 months.

Evidence of primary non-response was not seen in this subgroup (n=21).

Pretreatment characteristics of CHB patients of Tenofovir subgroup (n=21)

The total number of patients was 21. Mean age in given subgroup was 42,3±16,5 years. The number of males was 17, the number of females – 4. M/F ratio was 4,3/1.

95% patients (20/21) were tested for HBe antigen at the initiation of antiviral therapy. There were 50% (10/20) HBeAg-positive patients and other 50% (10/20) patients had negative HBeAg status. 67%

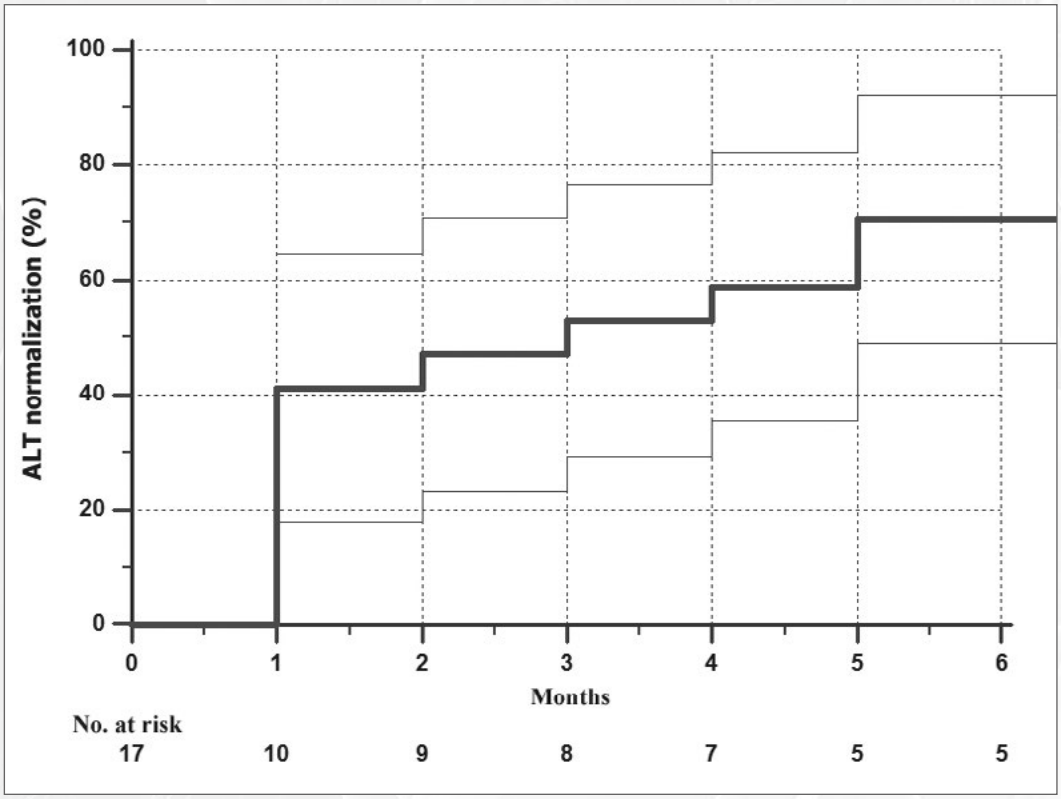

Fig. 4. Biochemical response to antiviral therapy in Tenofovir subgroup (n=17)

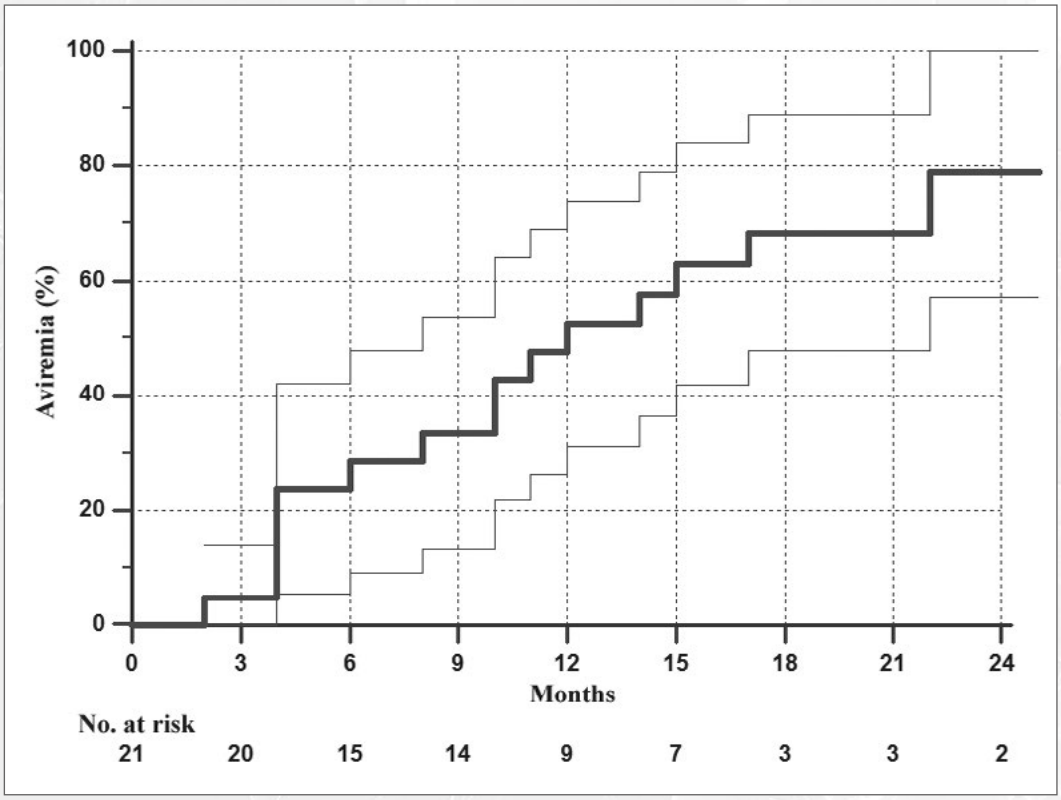

Fig. 5. Virological response to antiviral therapy in Tenofovir subgroup (n=21)

patients (14/21) were tested for anti-HBcore IgM at the initiation of antiviral therapy. Anti-HBcore IgM appeared in 43% (6/14) patients, in 57% (8/14) patients anti-HBcore IgM were absent.

Mean follow-up time comprised 25,3±2,0 months [95% CI 20,4-29 months].

48% (10/21) patients of Tenofovir subgroup had prior antiviral therapy with lamivudine in anamnesis. The main reason of lamivudine discontinuation was forming of drug resistance and subsequent virological breakthrough. Mean time before drug resistance appearance was 8,4±1,4 months [95% CI 5,3-11,6 months] including minimum of 2 months and maximum of 14 months before forming of drug resistance. It should be noted that among the patients of the Tenofovir subgroup with prior lamivudine therapy in anamnesis (10/21) there were no patients included to Lamivudine subgroup.

Median baseline ALT level in Tenofovir subgroup was 2,38 times above the upper limit of normal [95% CI 2 – 3,9] (interquartile range 1,27 [95% CI 0,49 – 2,27] to 4,27 [95% CI 3,14 – 6,56]). Baseline ALT level exceeded the upper limit of normal in 81% (17/21) patients (normal ALT levels in our laboratories were less than 65 U/L).

Median viral load level (DNA HBV) was $3,6x10^6$ IU/ml [95% CI $0,94x10^5$ – $20x10^6$ IU/ml].

Characteristics of antiviral therapy effectiveness in Tenofovir subgroup (n=21)

Biochemical response was evaluated with Kaplan-Meier survival analysis among 17 patients with initially increased ALT level (Fig. 4).

Normalization of ALT serum level occurred in 41% (7/17) patients at the end of 1 month of antiviral therapy, in 47% (8/17) patients at the end of 2 months, in 59% (10/17) patients at the 4 months, and in 71% (12/17) patients at 6 months.

HBeAg seroconversion appeared in 40% (4/10) initially HBeAg-positive patients.

Aviremia in patients on two-year (24 months) antiviral therapy with tenofovir occurred in 71% (15/21). On average, aviremia was reached after 9,5±1,5 months [95% CI 6,34-12,72 months], including minimum of 2 month and maximum of 22 months. Aviremia was estimated with Kaplan-Meier survival analysis, derived data was rendered at survival curve (Fig. 5). In Tenofovir subgroup (n=21) aviremia frequency comprised 4,71% [95% CI 0-13,87%] at 3 months of therapy, 33,25% [95% CI 13,1-53,4%] at 9 months, 52,36% [95% CI 30,9-73,82%] at 12 months, and 78,8% [95% CI 57,1-99,5%] at 24 months. Consequently, up to 78,7% events of aviremia may be estimated during two-year antiviral therapy with tenofovir in this subgroup.

Partial virological response (defined as a decrease in HBV DNA of more than 1 log10 copies/ml but detectable HBV DNA after 6 months of therapy) was observed in 29% (6/21) patients.

Signs of primary non-response were absent in this subgroup (n=21).

Characteristics of CHB patients of Others antiviral therapies subgroup (n=9)

Mean age in given subgroup equaled 35,3±1,5 years. Number of males 5, number of females 4. M/F ratio was 1,25/1.

56% (5/9) patients were treated with telbivudine.

Table 1

Baseline characteristics for CHB patients treated with lamivudine (n=21) and tenofovir (n=21)

	Lamivudine (n = 21)	Tenofovir (n = 21)	P
Age (years)	48,9±11,3	42,3±16,5	0,14
Male	12 (57%)	17 (81%)	0,18
Follow-up time (months)	21±3	25±2	0,37
HBe antigen	4/19 (21%)	10/20 (50%)	0,12
Anti-HBcore IgM	9/15 (60%)	6/14 (43%)	0,59
ALT median (times above ULN[a])	1,87	2,38	0,51
Patients with ALT higher ULN	12/21 (57%)	17/21 (81%)	0,18
DNA HBV median (copies/ml)	$29,5x10^6$	$18x10^6$	0,71
Cirrhosis	3/21 (14%)	4/21 (19%)	0,98

[α] ***ULN denotes "upper limit of normal"***

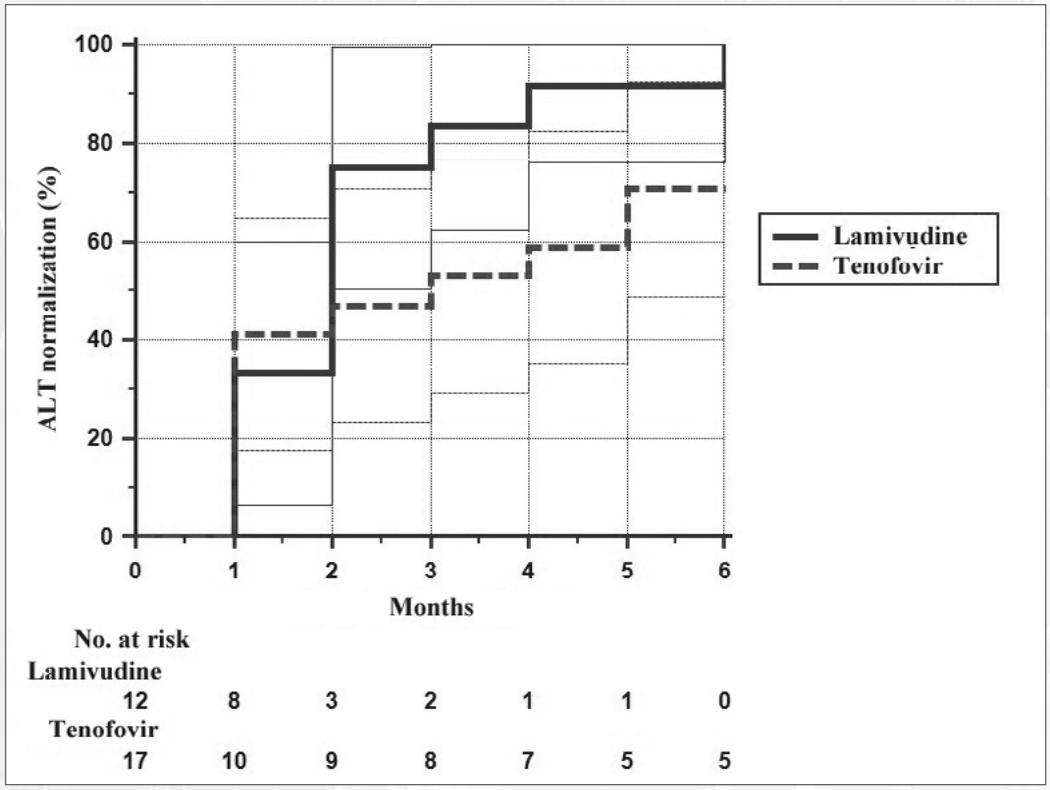

Fig. 6. Biochemical response, tenofovir (n=21) vs. lamivudine (n=21)

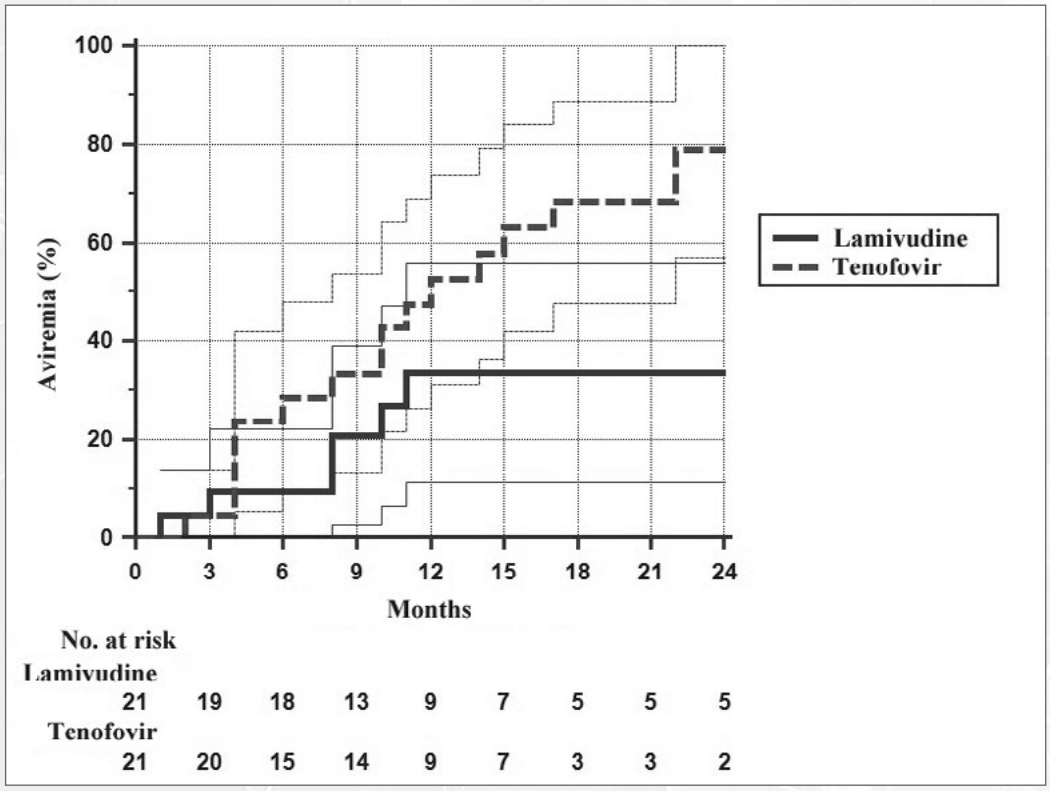

Fig. 7. Virological response, tenofovir (n=21) vs. lamivudine (n=21)

Table 2

Estimated rates of aviremia, Lamivudine (n=21) subgroup and Tenofovir (n=21) subgroup

	Months			
Treatment	3	9	12	24
Lamivudine (n=21)	9,5% [0-22,0%]	20,7% [2,6-38,9%]	33,5% [11,3-56%]	33,5% [11,3-56%]
Tenofovir (n=21)	4,71% [0-13,87%]	33,25% [13,1-53,4%]	52,36% [30,9-73,8%]	78,8% [57,1-99,5%]

80% patients (4/5) were tested for HBe antigen at the initiation of antiviral therapy and only 1 patient had positive HBe antigen test.

Baseline ALT level exceeded the upper limit of normal in 60% (3/5) patients.

Normalization of ALT occurred in 67% (2/3) patients with initially increased ALT level at 6th month of antiviral therapy. The only HBeAg-positive patient seroconverted at third month of telbivudine therapy. 40 % (2/5) patients achieved aviremia, partial virological response occurred in 40% (2/5) patients.

In a part of patients in given subgroup – 44% (4/9) – lamivudine antiviral therapy was enhanced with adding tenofovir into scheme of treatment. Tenofovir was started at 2, 8, 9 and 11 month after initiation of lamivudine. Reduction of DNA HBV of more than 1 log10 copies/ml was observed in all patients soon after tenofovir initiation. One patient (male, age at initiation of antiviral therapy 39, HBeAg-positive, HBV genotype A2, tenofovir added to lamivudine after 8 months of therapy) had simultaneous HBeAg and HBsAg seroconversion at 15th month of antiviral therapy. Seroconversion of HBsAg was accompanied by ALT normalization and aviremia. As a result of follow-up during the next 11 months this patient had antibodies to HBsAg, no detectable HBsAg and negative PCR assay for DNA HBV.

Effectiveness comparison between Lamivudine (n=21) and Tenofovir (n=21).

Pretreatment characteristics were similar among both Lamivudine and Tenofovir subgroups at the moment of antiviral therapy initiation (Table 1).

Kaplan-Meier survival analysis for two subgroups with subsequent log-rank test was used in order to compare both biochemical and virological effectiveness of lamivudine and tenofovir.

As a result of log-rank test there was no significant difference in probability of ALT normalization between Lamivudine subgroup and Tenofovir subgroup (hazard ratio, 0,55; 95% CI 0,24 – 1,3; P=0,0721) (Fig. 6).

Log-rank test was applied to K-M survival curves of aviremia probability in both subgroups, Lamivudine (n=21) and Tenofovir (n=21); significant difference was found in probability of aviremia (hazard ratio, 2,46; 95% CI 1,05 – 5,79; P = 0,0484) (Fig. 7).

Estimated rates of aviremia with [95% CI] for Lamivudine and Tenofovir subgroups are listed in Table 2.

Consequently, we found statistical significant difference in virological effectiveness between Lamivudine and Tenofovir subgroups (P=0,0484). This fact may be the evidence of more potent antiviral effectiveness of tenofovir.

Conclusions

A high prevalence of genotype D, subtype D2 HBV was observed.

As a result of comparison between tenofovir and lamivudine in normalizing ALT at 6 months in CHB patients there was no significant difference (hazard ratio, 0,55; 95% CI 0,24 – 1,3; P=0,0721).

We found statistically significant difference in probability of complete virological response at 24 months between antiviral therapy with tenofovir and lamivudine (hazard ratio, 2,46; 95% CI 1,05 – 5,79; P = 0,0484). There is evidence of tenofovir superiority to lamivudine in suppression of hepatitis B virus replication.

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