NASVAC: a therapeutic vaccine with potentialities to improve the quality of life of chronic hepatitis B patients

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*I*ntroduction

Here we show the show the points of view of Julio Cesar Aguilar PhD, who kindly accepted to share with us his points of view on the current development of therapeutics against hepatitis B. He is the scientific leader of the NASVAC vaccine project at the Vaccine Department, in the Center for Genetic Engineering and Biotechnology (CIGB) of Havana, Cuba.

*W*hat is the global situation of Hepatitis B disease in 2011 and what is the disease expectative in the next five years?

The Hepatitis B Virus (HBV) is a widely spread virus. According to the World Health Organization (WHO) more than one third of the world population has been infected with the Hepatitis B Virus. As a result, 350 to 400 million individuals are chronically infected -defined as persons with positive serology to HBsAg for more than 6 months. However, the prevalence of chronic hepatitis B (CHB) is higher in the southeast of Asia, sub-Saharan Africa and the Amazonia [1]. As you can easily realize, this is a problem starting in the viral infectivity and ending in the economic arena with a little bit of everything.

The infection usually occurs early in life in countries with high prevalence as the virus can be transmitted from mother to child. In addition, parenteral and sexual routes of transmission are also very efficient. The long-term sustained HBV chronic infection leads to a progressive hepatic disease that could result in the development of more severe complications like liver cirrhosis and/or cancer in approximately 25% of carriers. In the last decade it was considered that more than one million HBV related deaths were produced worldwide due to the different forms of progression of this viral infection [2]. Current picture is not very different as the progression of the disease depends on the pool of already infected patients and the current treatments have several limitations.

The treatment with alpha interferon (IFN-α), its polyethylenglycol-conjugated variant (PEG-IFN) and nucleos(t)ide analogs such as Lamivudine, Adefovir-dipivoxil, Entecavir, Tenofovir and Telbivudine. These drugs/treatments have a poor efficacy in terms of sustained virus clearance (from 7 to 20% of patients according to patients' characteristics) and they produce important side effects [3]. The situation in poor countries is really dramatic as the inefficacy of drugs is linked to the high cost of treatments and to inadequate diagnostic and patient follow-up.

The development of the anti-HBV vaccine, efficient to prevent HBV infection in a large percentage of cases, represents one of the most important medical achievements of the last century. At the present time more than 150 countries offer the anti-hepatitis B vaccine through immunization programs to children, adolescents and high risk groups. The next five years will show a reduction in the incidence of new infections, mostly in children. However, according to the current situation and the characteristics of the viral infection and treatments, the CHB will remain as a serious health problem for a long time.

*W*hat is missing worldwide to control Hepatitis B: political will of authorities? Funds? Technical capabilities? or a little bit of everything?

Based on the vaccine implementation programs for prevention in most countries, the epidemiological situation will improve. However, the poor efficacy of current treatments, their cost and limited accessibility for patients, the individual and national economic problems, as well as the political willing of governments will modulate this improvement in the future. The prevention will be the motor for global epidemiological improvement, no doubt; however the huge pool of patients with the virus will remain for a long time based on the previously explained factors.

To give you some details, I can tell you that the control of hepatitis B disease is a hard task and requires a strong commitment from governments. The organization of society reducing the role and power of the state in the poor countries (neoliberalism) is undoubtedly the worst enemy in CHB control. At present, the situation of poor countries is dramatic. Treatments are expensive, only a small percentage of patients requiring therapy are under treatment in these countries with the higher prevalence only because of the cost. The pegylated interferon reach 300 USD per injection and one year treatment requires 48 injections. In countries like the US, where insurance companies partially cover the expenses, patients cannot afford to cover their part and this is one of the main reasons of poor retention in therapy. But, lets imagine the case you have the money,…this is not the end, the efficacy of current therapies are limited to the period "on-therapy" but the virus will rebound in about 80% of patients "off-therapy" and the virus will rebound -sometimes with ALT flares. Also an important number of patients develop mutants, which is associated also to disease exacerbations [4]. A minority of patients remain with undetectable viral levels after therapy.

Usually, a person from the third world doesn't have support from their governments in any aspect, sometimes with some programs they will be detected as HBsAg positive, however, they will probably remain untreated based on the lack of medical advice/access,

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or the lack of correct follow-up. The disease requires specific virological, biochemical, histological, serological and hematological determinations, reaching several hundreds of dollars and related expenses like hospitalization costs, transportation costs, etc. In addition liver function tests, ultrasound and hematological studies are also required before the histological examinations, and hematological tests are required during treatment and follow-up… you need a lot of money only to know if you require treatment or not. This is important because the current treatments are limited due to the lack of efficacy in some specific conditions and due to adverse effects. Sometimes the doctors have to decide about patient therapy with few studies without accomplishing the international guidelines as they cannot afford paying several diagnostic rounds… and then patients are lost during follow-up, only due to the expenses, leaving doctor attention without therapeutic advice.

If patient's money is enough to cover the diagnostic procedures and medical attention (10 to 30% of patients in poor countries), then you need to pay for therapy. Doctors' recommendation should be a minimum of one year therapy, as this is the minimum time for antivirals, however companies sell the antivirals at daily basis -due to high price- and patients take the pills only for few weeks. Why? Patients think they are cured when some transitory symptoms improve (probably the symptoms improved just because of the variable nature of the disease) and they abandon the therapy as a result of economic problems. In summary, the expenditure of thousands of dollars to tackle a disease that is asymptomatic or fluctuates with spared flares over time for a number of years results in a non-critical decision for persons without money to cover some other fundamental or urgent activities of life. This is the picture of most poor countries today. This is a miserable way to nowhere.

The Cuban health system, still with some limitations in high-tech diagnostics, offer several possibilities at the level of prevention, diagnostic and therapy that have contained the spreading of the virus even in a region with an important level of prevalence. The case of Cuba is an important experience for the third world and offers a hope. The dramatic reduction in the incidence of the disease and the containment in the prevalence of CHB in the low level range are positive scenarios. Our group is also fighting in parallel for overcoming some of these problems.

What is your view on the use of a therapeutic Hep B vaccine? Are these vaccines following a common strategic path design? How many groups are working worldwide in anti HB therapeutic vaccines? How to characterize NASVAC as a future product versus other therapeutic vaccines and other therapeutic drugs against chronic Hepatitis B?

Since the last years of the XX century researchers are undergoing the assessment of a vaccine as a treatment against chronic HBV infection. This therapeutic strategy has attracted remarkable interest, based on results evidencing the fundamental role of the immune response in the control of this virus. The strategy of the different groups working in this topic is subverting the HBV immune-tolerance by administering commercially available or newly designed vaccine formulations.

Almost all preventive vaccines commercially available have been used in chronic hepatitis B patients in order to explore their potentialities. The results in the field of immunotherapy using conventional preventive vaccines, basically from 1990 to 2005, have been inconclusive, suggesting the need for more potent vaccine candidates including new antigens, adjuvants, administration routes and rationally combined therapies [5].

It is considered today that the design of optimal vaccine candidates must take into account the development of the antigenic component as well as those related with the adjuvant strategy of the formulation, as well as the optimal route and schedule of immunization. The importance of cell immunity against the HBV nucleocapsid antigen for the HBV chronic infection control was demonstrated by means of adoptive immunity transfer techniques [6]. Specifically, NASVAC strategy is aimed at improving and broadening the anti-HBV specific immunity by a) inserting a second and probably more important antigen (HBcAg) to the formulation and b) by the stimulation of a broad immune response including mucosal in addition to systemic compartments. This approach promotes the recruitment of a larger number of immunocytes against a wider representation of HBV T-cell epitopes.

If a new product like the therapeutic vaccine formulation NASVAC is registered, it would be a very valuable one. In the existing scenario, it has potentiality to be used as a first line therapy. NASVAC can be administered before starting more reactogenic therapies like IFN or before quasi-eternal treatments like taking nucleos(t)ide analogs for several years. The toxicological pattern of NASVAC will definitively be different and potentially safer according to preclinical and clinical results and also according to the experience with other products in CHB patients. For example, the induction of mutants won't be an expectable risk.

The specific value of the product will be better appreciated after phase III controlled clinical trials. The results not necessarily need to be better, even in case of similar efficacy to conventional treatments; it will be a highly valuable product because the therapeutic effect will be obtained with minimum reactogenicity –as much as we know today. In case of superiority, the value will be much greater as it will be a finite treatment that could lead to relatively rapid and safe responses for patients. A potential benefit to further intervention could also be expected.

Another valuable issue of NASVAC is that it can be administered simultaneously with other therapies, with potentialities to improve the efficacy of existing therapies. In the case of NASVAC-IFN combination it represents complementing specific and non-specific immune-stimulation; in the case of combination with antivirals, it would enable the patients to safely withdrawn therapy while sustaining the virus at low levels -avoiding the risk of viral rebound associated to liver failure.

In summary, a product like NASVAC, according to its characteristics, has the potential to be safer, cheaper, and effective in the context of the current therapeutic scenario.

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