



ABX203, a novel therapeutic vaccine for chronic hepatitis B patients

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Despite the existence of effective prophylactic vaccines, chronic hepatitis B remains a major public health problem, with more than 350 million people infected worldwide. Chronic infection increases the risk of serious liver diseases such as cirrhosis and hepatocellular carcinoma. Available therapies for chronic hepatitis B have limited efficacy and require long-term continuous treatments; that is why the development of therapeutic vaccines has been investigated as promising approach. In this sense, a novel vaccine formulation called ABX203 (HeberNasvac), based on the combination of the hepatitis B virus nucleocapsid and surface antigens, was developed. ABX203 has been studied in phase I,

phase II and phase III clinical trial in treatment-naïve chronically infected patients in Bangladesh and in healthy volunteers in Cuba with promising results. In the present work we reviewed the main preclinical and clinical results of ABX203 development. Altogether, the data demonstrates safety and immunogenicity of ABX203 vaccine and support its use as a novel and competitive treatment alternative for chronic hepatitis B. The vaccine has been granted marketing authorization in Cuba.

Key words: ABX203, hepatitis B, vaccine

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Despite almost universal vaccination of neonates and infants in more than 180 countries, with more than 80% coverage and the subsequent reduction in the incidence of new infections with hepatitis B virus (HBV), chronic HBV infection remains a significant public health problem worldwide. Nowadays more than 350 million people are persistently infected, and two billion people show evidence of past or current infection. These individuals act as a reservoir for viral spread. Chronic infection also increases the risk of severe liver complications such as cirrhosis and hepatocellular carcinoma. One million people die each year worldwide as a consequence of chronic hepatitis B (CHB) complications [1].

Currently available treatments for CHB include the use of standard and pegylated interferon alpha (Peg-IFN), and several nucleos(t)ide analogues, such as lamivudine, adefovir, telbivudine, entecavir, and tenofovir. Less than half of World Health Organization's Member States included antiviral drugs in the essential medication list [1]. These antiviral therapies are not effective for HBV elimination; they require long treatments and induce undesirable side effects [2].

Viral persistence has been associated with a defect in the development of HBV-specific cellular immunity. Limitations of the currently available therapies underline the need for alternative ones. Specific immunotherapeutic strategies target not only the induction or stimulation of CD4(+) and CD8(+) T-cell responses, but also the induction of pro-inflammatory cytokines capable of controlling viral replication. The use of vaccine formulations in the treatment of CHB constitutes an attractive approach. The first generation of CHB therapeutic vaccine was based on the use of hepatitis B surface antigen (HBsAg) formulations similar to the current HBV prophylactic vaccines. Although this strategy induces an effect on CHB patients, the immune response generated was not completely effective and sustained [3, 4]. More recently, several clinical trials have been performed using different vaccine formulations; however none of them has demonstrated a sufficient level of clinical efficacy [5].

ABX203 (HeberNasvac) was developed by the Center for Genetic Engineering and Biotechnology from Cuba. The vaccine is based on a combination of the HBsAg and the HBV nucleocapsid (HBcAg) antigens and is simultaneously administered by the intranasal and subcutaneous routes [6, 7]. ABX203 has been studied in phase I, phase II and phase III clinical trials with promising results [8–10]. In the present

work we reviewed the results of the main preclinical and clinical trials of this product.

Rationale for ABX203 vaccine design

The working hypothesis of this product suggests that repeated administration of ABX203, simultaneously administered by intranasal and subcutaneous routes to CHB patients, would be able to subvert the HBV specific immune tolerance, inducing specific immune responses (specifically Th1-related) in systemic and mucosal compartments, as well as the activation of antigen presenting cell (APC) to a level enough to control viral replication and normalize the transaminases in a significant number of patients, without severe adverse reactions.

The inclusion of the complete HBcAg as a virus-like nucleoparticle in the formulation allows the development of a more potent and multifaceted immune response [3]. The anti-HBcAg specific cellular response has been associated with HBV control [11]. It has been also described that HBcAg induces a Th1-pattern of immune response [12], which correlates with the immune response required for HBV control [13, 14]. In addition, the recombinant HBcAg present in ABX203 vaccine has the capacity to encapsulate bacterial nucleic acid, which acts as a potent Th1 adjuvant [12]; all these properties circumvent the need in external adjuvant in the formulation.

Other novelty of ABX203 vaccine formulation is the use of the intranasal route of administration. Involvement of the mucosal immune system in response to ABX203 vaccine allows stimulating a new pool of immune cells that could be less affected by the HBV tolerance established in chronic patients [15]. The fact that both antigens in the formulation (HBsAg and HBcAg) are virus-like particles around 20–30 nm in diameter [16] facilitates their uptake by nasopharyngeal physiological mechanisms [17]. In addition, the combination of parenteral and mucosal routes for the vaccine administration constitutes another approach to further potentiate the immune response in chronic patients. This strategy has been recently used with promising results in HIV vaccine studies [18, 19].

Pharmacological studies in animal models

Immunogenicity of ABX203 has been extensively studied in normal and transgenic mice [6, 7, 20–23]. In Balb/c mice, immunogenicity of this combination formulation at different doses and antigen ratios was explored using parenteral and mucosal immunization routes [6, 7, 20, 24]. In these studies ABX203 formulation induced a potent humoral immune response against both antigens and secretion of interferon



gamma (IFN- γ) by T CD8⁺ cells. A strong lymphoproliferative response in total spleen cells was also detected. A similar behavior was observed in C57/Bl6 mice [6]. Knowing the relevance of the IFN- γ secretion response as the main effector mechanism for HBV control in humans [25, 26], these results support the evaluation of ABX203 formulation as a potential effective treatment against CHB.

In addition, immune response induced by ABX203 immunization was also studied in hepatitis B transgenic mice models [21–23]. Two different transgenic mice models of CHB were used. The first model showed high levels of HBsAg expression in blood and some organs [27]. However, a humoral and cellular immune response against the HBsAg could be detected after five doses of ABX203 using the intranasal/subcutaneous combined schedule for the immunizations [21, 28]. Other authors reported difficulties to induce a HBsAg-specific immune response in hepatitis B transgenic mice with the use of potent adjuvanted formulations [29, 30]. Considering this point and high levels of HBsAg present in the circulation of the currently employed transgenic mice, the results pointed out the promising profile of ABX203 vaccine. Additionally, it is important to say that any potential damage that could be generated by a strong immune response in mice expressing HBsAg in their main organs, such as liver and kidneys, was evaluated in various histopathological studies (with up to 25 immunizations); no evidence of toxicity was observed [21, 22, 28]. Using the same transgenic model, a number of complementary

studies on adoptive transfer of ABX203 immune splenocytes was carried out. The results obtained confirm the immunogenicity and safety profile of ABX203 vaccination strategy [22]. ABX203 formulation has been also evaluated in a humanized hepatitis B surface antigen transgenic mouse model [23, 31]. These studies demonstrate that ABX203 formulation is capable to elicit humoral immune response against both antigens and a predominantly T CD4⁺ cellular immune response. In general, the results obtained in transgenic mice indicate recovery of T-cell function mediated by antiviral cytokine production, such as TNF- α and INF- γ .

Being analyzed together, the preclinical data obtained with ABX203 indicates that this vaccine candidate is highly immunogenic and shows good evidence of immune stimulation in CHB infection animal models.

Toxicological studies

To support the safety profile of ABX203 formulation, several toxicological studies have been performed fulfilling Good Laboratory Practice requirement. Table 1 summarizes general characteristics of each study. Altogether, this battery of toxicological studies demonstrated safety and tolerability of ABX203 use by intranasal route alone or with simultaneous subcutaneous administrations.

Clinical phase of development

So far, several clinical trials with ABX203 vaccine have been carried out (Table 2). All volunteers gave

Table 1. Toxicological studies carried out for HeberNasvac safety evaluation

Study	Animal specie	Route
Acute toxicity	Sprague Dawley rats	Intranasal
Irritability	Sprague Dawley rats	Intranasal
Local tolerance	Sprague Dawley rats	Intranasal
Acute toxicity – single dose	Sprague-Dawley rats	Intranasal
Acute toxicity – single dose	Sprague Dawley rats	Intranasal/subcutaneous simultaneous administration
Local tolerance	Sprague Dawley rats	Intranasal/subcutaneous simultaneous administration
Repeated doses	Sprague Dawley rats	Intranasal/subcutaneous simultaneous administration
Acute toxicity – single dose	First generation rabbits (New Zealand \times Semi-Giant)	Intranasal/subcutaneous simultaneous administration
Repeated doses	First generation rabbits (New Zealand \times Semi-Giant)	Intranasal/subcutaneous simultaneous administration



Table 2. Completed clinical trials with HeberNasvac

Study	Study subjects	N	HeberNasvac doses	Route	Reference
Randomized, double blind, placebo controlled Phase I	Healthy adult	19	5 doses (50 µg of each antigen per dose)	Intranasally	[8]
Open-label Phase I/II	CHB patients refractory or intolerant to IFN-α	6	10 doses (100 µg of each antigen per dose)	Intranasally	Unpublished
Open-label Phase I/II	Treatment-naïve CHB patients	18	10 doses (100 µg of each antigen per route)	5 doses intranasally + 5 doses intranasally / subcutaneously	[9]
Randomized, open-label, Peg-IFN controlled Phase III	Treatment-naïve CHB patients	160	10 doses (100 µg of each antigen per route)	5 doses intranasally + 5 doses intranasally / subcutaneously	[10]

CHB chronic hepatitis B, IFN-α interferon alpha, Peg-IFN pegylated interferon

their written informed consent before enrollment, and the studies were conducted according to the principles set in the Declaration of Helsinki and in accordance with Good Clinical Practice requirements.

First, the vaccine was evaluated in a phase I trial in healthy male adults [8]. In this initial trial all the adverse events reported were categorized as mild in intensity and self-limiting. The rates of adverse events observed were similar or below those reported for other commercial products with intranasal administration, Nasal-flu and calcitonin spray [32, 33]. Additionally, 100% seroconversion was attained against HBcAg and a 75% against the surface antigen. These results were encouraging and suggested that the intranasal administered dose could be increased to obtain a higher humoral immune response. This clinical trial with ABX203 vaccine was the first ever to demonstrate seroprotection in healthy adult individuals against HBV after intranasal administration.

Later on two clinical trials were conducted in CHB patients in Cuba and Bangladesh to evaluate preliminary safety and efficacy. The Cuban study enrolled six patients previously treated with interferon-α, showing detectable levels of viral load at the start of vaccination (unpublished data). These six patients received a vaccination schedule of ten doses each, intranasally. The trial demonstrated that ABX203 was safe and well tolerated. At the end of the study, all patients demonstrated a reduction in their viral load to undetectable levels (assessed quantitatively). The viral load remained constantly reduced up to three years after the end of treatment. In addition, signals of serological response against the HBeAg were observed

in three patients who were HBeAg-positive at the beginning of the study.

The phase I/II trial in Bangladesh enrolled 18 treatment-naïve patients [9]. The vaccine was administered ten times at 2-weekly intervals, the first five doses via nasal route only and the subsequent five doses via both nasal and subcutaneous routes. This study demonstrated the safety profile of ABX203 administered simultaneously by intranasal and subcutaneous routes. No flare-ups of HBV DNA or alanine aminotransferase were recorded in any patient. In general, sustained transaminases normalization was observed in 100% of patients, followed by a significant reduction of viral load to undetectable levels in 50% of them. Moreover, an increment in secretion of pro-inflammatory cytokines was observed after the end of the first treatment cycle.

Subsequently, a randomized, open-label, treatment controlled Phase III trial was carried out in Bangladesh [10]. A total of 160 CHB patients were enrolled and randomly assigned to receive either a ABX203 therapeutic vaccine or Peg-IFN. The vaccine administration schedule was similar to the described above for the phase I/II trial. Treatment with Peg-IFN was used as a control, at dose regimen of 180 microgram subcutaneously once weekly for 48 consecutive weeks. The results confirmed safety of ABX203 therapeutic immunization; no serious or severe adverse events were detected. In terms of efficacy, 61% of ABX203 treated patients reduced their HBV DNA levels below 250 copies/mL (undetectable HBV DNA) at end of treatment and a similar proportion remained undetectable after 24 weeks of treatment-free follow up. In the Peg-IFN group,

Conflict of interests

Authors are employees of the Center for Genetic Engineering and Biotechnology, and have been working in the development of HeberNasvac vaccine.



67% of patients reduced their HBV DNA levels below 250 copies/mL at end of treatment; however, only 39% remained at the same level after 24 weeks of treatment-free follow up. A generalized and sustained normalization of alanine aminotransferase values in the majority of patients was observed. These promising results support future clinical trials with ABX203.

In summary, the clinical data obtained demonstrated safety of ABX203. The most frequent systemic adverse events were flu-like symptoms. At local level, sneezing and rhinorrhea after intranasal

administrations and pain at injection site after subcutaneous administrations were registered. In terms of efficacy, the main achievements of the product are a significant and sustained off-treatment reduction of the viral load, and normalization of transaminase levels in all treated patients.

Conclusion

Altogether, the results provide the strong evidence that vaccination with ABX203 (HeberNasvac) is safe and efficacious, supporting its use for therapy of CHB infection. ☺

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ABX203, инновационная терапевтическая вакцина для больных хроническим гепатитом В

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Несмотря на существование эффективной вакцинопрофилактики, хронический гепатит В, которым во всем мире инфицировано более 350 млн человек, остается одной из основных проблем здравоохранения. Хроническая инфекция увеличивает риск серьезной печеночной патологии – цирроза и гепатоцеллюлярного рака. Существующие методы лечения хронического гепатита В недостаточно эффективны и требуют длительной непрерывной терапии. Вот почему в качестве перспективного подхода изучается возможность разработки терапевтических вакцин. В этих целях был создан инновационный вакцинальный препарат ABX203 (Назвак), в состав которого входят сердцевинный (HBcAg) и поверхностный (HBsAg) антигены вируса гепатита В. Терапевтическая

двухкомпонентная вакцина ABX203, зарегистрированная на Кубе, изучалась в клинических исследованиях I, II и III фазы у ранее не леченных хронически инфицированных пациентов в Бангладеш и у здоровых добровольцев на Кубе и показала многообещающие результаты. Эта статья представляет собой обзор основных результатов доклинических и клинических исследований вакцины ABX203. На основании анализа представленных данных можно говорить о безопасности и иммуногенности вакцины ABX203, что позволяет применять ее как инновационный и конкурентоспособный вариант лечения хронического гепатита В.

Ключевые слова: ABX203, гепатит В, вакцина

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