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HEPLISAV™

Hepatitis B Vaccine

HBV-ISS
HBsAg-ISS
V-270

Hepatitis B vaccine consisting of recombinant hepatitis B virus surface antigen (rHBsAg) coadministered with an immunostimulatory phosphorothioate oligonucleotide (1018 ISS)

EN: 384028

ABSTRACT

Universal immunization against hepatitis B virus (HBV) is an effective strategy to reduce the global morbidity and mortality burden of HBV disease. However, with the three-dose series of the current commercial HBV vaccine (alum-adjuvanted recombinant hepatitis B surface antigen [HBsAg]), many individuals do not respond, and of the responders, most do not achieve a protective antibody response until after the second or third dose. The efficacy and durability of this seroprotection varies among different patient populations and has been noted to be greatly diminished in immunodeficient hosts. Immunostimulatory DNA sequences (ISS) are emerging as useful tools for modulating immune responses. Combined administration of two doses of 1018 ISS and rHBsAg (Heplisav™) has been shown to be more immunogenic than the conventional vaccine and is well tolerated. This accelerated two-dose regimen may help achieve improvement in the rate and durability of HBV immunity. The addition of ISS increases the immunogenicity of the vaccine. The new vaccine may be useful for individuals who are nonresponders to presently available HBV vaccines or have comorbid factors such as older age, obesity, smoking, diabetes or renal disease, which are all associated with decreased immune response. Earlier this year, a case of vasculitis reported in a single phase III trial subject prompted the FDA to put a clinical hold on Heplisav™. This patient had received two doses of the vaccine in the summer of 2007 and was diagnosed with Wegener's granulomatosis in early 2008. Since that time, Dynavax has reported results showing two cases of systemic vasculitis in this phase III trial: the case of Wegener's granulomatosis, or c-ANCA vasculitis, in the Heplisav™ group, and a case of p-ANCA systemic vasculitis in the Engerix B® control group.

BACKGROUND

Acute and chronic infection with hepatitis B virus (HBV) is responsible for significant morbidity and mortality globally (1, 2). About 2 billion people are estimated to have been infected by HBV and about 350 million are chronically infected. Active disease manifestations are seen in about 5-15% of acutely infected young children and 33-50% of older children and adults. About 5-10% of adults and up to 90% of infants acutely infected with HBV may not clear the infection after the initial phase of illness (3). Approximately 1 in 4 patients in the adult cohort eventually develop chronic active hepatitis. This group of patients also stands at a higher risk of developing hepatocellular carcinoma (4). HBV-related liver disease results in about 1-1.5 million deaths each year from an estimated pool of more than 350 million HBV carriers (5, 6). Immunization against HBV effectively prevents chronic infection, as well as mother-to-infant transmission of the disease, with a concomitant reduction in the incidence of hepatocellular carcinoma and global morbidity and mortality from the disease (7).

Current HBV vaccines consist of recombinant hepatitis B surface antigen (rHBsAg) that is adsorbed onto an adjuvant such as aluminum hydroxide or aluminum phosphate. Postimmunization antibody levels against HBsAg of ≥ 10 mIU/mL are considered protective (8). These antibody titers are achieved in more than 90% of healthy adults after a three-dose vaccination series at 0, 1 and 6 months. However, in the presence of comorbid factors such as older age, obesity, smoking, diabetes or renal disease, the rates of seroprotection are considerably reduced (9).

With the conventional HBV vaccine, higher antibody levels are achieved with longer intervals between the second and third injection compared to an accelerated schedule with only 1 month between the second and third doses (10). It has been proposed that a single-dose or an accelerated two-dose regimen would be useful to promptly achieve higher rates of seroprotection in hyporesponsive or suboptimally compliant populations and in areas of the world where hepatitis B remains a significant cause of morbidity and mortality (11, 12). Unfortunately, none of these strategies has optimally answered the issues related to vaccine hyporesponsiveness or durability of seroprotection. This has led to ongoing research for a more immunogenic vaccine that is effective in high-risk individuals who fail to respond to the standard HBV vaccination series.

DNA immunostimulatory sequences (ISS) have emerged as useful instruments for immune response modulation. ISS are cytosine

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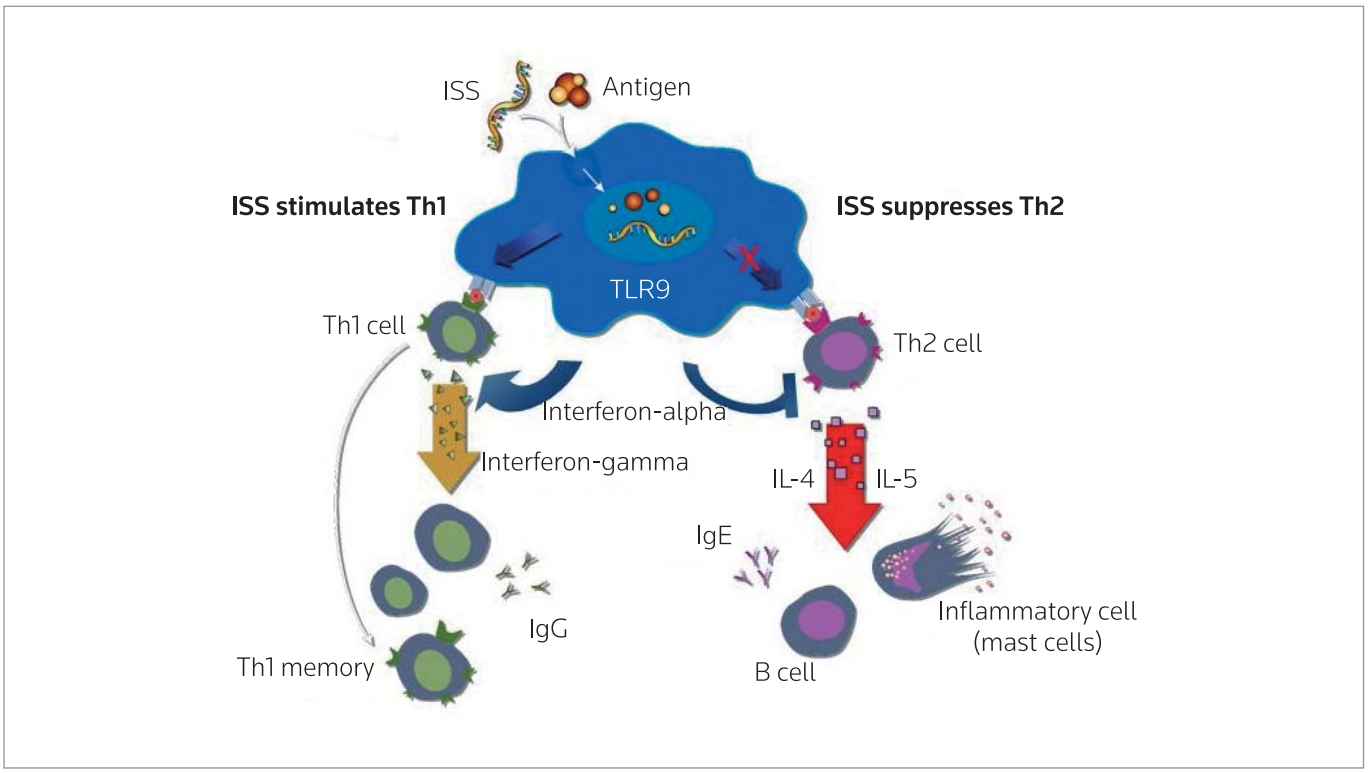

Figure 1. Mechanism of action of immunostimulatory sequences (ISS).

phosphoguanosine (CpG) motifs containing components of bacterial (invertebrate) DNA that have potent natural killer (NK) cell-activating and interferon-inducing properties (13). These properties can be reproduced by certain synthetic oligonucleotides containing these motifs (14, 15). ISS stimulate the production of Th1-type cytokines such as interferon alfa and beta, IL-6, IL-12 and IL-18, as well as interferon gamma secretion from NK cells (1, 16-18). These motifs also stimulate the proliferation of B cells and immunoglobulin secretion (19-21) and activate antigen-presenting cells (22-24). ISS have potent Th1 adjuvant properties when used for immunization with DNA (25, 26) and protein vaccines (18, 26-29). These molecules are thought to work, at least in part, by specifically targeting Toll-like receptor 9 (TLR9) found on cellular membranes and the cytoplasm of certain human immune cells.

TLR9 is one of the most prominent and well-characterized pattern recognition receptors (PRRs), the cellular distribution of which follows a species-specific restricted pattern. ISS contain repeat units of unmethylated cytosine and phosphoguanosine oligodeoxyribonucleotide (CpG) dinucleotide motifs. CpG-containing short, synthetic oligodeoxynucleotide sequences effectively work as pathogen-associated molecular patterns (PAMPs) that bind avidly to TLR9. The resulting recognition of ISS by TLR9 leads to activation of innate immune responses followed by an amplification of the adaptive immune response. With this background, synthetic ISS have generated significant interest as effective adjuvants that can potentially enhance both humoral (improved antigen-specific B-cell responses, immunoglobulin class switching and potential reduction in B-cell apoptosis) and cellular immune responses in multiple clinical situations with diverse immune and infectious etiologies, including vaccine-hyporesponsive patient populations (30, 31).

ISS work by changing or reprogramming the immune responses that cause disease rather than just treating the symptoms of disease. When administered along with an antigen, ISS help generate memory Th1 cells, allowing the immune system to respond appropriately to each future encounter with a specific pathogen or allergen, leading to long-lasting therapeutic effects (Fig. 1).

With better characterization of signaling pathways and patterns of TLR9 expression, coupled with an understanding of the differential activity of various ISS classes, it is now potentially possible to selectively tailor ISS sequences to achieve improved antibody production or increased T-cell responses to induce the desired effector response, such as that in a Th1 direction, in specific disease states.

Interferon administration has been shown to be effective in the treatment of several viral infections, such as HBV, hepatitis C (HCV), herpes simplex virus (HSV) and human papillomavirus (HPV). However, systemic exposure to such an agent carries a considerable risk of toxicity. Higgins et al. (31) proposed that ISS adjuvant activity can be enhanced by delivering ISS and antigen to the same antigen-presenting cell, or in combination with other delivery vehicles. It has been suggested that ISS may promote very high levels of endogenous interferon alfa secretion from plasmacytoid dendritic cells (PDCs) without significant systemic effects associated with exogenous exposure. The concomitant presence of ISS enhances the affinity maturation process during antibody production, resulting in increased levels of high-avidity antibodies (32). ISS show low toxici-

ty and good tolerability in animal studies and human trials. The ISS-adjuvanted prophylactic HBV vaccine has been shown to significantly enhance seroprotection (defined as anti-HBsAg antibody titers ≥ 10 mIU/mL) compared to the currently licensed alum-adjuvanted vaccine in adults aged 18-70 years (30, 31, 33).

Heplisav™ is Dynavax's phase III HBV vaccine candidate for the prevention of hepatitis B. Early clinical studies have also been conducted by the company in patients with end-stage renal failure (predialysis). Heplisav™ contains HBsAg combined with 3 mg of 1018 ISS (in the form of a synthetic phosphorothioate oligonucleotide). 1018 ISS significantly increases the frequency and magnitude of seroprotective responses, and is well tolerated and immunogenic when administered with rHBsAg. Heplisav™ has the advantage of requiring only two injections compared to three injections with the current alum-adjuvanted HBV vaccine, and thus far has proved to be more immunogenic. In comparison with most other vaccines, Heplisav™ appears easier to administer and is well tolerated (34). The accelerated, improved and more durable antibody response elicited after one or two doses indicate that the 1018 ISS-rHBsAg vaccine may be useful for immunizing difficult-to-access populations, individuals with high-risk behaviors that increase their risk of acquiring HBV, as well as in those with immune hyporesponsiveness secondary to older age, obesity, smoking, diabetes, renal disease, immunosuppression, etc. (35-38).

SAFETY

Initial clinical evaluations demonstrated overall good tolerability for Heplisav™, as evidenced by clinical and laboratory indices. The overall incidence of adverse effects and the incidence of specific adverse events were generally similar for Heplisav™ and the current alum-adjuvanted vaccine. There was no significant difference in the incidence of the most commonly reported adverse events (fatigue, headaches and myalgia) between the two groups (5, 39). The most frequently reported local adverse events included mild to moderate injection-site erythema and pain in both groups (75-77% and 34-35%, respectively, for Heplisav™ and the alum-adjuvanted vaccine). There was no difference between the groups in moderate or severe injection-site tenderness (39). There were no observed differences in biochemical, hematological, urinary, hepatic or rheumatological laboratory marker abnormalities between the two groups.

At least one previous author has alluded to the theoretical risk of unmasking underlying autoimmune conditions by this immunomodulator that may not have been identified due to the relatively small numbers of subjects in the above trials (34).

Interestingly, in 2008, a case of vasculitis was reported from among the vaccinees. This involved a single phase III trial subject who had received two doses of Heplisav™ in the summer of 2007 and was diagnosed with Wegener's granulomatosis in early 2008. Since that time, Dynavax has unblinded and reported results showing two cases of systemic vasculitis in this phase III trial: the case of Wegener's granulomatosis, or c-ANCA vasculitis, in the Heplisav™ group and a case of p-ANCA systemic vasculitis in the Engerix B® control group (40).

CLINICAL STUDIES

A good correlation between antibody response to HBsAg in nonhuman primates versus human subjects, as well as excellent tolerability and safety of the 1018 ISS, have been demonstrated (41, 42). The safety and immunogenicity of coinjection of rHBsAg and 1018 ISS were confirmed in a phase I, observer-blinded, randomized study in healthy anti-HBsAg antibody-negative adults who received two doses of the vaccine 8 weeks apart. The average age of the participants was 33 years (18-52 years) and 63% were female. Study vaccines were reconstituted to contain 300, 650, 1000 or 3000 µg of 1018 ISS alone or mixed with 20 µg rHBsAg. Higher ISS doses were demonstrated to result in higher anti-HBsAg antibody levels. Seroprotective titers (≥ 10 mIU/mL) were noted 4 weeks after the first dose in 0%, 25%, 75% and 87.5%, respectively, of the study subjects stratified by increasing ISS doses ($P < 0.05$) for those who received the ISS + rHbsAg combination. These percentages rose to 62.5%, 100%, 100% and 100%, respectively, 4 weeks after the second dose of the vaccine. Progressively increasing geometric mean anti-HBsAg antibody levels were demonstrated after both doses and correlated with increasing ISS + rHBsAg dose. Injection-site reactions (tenderness and pain) were more frequent at higher ISS + HBsAg doses, although they were mild and self-limiting. Adverse events did not increase in frequency with the second dose. One subject withdrew consent because of local and systemic adverse events. All four ISS + rHBsAg doses tested were more immunogenic than HBsAg alone. It was concluded that vaccination with 1000 and 3000 µg of ISS induced rapid and high antibody levels after one or two injections (43).

In phase II clinical trials, immunization with Heplisav™ demonstrated faster seroconversion compared to the currently licensed alum-adjuvanted vaccine (39, 43). A group of 99 healthy seronegative adults aged 18-28 years (mean age 22.6 years; 65% females) were randomly assigned in equal numbers to receive two doses of HBV-ISS vaccine (0 and 8 weeks) and placebo (24 weeks) or Engerix B® (0, 8 and 24 weeks). Immunization with a single dose of Heplisav™ offered seroprotection to 79% of recipients compared to 12% of those who received the alum-adjuvanted vaccine within 4 weeks of administration. One week after immunization with the second dose of the respective vaccines, these percentages improved to 100% and 18%, respectively. About one-third of the subjects in each group reported headache and fatigue as the most common systemic adverse effects. Mild injection-site tenderness was more common with HBV-ISS (39).

In phase III trials in a hyporesponsive population aged 40-70 years, 97% of subjects developed seroprotective titers after two doses of Heplisav™ versus 23% of those who received the alum-adjuvanted vaccine. Overall, no immediate serious vaccine-related adverse effects were reported in over 400 patients immunized with Heplisav™ in these trials. Similar to the above trials, subjects receiving Heplisav™ reported a higher frequency of transient, mild injection-site tenderness compared to the alum-adjuvanted vaccinees; there was, however, no significant difference in the incidence and severity of systemic adverse events between the two groups. As of April 2, 2008, there were four trials involving Heplisav™ registered with the National Institutes of Health (NIH) (44-47). Three of the studies are ongoing and the results from the phase III trial were presented by Pecoraro et al. (44), while a phase II study (45) was terminated following the FDA clinical hold due to a reported adverse event.

More information is required with regard to the safety and efficacy of Heplisav™ in both healthy adults and immunocompromised and

likely hyporesponsive populations. Improvements in the definition of baseline characteristics of study populations in these trials may help identify subjects who may demonstrate better immune responsiveness to this novel vaccine.

CONCLUSIONS

CpG-containing short, synthetic oligodeoxynucleotide sequences effectively work as PAMPs that bind avidly to TLR9. The resulting recognition of ISS by TLR9 leads to activation of innate immune responses followed by an amplification of the adaptive immune response. These compounds stimulate the production of Th1-type cytokines, the proliferation of B cells and immunoglobulin secretion, and activate antigen-presenting cells. ISS have potent Th1 adjuvant properties when used for immunization with DNA and protein vaccines.

Heplisav™ is a recombinant anti-HBV vaccine containing 1018 ISS mixed with 20 µg rHBsAg per dose. High rates of seroprotection after one and two injections of 1018 ISS + rHBsAg may translate into a reduced need for multiple booster doses, while addressing associated noncompliance and the need for serial monitoring for drops in protective titers. Although initial clinical trials involving small numbers of subjects demonstrated good tolerability and immunogenicity, further safety data on this vaccine are awaited.

SOURCE

Dynavax Technologies (US).

DISCLOSURE

The author states no conflicts of interest.

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