# An overview on a novel adjuvanted prophylactic hepatitis B vaccine

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Worldwide it is estimated that ± 350 million people are chronic carriers of the hepatitis B virus and about 1 to 1.5 million are expected to die from the chronic sequelae-liver cirrhosis and primary liver cancer (1). Although no curative treatment exists, hepatitis B virus infection can be prevented by vaccination. Effective vaccines are available for nearly two decades and the first yeast recombinant hepatitis B vaccine was marketed in 1986 (2). This vaccine, Engerix B™, has been distributed in more than 140 countries and > 500 million doses have been administered.

Extensive follow-up of > 10 years of cohorts in highly endemic countries showed a good protective efficacy of this hepatitis B vaccine. More than 95% of the children vaccinated on a 0, 1, 2 and 12 month schedule still have protective antibody titres (≥ 10 mIU/ml) 10-12 years later, irrespective of a booster dose given at year 5 (3). In clinical trials in adults, children and neonates, seroprotection rates vary between 91% and 100% depending on the age (2). These results indicated that there appears to be limited risk groups of non-responding people (e.g. haemodialysis patients, elderly) who could benefit from a more immunogenic hepatitis B vaccine. Several strategies to enhance the immune response have been proposed among which the use of novel adjuvant systems. Adjuvants are thought to improve immune responses by (1) causing depot formation at the injection site ; (2) increasing the interaction between immunogen and macrophage ; and (3) improving antigen presentation to T cells (4).

SmithKline Beecham have developed a new adjuvant system containing alum and 3-deacytelated monophosphoryl lipid A : SBAS4 (SmithKline Beecham Adjuvant System 4). Lipid A is a component of the gram negative Salmonella minnesota lipopolysaccharide (LPS), which together with its lipid A component, are well known as possessing strong adjuvant effects. However, their toxicity has precluded their use in vaccine formulations. It was shown that a monophosphorylated form of lipid A (MPL) retains its adjuvant function while almost completely losing its endotoxin effects. More recently a 3-deacylated form has been shown to have a further decrease in toxicity as tested in small animals, while retaining its immunopotentiating effect. It is suggested that the adjuvant effect of lipid A is linked to its ability to activate macrophages. Activated macrophages have an increased capacity for antigen processing and antigen presentation to T cells, which in turn results in a potentiation of effector T cells induction and improves B-cell response (4 and refs therein).

A first study assessed the safety and immunogenicity of a hepatitis B vaccine formulated with SBAS4, administered according to a 0, 1, 6 month schedule[4). The study showed that SBAS4 improved *in vivo* humoral and *in vitro* cellular immune responses. All HBV/SBAS4 vaccinees (n = 15) were protected by day 90 while in the control group (receiving a commercially available hepatitis B vaccine) a 100% seroprotection rate was only reached at day 210, 1 month after the 3rd dose. At this point in time the GMT in the HBV/SBAS4 group was threefold higher than the control group. Extensive clinical, haematological and biochemical follow-up demonstrated that this vaccine was safe and well-tolerated. No serious adverse events were reported.

A second study (5) investigated the HBV/SBAS4 vaccine in a larger group of volunteers (aged between 18-40 years) on a two dose schedule. 50 volunteers were randomly attributed to a HBV/SBAS4 group and twice 50 volunteers to two groups receiving hepatitis B vaccines formulated on alum only. Subjects receiving the HBV/SBAS4 reported more symptoms than those receiving the other HBV vaccines. This higher incidence could be attributed solely to the differences in local soreness and swelling. Although higher in incidence only 3 subjects scored the swelling as severe. All these symptoms resolved within the follow-up period of three days. The general symptoms were reported similarly in all 3 study groups, with fatigue and headache the most frequent. Overall, very few general symptoms were scored as grade 3 and all were transient and resolved without sequelae. No related serious adverse events were reported during this clinical trial. At month 1, a higher percentage of subjects in the SBAS4 group were protected (≥ 10 mIU/ml) levels : 38% versus 20 and 17%. Prior to the second dose 95% of the vaccinees in the SBAS4 group had protective levels of anti-HBV antibodies versus 35 and 42%. At month 7, all vaccinees in all 3 groups were protected. However, there was a great difference in GMTs at this point in time : 13,271 mIU/ml for the SBAS4 group versus 1203 and 1823 mIU/ml. At month 30 seroprotection rates were 100, 87 and 89%

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respectively (GMTs were 733, 117 and 116 mIU/ml). At month 30, cellular mediated immune responses were assessed : for all three groups a lymphoproliferation was observed but this was stronger in the group receiving HBV/SBAS4 (5).

A third study (6) assessed the profile of the HBV/SBAS4 vaccine in non-responders. These were defined as subjects who, after being vaccinated with three doses of a commercial available hepatitis B vaccine, still had a anti HBsAg titre ≤ 10 mIU/ml. The volunteers were aged between 20 and 60 and the two groups (one receiving HBV/SBAS4 and one receiving Engerix B™) were vaccinated on a 0, 1, 6 month schedule. One month after the first dose the SP rate was 44% for group 1 (58 subjects) receiving Engerix™-B versus 66% for group 2 receiving HbsAg, SBAS4 (57 subjects). One month after the second dose this was 58 and 81% respectively and one month after the third dose this was 68 and 98% respectively. Geometric mean titres were (one month after each dose) 34, 56 and 111 mIU/ml for the Engerix™ group versus 123, 222 and 1937 mIU/ml for the HbsAg, SBAS4 group. Pain at the injection site was the most common reported local symptom (per dose analysis) : very few were scored grade 3 (preventing normal day activities) : none in group 1 and 1.3% in group 2. Fatigue was the most common reported general symptom with 0.0% and 2.0% scoring grade 3 respectively.

Concluding, the hepatitis B vaccine formulated with the novel adjuvant SBAS4 shows to be well tolerated in the different populations tested. Experience from other vaccines where SBAS4 is used as an adjuvant shows a similar safety record. The HBV/SBAS4 vaccine is highly immunogenic : subjects are protected fast, the GMTs are high and CMI responses are vigorous. This novel vaccine would be indicated for example in immunocompromised subjects (e.g. haemodialysis patients) and in non- responders to classical hepatitis B vaccines.

## References

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