Long term protection after hepatitis A and B vaccination : an update

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Introduction

Viral hepatitis continues to be a cause of considerable morbidity and mortality in the world. On worldwide basis, approximately 1.4 million cases of hepatitis A are reported every year. The true incidence, however, has been estimated to be 3 to 10 times higher.

Regarding hepatitis B, more than a third of the world's population has been infected. The World Health Organization has estimated (2002) that there are 367 million chronic carriers of hepatitis B worldwide, and approximately 1 million deaths per year as a consequence of chronic complications and acute fulminant disease.

Hepatitis B vaccines have been licensed since 1982, hepatitis A vaccine since 1992. In 1996, a combined hepatitis A and B vaccine became available. An update on the long term protection conferred by hepatitis A and hepatitis B vaccines is given in the following paragraphs.

Hepatitis B vaccine and long term protection

Hepatitis B vaccines have been shown to be very effective and safe. The primary course can consist of 3 or 4 doses, administered according to a 0, 1 and 6 month schedule or a 0, 1, 2 and 12 month schedule. A booster dose of vaccine, offered 5, 7 or 10 years following the administration of the primary course, has been recommended for years by most national bodies. In addition, recommendations in European countries and the US varied considerably as to whether administration of a booster dose relates to the anti-HBs level as well as to the interval between primary course and the booster dose (1). This variability probably reflects national bodies focussing undue attention to declining anti-HBs levels as well as failure to understand the distinction between protection against subclinical and break through infection and between antibody persistence and cellular immunity.

These distinctions are very important : from a public health point of view we have to keep in mind that the major objective of vaccination against hepatitis B is to prevent the development of the persistent carriage of HBV, thereby also preventing HBV induced chronic liver disease and to eliminate the pool of chronic carriers, thereby limiting transmission of infection to susceptible contacts.

Today, the accumulating results of long term studies in vaccinated cohorts as well as the assessment of the role of immunological memory in vaccinees question the necessity of providing booster doses following a successful course of primary immunization.

Declining anti-HBs levels to low or undetectable low levels are not uncommon (2). Rather than a particular level of anti-HBs, the degree of protection afforded by the vaccine, in terms of generating immune memory, is much more relevant. Protection against hepatitis B virus infection is dependent on a complex interplay between memory B cells, memory T helper cells, memory cytotoxic T lymphocytes and antigen antibody complexes.

This explains why an individual successfully vaccinated 10 years or more ago, has a pool of memory B lymphocytes to HBsAg within 3 to 5 days, as a response to exposure to HBsAg, even if the remaining concentration of circulating anti-HBs is low or undetectable.

The accumulated data from 12 follow-up studies involving more than 5000 infants, older children and adults showed that although a certain number of vaccinees had lost their antibodies, none developed clinical manifestations of disease (3-7). Recently, a 14 year follow-up study on vaccine efficacy in Gambian children described a few break through infections in vaccinated children ; it must be stressed, however, that it is difficult to assess the significance of these infections, as some children were vaccinated intradermally, with low dose hepatitis B vaccines, and in others co-morbidity was not excluded (e.g. co-infection with HIV). In addition, although no break through infections due to HBV escape mutants have been observed in successfully vaccinated individuals so far, the possibility of such infections was not ruled out in this study neither.

Further evidence of immune memory comes from the demonstration by SPOT ELISA of circulating B cells able to produce anti-HBs, in a cohort vaccinees followed up to 15 years. Although 30% had no detectable anti-

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HBs anymore, all showed B cell memory by SPOT ELISA or by an anamnestic response following administration of a further dose of hepatitis B vaccine (8,9).

More recent data has confirmed the above findings : 64 healthy persons who had previous documented hepatitis B vaccination and developed antibody levels above the protective threshold, but whose responses had declined over time to < 10 mIU/ml, showed a rapid and powerful anamnestic response when given a dose of HBsAg as a booster. In order to simulate natural exposure, the challenge dose of HBsAg was prepared without an adjuvant (10).

All these data provided the basis for the recent European consensus statement which concluded that, as immunological memory lasts for at least 15 years in immunocompetent subjects, hepatitis B booster doses are not recommended in those who have responded to a completed primary vaccination course (1). As younger age groups respond perfectly to hepatitis B vaccines, booster doses are not recommended for infants, children and adolescents.

This applies also to adults, provided post-vaccination testing has demonstrated immunocompetence (> 10 mIU/ml).

Hepatitis A vaccine and longterm protection

High anti-HAV antibody levels and seroconversion rates have been observed in longterm follow-up studies in adults following the administration of a primary vaccination course (0-6 ; 0-12 ; or 0-18 months schedule). Follow-up data show longterm persistence (12 years) of vaccine-induced anti-HAV antibodies (11). Mathematical models estimate the long-term persistence of anti-HAV antibodies to be more than 25 years (12).

As for hepatitis B, anti-HAV antibody persistence has long been considered as a marker for vaccine protection. However, a better understanding of immunology has led to the realisation that long-term protection is conferred by underlying immune memory.

Studies on HAV vaccination in adult travellers have shown that a delay in the timing of the second dose (24–72 months after the first dose) does not appear to affect the immune response (13,14). A significant anamnestic response has been demonstrated in 25 travellers aged 36–50 years given a booster dose 48-72 months after the first dose. Even when there is no detectable level of antibody before the booster dose, an anamnestic response is observed indicating the involvement of immune memory (13,14).

Studies in chimpanzees provided early evidence of immune memory to HAV post-vaccination. When chimpanzees were immunized with formalin-inactivated HAV antigen, they were protected against challenge with infectious HAV, even in the absence of detectable levels of anti-HAV antibody (15). These data indicate that detectable levels of anti-HAV antibodies are not an absolute requirement for protective immunity.

Early cellular immunity studies using Spot ELISA techniques demonstrated that HAV vaccine has the ability to generate memory B-cells producing IgG anti-HAV (16). In addition, a T-cell response is exhibited 2-3 years after primary vaccination (demonstrated by lymphocyte proliferation and T-cell activation to HAV *in vitro*). The T-cell mediated response is thought to play an important role in long-term protection after natural HAV infection as well as after HAV vaccination (17).

Follow-up data in 31 adults (aged 32-40 years) demonstrate long-term persistence (12 years) of antibodies after completion of a primary HAV vaccination course (11). When challenged 12 years later with half of an adult booster dose of HAV vaccine GMTs rose from 242 at day 0 to 877 mIU/ml, 3831 mIU/ml and 5282 mIU/ml after 7, 14 and 30 days, respectively. These data also confirm the persistence of immune memory.

Available data show that HAV vaccines provide long-lasting protection in immunocompetent subjects. Evidence of immunity, in the form of persisting anti-HAV antibodies and/or an anamnestic response to a vaccine challenge, has been demonstrated in adults up to 12 years after receiving a full course of HAV vaccine. Therefore, based on the accumulating evidence showing that HAV vaccine elicits immune memory that persists even after loss of detectable antibodies, no booster hepatitis A immunization is recommended provided a complete primary course was given.

Conclusion

By abandoning the administration of hepatitis A and hepatitis B booster doses among immunocompetent persons, considerable savings will be achieved and implementation of universal programmes facilitated and prove more attractive.

Available data shows that the immunogenicity of a combined hepatitis A and B vaccine is comparable to that of the monovalent vaccines (18). This indicates that there is no support for hepatitis A or hepatitis B booster when a combined hepatitis A and B vaccine is used for the primary vaccination course.

In general, what remains important in assessing protection, is that attention is given to monitoring immunological memory in those whose antibody responses, although initially present, have declined to undetectable levels.

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