Review

Lessons learnt over two decades of vaccination against hepatitis B in Italy

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Summary

This article reviews topics covered and discussed at the Meeting: "Vaccini e vaccinazioni. Migliorare l'oggi e preparare il domani", held in Genoa, Italy, on 12 September 2014. Data presented at the meeting, clearly showed that: 1) hepatitis B vaccination can confer long-term protection and there is no need for booster in immunocompetent vaccinees; 2) vaccination is highly effective in protecting population from clinical acute or chronic HBV infections, including hepatocellular carcinoma; 3) children vaccinated as infants with hexavalent vaccines maintain immunological memory 5 years after priming, but further studies are needed to assess whether immunity persists during the adolescence and adulthood when risk of exposure to HBV becomes higher; 4) the emergence of vaccine-escape mutants and Pol-gene mutants during antiviral therapy – which can result in changes in the S-gene – is of some concern, but at present there is no evidence that such mutants may pose a threat to the established programs of vaccination.

Introduction

Viral hepatitis B is a serious health problem throughout the world, being a leading cause of acute and chronic liver disease including cirrhosis and primary liver cancer, which ranks as the 3rd cause of cancer deaths worldwide. Globally, over 350 million people are chronic carriers of hepatitis B virus (HBV), more than 500,000 die each year from HBV-related diseases, and approximately 4.5 million people are newly infected yearly. The good news is that hepatitis B is now considered a largely treatable and preventable disease thanks to the availability of effective antiviral drugs and the implementation of several public health measures, including vaccination. Effective vaccines have been available since the early '80s and have proved highly successful to control and prevent hepatitis B and its severe sequelae. Following WHO recommendations, at present 181 countries in the world have implemented programs of hepatitis B vaccination with success both in term of safety and effectiveness.
This article reviews topics covered and discussed at the "Vaccini e vaccinazioni. Migliorare l'oggi e preparare il domani" Meeting held in Genoa, Italy, on 12 September 2014.

Is a booster dose of hepatitis B vaccine required to maintain long-term protection?

Hepatitis B vaccination has been administered to hundreds of milion people of all ages showing an excellent level of safety and effectiveness in protecting people from developing clinical acute or chronic HBV infection. Following a complete course of vaccination (3 doses given at 0, 1, and 6 months), seroprotection rates (anti-HBs antibody at level ≥ 10 mIU/ml) are reached in > 95% of healthy children and adolescents, and in > 90% of healthy adults. Evidence shows that hepatitis B vaccine-induced anti-HBs antibody concentration declines over time and that the kinetics of decay depends on the magnitude of the peak antibody level achieved after primary immunization. In other words, the higher is the titer after primary vaccination course, the longer the antibody persists. Loss of protective antibody over time does necessarily means loss of protection since the immunological memory for HBsAg (hepatitis B surface antigen) can outlast the presence of antibody. Indeed, memory B and T cells are likely to persist beyond detectable anti-HBs antibody. Vaccinees who lost antibody usually show a rapid and strong anamnestic response when boosted or exposed to HBV [1-5].
These data clearly indicate that a strong immunological memory persists more than 20 years after primary immunization providing protection against clinical disease and the development of the carrier state [6-8]. Thus, based on current scientific evidence there is no need to administer booster doses of vaccine to sustain long-term protection in the general population. Such conclusion is based on data collected during the past 15-20 years and applies to both low and hyper-endemic areas of the world.
However, a booster dose could be provided to non- responders and some "at risk groups" (e.g., health care workers and immunocompromised individuals).
Recently, an increased number of failures to develop a response following a booster dose (the so-called boost-

ability) has been reported in some Asiatic countries. Waining of the ability to respond a booster dose seems to be more frequent in individuals vaccinated at birth with poor responses to priming.
Surveillance and additional follow up are needed to clarify this issue.

Do children immunized as infants with hexavalent vaccines maintain protection over time?

In 2000, two hexavalent vaccines (Hexavac and Infanrix Hexa) were licensed in Europe for vaccinating children against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B and invasive infections caused by *Haemophylus influenzae* b. In 2005, Hexavac was suspended as a precautionary measure due to concern about long-term protection against hepatitis B, while no actions were taken over Infanrix Hexa [9]. Until suspension, approximately 10 million doses of Hexavac had been distributed globally, especially in Germany, Austria, and Italy. A crucial question is whether infants vaccinated with Hexavac maintain protection over time or require a booster vaccination to sustain immunity.
A large randomized, multicenter study carried out in over 1500 Italian children primed as infants with hexavalent vaccines 5 years earlier showed that 83.2% of those vaccinated with Infanrix Hexa maintained antibody over the protective level (≥ 10 mIU/ml) compared to 38.4% of those who were treated with Hexavac. Also GMC was higher in the former than in the latter group (61.3 mIU/ml *vs* 4.5 mIU/ml; $p < 0.0001$). Following a booster with a single dose of monovalent vaccine, both groups of vaccinees (either treated with Infanrix Hexa or with Hexavac) had similar good anamnestic responses both in terms of percentages of responders and GMCs, regardless of which hexavalent vaccine they had been primed with [10]. These data were confirmed and extended by other studies [11, 12].
The conclusion from these data is that routine booster doses of vaccine do not seem necessary to sustain immunity in children primed with hexavalent vaccines, even though follow-up beyond 5 years is necessary to assess whether protection can last during adolescence and adulthood when risk behavior of exposure to HBV through sexual activity or intravenous drug-taking is expected to increase.
A follow up study carried out in adolescents primed as infants 10 years before is currently in progress in Italy, and results will be available in 2015.

Are HBV-escape mutants a matter of concern?

Hepatitis B neutralizing (protective) antibodies (anti-HBs) induced by vaccination are targeted largely towards the amino acid hydrophilic region known as the common a determinant which is present on the outer protein coat or surface antigen (HBsAg), spanning amino acids 124-147. This provides protection against all HBV genotypes (from A to H) and is responsible for the broad immunity afforded by hepatitis B vaccination. Thus, alterations of residues within this region of the surface antigen may determine conformational changes that can allow replication of the mutated HBV in vaccinated people.
An important mutation in the surface antigen region was identified in Italy some 25 years ago in infants born to HBsAg carrier mothers who developed breakthrough infections despite having received HBIG and vaccine at birth [13-15]. This virus had a point mutation from guanosine to adenosine at nucleotide position 587, resulting in aa substitution from glycine (G) to arginine (R) at position 145 in the a determinant. Since the G145R substitution alters the projecting loop (aa 139-147) of the a determinant, the neutralizing antibodies induced by vaccination are no longer able to recognize the mutated epitope. Besides G145R, other S-gene mutations potentially able to evade neutralizing anti-HBs and infect vaccinated people have been described worldwide [16-19].
In addition, the emergence of polymerase mutants associated with resistance to treatment with nucleos(t)ide analogues can select viruses with crucial changes in the overlapping S-gene, potentially able to alter the S protein immunoreactivity [20-22]. Thus the increasing use of such drugs may cause the emergence of mutants potentially able to escape vaccine-induced immunity and to infect vaccinees.
Despite concern, at present the overall impact of such mutants seems to be low and they do not pose a public health threat or a need to modify the established hepatitis B vaccination programs.

Is hepatitis B vaccination effective in preventing liver cancer?

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer death in humans and hepatitis B virus (HBV) is the most common etiological cause of HCC in the world, particularly in Asia, the Middle East, Africa and southern parts of Eastern and Central Europe. Chronic HBV infection can lead to chronic hepatitis, cirrhosis and HCC; it is estimated that chronic carriers of HBV are 100 times more likely to develop HCC than uninfected people. Thus prevention of chronic hepatitis B – through vaccination – can successfully prevent the risk of developing HBV-related cancer. Taiwan, a country where the universal HBV vaccination of newborns was implemented in 1984, is perhaps the best example of an area with previously high endemicity showing a substantial decrease over time of the burden of hepatitis B and HBV-related diseases, including HCC [23-26]. A study carried out by Chien et al, showed striking differences in HCC incidence (0.293 *vs* 0.117 per 100,000 person-years) between vaccinated and unvaccinated newborns 20 years after the implementation of vaccination, providing evidence that hepatitis B vaccination can

significantly prevent the long-term risk of HCC [27]. In Alaska, McMahon et al showed that following vaccination, the incidence of HCC in people < 20 years dropped from 3 per 100,00 in 1984-1988 to zero in 1995-1999, and no cases have occurred since 1999 [28].
All this clearly shows that anti-hepatitis B vaccination is a successful way to control and prevent HCC, indicating the hepatitis B vaccine as the first vaccine against a major human cancer.

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