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CURRENT VIEWS ON THE PERSISTENCE OF IMMUNITY FOLLOWING HEPATITIS B VACCINATION

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ABSTRACT

This paper presents current views on the persistence of immunity following vaccination against hepatitis B. Very high effectiveness of hepatitis B vaccination has been reported in a number of studies worldwide. Standard vaccination with approved schedule induces protective antibody titers in healthy newborns, children, adolescents and adults in more than 96% and 90% of cases, respectively. A number of studies have also confirmed the occurrence of anamnestic response to a booster injection of HB vaccine even after 20 years following primary immunization. From the numerous studies transpires that cellular response following hepatitis B vaccination persists longer compared to humoral response. Irrespective of gradual decline and loss of anti-HBs antibodies, adequately performed primary immunization in healthy persons ensures long-term protection against acute and chronic stages of hepatitis B. In fact, T and B lymphocytes, whose responsiveness prevails the presence of anti–HBs antibodies in serum, are true markers of immunity. A special attention should be given to persons with secondary immunodeficiencies or immunosuppressed patients whose immunization against hepatitis B raises difficulties.

Key words: *hepatitis B, vaccine-induced immunity*

INTRODUCTION

Effectiveness of vaccination against hepatitis B has been of interest in the past as well as present times (1). Determination of the persistence of immunity following hepatitis B vaccination was a very important issue. In 2002, information on it as of the end of 90s of the last century was published in the Epidemiological Review (2). Since that time, immunogenicity of vaccines and vaccination schedules were subject to modifications, especially in case of persons with immunodeficiencies.

Hepatitis B virus (HBV) is one of the most prevalent etiological agents of acute and chronic stages of liver infection. According to the World Health Organization (WHO) data, en estimated 600,000 persons die annually due to the consequences of infection with HBV such as liver cirrhosis or hepatocellular carcinoma (HCC). Hepatitis B is transmitted through contact of infected blood or other body fluids with broken tissues. A list of risk factors of infection with HBV include: medical procedures (i.e. surgeries, dental procedures, endoscopy) or cosmetic procedures (tattooing, piercing) provided single use disposable equipment or sterile devices are not applied. High risk of HBV infection is also attributed to nasal or injecting drug use as well as sexual contacts with infected partner. HBV may be also vertically transmitted, i.e. from infected mother to foetus in perinatal period or at the delivery.

Incidence of hepatitis B in Poland decreased significantly in the last years. At the beginning of 80s, it amounted to 45.1/100,000 inhabitants. In the present time, its value ranges from 3.5 to 4.0/100,000 inhabitants. Improvement of epidemiological situation results from the changes in the usage of medical equipment (single use disposable equipment and sterilization of medical devices in autoclaves). Introduction of effective vaccination of the selected groups and then the whole population, however, contributed to such situation to the largest extent. In 1993, Poland joined the Expanded Program on Immunization (EPI) which was implemented by the Word Health Organization. On a basis of this program, newborns were covered by this integrated immunization system. In Poland, primary immunization of newborns and infants include 3-dose series on a 0-, 1-, 6-month schedule. First dose is administered within 24 hours following child's birth (most

preferably within 12 hours). Second dose of primary series should be given 4 weeks after the first dose while the third one, complementary to primary vaccination, should be given 6 months following the first dose. A 4-dose series on a 0-, 1-, 2-, 12-month schedule (or 0-, 1-, 2-, 6) should be administered to newborns with low birth weight (<2000 g). In 2000, obligatory vaccination for adolescents aged 14 years (0-,1-,6-month schedule) was introduced. It is estimated that up to 2008, the percentage of adolescents and young adults aged up to 24 years who gained immunity to HBV exceeded 95%. The remaining percentage (ca 5%) in this age group is protected by herd immunity which reduces the risk of infection of unvaccinated person due to increased proportion of vaccinated persons in Polish population (3).

In case of healthy persons, there are two vaccination schedules against HBV, i.e.: 0-,1-,6 and 0-,1-,2-,12-month schedule. To determine the effectiveness of vaccination, the presence of anti–HBs antibodies 1 month after the administration of last dose is assessed. In the study of *Gesemanna* and *Scheiermanna*, whose mathematical model was developed in Poland, the highest and the most rapid decline of antibody titers was observed at one month and one and a half year following a standard course of vaccination, respectively (4). In the similar study, conducted in Thailand, the highest antibody titers was reported not until 12 month following vaccination (5). In a number of studies, long-term immunogenicity was confirmed by eliciting the persistence of anti-HBs antibodies 10, 15 and even 20 years after vaccination (6–8). From the longest observations transpires that of the newborns who received a 4-dose series (0-, 1-, 2-, 12-month schedule) and concomitantly a single dose of hepatitis B immunoglobulin, high percentage demonstrated immunity, marked by anti-HBs antibody titer at the age of 20 years. Namely, 64% and 92% of study participants had anti-HBs antibody titer equal to ≥10 mIU/mL and ≥ 3.3 mIU/ml, respectively (5).

FAILURE TO RESPOND TO VACCINATION

Irrespective of the fact that the majority of healthy persons (children as well) respond correctly to vaccine against hepatitis B (>100 mIU/mL), there is also a small proportion of persons whose response to HB vaccine is poor or none with the titers of anti-HBs amounting to 10–100 mIU/mL and <10 mIU/mL, respectively. In the study of *Migdał* et al., the percentage of adults who failed to respond to vaccine was 3.8% (9). In case of children, this percentage ranges from 0.5 to 4.0% (10). A person with anti–HBs titers below 10 mIU/mL following two vaccination series is defined as unresponsive. Consequently, the protection of such persons against infection may be contested.

Available data suggest that the reasons of poor or failed immune response to HB vaccine are demographic factors (age, gender) and health behaviours (obesity, tobacco smoking) (11). A separate issue is a group of persons with primary or secondary immunodeficiencies, including i.a. persons diagnosed with leukemia, bone marrow recipient, patients with cirrhosis or a history of liver transplantation, persons infected with HIV,

Table I. Immunization schedule for persons with impaired immunity against hepatitis B and the percentage of persons who responded to vaccination, based on the available data.

	ALL	Tx bone marrow	Liver cirrhosis	Tx liver	HIV - coinfection	ESRD and HD
Immunization schedule	0-1-2 months	0-1-6 months	0-1-2 months	0-2-4-16-18 weeks + HBIg	0-1-6 * months	0-1-6 * months
	0-1-2 months	n.d.	n.d.	n.d.	0-1-2-6 ** months	0-1-2-6 ** months
Vaccine dose	40µg	20µg	20µg	20µg	40µg	40µg
Booster dose	1 year/ 6 months following the last dose	n.d.	n.d.	up to 3x in monthly intervals	up to 3x in monthly intervals	n.d.
Immune response to vaccination (%)	48.8-60%	64%	60% very good response	n.d.	50.7-60% ^	47-73% ^
			19% good response			
			21% failed response		89% ^^	82.6-89.6% ^^
Source	(12)	(13)	(14)	(15)	(16)	(17;18)

ALL – acute lymphoblastic leukemia
Tx bone marrow – bone marrow transplantation
Tx liver – liver transplantation
n.d. – no data
ESRD – end-stage renal disease
HD – hemodialysis
* Immunization 0-1-6 months
** Immunization 0-1-6 months
^ response after 0-1-6 immunization
^^ response after 0-1-6 immunization

those with end-stage renal disease or hemodialyzed. Compared to healthy persons, different HB vaccination schedules are to be frequently adopted in such patients as immune response following vaccination is considerably lower. Due to the multiplicity of disorders, patients with immmunodeficiencies require, i.a. administration of double doses, booster doses or HBIg (passive immunization) to enhance the immune response rate following vaccination (Table I).

Of patients for whom immunization is hard to achieve, including patients with immunodeficiencies, the greatest challenge are patients diagnosed with acute lymphoblastic leukemia, end-stage renal disease and those hemodialyzed and coinfected with HIV who require the administration of double vaccine doses (Table I). Irrespective of the fact that in a proportion of cases, even more than 50%, immunity response is achieved (Table I); persons with immunodeficiencies do not gain long-term immunity against hepatitis B.

Researchers suggested that immunogenetic phenomena may be fundamental in responsiveness to HBsAg. From one of the first studies, which was conducted by *Walker* et al. in 1981, excessive expression of HLA–DR7 and concomitant lack of HLA–DR1 were reported in persons who failed to response to HB vaccine (19). It was an important study, in which Dr Wolf Szmuness participated, alumnus of the Medical University of Lublin and then researcher who in the United States conducted significant studies on the immunization against hepatitis B in hemodialyzed patients and homosexualists. This study initiated research on the successive stages of immune response to vaccine, i.e. defect in antigen presentation by antigen presenting cell (APC), proliferation of the T cell lines, activation of the T lymphocytes and memory B cells. Studies conducted so far demonstrate that for poor-or non-responders to vaccine, a characteristic feature is a defect of T lymphocytes, which have receptors to recognize HBsAg. According to *Desombere* et al., T lymphocyte response to HBsAg in these persons may be oligospecific and oligoclonal (20).

IMMUNE MEMORY FOLLOWING VACCINATION

From numerous studies conducted so far transpires that standard vaccination against hepatitis B with approved schedule induces protective antibody titers in healthy newborns, children, adolescents and adults in more than 96% and 90% of cases, respectively. According to *Leuridan* and *Van Damme,* primary immunization provides long-term protection in case of adequately vaccinated persons due to immune memory. It demonstrates rapid anamnestic response to a booster vaccine and low percentage of persons infected with HBV in vaccinated population (21). An expected effect following vaccination is the activation of immunity protecting against infection. A number of observations were conducted with an objective to determine the prevalence of hepatitis B markers as markers for breakthrough infection in vaccinated persons. In study groups, the prevalence of breakthrough infections was low. These infections were most frequently associated with an increase of anti–HBc: from 1.0% to 13.8%; transient appearance of HBsAg: 0.7% - 5.4% and presence of HBV DNA: 0.19% - 0.9% (8,21).

Numerous studies confirm that anamnestic response to a booster vaccine administered 10, 15 and even 20 years after primary immunization occurs in persons whose anti–HBs titers decreased below the protective level (< 10 mUL/mL) (5,6,22–25). Occurrence of anamnestic response after vaccination is dependent on the group studied. In case of children, its percentage amounts to even 99%. According to researchers, higher percentage of non-responders to booster doses in older persons results from age-related waning of immune memory (23).

ROLE OF CELLULAR RESPONSE IN MECHANISM OF IMMUNE MEMORY

Observation of gradual waning of anti–HBs antibodies (<10 mIU/Ml) following a standard course of vaccination and possibility of effective secondary immunization initiated the research on the role of cellular response (5). Due to a number of *in vitro* experiments, it was possible to understand the mechanisms of immune memory. Pioneer in this respect was the team presided by *van Hattum* and *Boland* (26). In the study group, anti-HBs titers were investigated 10 years following vaccination. Peripheral mononuclear cells were also collected to test lymphocyte proliferation to HBsAg. From study transpires that T lymphocyte proliferative response to HBsAg was positive in the majority of vaccinated persons whose anti–HBs titers were less than 10 mIU/mL. These results confirmed that T lymphocyte response persists longer compared to humoral response (26). On a basis of T lymphocyte proliferative response, *Leuridan* and *Van Damme* proved the responsiveness of B and T lymphocytes to antigens of vaccine in vaccinated person (21). Long-term persistence of cellular response was also confirmed by *in vitro* measurement of the secretion of cytokines—interferon (IFN)-γ and interleukin (IL)-5 by Th1 and Th2 lymphocytes following HBsAg stimulation (HBsAg) (8). Similarly, the presence of memory B cells and anti–HBs-producing cells using 'ELISPOT' was reported in persons for whom specific antibodies were not detectable (27). As

early as in 2000, a paper suggesting that adequately performed primary immunization - due to long-term immune memory - provide life-long protection against hepatitis B was published. This paper was accepted by the majority of the EU countries (28).

SUMMARY AND CONCLUSIONS

Above all, studies discussed and their findings demonstrate very high effectiveness of vaccination against hepatitis B. Irrespective of gradual decline and loss of anti-HBs antibodies, adequately performed primary immunization in healthy persons provides long-term protection against acute and chronic stages of hepatitis B (29). It suggests that there is no need for periodic testing for anti-HBs (each 5 years) which recently was a routine practice in Poland. In fact, T and B lymphocytes, whose responsiveness prevails the presence of anti–HBs antibodies in serum, are true markers of immunity. A similar opinion is expressed by the team of *Bernatowska* et al. They stated that antibody titers less than <10 mIU/mL do not suggest the lack of immunity. Furthermore, recommendations promoted worldwide suggest more than 20-year-lasting protection against hepatitis B following primary immunization (30).

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