

Association of HLA Phenotype with Primary Non-response to Recombinant Hepatitis B Vaccine: A Study from North India

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Introduction

Hepatitis B vaccination has been one of the success stories in the prevention of hepatitis B virus (HBV) infection and related complications. Recombinant hepatitis B vaccine is highly immunogenic and has a good safety record in various countries around the world including India.¹⁻⁴ Most studies have found the primary non response rate to recombinant hepatitis B vaccination to range between 5% and 10%. Factors that have been linked to non-response include age, sex, obesity, smoking, diabetes and chronic renal failure.^{1,4,5-7} But these factors alone cannot explain all causes of non-response. It has been suggested that non-response may be related to certain human leucocyte antigen (HLA) phenotypes such as DR4, DR7, FC31, B44, DQ3 etc.⁸⁻¹¹ This is because the immune response to the virus has been found to be influenced by HLA phenotypes.¹⁴⁻¹⁶ Ethnic differences in HLA Phenotypes are responsible for non-responsiveness to hepatitis B surface antigen (HBsAg) has been documented in the literature.¹⁷ Since HLA phenotypes of Indians have been found to be different from those of both Caucasians and orientals,¹⁸ we decided to design a study to characterize the HLA phenotypes associated with non-responsiveness to hepatitis B vaccination in Indian population.

Materials and Methods

The study was conducted at the L.N.Hospital, New Delhi during April 1998 to March 1999. A total of 107 healthy volunteers were selected from 387 healthy non-obese non-smokers attending the medical outpatient services using the random sampling method. The volunteers were re-tested for markers of HBV infection. The 102 volunteers negative for hepatitis B infection agreed to participate. The serological tests in the study included HBsAg (Ranbaxy Diagnostics, Bombay, India). IgG anti-HBe (Meltec, Spain), anti Hbs (AUSAB, Abbot Lab USA) and anti-HBc (Melotec, Spain) using commercially available ELISA kits. Among the 102 volunteers who completed the trial, there were 87 responders (age and sex matches) were included in the study using the random sampling method after obtaining informed consent. The schedule of the recombinant HBV vaccine was 0, 1 and 6 months.

Testing for anti-HBs antibody titres was done on days 90 and 210 after administration of first vaccine dose. Non-responders were defined as volunteers with anti-HBs antibody global mean titres (GMT) <10mIU/ml at day 210. HLA A/B/C/D typing was carried out by standard microlymphotoxicity tests. All the volunteers were administered a questionnaire and those positive for known factors that could confound the rate of response were not included. Statistical analysis was done using the standard student's and Chi-square test with Yates correction.

Results

The average age of the responders was 44.6 ± 6.9 years. The male-to-female ratio in the responder population was 4:1 while in the non-responder population it was 8:7. Table 1 shows the frequency of specific HLA types among responders and non-responders. Haplotypes with the highest frequencies among non responders (compared to responders) were HLA A1 and B15 (5-times) followed by B40 (3 times), and A10 and DQ2 (2.5 times). DR 52 was present in a frequency of 11/15 (73.3%) in equal measure in both groups. HLA A1 and B15 were present among 5/15 of the non-responders (33.3%) but only 1/15 of the responder population (6.7%). HLA DR53 was more frequent in the non-responders (7/15, 46.7%) compared to the responders (5/15, 33.3%). The most common HLA phenotypes in the responder population were HLA – A11, C3, DR10 and DR51. These differences in frequencies were however non-significant ($p > 0.05$).

Discussion

On the basis of HLA phenotypes, Indians occupy a middle position between Caucasians and Orientals. This conclusion is based on the findings of HLA phenotype studies conducted in India as well on Indians in other countries. Indians have patterns similar to Caucasians for HLA phenotypes A1, A3, A7, 6b and A8; HLA A2 and 6a are lower among Indians while HLA A9, Lc17, AS and D-66 are higher among Indians compared to Jews or Japanese.¹⁸⁻²¹ HLA A1, A3, A9 and A5 are observed with increased frequency in Indian population.¹⁸⁻¹⁹ A2 is significantly lower while similar frequencies occurred for HLA A7, Lc17, 6b and A8. Further, HLA W19. (Thomson factor) was also absent in our study group.¹⁸⁻²¹ Previous investigations have correlated the non-response to hepatitis B vaccine in Caucasians to extended haplotypes B44, DR7, FC31 and B8^{10, 17, 20, 23, 25} and reported an increased prevalence of HLA A1, DQ2, DQ3, DR3, B44, B15, DR4 and DR53 in responders. In our study,

response to hepatitis B vaccinations was associated with certain HLA phenotypes such as HLA A1, DQ2 and B15 as reported by other investigators. HLA B40 and A10 haplotypes was associated with non-response to vaccination in our subjects, which has not been reported from the west. Interestingly, certain HLA phenotypes such as DR4, DR7 and DQ3 were found to be lower in our non-responder population, but have been reported in other ethnic among non responders to hepatitis B vaccination.^{3,8,17,25} Some of the haplotypes such as HLA 44 and B46, which have been described among non-responders by other investigations,²⁴ were absent in our population. Also, there certain haplotypes such as A10 and DR3 which were found with increased frequency among non-responders in our study group but were not reported by other investigators. So far, HLA B40 and A10 studies to identify the relationship between HLA phenotypes and diseases such as tuberculosis and Kalazar^{26, 27} in an Indian population have not yielded any specific haplotype associated among individuals.

Table 1 : Selected HLA Phenotypes in responder and non-responder populations.

HLA Types	Responder (n=15)	Non-responder (=15)
A1	1 (6.7)	5 (33)
A10	2 (13.3)	5 (33)
A11	6 (40)	4 (26.7)
B8	1 (6.7)	3 (20)
B15	1 (6.7)	5 (33)
B40	1 (6.7)	3 (20)
C3	8 (53.8)	4 (26.7)
B4/B6	15 (100)	15 (100)
DQ2	2 (13.3)	5 (33)
DQ6	3 (20)	1 (6.7)
DR10	3 (20)	1 (6.7)
DR51	4 (26.7)	1 (6.7)
DR52	11 (73.3)	11 (73.3)
DR53	5 (33)	7 (46.7)

Values in parentheses are percentages

Our Study revealed certain interesting observations that lead us to believe that certain haplotypes such as HLA A1, B8, B15 and Bq12, which have been recognized as universal, do occur in an Indian population and may be associated with non-responsiveness to HBV vaccination. At the same time, certain other haplotypes such as HLA B40 and A10 were also detected among non-responder to HLA vaccination, which has not been observed earlier. These results emphasize the need for larger studies to study HLA phenotypes with respect to responders and non-responder in different ethnic groups within the Indian population.

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