Abstract #:804

IMMUNOLOGICAL RESPONSES AFTER A BOOSTER DOSE OF HBV VACCINE IN HIV-INFECTED YOUTH

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Abstract

Background: Three doses of vaccine against HBV induce the production of protective antibody (Ab) levels (>10 IU/mL) in 95-100 % of healthy children but in only 23-56% of HIV-infected children. Ab titer elicited by vaccination decreases over time in both populations with a faster slope observed in HIV-infected patients. This decline protection against HBV is known to last almost three decades after vaccination in immunocompetent children, these data are limited in HIV-infected children.
Methods: 53 HIV-infected patients (aged 8-25 years old) in whom HBV vaccination according the Italian schedule did not elicit the generation of protective Ab titers were enrolled in the study at Paediatric Infectious Diseases Unit, L. Sacco Hospital, University of Milan. All patients had undergone ART for at least 1 year; HIV viral load was undetectable in all of them, median CD4+ count 718 mm^3. All patients received a booster dose of HBV vaccine (HBVAXPRO 10 micrograms i.m.). HBV-specific Ab titer, viral load and CD4 + were measured in all subjects at baseline (T0), at 1 (T1), 6 (T6) and 12 (T12) months after the booster dose. In a subgroup of 16 patients HBV-specific cell mediated immune (CMI) responses were evaluated at baseline and at T6.
Results: The booster HBV vaccine dose resulted in a seroconversion rate (anti-HBs ≥ 10 IU/mL) in 51% of patients at T1, 57% at T6 and 49% at T12; seroconversion rate was significantly correlated with CD4+T lymphocyte counts at T0 and to CD4 nadir (p<0.05). HIV viral load was undetectable at each time. CMI responses were evaluated in 9 responders (HBsAb >10 IU/mL) and 7 non-responders (HBsAb <10 IU/mL). Upregulation of HBV-specific CMI compared to baseline values was observed at T6 in responders alone. Memory (p= 0.007), Effector Memory (p= 0.003), TNFα- (p= 0.041), IFNγ- (p= 0.004), and granzyme-secreting CD8+ T cells (p= 0.003), Central Memory (p= 0.005) and IL2-secreting CD4+ T cells (p= 0.015) were significantly increased in responders compared to baseline values. Activated CD8+CD38+CD45RO+ T cells (p= 0.004) were significantly reduced as well at T6 in these individuals. No significant differences were observed when T0 and T6 data were compared in non responders.
Conclusions: In HIV+ patients no responding to the standard HBV immunization protocol, seroconversion induced by a booster dose of vaccine (Ab titers <10 IU/mL) correlates with the development of T cell immunological memory. Alternate immunization schedules should be designed for those individuals who don't respond even to a booster dose of vaccine.

Background

- Suboptimal HBV vaccination responses in HIV-infected individuals have been documented in literature *(reviewed in Mena G. et al., 2015)*
- HBV vaccination induces the production of protective antibody levels only in 23-56% of HIV-infected children. *(Abzug M. et al., 2010)*
- Decline in Ab titer has been reported to decrease over time both in healthy and HIV-infected individulas, with a faster slope observed in HIV-infected patients. *(Whitaker J. et al., 2014)*
- Despite the decline in Ab titers, HBV vaccination has been shown to last almost three decades in heathly individulas. *(Mena G. et al., 2015)*
- Nontheless, data on HBV vaccination efficacy in HIV-infected children is still limited.

AIM

To evaluate immunological responses after a booster dose of HBV vaccination in HIV-infected young individuals

Materials and Methods

Study Population and Inclusion Criteria:
53 HIV-infected young individuals (aged 8-25 year old) non responders to standard HBV vaccination regimen were enrolled in the study. All subjects were under HAART and with undetectable viral load.

A booster dose of HBV vaccine (HBVAXPRO 10 µg i.m.) was administered to each enrolleld patient

Analyses performed:
- Evaluation of Ab titer, viral load, CD4+ T cells count and percentage at T0, T1, T6 and T12
- Cell-mediated immune response analysis (CMI) was evaluated at T0 and T6 in a subgroup of 16 patients responders (n=9) or non-responders (n=7) to the booster dose of HBV vaccine.

  - T cells maturation subsets were evaluated by flow cytometry: Naive T cells were identified as CD45RA+/CCR7+, central memory were identified as CD45RA-/CCR7+, effector memory were identified as CD45RA-/CCR7- and terminally differentiated were identified as CD45RA+/CCR7-.

  - PBMCs isolated by density gradient were stimulated with a recombinant HBsAg (adw) antigen (1µg/ml) (Acris Antibodies) for 18 hours. HBV CD8+ specific T cells responses were evaluated by flow cytometry.

Results

	NSR baseline	NSR T1 number (%)	NSR T6 number (%)	NSR T12 number (%)
7-12 years	7	2 (29%)	1 (14%)	2 (26%)
13-18 years	15	8 (29%)	6 (40%)	8 (53%)
> 18 years	31	16 (52%)	16 (52%)	17 (54%)
total	53	26 (49%)	23 (43%)	27 (51%)

Table 1: Stratification by age of patients with non protective antibodies titer (HBAb<10 UI/mL, non responder, NR) for each time of the study (T1, T6, T12)

	P 50	P 25	P 75
CD4 T0 absolute number cell/mm^3 (%)	713,5 (34,5%)	608,5 (28,9%)	910,5 (40,32%)
CD4 T1 absolute number cell/mm3 (%)	750 (34,5)	535,25 (29,35%)	923,5 (42,82%)
CD4 T6 absolute number cell/mm3 (%)	737,5 (34,75%)	561,5 (28,2%)	878,5 (43,62%)
CD4 T12 absolute number cell/mm3 (%)	728 (36,2%)	587 (28,8%)	887 (42,87%)
Nadir CD4 absolute number cell/mm3 (%)	306 (17,5%)	180 (11,6%)	397 (26,42%)

Table 2: Median and percentiles of CD4 count values in absolute number and percentages at T0, T1, T12 and nadir. Tobit analysis showed positive significative relationship between CD4 nadir (absolute number) and HbsAb serorevertant rate at T1(p< 0.1), T6 (p< 0.1) and al T12 (p<0,05).

	HBsAb T1 (UI/mL)	HBsAb T6 (UI/mL)	HbsAb T12 (UI/mL)
CD4+ count T0	p<0.05 (0.570)	p<0.1 (0.720)	p<0.05 (0.626)
CD4+ count nadir	p<0.1 (0.309)	P<0.1 (0.197)	p.0.05 (0.165)

Table 3: Correlation between CD4+ count (absolute number) and seroconversion rate at T1, T6, T12: p value (standard errors)

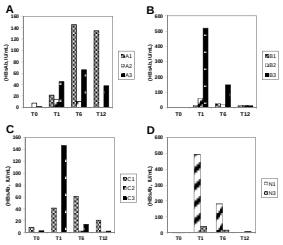


Figure 1: Average values of HBsAb trends according CDC stages. CDC A (Panel A), CDC B (Panel B), CDC C (Panel C), CDC N (Panel D).

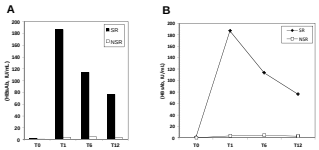
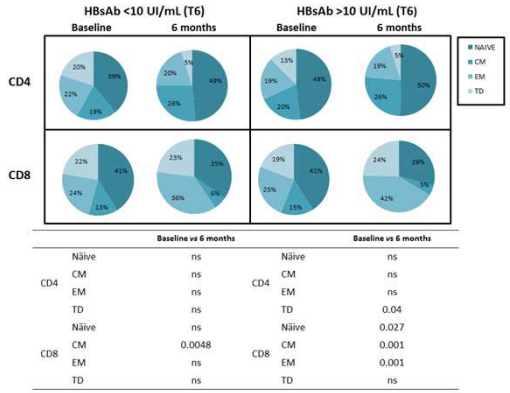


Figure 2: Mean HBsAb titers (UI/mL) of serorevertants patients (SR) and non-serorevertant (NSR) at T0, T1, T6 and T12. Histograms (Panel A) and trend lines (Panel B).



		HBsAb <10 UI/mL (T6) Baseline vs 6 months		HBsAb >10 UI/mL (T6) Baseline vs 6 months
CD4	Naïve	ns	Naïve	ns
	CM	ns	CM	ns
	EM	ns	EM	ns
	TD	ns	TD	0.04
CD8	Naïve	ns	Naïve	0.027
	CM	0.0048	CM	0.001
	EM	ns	EM	0.001
	TD	ns	TD	ns

Figure 3: CD4+ and CD8+ T Cells maturation subsets. Proportion of CD4+ and CD8+ T-cell subsets. Immunological parameters analyzed in vaccine recipients are shown at baseline and in response to HBV vaccine dose. Mean values, SE and statistically significant differences are indicated. NS, not significant. CM, central memory; EM, effector memory; TD, terminally differentiated.

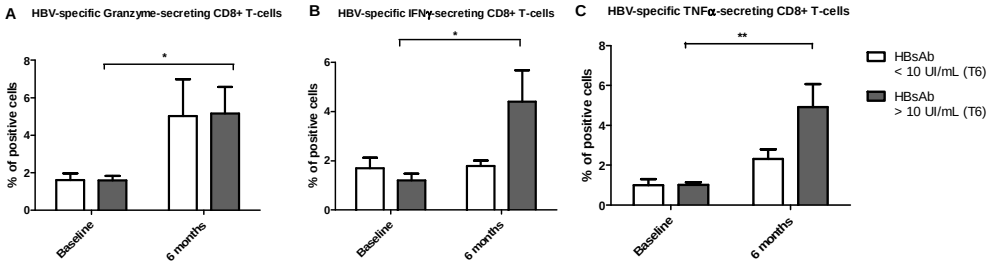


Figure 4: HBV-specific CD8+ T cell responses. Percentage of HBV-specific Granzyme- (Panel A), IFNγ- (Panel B), and TNFα- (Panel C) secreting CD8+ T-cells analysed in Responders and Non-Responders HIV-infected individuals at Baseline and in response to HBV vaccine booster dose. * p<0.05, ** p<0.01. Mean values and SE are indicated.

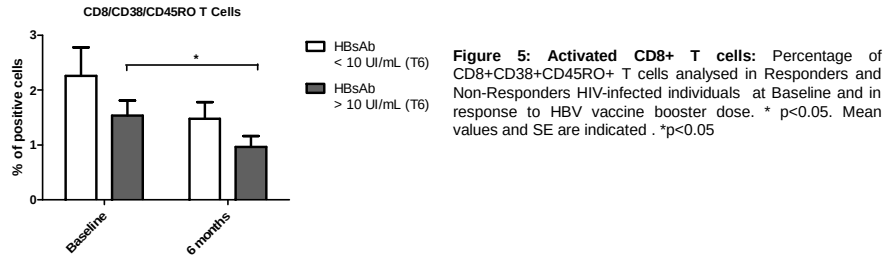


Figure 5: Activated CD8+ T cells: Percentage of CD8+CD38+CD45RO+ T cells analysed in Responders and Non-Responders HIV-infected individuals at Baseline and in response to HBV vaccine booster dose. * p<0.05. Mean values and SE are indicated . *p<0.05

Conclusions

In HIV-infected young patients no responding to the standard HBV immunization protocol, seroconversion induced by a booster dose of vaccine (Ab titers >10 IU/mL) correlates with the development of T cell immunological memory, characterized by higher percentages of HBV specific granzyme, INFγ and TNFα secreting CD8+ T cells.
Alternate immunization schedules should be designed for those individuals who don't respond even to a booster dose of vaccine