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Varicella Zoster Virus Vaccination in immunocompromised patients with haematological and rheumatological diseases: specific T-cell response measured with an in-house Interferon Gamma Release Assay

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Background

The reactivation of varicella-zoster virus (VZV) causes herpes zoster (HZ).

VZV-specific T-cell –mediated immunity (CMI) is considered fundamental to prevent HZ. Age and immunomodulating drugs can impair VZV-specific CMI and contribute to HZ occurrence. A new adjuvanted recombinant subunit vaccine (HZ/su) has been recently approved for the prevention of HZ in adults with immunosuppression.

Our study aimed to investigate VZV-specific immunity in haematological (HE) and rheumatological (RH) patients under immune modulating treatments or chemotherapy after HZ/su vaccination.

Material and Methods

HE and RH patients under active treatments were enrolled in the study.

Two doses of HZ/su were administered 1 month apart (T0 and T1 respectively), with a follow-up visit 1 month after the second dose (T2).

T-cell responses were assessed at T0 and T2 with an in-house Interferon Gamma Release Assay (IGRA), consisting of heparin whole blood stimulation with VZV gE and Immediate Early (IE)-63 peptide libraries. Each test included a negative (NC) and positive (phytohemagglutinin, PHA) control. IFN-gamma production was measured with the automated ELLA platform. *Figure 1*

Data were represented as median (interquartile range, IQR).

Medians were compared using the non-parametric Wilcoxon matched-pairs signed rank test.

Results

We enrolled 19 patients (14F/15M) with severe immunodeficiency who completed the vaccination schedule and with at least 1 month of follow up after the second dose.

13 (68%) had HE disease (2 multiple myeloma [MM], 11 B-cell lymphoma [BCL]); 6 (32%) had RH disease (all with rheumatoid arthritis) under corticosteroid and Jak-2 inhibitors treatment. Median age was 63 years (IQR 56-71). *Tab.1*

All patients were under active treatments.

Sex		Age y/o	Pathologies		
F	(14) 74%	63.6	H	13	68%
M	(5) 26%	63 (56;71)	R	6	32%

Tab.1

Median IFN-gamma production after gE stimulation was 1.1 pg/ml, and 46.7 pg/ml at T0 and T2, respectively (Wilcoxon p<0.001). Median IFN-gamma production after IE-63 stimulation was 1.3 pg/ml, and 1.1 pg/ml at T0 and T2, respectively (Wilcoxon p=0.1) (*Figure 2*). An effective vaccinal response was defined as a 4-fold increase in IFN-gamma production in the gE stimulated condition, from T0 to T2. 5/19 (26%) patients were considered as non-responder (all of them with HE malignancy, 1 MM and 4 BCL)

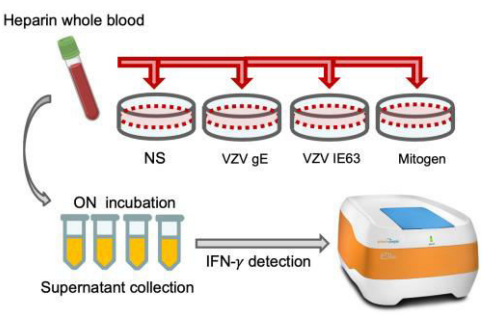

Figure 1: 500µl of fresh heparinized blood were incubated overnight at 37° C and 5% CO2, after stimulation with glycoprotein (g)E and immediate Early (IE)63 peptide libraries of VZV, at a final concentration of 1µg/ml. For each patient a negative and positive (phytohemagglutinin (PHA) 5µg/ml) control was also included. After 18 hours, supernatants were collected and stored at -80° C. IFN-γ production was assessed with the automated ELLA platform. FN-γ response was defined as peptide or PHA stimulated condition minus unstimulated condition.

Figure 2: VZV-specific cell-mediated responses in Haematological and Rheumatological patients before (T0) and after (T2) HZ/su vaccination

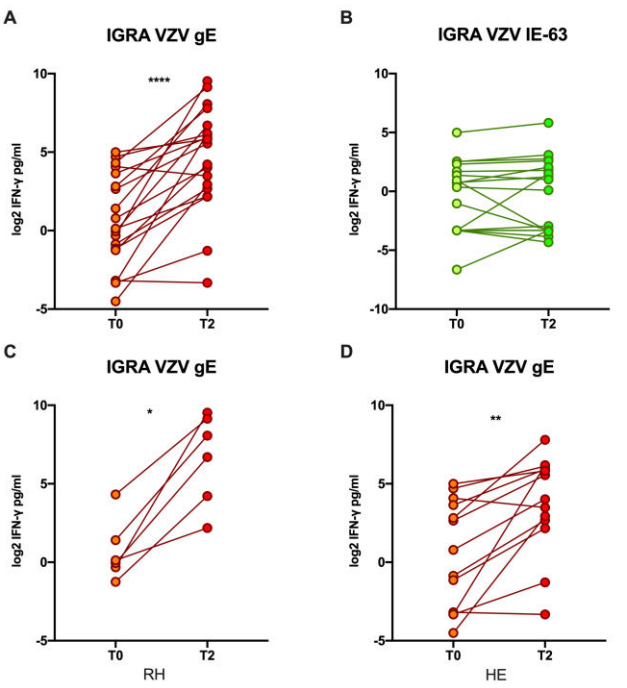

Figure 1: **A)** Interferon-gamma (IFN-γ) production after stimulation with gE peptide libraries of VZV at T0 (pre-vaccination) and T2 (one month after second dose of HZ/su vaccine), in the overall study population; HZ/su vaccine is based on VZV-gE protein; Wilcoxon test p<0.0001. **B)** IFN-γ production after stimulation with IE-63 peptide libraries of VZV at T0 (pre-vaccination) and T2 (one month after second dose of HZ/su vaccine), in the overall study population; IE-63 protein is not contained in HZ/su vaccine; Wilcoxon test p=0.1. **C)** IFN-γ production after stimulation with gE peptide libraries of VZV at T0 (pre-vaccination) and T2 (one month after second dose of HZ/su vaccine), in rheumatological patients (RH); Wilcoxon test p=0.03. **D)** IFN-γ production after stimulation with gE peptide libraries of VZV at T0 (pre-vaccination) and T2 (one month after second dose of HZ/su vaccine), in Hematological patients (HE); Wilcoxon test p=0.002.

Conclusion

VZV gE IGRA is a sensitive and specific tool to assess CMI after HZ/su vaccination in HE and RH patients.

HZ/su elicited a significant T-cell response in all patients with RH diseases and more than 60% of patiens with HE malignancy. However, 5 patients had a limited or absent increase of IFN-gamma production from T0 to T2.

This aspect highlights the importance of assessing VZV-specific after HZ/su vaccination CMI in patients with HE malignancy receiving immune modulating treatments or chemiotherapies to verify protection from VZV reactivation and HZ development.

References

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