A novel immunotherapy regimen: Safety, immunogenicity and clinical response in HPV16-positive vulvar intraepithelial neoplasia

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Introduction

Vulvar intraepithelial neoplasia (VIN) is a premalignant skin disorder. Usual type VIN (uVIN) is caused by infection with high risk human papillomavirus (HPV). Persistence of oncogenic HPV proteins E6 and E7 are required for carcinogenesis, and thereby form an exquisite target for immunotherapeutic intervention. We developed a vaccine consisting of fusion of HPV E7 (shuffled) and Tetanus Toxin Fragment C (TTFC-E7SH).

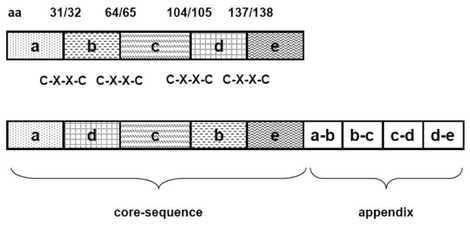

Fig. 1. Vaccine format: fusion of HPV E7 shuffled and Tetanus Toxin Fragment C (TTFC-E7SH)

Furthermore, we developed a novel DNA vaccination strategy named DNA tattoo vaccination, which outperforms classical intramuscular DNA vaccination by 10-100-fold when tested in non-human primates.

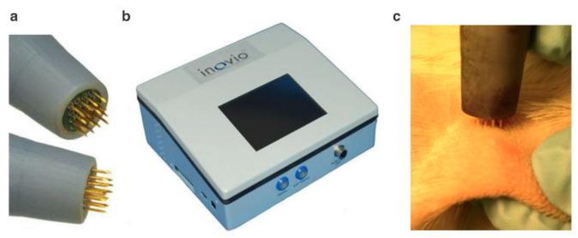

*Fig. 2. Skin electroporation procedure. (**a**) Surface EP device. Photo shows electrode configuration. (**b**) ELGEN pulse generator which is tethered to the surface EP device and delivers the electrical pulses. (**c**) Positioning of the surface EP device on guinea pig skin.*

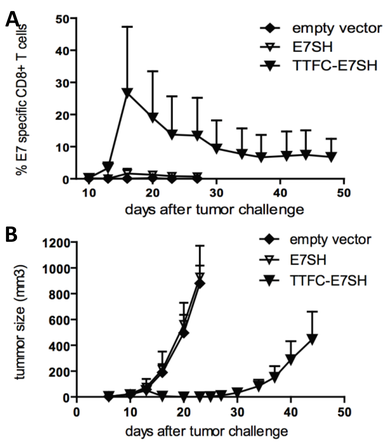

*Fig. 3. The addition of TTFC improves the immunogenicity of E7SH. Mice were tattoo-vaccinated on day 0, 3 and 6 with the indicated vaccines. **A**. Curve depicting the mean percentage +/- SD of peripheral blood E7 specific CD8+ T cells over time. **B**. Plot depicting the mean tumor diameter (mm) +/- SD over time.*

Aim

In this phase I trial we evaluate the toxicity, immunogenicity and clinical response of a HPV DNA vaccine (TTFC-E7SH), applied by DNA tattoo vaccination in uVIN patients.

Methods

Patients with histologically confirmed HPV16-positive uVIN were eligible. Patients who received prior treatment with an anti-HPV agent or who where immunosuppressed were excluded. Patients were vaccinated with a fixed dose of TTFC-E7SH. The first 6 patients received 0.2 mg in 2 cm^2 and the following 6 patients received 2 mg in 16 cm^2. TTFC-E7SH was injected intradermal, using a permanent make-up device, on days 0, 3 and 6 and patients received a boost vaccination at week 4 (days 28, 31 and 34). HPV16-specific T-cell immunity was evaluated by flow cytometry before start of vaccination and at day 14, 28, 42 and 56. A vaccine induced response is defined as a 2 fold increase in the T-cell response compared to baseline.

Results

All 12 patients received all vaccinations with TTFC-E7SH. No SAEs were observed, only mild toxicity grade I-II was shown.
In cohort 1, flow cytometry showed a limited CD8 vaccine-induced HPV16-specific T-cell response (see fig. 6 and 7).
The immunological results of the second dose cohort are in progress.
At 3 months follow-up, in both cohorts no clinical response was seen, so far.

Fig. 4. Vaccination spots in cohort 2, patient #12

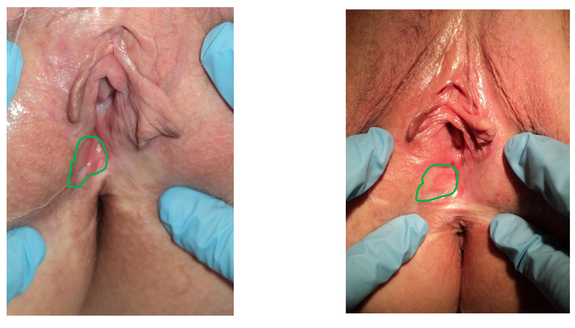

Fig. 5. uVIN at screening (left) and at 3 months follow-up (right).

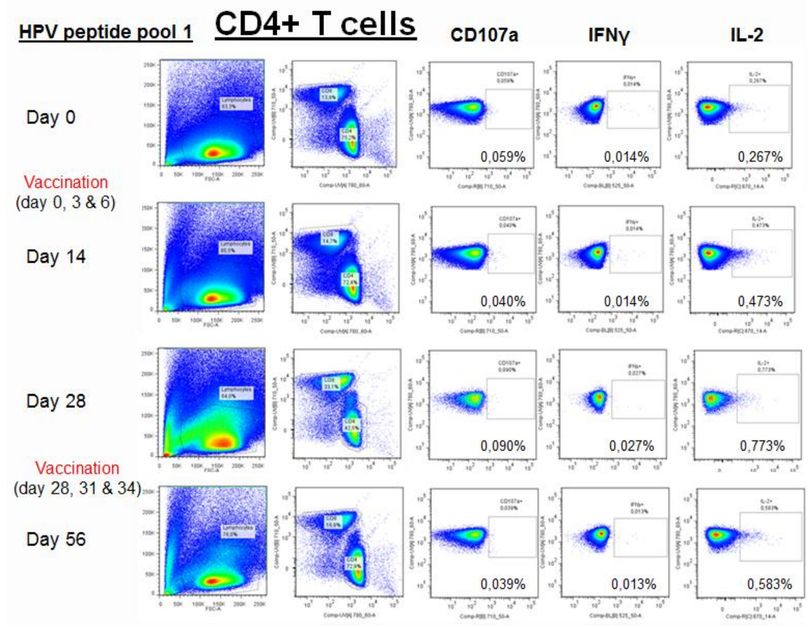

Fig. 6. A representative flow cytometry dot plot for HPV16-specific CD4+ T-cells on different time points in patient #3 of cohort 1. The graph shows no higher frequencies of CD107a, IFNy or IL-2 after vaccination with TTFC-E7SH.

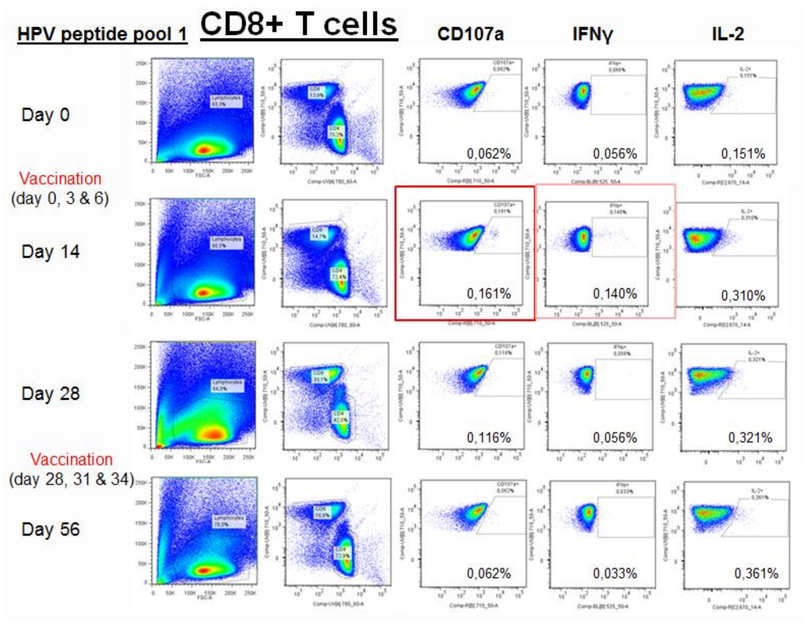

Fig. 7. A representative flow cytometry dot plot for HPV16-specific CD8+ T-cells on different time points in patient #3 of cohort 1. The graph shows a higher frequency of CD107a and IFNy after vaccination with TTFC-E7SH.

Conclusion

TTFC-E7SH is safe and shows a limited vaccine-induced immune response in the first dose cohort. So far, no clinical response has been observed.
More immunogenic vaccine formats are currently in development.

Disclosures

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