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Deficient H5N1 Intranasal Influenza Vaccine Lacking the NS1 Gene

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Background: Reverse genetics permitted us to develop a new generation of attenuated influenza vaccines based on the deletion of the major viral pathogenicity and immunosuppressive factors. Previously, we demonstrated that the removal of the NS1 protein (ΔNS1) abrogates the replication of influenza A and B viruses in interferon competent cells or organisms, but such viruses could be efficiently produced in Vero cells. Despite the replication-deficient phenotype, the seasonal intranasal ΔNS1 vaccine appeared to be immunogenic in animals and humans and is currently in phase II clinical trials. We applied the ΔNS1 approach for the construction of a pandemic H5N1 vaccine candidate and performed two clinical studies. Materials and Methods: The ΔNS1 H5N1 vaccine candidate was obtained by reverse genetics in Vero cells by using synthetic sequences corresponding to the HA, NA, and M gene segments from the A/Vietnam/1203/04 virus. These gene segments were co-transfected with the remaining 5 gene segments which originated from the Vero adapted NS1 IVR-116 strain. The polybasic cleavage site of the HA was modified to reveal a trypsin dependent phenotype. The phase I clinical trials were performed as randomized, double-blind, placebo-controlled dose-escalation studies (6.8 log10, 7.2 log10, and 7.5 log10 TCID 50/dose). The study medication was administered intranasally once or twice with a 4 week interval. Results: Clinical laboratory evaluations, physical examinations, and vital signs did not reveal any safety concerns. No vaccine virus shedding was detected later than 24 hours after vaccination. After two immunizations, in both dose groups, all of the volunteers (12 out of 12) responded to the vaccine with either local or systemic immune responses. There were no responders in the placebo group. The HA1 seroconversion rate was higher after 2 vaccinations (92% in both dose groups) than after one vaccination (42% low dose group, 75% high dose group). 83% of all vaccinees receiving the low dose and 75% of receiving the high dose showed an at least four-fold increase in MNA antibody titres after two immunizations. The GMT increase was 10.7-fold in the low dose group and six-fold in the high dose group. In line with the HA1 and MNA results, the nasal IgA response was higher after two vaccinations (IgA: 46% for both dose groups) than after the first vaccination (IgA: 0% lowdose group, 18% high dose group). Moreover, a systemic influenza A virus-specific T-cell mediated response was detected by a ranzyme B ELISPOT assay in several (HLA matching) volunteers. Conclusions: Overall, the H5N1 ΔNS1 rototype vaccine was safe, well tolerated, and highly immunogenic, despite its replication-deficient phenotype.