Epicutaneous Immunotherapy Using Plasma-Derived Factor VIII Reduces the Inhibitor Immune Response to Therapeutic Factor VIII in Experimental Hemophilia a

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Rationale: Hemophilia A is a rare X-linked bleeding disorder that results from a lack of functional pro-coagulant factor VIII (FVIII). Treatment of bleeding by administration of exogenous FVIII is complicated by the onset of inhibitory anti-FVIII antibodies in up to 30% of the patients. Here, we hypothesized that the epicutaneous delivery of FVIII imposes immune tolerance to FVIII

Method: FVIII-deficient C57BL/6 mice were sensitized by intravenous administration of recombinant human FVIII (2 µg/mouse, rFVIII) once a week for 3 weeks. Mice were then treated with epicutaneous patches containing PBS (sham) or 25 µg of plasma-derived FVIII (pdFVIII) once a week for 48 hours over 8 weeks. Two weeks after the last treatment, mice were injected intravenously once a week for 4 weeks with rFVIII (0.5 µg/mouse) to mimic replacement therapy. Plasma levels of FVIII inhibitory antibodies were measured in a coagulation assay. FVIII-specific cellular responses were evaluated in spleen following in vitro stimulation.

Results: Mice exposed to pdFVIII-containing patches developed significantly lower levels of FVIII inhibitors than sham mice (1034±356 vs 2715±1025 Bethesda Units/mL, p=0.041). Likewise, following stimulation of splenocytes, numbers of IL-10+CD4+ T cells were greater in mice exposed to pdFVIII-patches than in sham animals (13.2±5.4 vs 7.1±1.6 cells/10^6 splenocytes, p=0.031).

Conclusion: Epicutaneous exposure to pdFVIII of hemophilic mice sensitized to FVIII, reduces the immune response to therapeutic FVIII during replacement therapy. Further experiments are required to optimize the dose and duration of epicutaneous FVIII exposure, and to investigate the potential regulatory role of the induced splenic IL-10+CD4+T cells.