CLEARANCE OF INHIBITORS IN ACQUIRED HEMOPHILIA-A DURING PREDNISONE THERAPY IS ASSOCIATED WITH REDUCED IFN-γ AND LT-α PRODUCTION

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Acquired hemophilia A (AH) is an auto-immune disorder caused by polyclonal auto-antibodies (inhibitors) to clotting factor VIII (FVIII). Glucocorticoids (GC) are a standard initial approach to elimination of these inhibitors and are successful in approximately 30% when used alone and about 60% when used in combination with other immuno-modulating therapies. However, the mechanism of action and effect of GC on the immune system are not fully understood. Furthermore, a Th1 (IFN-γ) polarization of the immune response has previously been shown to be associated with inhibitor development. In this report, we delineate the effect of prednisone on the main Th1 cytokine IFN-γ and also on LT-α which has been shown to play a pivotal role in B cell maturation.

Blood samples were collected on two male patients diagnosed with AH, a 77-year-old (A) and a 68-year-old (B) at baseline and at various time points. Patients A and B, both presented with hematuria and were treated with prednisone (100 mg/kilogram/day). Peripheral blood mononuclear cells (PBMCs) were isolated and stimulated during 96 hours in-vitro by immobilized anti-CD3 and anti-CD28 antibodies. Messenger RNA (mRNA) expression was measured using RT-PCR, and cytokine concentrations in the culture supernatants were evaluated by ELISA.

Patient A's inhibitor was initially 160 Bethesda Units (BU) and disappeared by day 54, patient B's inhibitor went from 38 BU to undetectable within 32 days. Analysis of mRNA expression by PBMCs showed an initial increase in IFN-γ and LT-α in both patients (patient A: 100-fold increase in IFN-γ and a 35-fold increase in LT-α levels at day 5; patient B: 246-fold increase in IFN-γ and 12-fold increase in LT-α mRNA levels). The increase in IFN-γ and LT-α mRNA expression did not translate into higher concentrations of these cytokines in the supernatants. Initially, there was no significant change in concentration of IFN-γ in the culture supernatant but a significant decrease by the time of inhibitor disappearance was observed. Concomitantly, LT-α concentration gradually decreased from day 0 to day 54 (p=0.004) in patient A and from day 1 to day 32 (p=0.0004) in patient B. The clearance of inhibitors coincided with a reduced expression of IFN-γ and LT-α at the mRNA as well as at the protein levels.

These results show a possible mode of action, by which prednisone works to reduce inhibitor production. It appears that in the context of this therapy, prednisone interferes with T cell function by reducing the ability of T cells to produce IFN-γ and LT-α.

*This work was supported by the Louisiana Comprehensive Hemophilia Care Center.*