Intolerable: Inhibitors to Factor VIII

By Margaret Ragni, MD

Shakespeare could have been describing inhibitors when he said, "She's intolerable" in *The Taming of the Shrew.* From mechanism to management, coagulation inhibitors are the focus of the Education Session on Bleeding Disorders (held yesterday and again today from 9:30 - 11:00 a.m.), chaired by David Lillicrap, Queen's University, Canada. Although there is uniform agreement that inhibitors to factor VIII — whether alloantibodies complicating hemophilia treatment or *de novo* autoantibodies in those with no previous bleeding — cause major morbidity and mortality, there is no uniform agreement as to their treatment, given the absence of definitive evidence-based studies.

David Lillicrap, MD, focuses on the pitfalls of current treatment and potential new approaches to treatment of inhibitors, including von Willebrand factor (VWF) concentrates, the CD20 monoclonal antibody rituximab, and new, less immunogenic FVIII molecules with porcine sequences substituted for the C2 immunogenic epitopes. Also under evaluation is FVIII tolerogenic delivery in pre-clinical models by the nasal and gastrointestinal routes, and by immature dendritic cells. In general, the best response to immune tolerance (eradicating inhibitors) occurs in those with inhibitor titer < 10 Bethesda units, peak historic titer < 200 BU, and presence for < two years. Following tolerance, it is recommended that patients be maintained on prophylaxis regimens (every-other-day factor) indefinitely, although this approach is not evidence based.

In the second presentation, Keith Hoots, MD, University of Texas, Houston, reviewed the "off label" use of recombinant factor VIIa (rVIIa) for indications other than hemophilia inhibitors. Off-label indications now account for at least half of its use. Dr. Hoots showed that in the few randomized clinical trials using rVIIa after prostatectomy, partial hepatectomy, trauma, cirrhotic GI bleeding, and intracranial hemorrhage, thromboembolic risk increases. This may be related to baseline, innate capacity for thrombin generation. So, for example, use of rVIIa in hemophilia inhibitor patients rarely leads to thrombosis, because their thrombin generation is greatly reduced. In the latter, infused rVIIa augments thrombin generation through activation of FX, i.e., in a *TF-independent* fashion. By contrast, in off-label use of rVIIa, i.e., in the absence of a congenital coagulation defect, thrombin is already generated through FX activation (after initial TF-activation) in a *TF-dependent* fashion. In this setting, rVIIa binds TF wherever it is expressed, and this dramatic VIIa increase may be responsible for the occurrence of thrombotic complications. Thus Dr. Hoots suggested that rVIIa in the off-label setting should be reserved for use after other hemostatic agents have failed, with careful assessment of fibrinogen, platelets, and D-dimer levels.

In the concluding talk, Alice Ma, MD, University of North Carolina, Chapel Hill, summarized the diagnosis and management of acquired auto-antibodies to factor VIII. Auto-anti-VIII are uncommon, occurring in fewer than one in a million patients. These auto-antibodies typically occur in elderly patients with no previous bleeding. Associated with high morbidity, the management is difficult, and with few trials, not evidence-based. Recognized as a T cell-independent immune response directed against factor VIII, cytotoxic agents (including cyclophosphamide, prednisone, and the anti-CD20 monoclonal antibody, rituximab) have shown efficacy, individually and together. With rituximab given in four weekly infusions, as for lymphoma, if relapse occurs, re-induction may be effective in successfully eradicating the inhibitor.

An important oral abstract to be presented today (#765) by Tom Howard in the Coagulation and Hemophilia Session reports on findings from the Pharmacogenetics of Inhibitor Risk (PIR) Study. The high prevalence of inhibitor formation in African-restricted H3, H4, H5 factor VIII haplotypes potentially reflects the primarily Caucasian donor base for infused plasma, with H1 and H2 factor VIII haplotypes.