

# AHCDC Inhibitor Subcommittee Report 2004

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**Mission:** To evaluate the development of inhibitors in Canadians and develop guidelines for the clinical management of such patients. Additionally to conduct and co-ordinate research into the development of inhibitors and their management.

## **Resources available to subcommittee and main subcommittee members responsible for these:**

**CHARMS and CHR data collection systems (I. Walker)** – facilitates the tracking of inhibitor development and its prevalence in Canada.

**National Hemophilia Reference Laboratory in Kingston (D. Lillicrap):** A reference laboratory for inhibitors in Canada. Laboratories at the various Hemophilia Treatment Centers in Canada can use this laboratory to confirm inhibitor test results. Additionally this lab acts as a research lab in multicenter research clinical trials on inhibitor development and management. Funding is secure for this laboratory for this year and next but after that funding will need to be once again arranged.

## **2003-2004**

This past year has been a year of acknowledging our accomplishments but recognizing that Canada is losing its lead to other countries in the area of inhibitor surveillance and research. This past year the Inhibitor Subcommittee was asked to present the Canadian experience of inhibitor surveillance at 2 major international events:

1. *"The Canadian Inhibitor Surveillance Program"* – presented at the meeting of the Factor VIII/IX Subcommittee of the ISTH, Birmingham, UK
2. *"Canadian Experience with FVIII Inhibitors during conversion to recombinant products"* presented at the Workshop on FVIII Inhibitors sponsored by the FDA - Bethesda, USA.

Additionally the Inhibitor Subcommittee took on a small 10 year retrospective study on immune tolerance therapy in Canada – Study sponsored by Bayer Inc. Preliminary study results presented in October, 2003 at an International Workshop on Immune Tolerance in Hemophilia in Venice, Italy. In addition to the Inhibitor Subcommittee members several other AHCDC members (Drs. Man Chu Poon, Mohan Pai and Victor Blanchette) were also involved in the study. This study is now completed and a manuscript is being written. Additionally abstract being sent to the WFH meeting.

The inhibitor subcommittee also developed a protocol/study for the use of Rituximab in patients who have failed conventional immune tolerance. 3 patients have been treated with this protocol (2 in Montreal and 1 in Toronto). This experience will be written up in an abstract for WFH and a manuscript is also to be written up.

It is clear from various meetings that Canada is now beginning to lose its lead in the area of inhibitor surveillance as other countries become more organized in inhibitor surveillance. As such we need to re-evaluate how we are going to do inhibitor surveillance to remain a leader in this area. Also more research (both clinical and laboratory research) is required.

#### **“Inhibitor”-related publications by Inhibitor subcommittee members (2003-04)**

*Successful treatment using recombinant factor VIIa for severe bleeding post cardiopulmonary bypass.* Naik VN, Mazer CD, Latter DA, **Teitel JM**, Hare GM. Can J Anaesth. 2003; 50(6):599-602.

*Optimization of storage conditions for diluted working solutions of porcine FVIII and performance of the Bethesda assay for the determination of antiporcine FVIII inhibitor titres.* Winikoff R, Boulanger A, Robinson P, St-Louis J, Lacroix S, **Rivard GE**. Haemophilia. 2003; 9(1):104-9.

*An evaluation of the stability of FVIII inhibitors in plasma and plasma dried on filter paper discs stored at room temperature.* Winikoff R, Boulanger A, St Louis J, Lacroix S, **Rivard GE**. Haemophilia. 2003; 9(1):57-9.

*Intensive exposure to FVIII is a risk factor for inhibitor development in mild hemophilia A.* Sharathkumar A, **Lillicrap D**, Blanchette VS, Kern M, Leggo J, Stain AM, Brooker L, **Carcao MD**. J Thromb Haemost. 2003; 1(6):1228-36.

*Central venous catheter-related thrombosis presenting as SVC syndrome in a haemophiliac with inhibitors.* **Carcao MD**, Connolly BL, Chait P, Stain AM, Acebes M, Massicotte P, Blanchette VS. Haemophilia. 2003; 9(5):578-83.

*Elective orthopaedic surgery for inhibitor patients.* Rodriguez-Merchan EC, Wiedel JD, Wallny T, Hvid I, Berntorp E, **Rivard GE**, Goddard NJ, Querol F, Caviglia H. Haemophilia. 2003; 9(5):625-31.

*Immunoabsorption for coagulation factor inhibitors: a retrospective critical appraisal of 10 consecutive cases from a single institution.* **Rivard GE**, St Louis J, Lacroix S, Champagne M, Rock G. Haemophilia. 2003; 9(6):711-6.

*Elective orthopedic surgery for hemophilia patients with inhibitors: New opportunities.* Rodriguez-Merchan EC, Wiedel JD, Wallny T, Caviglia H, Hvid I, Berntorp E, **Rivard GE**, Goddard NJ, Querol F. Semin Hematol. 2004; 41(1 Suppl 1):109-16.

AHCDC members – underlined

Inhibitor Subcommittee members - bold

## Plans for 2004-05:

### Complete/publish the following studies:

1. **A study of FVIII Inhibitors in Canadian Hemophilia Patients who switched to Kogenate-FS.** PI: **Rubinger M** and the **Inhibitor Subcommittee of the AHCDC**. A study evaluating inhibitor development with the switch from Kogenate formulated in albumin to Kogenate formulated in sucrose. The study is now complete, data being analyzed and to be published.
2. **A 10 year Canadian multi-institutional survey of immune tolerance therapy (ITT).**
3. **Write up the rituximab experience in Canadian congenital hemophiliacs.**

Other projects/studies to be done.

#### 1. **Institute a National Inhibitor Surveillance Protocol for all Factor VIII products.**

The need for this has recently become more apparent. Without a systematic, rigorous comprehensive program for ongoing inhibitor surveillance the incidence of inhibitor development in PTPs is grossly underestimated as most cases fail to be reported to companies or regulatory agencies.

This program would involve 2 components. First - companies marketing FVIII concentrates in Canada would provide (fixed) funds for the support of the National Inhibitor Laboratory in Kingston. (Done). Second manufacturers would be billed the cost of yearly testing (q6 mos in the first 2 years of exposure to product) for inhibitor development in patients receiving their FVIII product. These funds would support – individual clinic and laboratory costs for testing at all Hemophilia Treatment centers, confirmatory testing for inhibitors in Kingston and a National Inhibitor Data Coordinator. Funds for this endeavor would be administered through the AHCDC.

This is particularly important to get this done ASAP due to the introduction of Advate. A protocol **should be available** (hopefully) for all clinics by June 1.

#### 2. **Update the Guidelines for management of patients with inhibitors**

Last updated 1999 (3<sup>rd</sup> edition) and published in *Hemophilia 2000*

3. **Improve Canadian participation in International Collaborative Studies:** e.g. the International Immune Tolerance Study: International, randomized, controlled trial comparing 2 regimens of immune tolerance induction (ITI; a high dose - 200 U/kg/day vs. a low dose - 50 U/kg/3 days/wk of FVIII) for patients with high titre inhibitors to FVIII. The study is assessing the efficacy and economics of the 2 regimens and will identify predictors of successful immune tolerance. PI. Hay, Mauser-Bunschoten, DiMichele. (*Information and Consent forms available - see M. Carcao*)

### **Other potential projects**

Evaluate the development of Inhibitors in Mild Hemophilia A and in all hemophilia A patients following continuous/intensive exposure to FVIII.

Evaluate the relationship between age of first FVIII exposure to inhibitor development in hemophilia A and assess a strategy of avoiding FVIII exposure at an early age on inhibitor incidence.

Consider adopting a **Canadian standard salvage ITI protocol** for inhibitor patients who fail primary ITI. – e.g. Rituximab