

AHCDC Inhibitor Subcommittee Report 2003

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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.

Past Accomplishments: The inhibitor subcommittee has during its lifetime accomplished much and its efforts have resulted in the world hemophilia community regarding Canada as a model for national inhibitor surveillance. Much of the past accomplishments of this committee was conducted by many of the current senior members of the committee along with some past prominent Canadian hemophilia treaters/researchers. Particular mention has to go to Dr. Alan Giles. (below are some key contributions of this group)

Giles AR, Rivard GE, Teitel J, Walker I. *Surveillance for FVIII inhibitor development in the Canadian Hemophilia A population following the widespread introduction of rFVIII replacement therapy*. Transfus Sci. 1998;19(2):139-48.

Giles AR, Verbruggen B, Rivard GE, Teitel J, Walker I. *A detailed comparison of the performance of the standard versus the Nijmegen modification of the Bethesda assay in detecting factor VIII:C inhibitors in the haemophilia A population of Canada*. Association of Hemophilia Centre Directors of Canada. Thromb Haemost. 1998; 79(4):872-5.

2002-2003

This past year has been a year of transition. One year ago Manuel Carcao took over as chair of the subcommittee from Morel Rubinger. The most important undertaking of the past year has been to find a permanent solution to the ongoing funding of the National Hemophilia Inhibitor Surveillance Laboratory in Kingston. The cost of running this lab is substantial (approx. \$100 K/yr) and in the past funding for this was not guaranteed. One year ago there was concern regarding whether this lab was in jeopardy of folding given that funds for it were running dry. A 3-yr plan for funding was developed and 4 companies agreed to provide \$25,000.00/yr each for the next 3 yrs.

The other major issue that the Inhibitor Subcommittee has been dealing with is the issue of inhibitor development in PTPs. This surfaced as an important issue at the end of 2002. Many teleconferences and meetings were held regarding this issue and a report will be presented at this AHCDC meeting.

“Inhibitor”-related publications by Inhibitor subcommittee members (2002-2003)

1. *Recombinant FIX recovery and inhibitor safety: a Canadian post-licensure surveillance study.* Poon MC, **Lillicrap D**, Hensman C, Card R, Scully MF. A study evaluating the effectiveness and risk of inhibitor development with Benefix. *Thromb Haemost.* 2002; 87(3):431-5.
2. *A 4% solution of bovine serum albumin may be used in place of factor VIII:C deficient plasma in the control sample in the Nijmegen Modification of the Bethesda factor VIII:C inhibitor assay.* Verbruggen B, van Heerde W, Novakova I, **Lillicrap D**, Giles A. *Thromb Haemost.* 2002; 88(2): 362-4.
3. *Dangerous liaisons: the role of "danger" signals in the immune response to gene therapy.* Brown BD, **Lillicrap D**. *Blood.* 2002;100(4):1133-40.
4. *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.
5. *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.
6. *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**. Study evaluated patients with mild hemophilia A at the Hospital for Sick Children to determine the incidence and risk factors for inhibitors in such patients. *J Thromb Haemost.* (in press)
7. *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. An unusual case report and literature review on symptomatic clots in hemophiliacs. *Haemophilia.* (in press)

Plans for 2003-04:

Complete 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 ready for final samples to be obtained, data to be analyzed and published.
2. **Improve Canadian participation in International Collaborative Studies:**

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*)

Malmö International Brother Study (MIBS): A study to evaluate brothers with hemophilia A to determine genetic predisposing factors to inhibitor development. PI. J. Astermark and E. Berntorp (Malmö, Sweden). (*Information and Consent forms available - see M. Carcao*)

Update the Guidelines for management of patients with inhibitors

Last updated 1999 (3rd edition) and published in *Hemophilia 2000*

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. So far one company has agreed to this proposal.

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 standard salvage ITI protocol for inhibitor patients who fail primary ITI.