

**Canadian Experience with FVIII  
Inhibitors during Conversion to  
Recombinant Products**

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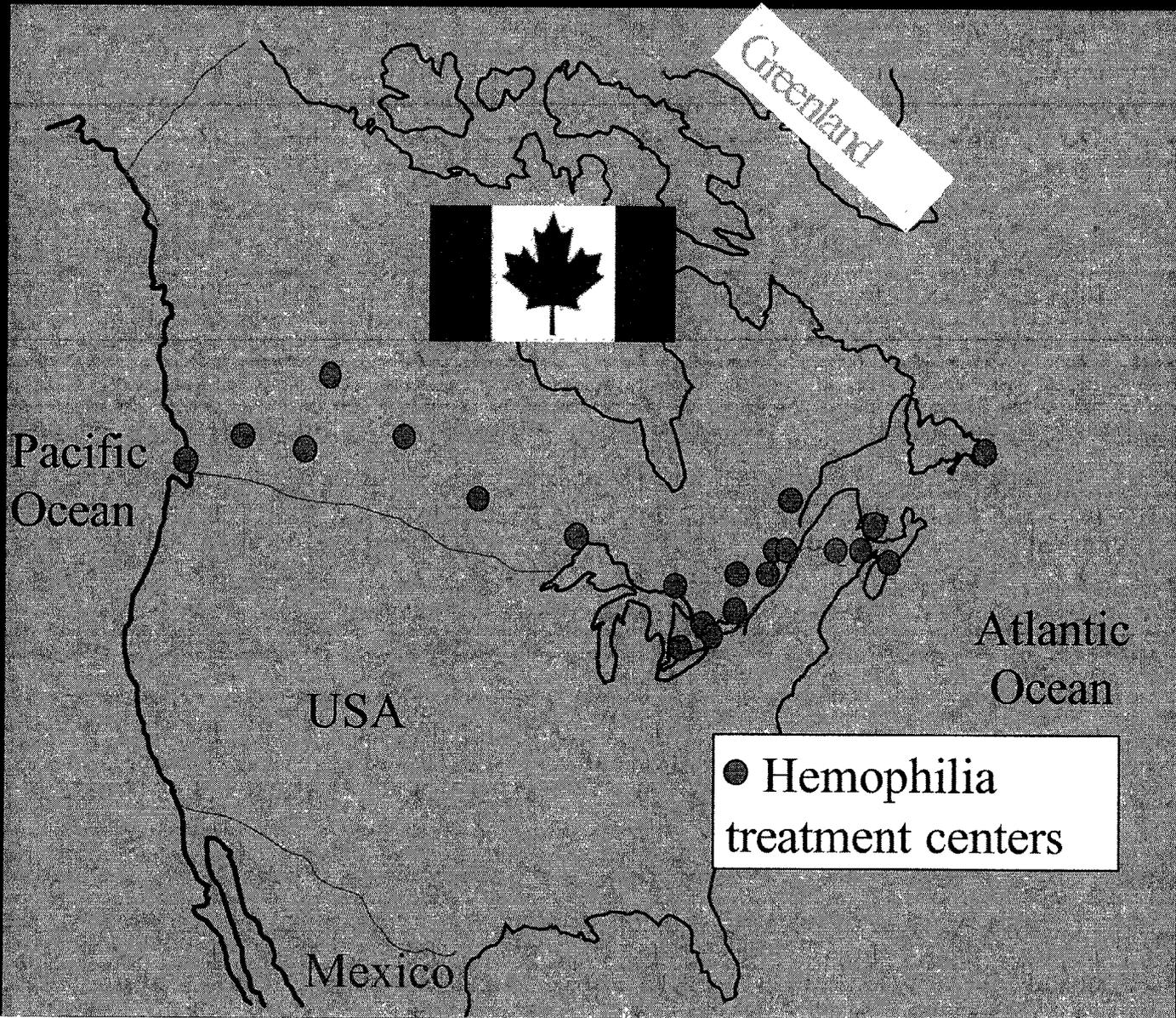
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# HEMOPHILIA IN CANADA (2003)

- **2561 hemophiliacs**
  - **2063 (81%) with Hemophilia A**
  - **498 (19%) with Hemophilia B**
  - **virtually all followed 25 hemophilia treatment centers**
- **Prevalence of hemophilia among Canadian males: 1 in 5740**
- **Most hemophiliacs (>90%) receive recombinant factor concentrates**

# HEMOPHILIA A

- **Total = 2063**
  - **Severe (n= 614; 30%)**
    - **No inhibitors** 542
    - **With inhibitors** 72 (12% of severe)
  - **Moderate (n=250; 12%)**
    - **No inhibitors** 243
    - **With inhibitors** 7 (3 % of moderate)
  - **Mild (n=1199; 58%)**
    - **No inhibitors** 1195
    - **With inhibitors** 4 (0.3 % of mild)
- **Inhibitors** 83 (4% of all Hemophilia A)



# INHIBITORS IN CANADA

- **Inhibitor prevalence**
  - 4% for Hemophilia A (12 % for severe)
  - 0.8% for hemophilia B (2% for severe)
- **Patients currently with inhibitors**
  - 83 hemophilia A
  - 4 hemophilia B
- **Inhibitor incidence is not known**
- **Data entered into and analyzed within a data management software program (CHARMS; Canadian Hemophilia Assessment and Resource Management System)**

# CHARMS

- **Computer software program designed for data entry, management and analysis by all 25 Canadian hemophilia clinics**
- **Tracking distribution of factor concentrates from clinics to patients and usage by patients**
- **Data entered at individual clinic site and available as aggregate national data**
- **In existence for 5 years**

**Surveillance for FVIII Inhibitor  
Development in the Canadian  
Hemophilia A Population Following  
the Widespread Introduction of rFVIII  
Replacement Therapy**

GILES ET AL. TRANSF SCI 98; 19: 139-48

# **GILES ET AL: pd-FVIII SWITCH TO rFVIII STUDY**

- **Funding: Canadian Blood Agency**
- **Population: Previously treated Hemophilia  
A patients felt by individual clinics to be  
inhibitor negative converting from pd-FVIII  
to rFVIII**
  - **Range: minimally treated to heavily treated**
  - **814 patients - converted to rFVIII**
  - **478 patients - data obtained**

# METHODS

- Plasma samples obtained pre switch and then 1 year and 2 years post switch
- Testing: single central reference laboratory (Kingston, Ontario; Alan Giles – David Lillicrap)
- Bethesda assay used for pre and 1 year samples; Bethesda assay and Nijmegen modified Bethesda assay done in parallel for 2-year sample
- Positive test =  $>0.5$  BU

# RESULTS

- **For inhibitor neg. patients (pre switch)**
  - 1 yr (478 pts tested) 9 patients (1.9%) Inhibitor +
  - 2 yr (339 pts tested) 10 patients (3%) Inhibitor +
  - All inhibitors low titer
- **Inhibitor prevalence did not change following switch to rFVIII**
- **Incidence (over 2 yrs) of inhibitors in all PTPs (minimally & extensively treated) was < 2-3% - many inhibitors were transient**
- **No attempt to correlate inhibitors with patient age or genetics, dose or intensity of treatment**

# CANADIAN EXPERIENCE SINCE GILES ET AL, 1998

- **Prospective Surveillance Study of FVIII Inhibitors in Canadian Hemophilia Patients who switched to FVIII formulated in Sucrose**
  - **To be presented by Peter Larson - Bayer**
- **Sporadic reports in CHARMS of inhibitor development in PTPs**
- *There has not been a systematic tracking and reporting mechanism for such patients*

# **FUTURE DIRECTIONS**

- **How to study current factor concentrates for inhibitor development**
  - **CHARMS – refinements – maintain date of first + inhibitor test (to obtain incidence data) and encourage improved data entry by individual clinics**
  - **Promote the role of central reference laboratory to confirm all new inhibitors**
- **How to study future products and address current limitations of post marketing surveillance**

# POST-MARKETING INHIBITOR SURVEILLANCE

Options to study new FVIII concentrates

- Separate studies for different FVIII concentrates that become licensed

OR

- Common Inhibitor Surveillance for all FVIII concentrates

# SEPARATE STUDIES

- **Advantages**

- **Easier to track costs**

- **Disadvantages**

- **Repetitive and duplicative efforts**

- **Develop separate protocols, consent forms and data collection forms**
  - **Would lack comparability data – between different factor concentrates**

# **COMMON NATIONAL INHIBITOR SURVEILLANCE PROGRAM**

- **Companies marketing FVIII would provide fixed funds for the support of the Canadian National Inhibitor Laboratory (Implemented)**
- **Global protocol for inhibitor surveillance for all FVIII concentrates - modified for individual FVIII product**
  - **Would apply to all PUPS beginning on a product (including current products), to all PTPs switching to a product (this would cover all new products) - in both cases for 3 years post starting the product**
  - **Manufacturers would be billed for q6 mo inhibitor testing for patients receiving their particular FVIII**

# COMMON NATIONAL INHIBITOR SURVEILLANCE PROTOCOL

- **The Need**
  - **Without systematic, rigorous program for inhibitor surveillance**
    - **Most cases of inhibitors fail to be reported**
    - **Incidence/ prevalence/ risk factors for inhibitor development are inaccurate**

# COMMON NATIONAL INHIBITOR SURVEILLANCE PROTOCOL

## ▪ Advantages

- All companies would need to commit to have products used in Canada
- Avoid duplication of efforts to develop separate surveillance studies
- Insure that all companies contribute to supporting a National Inhibitor Laboratory – for confirmation of inhibitors

## ▪ Disadvantages

- Costs and logistics
- Requires large commitment from Hemophilia treatment centers to insure data collection and samples being sent to National Laboratory