ATHN 3 – Radionuclide Synovectomy – A Multicenter Collaboration Using the ATHNdataset

Amy L. Dunn
Nationwide Children’s Hospital
Background

• Radionuclide/Radio-isotopic synovectomy/synoviorthesis has been utilized for many years in the bleeding disorder community
• Several complications have been reported
• The ATHNdataset had never been interrogated for outcomes or adverse events related to this procedure
Subject Definitions

- **Case** = subject who had RS and consented to the ATHN dataset
- **Control** = subject who has not had RS but consented to the ATHN dataset
Hypothesis 1:
Patients with severe bleeding disorders are more likely to have RS than those with mild bleeding disorders

• Aim 1: Interrogate the ATHN dataset to identify the numbers and diagnoses of patients with bleeding disorders who have undergone RS and have agreed to share their data

• Aim 2: Interrogate the ATHN dataset to identify the numbers of RS procedures that have been performed in consented patients
Hypothesis 2:

Patients with bleeding disorders who have undergone RS may be at increased risk of hematologic/oncologic complications

• Aim 1: Utilize the ATHN dataset to identify non bleeding related hematologic or oncologic complications in patients who have undergone RS

• Aim 2: Compare complication rates with Surveillance, Epidemiology and End Results Program (SEER) data
Hypothesis 3:

Case patients are at risk for decreased ROM compared to control subjects and compared to the non–bleeding disorder population

• Aim 1: Utilize the ATHN dataset to evaluate last available ROM of the involved joint in case patients and compare to age and sex matched normal ranges

• Aim 2: Utilize the ATHN dataset to evaluate last available ROM of the involved joint in case subjects and compare to age and disease matched control subjects
Hypothesis 4:

Patients who have had RS are at increased risk for requiring subsequent joint intervention/surgery

- Aim 1: Utilize the ATHN dataset to determine the proportion of patients who have had RS who subsequently required additional surgical/procedural intervention
- Aim 2: Utilize the ATHN dataset to evaluate time from RS and age of case patient on subsequent procedures
Hypothesis 5:
Published literature regarding complications of RS may influence the frequency of RS procedures in the bleeding disorder population

- AIM 1: Compare rates of RS in the ATHN dataset before and after seminal publications
  - Leukemia #1-2002
  - Leukemia #2-2005
  - MASAC guidelines-2006
  - MedWatch warning-2008
  - Aplastic anemia-2012
  - Canadian RS report-2012
  - Ewing Sarcoma-2013


MASAC Document #163

MedWatch August 29, 2008, Phosphocol P 32 (Chromic Phosphate P 32 Suspension)

N. Karadas, C. Zihni, D. Karapinar, K. Kavakl I, And C. Balkani Severe aplastic anemia in a patient with severe hemophilia A Haemophilia (2012), 18 (Suppl. 3), 66


Study Population/Design

• Patients with any bleeding disorder who have authorized the sharing of their demographic and clinical information through the ATHN dataset
  – Cases are those who had RS, controls are those who have not had RS

• Study design: Multi-institution, observational cohort
Methodology

- eWeb Report with key data elements was created
- Participating HTCs reviewed the report to confirm data for cases was correct and complete
- ATHN biostatistician executed analysis per investigator input
Results

Hypothesis 1: Patients with severe bleeding disorders are more likely to have RS than those with mild bleeding disorders
Demographics of cases and controls with ATHNdataset Participation

- Patients: 24,328 control (non RS) subjects
- 194 case (RS) subjects
  - 79% HA, 15% HB, 4% VWD, 2% other
  - Age 4-72 years (median 15 y/mean 18 y)
  - 97% male
RS Procedure Numbers

• 194 cases had 360 injections
  – 51% had 1 injection
  – 29% had 2 injections
  – 20% had >2 injections

• Right sided procedures were more common than left-sided procedures
Injected Joints

- Left Ankle: 27
- Right Ankle: 74
- Left Elbow: 31
- Right Elbow: 102
- Left Knee: 22
- Right Knee: 78
- Right Shoulder: 11
Demographic Related Outcomes

• Differences (p<0.001)
  – Patients with severe disease more likely to undergo RS than those with mild or moderate disease
  – HIV (11.3% vs. 2.6%) and hepatitis C (38.1% vs. 8.4%) positivity more common in cases
  – Positive inhibitors more common in cases (29.4% vs. 4.5%)
  – Southeast region had more cases than other regions

• Similarities
  – No difference in race or ethnicity between cases and controls
  – Severe HA and severe HB case proportions were equivalent
Results

Hypothesis 2 Patients with bleeding disorders who have undergone RS may be at increased risk of hematologic/oncologic complications that are not directly related to their bleeding disorder.
Outcomes: Malignancy and Myeloproliferative Disorders (MPD)

• No significant difference in rates of cancer:
  – 1 (0.5%) case patient was diagnosed with colon cancer
  – 222 (0.9%) control subjects were diagnosed with cancer
    (mean age at diagnosis 52y)

• Significant difference in rates of MPD in the control patients:
  – 5 controls with polycythemia vera, 2 essential thrombocytopenia, 1 myelofibrosis
  – No control patients with MPD had HIV, HCV or HBV
  – No case patients with MPD
Outcomes: MPD

• ATHN dataset compared to age – adjusted incidence rates of MPD with SEER data
  – Significantly more MPD in ATHN dataset subjects <50 years of age (p=0.001)
  – Significantly higher rates in Caucasian patients (p=0.002)
Results

Hypothesis 3: Case patients are at risk for decreased ROM compared to control subjects and compared to the non–bleeding disorder population
RS Outcomes: ROM

• Cases had significantly decreased ROM than age matched normal subjects without bleeding disorders (p<0.001)
• Cases had significantly decreased ROM compared to age and disease matched controls except in elbow extension age 9-19y and knee flexion age 20-44y (p<0.01)
• Most control subjects had worse ROM than normal subjects except for ankle dorsiflexion and elbow flexion in age 9-19y (p<0.01)
Results

Hypothesis 4 Patients who have had RS are at increased risk for requiring subsequent joint intervention/surgery
RS Outcomes: Repeat Procedures

• 52 cases (28%) were re-injected (mean 2.9 y later)
  – Mean age at second RS = 20 y

• 31 cases (16%) had other subsequent procedures
  – 10 cases had open synovectomy
  – 12 cases had arthroscopic synovectomy
  – 4 cases had ankle arthrodesis
  – 7 joint replacements
Results

Hypothesis 5 Published literature regarding complications of RS may influence the frequency of RS procedures in the bleeding disorder population
Impact of Publications

- 181 (53%) of procedures were performed before the first leukemia publication
- 147 (43%) were performed between the first leukemia report and the Canadian safety report
- The mean # of annual procedures increased between the first and second leukemia reports (from 18 to 20)
- The mean annual number of procedures decreased slightly after the MASAC report in 2006 and has continued to decline (7)
What Did We Learn from this Process
The Good News

19 centers collaborated to address this question

- CHLA
- CHOC
- Children’s Mercy
- Cincinnati Children's
- Cornell
- Fort Worth Bleeding Disorders Program at Cook Children’s Medical
- Emory/CHOA
- IHTC
- ILBCDI
- Medical University of South Carolina
- Nationwide Children’s
- Northwest Ohio Hemophilia Treatment Center
- Phoenix Children’s
- Rainbow Babies
- University of North Carolina
- University of Michigan
- University of Miami
- University of Minnesota
- Vanderbilt
The Good News

• This is an increasingly robust dataset
• ATHN has biostats and operations resources to help facilitate this, other current and future projects
  – Dunlei Cheng PhD-Associate Director Health Services Research / Biostatistics
  – Crystal Watson-Director of Operations
  – Cathy Haupt-program coordinator
Limitations

Investigator initiated projects using the ATHN dataset require time and money

• Local data manager support is often insufficient
• Physician time limitations can be a barrier, if unfunded (clinical research does not generate RVUs)
• Data present in the dataset may not be adequate to address questions
  – Incomplete/inaccurate data
  – Data point not being collected
• Required consent process may introduce bias
Realistically, additional funding is needed to support investigators even for many ATHN dataset projects.

- Internal/external
- Research spending using local 340-B funds is an option; approval is required
ATHN dataset - Suggestions

• ATHN could review and possibly revise the process for collaborative projects and make this information easily accessible on the website
• ATHN could consider staging (twice yearly) or prioritizing projects so that centers are not overwhelmed and can plan local resources
• ATHN could consider developing a project funding mechanism perhaps in partnership with industry or government
Thank You !!!!!

• Investigators
• Data managers
• ATHN
• Patients