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Radionuclide Synovectomy/Synoviorthesis (RS) in Persons with Bleeding Disorders: A Review of Impact of National Guidance on Frequency of RS using the ATHNdataset.

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Radionuclide synovectomy/synoviorthesis (RS) is a procedure in which radio-active pharmaceuticals are injected into the joint space of someone affected by a proliferative synovial disorder in order to decrease synovitis. Radiation is delivered to the synovium with minimal penetration to deeper joint structures. Historically this was a fairly common procedure for persons with hemophilia and other bleeding disorders because it can be performed in an outpatient setting with relatively minimal clotting factor concentrate replacement (1). Numerous patients with bleeding disorders have had RS with various isotopes since this procedure was first described in 1963 with Phosphocol P32 (chromic phosphate P32 suspension), the most commonly utilized isotope in the US (2-9). However, patient safety concerns arose after 2 reports of acute leukemia in children with hemophilia within one year of RS were published in 2002 and 2005 (10, 11) which prompted the medical and scientific advisory council (MASAC) to the National Hemophilia Foundation to issue recommendation # 176 on October 15, 2006 (12). This recommendation suggested careful consideration of the risk benefit ratio of RS and utilization of a standardized RS protocol. On September 18, 2008 the Food and Drug Administration (FDA) issued a MedWatch regarding the use of P32 for intra-articular use indicating that P 32 may increase the risk for leukemia in certain situations and stating that it was not indicated in the intra-articular treatment of hemarthrosis (13). Subsequently in 2012 a large Canadian retrospective cohort study of cancer incidence after RS did not identify a correlation between RS and cancer (14). Finally, the first case of solid tumor-Ewing sarcoma diagnosed after RS was published in 2013 (9). With conflicting publications/recommendations about this procedure we hypothesized that the American Thrombosis and Hemostasis Network (ATHN) ATHNdataset which includes US individuals with bleeding disorders who are cared for in Health Resources and Services Administration (HRSA) hemophilia regions (Figure 1) and have authorized the sharing of their demographic and clinical information for research would

allow interrogation of rates of RS utilization related to selected publications/guidance documents.

Figure 1

ATHN3 is a working group of adult and pediatric hematologists and ATHN support staff with interest in RS. The ATHN3 working group designed and performed a retrospective multi-institution, observational cohort study utilizing the dataset that included any patient with a bleeding disorder who had undergone a RS procedure through 12/31/2014. The ATHNdataset includes data contributed from 135 HTC's from 8 regions. A standard data collection template was utilized by participating Hemophilia Treatment Centers (HTC's) to validate RS patient data in the ATHNdataset. The chi-square test was utilized to verify the hypothesis. The prevalence of RS in relation to 6 publications/guidance documents that were determined by the ATHN3 working group was considered. These included publications regarding: two cases of leukemia the first in 2002 and the second in 2005, the MASAC guideline on RS #176 in 2006, FDA P32 MedWatch warning regarding P32 in 2008, a comprehensive safety review of Canadian P32 cases in 2012 and a case of Ewing sarcoma in 2013.

As of 12/31/2014, the ATHN data set included a total of 19,735 bleeding disorder patients. Of the 135 HTCs contributing data to the ATHNdataset, 38 had reported 362 RS procedures in 196 patients. Age at RS ranged from 4-72 years (median 15 years). Ninety-five percent of patients who had RS had hemophilia A or B and 97% were male. Overall, the proportions of patients of different races and ethnicity who had RS did not differ from dataset participants who did not have RS.

The mean annual number of procedures increased between leukemia case #1 and leukemia case #2 from 18 to 21 (Figure 2). The mean number of annual procedures decreased slightly after MASAC guidance in 2006 and has continued to decline thereafter. Mean RS instillations decreased from 13 per year before the MedWatch warning in 2008 to 12 in 2012, and to 7 by 12/31/2014. 149 (43%) of injections were performed between the first leukemia report and the Canadian safety report in 2012. The annualized number of RS injections performed after the Canadian safety report in 2012 was 7 and the total number of RS procedures continued to decline after the Ewing sarcoma publication in 2013 to 3 in the year 2014.

Figure 2

There were significantly fewer patients who had repeated RS after the MASAC guidelines (17% vs. 83%; p<0.001).We did not find race or ethnicity related differences in RS rates after the first publication of MASAC in 2006. 27% of Caucasian and 25% of Non-Caucasian patients had RS after the MASAC guidelines (p=0.821). The percentage of procedures performed in Hispanic or non-Hispanic patients after MASAC guidelines did not differ too much, 32% vs. 25% (p = 0.480). MASAC guidance did appear to impact the use of RS in some regions but not others (p <0.001). After the MASAC guidelines the number of RS procedures dropped substantially for New England (from 31 to 3), Great Lakes (from 90 to 16), Mountain States (from 16 to 2), Great Plains (from 19 to 6) and the Southeast (from 80 to 38) regions. Northern States (from 8 to 6) and Western States (from 17 to 14) did not see the substantial reduction in the amount of RS procedures as the other regions. Interestingly enough, there was no significant difference between number of RS procedures performed in patients with inhibitors (32.8%) compared to patients without inhibitors (29.5%) after MASAC guidelines (p=0.658).

Our study was limited by its retrospective database design. Practice changes such as increasing use of primary and secondary prophylaxis with resultant decrease in arthropathy as well as difficulty in obtaining P32 after the MedWatch warning may have influenced RS rates and could not be independently evaluated. A potential study of the rates of surgical synovectomies over this period may help discern these variables. In our study, we were unable to evaluate this since some patients who underwent RS also had surgical synovectomies and these variables were not mutually exclusive. Additionally, the short supply of P32 may have been a confounder of the impact of MASAC guidelines on the regional change in procedure as well.

The data suggests that the MASAC guidelines may influence general practice. Another interesting observation was that the MASAC guidelines seem to be more impactful in certain regions as opposed to others. Regional differences may have been descriptive of individual preferences of groups of practitioners or institutions driven by factors including availability of someone to handle the radioactive isotope which is highly regulated, limited availability of experts to administer the injections and size of centers and patient volumes justifying purchase of the isotope. Additionally, the ATHNdataset was utilized as a high quality dataset in this study which paves the way for future studies using the ATHNdataset that may require evaluating a large population of patients with bleeding disorders in multiple centers.

Acknowledgement: The ATHNdataset, a HIPAA compliant limited data set under the stewardship of the American Thrombosis and Hemostasis Network (ATHN), was developed through collaboration with over 135 ATHN-affiliated Hemophilia Treatment Centers across the U.S.

Human Participant Protection: Patients opt in and provided written authorization for the sharing of their demographic and clinical data for research as part of the ATHNdataset.

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Author Contributions:

AD designed the research study and critically revised the manuscript. RS performed the research, analyzed the data and wrote the manuscript. DC conducted the statistical analysis and data interpretation. All ATHN investigators made substantial contributions to research design, conducted the research study and contributed research subjects. All authors approved the final and submitted versions of the manuscript.

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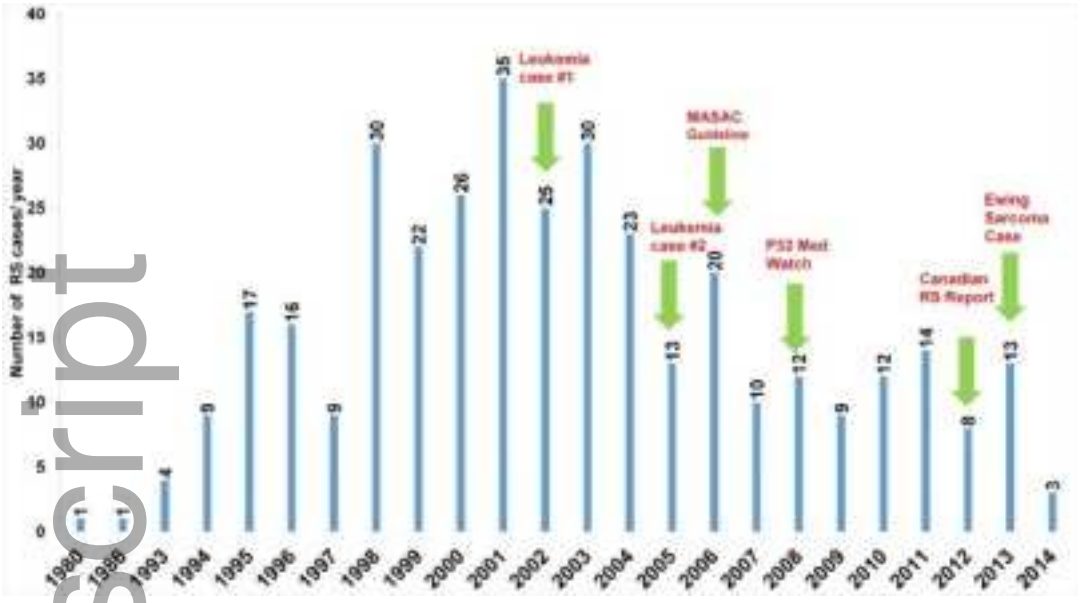

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