Joint Health Study

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Background

Hemophilia B is a congenital bleeding disorder caused by a mutation in the factor IX gene, resulting in low circulating clotting factor levels which has been associated with trauma induced and spontaneous bleeding into the joint space. Recurrent bleeding leads to risk for re-bleeding, hypertrophy of the synovium, progressive cartilage destructions and bony changes, resulting in hemophilic arthropathy, chronic pain and functional disability [Forsyth 2012]. Prophylactic treatment with clotting factor concentrates to prevent bleeding has been shown to reduce the risk for joint arthopathy [Manco-Johnson 2007] and has become standard of care.

Current prophylactic regimens, although very effective, do not completely prevent joint disease in a long-term perspective. Joint arthropathy in primary prophylaxis develops over many years, sometimes over a decade or even longer time periods. The ankle joints are the first and most severely affected joints in those patients and thus may serve in outcome assessment as an indicator of early joint arthropathy when followed by ultrasound or magnetic resonance imaging [Oldenburg, 2015].

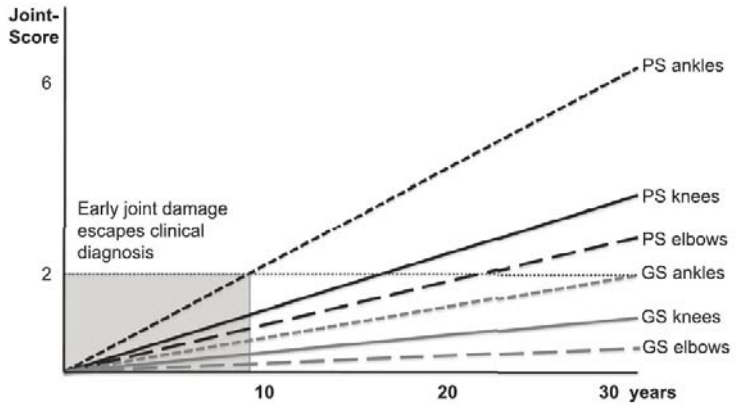


Figure 1. Development of ankle arthropathy in a cohort on intensive lifelong prophylaxis, GS, Gilbert score; PS, Pettersson score [Oldenburg, 2015].

Screening for hemophilic arthropathy is generally conducted during annual comprehensive visits in hemophilia treatment centers, and several tools have been developed to assess for and monitor progression of arthropathy. The Gilbert Score and the Hemophilia Joint Health Score (HJHS) are clinical scores. The World Federation of Hemophilia Pettersson score and Arnold-Hilgartner score are based on x-ray findings and tend to reflect later, irreversible bony damage. Magnetic resonance Imaging (MRI) is sensitive to soft tissue changes and detects pathologic findings such as effusions, synovial hypertrophy, hemosiderin deposition, and

osteochondral changes. Numerous scales have been developed over the years (Denver score is a progressive score, European score is an additive score, Compatible score is a combined Denver and European score, IPSG score is currently the standard). While more sensitive for soft tissue changes, MRI is costly, not-easily assessable, takes a significant time commitment and necessitates sedation in children. Thus MRI is difficult to incorporate in the assessment of acute/bleeding and chronically changing joint.

More recently, musculoskeletal ultrasound (MSKUS) has been used for diagnosis of joint disease in hemophilia. Like MRI, it can reveal joint effusion, proliferation of synovium and subtle cartilage and bone abnormalities. It is the imaging modality recommended by the American College of Rheumotology and is superior to physical exam, especially when evaluating synovitis [Foltz 2012, McAlindon 2012, Porta 2012]. It has been demonstrated that ultrasound helps in the correct and timely diagnosis of acute bleeding episodes [Ceponis 2013], along with other musculoskeletal changes in people with hemophilia [Kidder 2015]. Advantages of MSKUS are its wide availability and low cost. Ultrasound will allow more thorough longitudinal joint assessment [Aznar JA 2015], assisting in the prevention of disease progression, thereby potentially improving outcomes and decreasing cost. Soft-tissue changes such as synovial hypertrophy, which precede joint disease, especially can be effectively diagnosed. Standardized and simplified ultrasound scanning protocols for early arthropathy detection in ankles, knees, and elbows have been published [Martinoli 2013]

Research Question

Knowledge pertaining to the progression of hemophilic arthropathy of patients with Hemophilia B is limited since Hemophilia B is very rare. Only 1 in 25,000 live male birth is affected compared to patients with Hemophilia A, born at a ratio of 1:5000 male birth (ref). To date, and to the best of our knowledge, there are no prospective studies available to document the development of hemophilia arthropathy in patients with Hemophilia B. We therefore propose to study longitudinal joint changes in patients with moderate and severe Hemophilia B. Most patients are on episodic or prophylactic FIX replacement therapy, whereby patients have a choice to be treated with newer extended half-life (EHL) products or to remain on traditional short-acting FIX products. For example, recombinant FIX albumin fusion protein (rIX-FP) is the most recently approved EHL concentrate and has demonstrated an increase in circulating half-life and area of the curve (AUC) of greater than fourfold versus unmodified FIX. When infused weekly this kinetic profile allows for potential trough levels of greater than 10% [Santagostino 2016]. Such improvement in minimum trough levels could improve the incomplete protection observed with previous products. This study will test the hypothesis that an EHL FIX product (such as rIX-FP) could offer better protection than previous treatment concentrates. The primary research question is whether EHL-rIX with an intended trough level of >5% will improve the outcome of joint health of elbow, ankle and knee joints as assessed with ultrasound assessment in severe hemophilia B patients.

Study Design

Prospective, non-randomized controlled study, whereby patients will be included in 1 of 3 groups depending on their current treatments as outlined below. Patients will be assigned to a specific group by the clinician/PI based on their current regimen with the intent to stay on this regimen for the next 3 years.

- Group A - episodic treatment with FIX concentrates for bleeding episodes
- Group B - prophylaxis using any FIX concentrate with an intended trough of 1-5%
- Group C – prophylaxis with an extended half-life FIX with an intended trough of > 10%

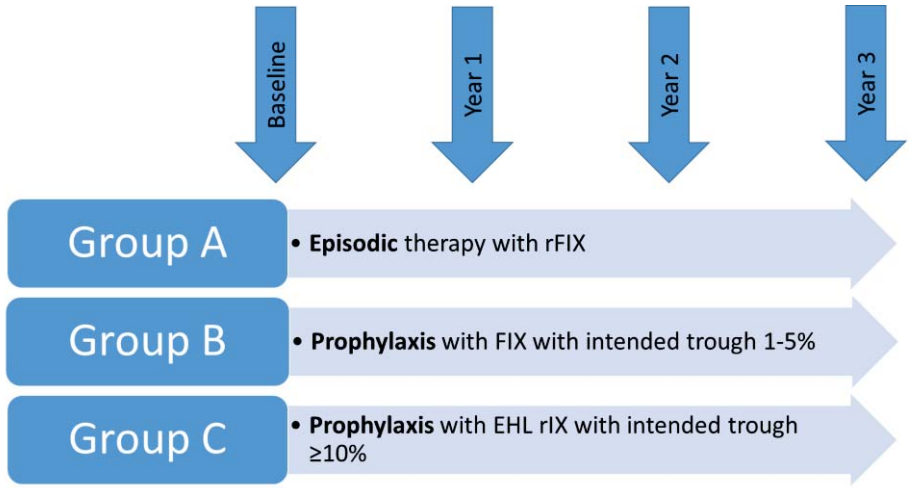
Primary Outcome

Joint health status in all 3 groups as assessed by MSKUS at 3 years.

Joint health will be assessed in all 6 major joints (elbows, knees and ankles), if possible, but at a minimum, target joints and the contra lateral joint will be included. During the exam the previously described Martinoli transducer positions will be used [Martinoli 2013]. To verify MSKUS, the first 10 patients will have parallel x-rays and MRI of the target joint and contra lateral joint.

Allocation of a comparison score of the MSKUS at baseline vs. year 3 will be done by a central, blinded person once all MSKUS images are available. The Joint Activity and Damage Exam (JADE) protocol will be documented to inform scoring. The scoring will be as follows:

MSKUS Assessment	Score
MSKUS imaging indicated improved joint status (decreased signs of arthopathy)	-1
MSKUS imaging indicated no change in joint status	0
MSKUS imaging indicated worsened joint status (increased signs of arthopathy)	+1



Secondary outcomes

- Observational assessment of joint and overall health status evaluated by activity level, functional assessment, pain assessment, joint examination, and adherence.
- Observational assessment of joint health at 1 and 2 years in the different groups
- Observational assessment of MSKUS findings during acute events/bleeding with an opportunity to follow longitudinally to gain understanding of natural evolution of bleeding on MSKUS
- Exploration of potential biomarkers for joint health

Patient Population

Inclusion Criteria

- Male gender
- Severe hemophilia B (factor IX < 1%)
- Age ≥ 16 year
- Either on demand or on prophylaxis with rFIX or EHL-rIX products with the intention to stay on the current regimen for the next 3 years
- For Group C start of this treatment regimen up to 6 months ago is permissible
- Willing and able to give written informed consent/assent
- Willing to undergo MSKUS and /or collection of blood sampling for biomarkers

Exclusion Criteria

- Other known bleeding disorder
- Other rheumatologic disorder affecting joints
- Other known neuromotor defect (making physical exam difficult)

Assessment at baseline and at annual exams**:** Patients will be consented and eligibility will be confirmed. The following will be collected:

- Baseline Form (Demographics, bleeding history, use of hemostatic agents, past medical/surgical history, vital signs)
- Rapid Assessment of Physical Function (RAPA – 1 page questionnaire) to assess physical activity level
- Hemophilia Activity List (HAL – 3 page self –administered questionnaire) and Time up and go (TUG – assessed by PT) to assess function
- VERITAS-Pro (24 question self-administered questionnaire) for Arm B and C to assess adherence to prophylaxis
- Brief Pain Inventory (BPI – 10 question self-administered questionnaire)
- Joint Assessment (Hemophilia Joint Health Score =HJHS)
- MSKUS: Full J.A.D.E. Protocol (prior exams up to 3 months are permissible)
- x-rays and MRI (first 10 patient only prior exams up to 3 months are permissible)
- Treatment Plan prescribed at visit
- Labs: Factor XI level, FXI inhibitor, hsCPR
- Plasma Sample for biomarkers for Bio Repository

Historical assessments up to 1 year will be allowed as long as all required data was collected.

Assessment of painful episodes: Patients participating in this study will be encouraged to come in for an assessment during a painful episode of either of their elbows, knees or ankles. They will be asked to classify the episode as a bleed vs. non-bleed. The pertinent joint will be examined by a healthcare practitioner as classified to be a bleed vs. non-bleed by the practitioner and a treatment will be determined according to the exam. The patient then will undergo MSKUS and the treatment plan will be reviewed. If changes are made based on the MSKUS finings, they will be noted. The patient is offered to have a sample for the biomarker repository drawn.

Assessment post-painful episodes: Patients who came in for a painful episode are encouraged to return to clinic in 1-2 weeks for repeat exam and MSKUS. The patient is offered to have a sample for the biomarker repository drawn.

Assessment Schedule:

	Baseline	Acute Pain Event	Post-Pain Event	Year 1,2	Year 3
Demographics (age, race/ethnicity)	X			X	X
History (including bleeding history, medications, hemostatic agents and regimen, surgeries, joint bleeding/injury/surgery)	X	X	X	X	X

Recent **joint bleeding/injury** history (over the last 1 year)	X			X	X
Activity level (e.g RAPA or fitbit)	X	X	X	X	X
Functional assessment (HAL)	X	X	X	X	X
Brief **Pain** Inventory	X	X	X	X	X
Physical Exam	X	X	X	X	X
HJHS	X	X	X	X	X
MSKU	X	X	X	X	X
Biomarkers	X	X	X	X	X
X-ray (1st 10 patients only)	X			X*	
MRI (1st 10 patients only)	X			X*	
Time to up and go	X	X (if appropriate)	X (if appropriate)	X	X
Veritas or Veritas-Pro - Adherence	X	X	X	X	X

*Year 1 only

MSKUS Assessment: MSKUS will be performed by a qualified person at each study site. To reduce operator dependence of results and ascertain uniform data collection, this person must have had sufficient training (took a course on hemophilia related MSKUS though Dr. Martinoli, through UCSD, or equivalent). Preferably, the MSKUS is performed by the same person at each time point. Assessment at each time point should be of bilateral elbows, knees and ankles, if possible – at a minimum, MSKUS of an acute or historical target joint (elbow, knee or ankle) and the contralateral join has to be performed at baseline and at 3 years to be included in primary endpoint analysis.

X-ray Assessment: The 1st 10 patient in the study will have x-rays of their target joint and contralateral joint using the following views:

- Knee – radiographs: standard AP and lateral, but also include a merchant view (3 views total)
- Elbow – radiographs: standard AP and lateral (2 views)
- Ankle – radiographs: standard AP, lateral, and mortise (3 views)

x-ray studies done within 6 months of study visit are permissible.

MRI Assessment: The 1st 10 patient in the study will have MRI images of their target joint and contralateral joint using the following protocol:

Preferably imaging should occur on a 3 Tesla machine and each site will have their own standard clinical MRI protocols using conventional 2D sequences in 3 imaging planes (typically fast spin echo [FSE]). In addition, add a sagittal 2D gradient echo sequence (to better visualize hemosiderin deposits) and also a 3D sequence. The 3D sequences are depending on particular MRI vendor at the individual sites. If available a 3D FSE should be performed (GE has CUBE, Siemens has SPACE, Philips has VISTA, Hitachi has isoFSE, and Toshiba has 3D MVOX). Acquisition for the 3D sequence should be in the sagittal plane and voxel size should be close to isotropic. The 3D sequence will be very useful for comparing specific planes with ultrasound (such as the femoral trochlea). The radiology consultant for this study will advise on sequencing at each individual site.

MRI studies done within 6 months of study visit are permissible.

Biomarker Repository: During all visits, including acute pain and pain follow-up visits, the patient will be approaches to contribute blood samples for the repository. Five citrated (blue top) tubes will be drawn, samples will be spun, aliquoted and frozen for potential later studies.

Cost to the patient: This study will cover the cost for the MSKUS performed, the x-ray and MRI validation exams for the first 10 patients. It will not cover the cost of the clotting factor and routine clinical laboratory.

Patient compensation: The patient will be compensated for his time for the baseline, year 1, year 2, year 3, acute pain episode and pain follow-up visit at $150.-/visit. Patients are allowed to get evaluation for more than 1 pain episode and data can be included in the analysis, but there is no compensation for these additional visits. There will also up to $50.-/visit in travel compensation for the baseline, year 1, year 2, year 3, and one acute pain episode and pain follow-up visit.

Statistical Plan

For first 10 patients do MRI, compare Ultrasound to MRI and X-ray at baseline and 1 year; and compute sensitivity and specificity and evaluate the rate of false negatives by ultrasound, with MRI as gold standard.

The primary outcome will be proportion of patients with improvement (compared to same or worse) between groups B and C, with analysis by Fisher's Exact Test. Given a feasible sample size of 20 patients per arm for groups B and C, we anticipate having 80% power to detect a 5-fold increase in the proportion of patients classified as improved (e.g., from 10% to 50%). Proportions in each group classified as worse, same, or improved will also be reported and compared by Fisher's Exact Test.

Sample Size

- Arm A: 10 patients
- Arm B: 20 patients
- Arm C: 20 patients

Potential Study Sites

- Washington Center for Bleeding Disorders at Bloodworks NW, Seattle, WA
- Hemophilia and Thrombosis Treatment Center, University California, San Diego, CA
- Seattle Children's Hospital, Seattle, WA
- Orthopedic Hemophilia Treatment Center, Los Angeles, CA
- Tulane University, New Orleans, LA
- Hemophilia and Thrombosis Center, Denver, CO
- Center For Inherited Blood Disorders, Irvine, CA
- Children's Hospital of Michigan, Detroit, MI
- Oregon Health & Science University, Portland, OR

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