Subclinical Cardiovascular Disease in Psoriatic Disease

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1. Synopsis

Cardiovascular disease (CVD) remains the leading cause of death in the US. Five modifiable risk factors: smoking, hyperlipidemia, diabetes, hypertension and obesity, account for 50% of CVD mortality between the ages of 45 – 79.[1] These traditional cardiac risk factors dictate who to treat with primary prevention measures but do not take into account patient-specific disease states such as psoriatic disease including psoriasis and psoriatic arthritis, which predispose to chronic inflammation. Patients with psoriatic disease have an increased risk of atherosclerotic heart disease and myocardial infarctions compared to matched controls.[2] Studies are needed on how the chronic inflammation seen in psoriatic disease translates into the increased atherosclerotic and thrombotic risk and how treatment reduces this CVD risk.

2. Background and significance

Psoriatic disease which includes psoriasis and psoriatic arthritis are chronic inflammatory disease states which have been shown to increase the risk of cardiovascular mortality.[3] Psoriasis has a prevalence of 2 to 3 percent, with a bimodal distribution affecting most those 30 – 39 and again between 50 – 69 years of age.[4] Meta-analysis on the association of CVD with psoriasis have yielded an overall relative risk (RR) of 1.5 for ischemic heart disease.[5] Young adults are at even higher relative risk (RR) higher risk, with a RR for myocardial infarction of 3.1 compared to age-matched controls.[6] Confounding this relationship is the increased prevalence of metabolic syndrome, obesity, HTN and hyperlipidemia within the psoriatic population.[5] Despite this, epidemiologic studies have noted the increased risk of CVD remains after adjustment for these traditional CVD risk factors.[6]

The mechanism(s) between psoriatic disease and CVD are still being characterized.[7] The systemic inflammation is linked to the production of numerous inflammatory cytokines such as interferon – γ, tumor necrosis factor (TNF), IL-17 and IL-22 with an overall activation of the innate immune system response.[8] Through systemic inflammation, the initial stages of atherosclerosis develop with upregulation of vascular endothelial adhesion molecules and leukocyte translocation, platelet activation and increased vessel wall permeability to lipoproteins and inflammatory mediators.[9]

There have been studies linking the earliest phases of atherosclerosis, endothelial dysfunction and psoriasis. Psoriatic patients have impaired flow-mediated dilation, increased arterial stiffness and increased carotid intima-media thickness.[10] Biochemically, a variety of extracellular microparticles, involved in both endothelial cell and platelet activation are elevated in those with moderate to severe psoriasis.[11] Platelet activation in particular through measurement of platelet-derived microparticles and soluble P-selectin are increased in psoriasis and linked to psoriasis severity.[12]

While there have been studies evaluating the effects of psoriatic specific treatment on endothelial dysfunction, there is a lack of evidence on the use of medications typically used for the primary prevention of CVD within the psoriatic population.[10] The goals of the proposed study are three fold: As a first step to assess endothelial dysfunction, we will assess vascular function in psoriasis patients through non-invasive ultrasound imaging and through a novel technique: direct analysis of endothelial cells with minimally invasive endothelial vein harvesting.[13] As a second goal, we will assess thrombotic risk through platelet activation and platelet – endothelial interaction. Finally, as a third goal, we will assess in patients with moderate to severe psoriatic disease changes to the endothelial function and platelet activation over time with the use of 81mg of aspirin and/or 40mg of atorvastatin.

3. Specific Aims

3.1 To evaluate the association between moderate to severe psoriatic disease and measures of vascular function.

3.2 To evaluate the association between moderate to severe psoriatic disease and measures of thrombotic risk.

3.3 To understand how traditional medications used in CVD prevention such as aspirin and statins affect vascular function and thrombotic risk in those with moderate to severe psoriatic disease.

4. Research Design

4.1 Recruitment

We will recruit patients across the spectrum of psoriatic disease (includes psoriasis and psoriatic arthritis and age and sex matched health controls).

4.2 Inclusion/Exclusion Criteria for Psoriatic Patients

Inclusion Criteria

1. Group 1: Subjects with a history of moderate to severe psoriatic disease
2. Age ≥ 18 & < 90
3. Able and willing to provide written informed consent for the study

Exclusion Criteria

1. Unable to speak Spanish or English
2. Active smoking (within the past year)
3. Autoimmune, rheumatologic or inflammatory disease which are not psoriasis or psoriatic arthritis
4. Known active cancer receiving treatment
5. Pregnancy
6. Anemia (hemoglobin < 9 mg/dl) or thrombocytopenia (Platelet count <75), or thrombocytosis (Platelet count >600)
7. A history of severe bleeding or bleeding disorders
8. Current medication use which interact with either aspirin or atorvastatin
9. Chronic kidney disease (CrCl < 30ml/min)
10. Congestive heart failure
11. Currently taking aspirin or a statin.
12. NSAID use within the past 48 hours

4.3 Inclusion/Exclusion Criteria for Healthy Controls

Inclusion Criteria

Group 2: Healthy subjects without known psoriatic disease or cardiovascular disease

1. Age ≥ 18 & < 90
2. Able and willing to provide written informed consent for the study

Exclusion Criteria

2. Unable to speak Spanish or English
3. Active smoking (within the past year)
4. Autoimmune, rheumatologic or inflammatory disease which are not psoriasis or psoriatic arthritis
5. Known active cancer receiving treatment
6. Pregnancy
7. Anemia (hemoglobin < 9 mg/dl) or thrombocytopenia (Platelet count <75), or thrombocytosis (Platelet count >600)
8. A history of severe bleeding or bleeding disorders
9. Current medication use which interact with either aspirin or atorvastatin
10. Chronic kidney disease (CrCl < 30ml/min)
11. Congestive heart failure
12. Currently taking aspirin or a statin.
13. NSAID use within the past 48 hours

Recruitment goals are listed in the schedule of assessments below. Both female and males will be recruited. Patients will be recruited from the outpatient general medicine, musculoskeletal/rheumatology and dermatology clinics at the NYU Faculty Group Practice (FGP) clinics including the Psoriasis, psoriatic arthritis ambulatory clinic, psoriasis and dermatology ambulatory care center and Bellevue Hospital Adult Clinics. We will also recruit from the Hospital for Joint Disease Psoriatic arthritis clinic which is staffed by NYU faculty. Patients fulfilling inclusion and exclusion criteria will be identified by their health care professional, who will obtain verbal consent for contact by a member of the research staff. Study brochures will also be left at the front desk of these practices in the even that subjects would like more information from study staff. Patients will be approached after their visit with the health care provider in the clinic setting. Subjects and healthy controls will also be recruited from posted fliers across the medical center. Additionally, subjects who have previously enrolled in any study (10-00607, S12-03123, S14-00531, s14-01418) by the co - PI (Jeffrey Berger) and who checked off the box that they may be contacted by a member of the study staff for potential enrollment will be included.

Additional recruitment will be done through posted fliers and approved brochures at private dermatology offices with dermatology office staff permission. We will also recruit through social media postings including Craigslist, Facebook, psoriatic support groups and national psoriatic society patient

advocacy groups as well the NYU approved research match The advertisement for these postings will contain the same content as noted on the IRB approved flyer. This social media advertisement will also includes the health-union psoriasis advocacy website.

Working with MCIT and DataCore we will be using *Epic's Reporting Workbench tool* to identify potential subjects that have psoriasis and present to the dermatology FGP, arthritis or phototherapy clinics. We will screen these subjects and then if they meet study inclusion criteria and has agreed to be contacted for potential studies then they will be contacted. *Contact will be initiated using Epic and the patient portal, MyChart, via Epic's Research Recruitment functionality. The information used to send the MyChart message will be the same as that used for other study advertisements.*

Only subjects that have the capacity to consent will be asked to consent.

Vulnerable Population

We will not be enrolling any vulnerable populations.

4.4 Informed consent

If a subject wishes to participate, a member of the research team will review the informed consent documents, answer any questions, and obtain written consent for participation in the study and obtain written consent for future analysis, contact, and sample storage. Subjects will be given a "Subject history form" to fill out asking for a complete medical history. They will also be given an appointment reminder sheet to bring with their consent form. They will bring the subject history form to their first baseline assessment appointment. Participants will consent to complete the baseline assessments (see table 1). Participants may opt to decline participation in any baseline assessment they feel uncomfortable with or time constraints do not allow. Follow-up assessments will be completed in those who agree to aspirin or atorvastatin usage for the longitudinal part of the analysis. Participation in follow-up assessment is not required for participation in the baseline assessment. The consent process will take place in private offices at the NYU FGP, CTSI, ambulatory care center, Seligman Center for Advanced Therapeutics and Bellevue adult clinics. Subjects will be given the opportunity to be contacted for future studies that they may qualify for as well. A member of the research team will conduct the baseline interview with the subject and review the clinical history, demographic information and medication use with the individual. All information including the consent will be kept under double lock and key at the PI's office in NYU Skirball 9th floor.

4.5 Methods

4.5.1 Schedule of assessments

At least one baseline assessment is required for all study participants where both a blood draw of 60ccs (for the use of platelet function testing, biospecimen collection), non-invasive vascular function imaging testing and endothelial vein harvesting will occur (table 1). A subject can choose not to participate in any baseline testing they feel uncomfortable with but must participate in one baseline assessment to be included in the study.

4.5.2 Longitudinal component (Group 1 only)

After baseline assessment, those with moderate to severe psoriatic disease will be offered by the study physician randomly the opportunity for longitudinal follow up and to take either aspirin and/or atorvastatin. For 2 weeks +/- 4 days, 1/4th of the subjects enrolled will be offered 81mg of aspirin, 1/4th of the subjects enrolled will be offered atorvastatin 40mg, ¼ will be offered both aspirin and atorvastatin and 1/4th will be offered nothing. Participants will be given the opportunity to only participate in the baseline assessment and opt out of the opportunity to take aspirin and/or atorvastatin and longitudinal component.

Both aspirin and atorvastatin are routinely used and approved in medical practice for the primary prevention of coronary artery disease. These medications are frequently used in the psoriatic population based on national guidelines when a calculated cardiac risk score is elevated (considered at moderate to high risk of cardiovascular events). These medications will be obtained from the Tisch outpatient pharmacy. They will be stored and dispensed with CTSI oversight. A drug accountability and storage log will be kept as per NYU research protocol.

A follow up assessment will be planed (table 1) at 2 weeks +/- 4 days and will include repeat blood draw (60 ccs, for the use of platelet function testing, biospecimen collection) and repeated endothelial vein harvesting. The end of the study is considered when the subject completes the follow up assessment. All study drugs will be stopped at this time. If the subject wishes to continue the study drugs they will be referred to their primary medical provider for further management.
A subject will be able to opt out of any part of the follow up assessment they desire. If a subject agrees to be started on aspirin and/or atorvastatin for the longitudinal part of the analysis and therapy for psoriasis is planned by the referring provider, we will attempt to perform the longitudinal follow up prior to their starting medication. Participation in this study will not impact planned treatment of the subjects by their primary provider.

All subjects may be asked to provide additional information about their medical history, update any interim history and provide additional samples as noted above. Health information will be monitored overtime by review of the medical chart. Additional questions may be asked by phone or during routine clinical follow-up, as appropriate.

Table 1. **Patient Group**		**Baseline**	**Longitudinal Analysis**	**Follow-up**
1 n = 40	Moderate to severe psoriatic disease	1) Blood 2) Endothelial vein harvesting 3) Vascular function imaging	Offered: 1) Aspirin 2) Atorvastatin	1) Blood 2) Endothelial vein harvesting 3) Additional medical history

				obtained
2 n = 10	Healthy Controls	1) Blood 2) Endothelial vein sampling 3) Vascular function imaging		1) Additional medical history obtained

4.5.3 Vascular function assessment

Vascular function may be assessed either using brachial artery flow mediated dilatation (FMD) or pulse wave velocity (PWV), both non-invasive ultrasound measures of vascular function. FMD and PWV will be measured using a duplex ultrasound imaging system (2D, grayscale B-mode imaging, pulsed Doppler and color flow Doppler) with a 11 MHz linear array probe (Sonosite Inc., Bothell WA). Collection of the ultrasound vascular function data will occur in the Clinical Research Center of the NYU Clinical and Translational Science Institute (CTSI), under the direction of Dr. Stuart Katz, who is on this proposal.

Before each study, participants will provide answers to a brief series of questions to determine eligibility for the FMD/PWV measurements and to determine which arm to use. Participants will rest supine for at least 20 minutes before measurements are made. We will attempt to use the right arm for imaging except in a few uncommon circumstances among patients eligible for this study (recent injury with or without casting on the right arm, right mastectomy with lymph node removal, or any other condition that results in immobility, pain, and/or swelling in the right arm or hand). The participants will be positioned to maximize their comfort and to facilitate image acquisition by the sonographer. A standard 3-lead electrocardiogram will be placed on the torso (right upper torso, left upper torso, and left lower torso) as per protocol. Resting supine blood pressure will be measured in the left arm and recorded.

Mean blood flow velocity (MBFV, cm/sec) will be determined by calculation of the area under the hand-traced curve of the spectral display. Brachial artery diameter and MBFV will be measured at rest, and after transient arterial occlusion induced by inflation of a forearm blood pressure cuff to suprasystolic pressure for 5 minutes. MBFV will be measured for 15 seconds immediately upon release of the occluding cuff; the first 5 beats after release will be averaged. Occlusion of brachial artery blood flow for 5 minutes with suprasystolic pressures may result in mild hand numbness and discomfort that resolves quickly with decompression of the blood pressure cuff without any known clinical sequelae. Brachial artery diameter will be measured over a 1 cm vessel length at end-diastole 60-75 seconds following release of the occluding cuff; 3 diameter measurements will be averaged. FMD will be calculated as the % change in brachial artery diameter after cuff release compared with the resting diameter. Internal and external landmarks will be used to make repeated measurements at the same vessel site. In our laboratory, mean FMD in normal adult subjects mean age 43 years is 5.89% (95% CI 4.53%, 7.23%). Intraobserver coefficient of variance for FMD measurements of the same vessel is 1-2%. Within-subjects coefficient of variance ranges from 5-10% for same day measurements (reliability coefficient for repeated measures 72%) and 15-30% for day-to-day measurements (reliability coefficient for repeated measures 46%). Carotid-to-femoral arterial pulse wave velocity as well as central arterial

pressure (Sphygmacor), a surrogate measure of vascular stiffness associated with long-term risk of cardiovascular event will also be recorded.

4.5.4 Endothelial cell harvesting

There will be a maximum of two time points for endothelial cell harvesting and biospecimen collection. Endothelial harvesting will take place either in the CTSI or in the NYU Seligman Center for Advanced Therapeutics. Both of these centers have access to nursing support and ancillary support staff including trained phlebotomists. All subjects will have their blood drawn and endothelial harvesting after informed consent and completion of the screening interview. If willing to the subjects will be preferably fasting > 4 hours and water intake is allowed. They will be in a reclined position with feet elevated. An angiocatheter ≤ 21 gauge will be inserted into a peripheral vein on the upper extremity using aseptic technique. A 0.021in. diameter J-shaped wire (Daig, Minnetonka, MN) or a 0.018in. diameter J-shaped wire (Arrow, Reading, PA) will be then advanced into the angiocatheter, to a distance of 4cm beyond the end of the angiocatheter. Angiocatheters and J shaped wire described above are routinely used for intravenous fluids and medication administration in this hospital. Venous endothelial cells will be scraped from the intimas of superficial forearm veins by repeated (3 times) insertion and removal of the wire. The distal portion of the wire will be transferred to a 50ml conical tube containing dissociation buffer (0.5% bovine serum albumin, 2 mM EDTA, and 100 microg/ml heparin in PBS, pH 7.4) and maintained at 4°C until study. Half of retrieved endothelial cells will be used for RNA extraction and a half for immunofluorescence.

The angiocatheter used will be a ≤ 21 gauge (typically 20 gauge) INSYTE autoguard IV catheter which is routinely used for clinical care, IV hydration and administration of medications. In this case we will using this angiocathter off label as a method to safety access the peripheral vein. This poses a non-significant risk for the device according to 21 CFR 812.3 (m) because: 1) There is NO implantation of the device. 2) This device will not be used to sustain human life and does not pose a serious risk to health or safety of the subject. 3) This device will not be used to diagnose, cure, mitigate or treat a disease. 4) This angiocatheter device is routinely used across the country in clinics and hospitals and does not pose a serious risk to health, safety or welfare of the subject.

The J – wire used will be either a 0.021in. diameter J-shaped wire (Daig, Minnetonka, MN) or a 0.018in. diameter J-shaped wire (Arrow, Reading, PA). This device will be used off label as a means of accessing and collected endothelial cells. In clinical practice these devices are typically used in hospital settings as a guidewire for accessing human veins and threading other catheters into the vein. These wires therefore routinely come into contact of vein walls during clinical care. HOWEVER, our use is to harvest endothelial cells that come into contact with these wires. Therefore, this is considered off label. This poses a non-significant risk for the device according to 21 CFR 812.3 (m) because: 1) There is NO implantation of the device. 2) This device will not be used to sustain human life and does not pose a serious risk to health or safety of the subject. 3) This device will not be used to diagnose, cure, mitigate

or treat a disease. 4) This j-wire device is routinely used across the country in clinics and hospitals and does not pose a serious risk to health, safety or welfare of the subject.

4.5.5 Biospecimen collection

Study blood will be collected by trained staff in the outpatient clinics, Seligman Center for Advanced Therapetucis or in the CTSI. This will occur immediately after endothelial vein harvesting using the same brachial IV site if the subject has agreed to endothelial vein harvesting. If the subject declined endothelial vein harvesting but agrees to a blood draw, then standard techniques of blood drawing will be used as follows. After cleansing of the venipuncture site with an alcohol wipe and removal of excess alcohol with sterile gauze, a tourniquet will be applied to the patient's bicep region. A 20G butterfly needle or less will be inserted into the antecubital vein, the tourniquet will be removed, and free-flowing blood will be collected with minimal trauma and stasis. The needle will be removed when blood collection is complete and sufficient pressure will be applied using sterile gauze at the puncture site until cessation of bleeding. A sterile band-aid will be applied to cover the venipuncture site. .

For each patient, no more than 60 ml (≈4 tablespoons and 1/8 of a standard blood donation) of blood will be collected at the baseline visit in red (no anticoagulant) top, lavender (EDTA anticoagulant) top, green (heparin) and blue (sodium citrate anticoagulant) top tubes). We believe this amount of blood is negligible and presents minimal risk for the patient. Approximately 30 cc of blood will be used for the different measurements of platelet function, lipid levels, coagulation, inflammation, and approximately 30 cc of blood will be used for isolation of RNA, microRNA and storage of DNA at -80C. . The samples will be stored in the PI's lab at the NYU Science building 7th floor without any identifying information other than a code number. These samples will be barcoded system and lab vantage and stored in a freezer with back-up power supply.

4.5.6 Longitudinal Follow Up Data Collection

Participants enrolled in the longitudinal part of this study will be offered the option to participate in follow-up biospecimen collection. This follow-up will allow us to assess how aspirin and/or atorvastatin affect platelet and endothelial function and inflammation. This follow-up component will consist of additional blood samples of ≈ 30ml (2 tablespoons or less) that will be collected for different measurements of platelet function, lipid levels, coagulation, inflammation, and approximately 30 ccs of blood will be used for isolation of RNA, microRNA and storage of DNA at -80C. The samples will be stored in the PI's lab at the NYU Science building 7th floorwithout any identifying information other than a code number. Repeat endothelial vein harvesting will also be performed as described above.

Overall, code numbers used for collection of samples will not be based on any information that could be used to identify the subject (for example, social security number, initials or birth date). The master list linking names to code numbers will be kept in a locked file cabinet, separate from all research information.

If participating in the optional follow-up collection, the total amount of blood withdrawn (baseline plus follow up) will be no more than 120 ml (approximately 7 tablespoons and 1/4 for a standard blood donation). This amount of blood collection is within established safety guidelines of research blood collection in adults. Blood collection at baseline and at the follow up time points will allow us to examine how the treatment of aspirin and atorvastatin modify 1) endothelial vein function in psoriatic disease, 2) changes to platelet activity and 3) alterations in coagulation and inflammation in those with psoriatic disease.

For all cases and controls, we will call 1 week after each procedure to assess how patients are feeling after endothelial vein harvesting. Adverse events will be managed as mentioned below.

4.5.7 Genetic Profiling

The blood and endothelial specimens will be analyzed upon completion of the study for RNA, microRNA, and DNA profiling. We will perform detailed molecular profile study, describing genetic arrays of patterns of platelet and endothelial vein analysis associated with atherosclerotic heart disease and psoriasis. We will be looking at specific transcripts in various cell types and endothelial cells associated with cardiovascular diseases. Platelet-rich plasma (PRP) will be isolated for platelet purification and subsequent genetic analysis will be performed. The samples will be stored in dedicated freezer space in the Marc and Ruti Bell Program for Vascular Biology (the NYU Science building 7th floor) for the PI without any identifying information other than a unique code number. The code number will not be based on any information that could be used to identify the subject (for example, social security number, initials, birth date, etc.). The master list linking names to code numbers will be kept in a locked file cabinet, separate from all research information. Genetic information will not be disclosed to anyone, including the participants and their physicians. Samples shall be destroyed at the end of the testing process.

4.6 Future Sample Storage

All patients will be offered an option to have their blood stored for future processing. If patient does not agree to store his/her blood for future tests not related to this study, then his/her blood will be destroyed after all planned laboratory tests have been performed.

Blood samples for future analysis will be assigned a unique code number and stored in the dedicated freezer storage by the PI without any identifying information other than a code number. The unique code number will not be based on any information that could be used to identify the subject (for example, social security number, initials, or birth date). The master list linking names to code numbers will be kept in a locked file cabinet, separate from all research information placed under double lock and key at PI's office. All confidential data will be stored with a unique code as an identifier and will be protected by a double electronic lock. All physical data will be kept under double physical lock. Access to the data will be given to the study personnel only.

Samples will be stored for no more than 10 years. The specimens for future analysis may be analyzed upon completion of the study for RNA, microRNA, and DNA as described above. Genetic information will not be disclosed to anyone, including the participants. Samples could also be used for testing other potential biomarkers in patient plasma and/or serum related to psoriatic disease and CVD that may occur with exception of those which are already part of the protocol. Results of the future research will not be shared with the subjects or their study doctor, and will not become part of the medical records.

In the future, other institutions or future collaborators at or outside of NYU Medical Center may want to study a portion of these samples, too. If that happens, samples would be sent to other places so other people interested in studying these diseases and conditions could do that. The samples sent to other researchers will be de-identified without PHI. Samples will be stored for no more than 10 years following completion of the study. At the end of the 10-year period, all samples will be destroyed.

Subjects can request for withdrawal of samples at any time by contacting PI Dr. Berger in writing. His mailing address is Faculty Practice Tower 9 R, 530 First Ave NEW YORK 10016. Withdrawing Authorization only affects uses and sharing of information after written request has been received, and subject may not withdraw his/her Authorization for uses or disclosures that have previously been made or must continue to complete analyses or report data from the research.

5. RISKS

The potential risks of phlebotomy are pain, bruising, fainting, or small infection at puncture site. The procedure to perform endothelial vein harvesting is identically to the placement of an IV and routine phlebotomy blood draw. These risks are pain, bruising, fainting or small infection at the puncture site.

Sterile gloves and sterile wires are used to harvest the endothelial cells. The wires are advanced < 5 inches. Our lab is partnering with a lab experienced with this technique and has published extensively on the technique for many years[14]. In their experience patients complain only on the routine discomfort of the IV insertion. There is a theoretical risk of vein thrombosis. In our collaborators experience, in over 10 years of sampling, not one thrombosis has occurred. To minimize this risk, we will encourage arm mobilization post procedure. We will be using our collaborators protocols and their consent language to ensure adequate patient knowledge on the risks of the procedure and we will train extensively prior to carrying out this low risk minimally invasive procedure to harvest endothelial veins. There lab has also agreed to help mentor and guide us to help with the appropriate and safe procurement of endothelial cells when performing this testing on our initial subject cohort.

Regarding non-invasive imaging of vascular function, there are no known risks associated with taking ultrasound pictures. The cuff on the forearm and the “pins and needles” sensation may be uncomfortable for participants. At their request, the cuff will be deflated and any discomfort should disappear within a few seconds. There are no known risks to the arterial tonometry measurements.

Treatment risks:

Aspirin and atorvastatin are standard medications used for the primary prevention of CVD. Nevertheless, there are risks associated with being on aspirin for 2 weeks. Use of aspirin has known side effects, including stomach irritation, ulcers, heartburn, easy bruising, and minor or major bleeding. Thus, we are using the lowest clinically effective dose (81mg) and for a very short period of time.

There is also a risk of being on 40mg of atorvastatin. There are known side effects to short term therapy which includes hepatotoxicity, myositis, muscle soreness, stomach irritation and interaction with other medications (such as antifungals) and foods (such as grapefruit). We are using a statin (40mg of atorvastatin) which has been widely studied with a low rate of interactions, hepatotoxicity and incidence of myositis.

Genetic risks:

Genetic testing can generate information about a subjects' personal health risks and can cause or increase anxiety, damage family relationships, and/or compromise insurability, employability and can even lead to discrimination. In general, results from studies that use data collected as part of this research will be preliminary, and the clinical implications of any findings may not be understood for years. Therefore, individual study results will not be shared with participants or their physicians.

Potential loss of confidentiality: Confidentiality will be preserved to the fullest extent by the research team but absolute confidentiality can't be guaranteed. All data will be stored with a unique code that does not identify the participant. Furthermore, data will be saved using a double electronic lock. All physical data will also be kept under double physical lock. Access to the data will be given to the study personnel only thereby greatly reducing the possibility of psychological or social risks that could arise from knowledge of this genetic information, such as risk for employability or insurability or the risk of discrimination.

6. BENEFITS

The proposed study will examine the relationships between psoriatic disease, endothelial and vascular function and markers of thrombotic and CVD risk. Further, we will examine how treatment with aspirin and/or statin will improve markers of inflammation and vascular function in those with psoriatic disease. The long-term goal is to develop a better understanding of the role endothelial function and thrombotic risk in those with psoriatic disease. Furthermore we hope to understand the use of accepted primary prevention CVD medications in those that show an elevated risk of CVD through chronic inflammation. This will lead to improved personalized medicine. There may be no direct benefit to enrolled subjects.

7. COST

There is no cost to the study participants. There is also no direct benefit expected from the participation in this study. This study may provide valuable information to medical/cardiovascular physician scientist's with minimal risk to study subjects. It is hoped that knowledge gained will be of benefit to others in the future.

8. Reimbursement:

Both control subjects and psoriasis subjects may be reimbursed up to 100 dollars.

9. STATISTICAL ANALYSIS

This is a pilot study designed to investigate a novel technique of endothelial vein sampling, vascular function, and assessment of thrombotic risk in a population that is under studied.

In the first publication of this endothelial vein harvesting technique comparing subjects with and without severe decompensated heart failure, an n = 5 per group showed differences in markers of endothelial dysfunction.[15] There is data on imaging techniques to assess endothelial dysfunction in psoriatic disease. For non-invasive vascular imaging techniques, previous studies have shown upwards of a 35% difference in measurements of endothelial dysfunction between those with psoriasis and healthy controls.[16]

Specific Power Analysis:

Based on the above study evaluating endothelial dysfunction in psoriatic patients, we have a power > 80% with an alpha level of 0.05 to detect a 35% difference using non-invasive vascular imaging in those with psoriatic disease compared to healthy controls with a goal n = 40 for the psoriatic group and n = 10 for the control group (G*Power 3.1.9.2). We do not have comparable data on the use of endothelial harvesting techniques to compare psoriatic disease to healthy controls. In previous studies using endothelial harvesting to study heart failure, staining for NF-kB (non-specific marker of inflammation and endothelial dysfunction) yielded a 16% difference between groups, a narrow standard deviation with an effect size d of 1.2. Extrapolating this measurement with an n = 40 for psoriatic disease and n = 10 for controls gives us > 90% power to detect baseline endothelial function differences between groups with an alpha level of 0.05 (G*Power 3.1.9.2). For the longitudinal component assessing endothelial function with endothelial vein harvesting and staining for NF-kB, n = 10 per group and pre and post aspirin/atorvastatin and assuming an effect size d of 0.8[17], we would have a 74% power with an alpha level of 0.05 to detect a difference between groups (G*Power 3.1.9.2). We believe given the pilot nature of this study, the sample sizes are adequate to detect both cross sectional and longitudinal trends which would then allow for further study proposals.

10. DATA ANALYSIS

All eligible subjects will be assigned a unique identification number upon enrollment in the study. Initial study data will be recorded on a printed form, which will be later converted to electronic database (Redcap). All potential identifiers will be kept separately in a safe location by the PI in a locked file cabinet in a locked room. After verification of entered data at completion of the study all potential identifiers will be stripped from the database.

a. **Aim 1**

To evaluate the association between moderate to severe psoriatic disease and measures of vascular function. Brachial artery reactivity will be modeled as a continuous variable in all analyses. Multiple linear regression will be used to estimate the difference in brachial artery reactivity between those with psoriasis and age and sex matched controls. Conventional adjustment for age and sex will be entered first into the model. Additional multivariable adjustment for other relevant covariates (e.g., body mass index, hypertension, renal function, LDL cholesterol) will then be performed.
A similar analysis plan will be undertaken for central pulse pressure (CPP) and pulse wave velocity (PWV) which will be modeled as continuous variables in all analyses. Multiple linear regression will be used to estimate the difference in CPP and PWV between those with psoriasis and age and sex matched controls. Conventional adjustment for age and sex will be entered first into the model. Additional multivariable adjustment for other relevant covariates (e.g., body mass index, hypertension, renal function, and LDL cholesterol) will then be performed.

For endothelial vein analysis quantitative Immunofluorescence will be performed. The human endothelial cells will be identified by staining with polyclonal rabbit antihuman VE Cadherin antibodies (Abcam), followed by secondary biotin-conjugated donkey antirabbit antibodies (Jackson ImmunoResearch Laboratories) preconjugated with Streptavidin oregon green (Molecular Probes). Nuclear NFkB (fluorescence intensity) and expression of MCP-1, ICAM-1, VCAM-1, iNOS, COX-2, eNOS, P-eNOS will be assed. Negative control slides will be generated by using preimmune mouse IgG (Sigma Chemical) as primary antibodies. Immunofluorescence analysis will be performed in a blinded fashion by numerically coding each slide. Staining will be visualized with ultraviolet light under a fluorescent microscope (Nikon ECLIPSE E600, Melville, NY) using a COHU charge coupled device camera (Danville, CA). Image processing will be performed by using ImageJ and expressed as fluorescence area in μm^2. Slides will be systematically read left to right and top to bottom. Only cells with both cellular and nuclear integrity will be analyzed. Cellular and nuclear integrity will be assessed morphologically. Intact cells will be defined as those with continuous, unbroken cell membrane delineated by VE Cadherine staining, as analyzed by phase contrast microscopy. Intact nuclei will be defined as well-circumscribed oval bodies as delineated by DAPI staining.

Additionally, real-time quantitative RT-PCR will be performed. One microgram of total RNA will be reverse-transcribed to cDNA with Superscript II reverse transcriptase and poly dT priming according to the manufacturer's instruction (Life Technologies). Real-time quantitative PCRs will be performed with a LightCycler thermal cycler (Idaho Technology, Salt Lake City, UT) as previously described.[40] We will assess mRNA expression of MCP-1, ICAM-1, VCAM-1, iNOS, COX-2, eNOS (fold change over healthy controls). Untargeted RNA-sequencing will also be performed for untargeted analysis to identify novel markers of psoriatic disease and activity.

b. **Aim 2**

We will evaluate the association between moderate to severe psoriatic disease and measures of thrombotic risk. As in Aim1, linear and nonlinear regression models will be employed to investigate the difference in platelet activity between those with and without psoriasis. This is gauged by monocyte platelet activity (MPA) and assessing monocyte – platelet interaction after adjusting for other covariates and applying model selection procedures. We will collect data including maximal aggregation (%), slope of the aggregation curve, and elapsed time between addition of agonist and onset of aggregation (lag phase). Regression models will unveil how these characteristics are influenced by those exposed to psoriatic disease, adjusting for other covariates.

c. **Aim 3**

We will then investigate how traditional medications used in CVD prevention such as aspirin and statins affect vascular function and thrombotic risk in those with moderate to severe psoriatic disease. We will assess baseline endothelial vein transcriptome data, genetic expression for routine markers of endothelial activation such as VCAM-1, ICAM-1, NF-kB and platelet reactivity data. Using paired t- tests, we will assess the changes to platelet reactivity and endothelial function with the use of aspirin, aspirin plus atorvastatin or atorvastatin therapy.

11. Safety and Adverse Events

11.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- <u>Suggests that the research places subjects or others at greater risk of harm</u> (including physical, psychological, economic, or social harm).

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious will be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events will be reported is the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 5 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator will notify the IRB of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

Abnormal Laboratory Values

A clinical laboratory abnormality will be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery will ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

11.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

11.3 *Reporting of Serious Adverse Events and Unanticipated Problems*

Investigators and the protocol sponsor will conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others
  (see definitions, section 8.1).

For Narrative Reports of Safety Events
If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

11.3.1 Investigator reporting: notifying the study sponsor
The following describes events that must be reported to the study sponsor in an expedited fashion.

Initial Report: within 24 hours:
The following events must be reported to the study sponsor by telephone within 24 hours of awareness of the event:

- Unanticipated problems related to study participation,
- Serious adverse events, regardless of whether they are unexpected.

Follow-up report: within 48 hours:
As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator will provide further information, as applicable, on the unanticipated device event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse device effects shall be provided promptly to the study sponsor.

Other Reportable events:

- **Deviations from the study protocol**
  Deviations from the protocol must receive the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.

- ***Withdrawal of IRB approval***
  An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but ***no later than 5 working days*** of the IRB notification of withdrawal of approval.

11.3.2 Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:
The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*

  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

11.4 Stopping Rules

In this study, if we encounter any serious adverse advents or > 5 adverse events in general we will interrupt the study and monitor for etiology and reasons behind the study. These events will be reported to the IRB as noted above.

11.5 Data and Safety Monitoring Plan

It is the responsibility of the Principal Investigator to oversee the data and safety monitoring plan. The PI as well as co-investigator Michael Garshick will be conducting the data safety monitoring review. We will review all endothelial sampling procedures for any adverse events after each one is performed. Important reviewable events include excess pain, significant bruising, or vagal responses in addition to those listed above in the adverse events section.
All serious adverse events will immediately be reported to the IRB along with a decision and plan on how to prevent these events in the future as detailed above in the reporting of adverse events section. A routine summary report will be sent to the IRB every three months to ensure adequate safety.

Safety will be monitored throughout the longitudinal phase of the study. For the control subjects, 1 week after endothelial vein sampling, a follow up phone call will be performed. For the longitudinal phase of the study with psoriatic subjects, subjects will get a phone call 1 week after the initial endothelial vein sampling, a follow up visit will occur at week 2 in the longitudinal cohort, not just for endothelial vein sampling but also to ensure safety and tolerability when on the aspirin and/or statin. Finally, a phone call will be performed at study week 3, 1 week after the second endothelial vein

sampling procedure was performed. On the consent form, all participants will have access to several phone numbers with the ability to leave a message to talk to study members including the PI, Dr. Jeff Berger's office, and co-investigator Michael Garshick's telephone number. Subjects will be counseled on the potential complications of aspirin and/or statin therapy as detailed above in the consent form and that for medical questions or problems they deem as emergencies including severe bleeding they should phone their own physician or report to the nearest emergency room .

12. Data Handling and Record Keeping

12.1 Confidentiality

This study is for research purposes only. Individual result will not be given back to study participant. This will include information from final results of the study, interim results of the study and incidental findings. Confidentiality will be preserved to the fullest extent by the research team. All data will be stored with a unique code that does not identify the subject. Initial study data will be recorded on a printed form, which will be later converted to an IRB approved electronic database, REDCap. Only study personnel will have access to this database. Furthermore, data will be saved using a double electronic lock. All physical data will also be kept under double physical lock.

12.2 Confidentiality and HIPAA

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). We are providing a consent form informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
    - Name, date of birth, MRN
- Who will have access to that information and why
    - Only IRB approved study investigators. Statisticians will have access to de-identified datasets.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Source Documents

Source documents will be stored for a minimum of 2 years after study completion. Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic

media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Case Report Forms

The study case report form (CRF) will be the primary data collection instrument for the study. All data requested on the CRF will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, "N/D" will be recorded. If the item is not applicable to the individual case, "N/A" will be noted. All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and enter the correct data above it. All such changes will be initialed and dated. ERRORS WILL NOT BE ERASED OR WHITED OUT. For clarification of illegible or uncertain entries, clarification above the item will be printed then initial and dated.

Signature and Delegation Responsibility Log

A signature and delegation of responsibility log will be kept. This log will list all of the study personal as well as their individual responsibilities, study – related tasks, and a description of these activities. This log will also hold a record of the signatures and initials of various research staff. This log will be kept in the regulatory binder.

Records Retention

We will retain case report forms and source documents for 2 years after study completion. After that, primary study documents will be discarded and stored in electronic form.

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