University of Pittsburgh & UPMC Scleroderma Center

COLLAGEN CONNECTION

Winter 2016

PEDIATRIC FREEZER FUNDRAISER UPDATE

Dr. Kathryn (Cassie) Torok, our pediatric scleroderma expert, is pictured below with the new pediatric scleroderma freezer purchased with your generous support of the recent "Freeze Out Scleroderma" fundraiser.

The new freezer will house 50,000 blood samples within the National Registry for Childhood Onset Scleroderma (NRCOS), and allow us to learn more about the disease as we work to improve treatment and outcomes.

Kaila Schollaert-Fitch

Kaila is originally from Youngstown, Ohio and holds a Bachelor's degree in Biological Sciences from the University of Cincinnati, where she participated in basic cancer research during and after her undergraduate studies. Kaila also earned a Master's degree in Microbiology from Indiana University (Bloomington) where she conducted thesis research on bacterial toxins, and supplemental research on bacterial fossilization in marine environments. Following her graduate training, she worked in the Allergy and Immunology Division at Cincinnati Children's Hospital studying eosinophilic disorders. She transitioned to clinical research at Cincinnati Children's in 2015, and served as a coordinator for the Biorepository for Childhood Neuromuscular Disorders as well as multiple Duchenne Muscular Dystrophy clinical trials.

Kaila joined the University of Pittsburgh Scleroderma Center in May 2016, and works as a clinical research coordinator for Dr. Torok. She currently coordinates the National Registry for Childhood Onset Scleroderma as well as additional ongoing and upcoming pediatric scleroderma studies at Children's Hospital of Pittsburgh.

Kaila lives in the South Hills with her husband Bradley and their daughter Olivia. In her spare time she enjoys baking fancy pastries and spending time outdoors with her family.

We would like to extend a big **THANK YOU** to both our monetary and blood donors for helping us #stopscleroderma!

If you would like to support our Scleroderma Center's research, please contact Rose Jandrasits at 412-864-1958 or krj13@pitt.edu.

IN THIS ISSUE

ASK THE EXPERT WITH DR. ROBERT LAFYATIS

Mary D from Columbus, Ohio asks:

What are the side effects of taking proton pump inhibitors (PPIs)?

PPIs are a group (class) of medicines that work on the cells that line the stomach, reducing the production of acid. Generally patients taking PPIs do not notice any side affects with taking them. Rarely patients experience headache, nausea, diarrhea, abdominal pain or joint pain.

Very rarely patIents develop an allergic type reaction by their kidneys called acute interstitial nephritis. Fortunately this serious problem is very rare, but unfortunately in early stages not associated with any symptoms. So a patient can have it damaging their kidney without knowing it.

Should I have any testing before or while taking PPIs?

Patients should keep in mind that they are at a somewhat higher risk for a condition known as Barrett esophagus, which sometimes becomes cancerous. Periodic endoscopy is still recommended to evaluate for this condition and, if present, to monitor for any progression.

I don't like taking medications anyway, do I really need to take my PPI?

It's important to consider the tremendous benefits associated with taking PPIs. Not only are they extremely effect at relieving heartburn, but they also protect the esophagus and lungs from acid burns. These advantages in most patients will far outweigh concerns about long term effects, which can in most cases be easily treated.

Do PPIs interact with other drugs I might be taking?

Methotrexate-PPIs as a group tend to increase levels of methotrexate. Since the dose of this medication is often matched to patient responses, a conversation with your physician is usually all that might be needed to consider whether any dose adjustment is needed.

Warfarin/coumadin, increased International normalized ratio (INR) and bleeding- PPIs tend to increase INR in patients taking warfarin. Patients starting PPIs should be monitored and their warfarin dose adjusted.

Clopidogrel-some PPIs, notably omeprazole, block conversion of clopidogrel into its active drug. Despite early concerns that this was a problem with all PPIs, current recommendations are to avoid only omeprazole and esomeprazole. Even for these drugs, several studies have suggested no difference in cardiovascular complications related to taking these PPIs with clopidogrel.

Patients taking citalopram and escitalopram should have an EKG as these drugs taken with a PPI are associated with rare but serious heart rhythm problems.

Some other drugs are affected by some but not other PPIs: clarithromycin, tacrolimus, phenytoin, digoxin, and diazepam. PPIs may also affect the absorption of some antibiotic, anti-fungals, anti-viral (particularly certain drugs for HIV) and anti-cancer medications.

Are there any long term problems with taking PPIs?

Long-term use of PPIs in some patients does appear to be associated with some complications, though these are typically mild and do not require stopping the medicine.

Some patients develop a stomach problem called atrophic gastritis, which mainly leads to a problem with absorbing Vitamin B12. This vitamin deficiency is easily treated with high dose oral supplementation.

Some patients on long term PPIs show decreased absorption of certain minerals that seem to need the acid environment of the stomach for proper absorption.

Iron(Fe): Stomach acid assists in Fe absorption and particularly in patients who might be iron deficient from scleroderma-associated gastric antral ectasia (GAVE, or watermelon stomach). The difficulty in replacing Fe can be significant and lead to or aggravate anemia.

Calcium - Although there has been some concern about the effect of PPIs on calcium absorption and related effects on bone strength and osteoporosis, recent studies have not supported an increased risk for osteoporosis in patients taking PPIs long-term.

Magnesium - Some patients have

been identified with low magnesium levels thought related to PPIs. There are many symptoms of low magnesium, but most common are muscle cramping, tremors, and nausea. Low magnesium can also be associated with heart rhythm problems and seizure. Although blood levels of magnesium can be measured easily, these do not necessarily reflect total body stores. Assessing total body stores requires more complex testing methods.

Infections. Several investigators have suggested that PPIs might lead to higher risks of infections from pneumonia to C. difficile, an intestinal infection. Most recent studies have not strongly supported these concerns. There may be a very slight increased risk for pneumonia. However, in patients with SSc this is largely outweighed by the beneficial effects not only on the stomach and esophagus as well as preventing stomach acid from getting into the lungs, which may occur at night even without patient awareness.

In summary PPIs are a mainstay of treatment for most patients with SSc. In most cases their value far outweighs their risks. Yet certain precautions should be considered particularly with prolonged use.

A PATIENT GIVES BACK

When Marla Bowen first began feeling the effects of scleroderma on her body, she had no idea what was happening. After having physicians tell her she had arthritis, she knew it was more. She recalls, " I literally felt like I was dying and no one would listen. I had many symptoms including Raynaud's, pain, fatigue, curling of my fingers, hard skin and just all over not feeling well."

Marla and Jamie enjoying their time in the Caribbean

She made an appointment with an orthopedic surgeon in Rochester, NY and that was the first time she heard scleroderma. She remembers her exact words, "Sclero what?" She was told to see a rheumatologist. Her primary doctor performed blood work in April 2013, and the test results were negative. She remembers feeling confused.

Marla was finally diagnosed with diffuse cutaneous scleroderma in June 2013. Her local rheumatologist wanted her to travel to Pittsburgh to see Dr. Thomas Medsger. She researched scleroderma specialists and agreed that Dr. Medsger was who she needed to see. Her first appointment at the UPMC Scleroderma Center was September 2013. She was relieved to know there was a Center that specialized in her disease and understood all of her symptoms. "I remember thinking; I'm in good hands."

In an effort to support scleroderma research, Marla has participated in research studies at the Center. "I feel it is important to be involved with research. If I can help someone or myself I'm willing to do all I can." During a visit at the Center, she was approached by Dana Ivanco, the Clinical Research Coordinator, to help design a shirt for her to wear in the Columbus marathon. Marla asked the help of her good friend, Marianne Mogon. "She had the computer and I had the idea of what I wanted and how I wanted it." Dana wore the shirt for the marathon and also set up an online store to sell them. The profit from the sales goes directly to the Center's research account.

Marla remains active and enjoys traveling with her husband, Jamie. They try to plan a yearly trip to the Caribbean. They also enjoy riding their motorcycle.

Her advice to newly diagnosed patients: "Stay positive! Everybody is different and so much is being done through scleroderma research. Be careful reading things on the internet. Make sure you get your information from a reputable source. Rest when you need it. There will be days that you just can't do what you normally do and that's ok. I also recommend joining a support group."

Marla and Dana Ivanco after Dana's marathon

CLINICAL DRUG TRIALS

Our Scleroderma Center is committed to participating in clinical trials. We feel it is vital step in working together to find a treatment for Scleroderma. Without clinical trials, our field will not advance. If you would like additional information regarding ongoing clinical studies at our Center, please contact one of our scleroderma research coordinators, Dana Ivanco at des2@pitt.edu or Maureen Laffoon at laffoonm@pitt.edu.

CURRENTLY ENROLLING PATIENTS:

Pilot Study To Assess The Efficacy And Safety Of Riociguat Vs. Placebo In Scleroderma-Associated Digital Ulcers (RESCUE):

This study examines the safety and effectiveness of Riociguat in scleroderma patients with digital ulcers. Riociguat is approved by the FDA for the treatment of pulmonary arterial hypertension (PAH). In this study half the patients will receive drug and half the patients will receive placebo. Patient must have an active digital fingertip ulcer at the time the trial starts. The first part of the trial is 8 weeks, followed by the potential for all patients to receive riociguat for an additional 8 weeks.

The Effect of Atorvastatin on Microvsacular Endothelial Function and Raynauds in Early Diffuse Scleroderma (TAMER):

This is a NIH-supported single-center study (being done only in Pittsburgh). The purpose of this study is to examine the effect of atorvastatin (trade name Lipitor) on Raynaud symptoms and small blood vessel function in patients with early diffuse scleroderma. Scleroderma is characterized by blood vessel injury, immune system activation and fibrosis. The blood vessel injury is thought to be important early in the disease, and many think this may be the reason most scleroderma patients experience Raynaud as the first symptom. While atorvastatin reduces cholesterol, it is recognized to have many positive effects beyond cholesterol reduction. These include improvement of blood vessel function and reduction of fibrosis. Because of these effects, it is believed that atorvastatin will improve blood vessel function and Raynaud symptoms in patients with early disease. Early disease means <3 years of scleroderma symptoms for this study. The trial is 16 weeks and half the patients will receive atorvastatin and half placebo. Atorvastatin (or placebo) is given as an "add-on" therapy. This means all medications can be continued while in this trial. There are only 3 visits over 16 weeks.

A Study of Subcutaneous Abatacept to Treat Diffuse Sclerosis (ASSET):

This study examines the safety and effectiveness of abatacept in patients with early diffuse scleroderma (<3 years of symptoms). Abatacept (trade name Orencia) is a medication which has been FDA-approved since 2005 for the treatment of rheumatoid arthritis. It is administered as an injection (at home) once weekly. In this study half the patients will receive drug and half the patients will receive placebo over one year. At the end of that year all patients are allowed to enter the open-label treatment where they are guaranteed to receive drug and not placebo.

Rituximab (Rituxan) Study:

Rituxan is an immunosuppressive drug originally designed to treat lymphoma, but has been FDA-approved to treat rheumatoid arthritis. Rituximab eliminates B cells from the blood stream. These cells participate in immune responses and may be responsible for some types of immune injury to tissues in patients with rheumatoid arthritis, lupus, and other related diseases, such as scleroderma. This study is directed at Scleroderma patients who have confirmed pulmonary arterial hypertension (PAH or high blood pressure in the lungs) regardless of how much skin thickening they have. Rituximab is given by vein twice, two weeks apart. Half of the patients will receive rituximab and half placebo. A right heart catheterization both before the study (to determine eligibility) and after 6 months on treatment (or placebo) is required. Other PAH medications can be continued throughout the study. Patients will be followed for 1 year or until the B cells in their blood have returned.

A Phase 2, Double-blind, Randomized, Placebo-controlled Multicenter Study to Evaluate Safety, Tolerability, Efficacy, and Pharmacokinetics of JBT-101 in Diffuse Scleroderma:

JBT-101 is an experimental (investigational) drug that is chemically similar to a chemical in cannabis, or marijuana. However, this drug has been designed to avoid the "high" feeling of marijuana. This research study is being done to test the safety, tolerability, and efficacy of JBT-101 when it is given to subjects with diffuse cutaneous scleroderma of < 6 years of disease. JBT-101 is entirely manufactured from chemicals, not plant or animal products. This is a 16 weeks study. Patients will be able to remain on their current scleroderma medications. 2 out of 3 will receive therapy in this study, and 1 in 3 will receive placebo. There is an open label extension study for this trial.

A Dose-Ranging Study of the Efficacy and Safety of Bardoxolone Methyl in Patients with Pulmonary Hypertension. (LARIAT):

The LARIAT study is a phase 3 study to examine the safety, tolerability, and efficacy of bardoxolone methyl in patients with pulmonary hypertension and pulmonary fibrosis on stable medication therapy. Bardoxolone methyl is an oral once daily antioxidant inflammation modulator that has been previously studied in pulmonary hypertension. It targets the inflammatory components of pulmonary hypertension, and has the potential to reduce the production of enzymes that cause fibrosis. This study is 16 weeks, with two-thirds of patients receiving drug and one-third of patients receiving placebo. If patients complete the trial, they are eligible for an open label phase where everyone will receive bardoxolone.

Dimethyl Fumarate, Tecfidera, In Pulmonary Arterial Hypertension Associated with Systemic Sclerosis (DMF):

The DMF study is a double-blinded, placebo-controlled study of Dimethyl Fumarate (DMF) in 34 SSc-PAH patients. The study medication will be added to stable background PAH medication(s). Subjects will be dosed for 24 weeks, will undergo examination every 8 weeks, and will be evaluated 12 weeks after completion of treatment. Dosage will be twice daily oral doses of 120mg for the first 7 days followed by the maintenance dose of 240mg twice a day. Participation will be for a total of 40 weeks, including a 4-week screening period, 24 weeks of drug, and a safety follow-up 12 weeks after the last dose.

WALK WITH TORI 2016

The 6th annual walk was held on September 11th in Hagerstown, Maryland. The outpouring of support is amazing every year. Tori, along with family and friends, have organized the walk to bring awareness about the disease and to raise money to support research at the Center. All monies raised at the event are used for scleroderma research. Over the past six years, Tori and her family and friends have raised over $180,000!

Thank you to all who came out to support the walk.

All photos from the walk are courtesy of Triple-T Photography, Hagerstown, MD

PEDIATRIC SCLERODERMA PATIENT EDUCATION CONFERENCE

The first ever PEDIATRIC only patient education scleroderma conference was held this Halloween weekend at Hackensack, NJ. This unique event aimed at providing both educational and social support to children and families affected by juvenile scleroderma, both localized scleroderma and systemic sclerosis. The event was a collaborative effort between Seattle Children's Hospital (Dr. Anne Stevens), Children's Hospital of Pittsburgh (Dr. Kathryn Torok), Hackensack University Medical Center (Dr. Suzanne Li) and the Scleroderma Foundation Tri-State Chapter (Mary Beth Bobik-Kadylak) (NJ, NY, CT).

The event was kicked off with a fabulous Halloween Costume Party Friday evening which gave families time to relax and get to know others. The evening included dinner, a photobooth and DJ. The doctors even dressed up (see image below)

The next morning, the conference was held at Hackensack UMC and included a keynote speaker, break-out sessions with parents, teens and younger children based on group needs and wrapped up with door prizes, ice cream sundae bar and the exchange of information between parents to keep the momentum going long after the day closed.

Specific contributions from Dr. Kathryn Torok, our Center's pediatric scleroderma expert, included organizing and developing the meeting program, giving a presentation and discussion of "Dealing with Scleroderma", for teens affected by scleroderma and a scientific presentation on "What do we think causes scleroderma" to the parents. With the teen group, she reviewed the findings from the focus interview group sessions held with LS patients and their parents (described in Collagen Connection 2015), and the main impacts on QoL revealed from this study. Also, Dr. Torok reviewed the impacts of gender, length of follow-up in clinic, and extra-cutaneous (or non-skin) manifestations of LS, like stiff joints or smaller limbs, on children and teens with LS. Dr. Torok also presented the social and physical function impacts of systemic sclerosis on the CARRA cohort of children and teens with scleroderma. The purpose of these studies is to gather information that is concerning or limiting the patient, so these concerns are addressed and potentially used as outcome measures in studies. The Research presentation was a summary of potential causes of scleroderma and focused mostly on the immune system problems that researchers are just starting to understand. Dr. Torok and her research team are hoping to understand the imbalanced immune system in pediatric scleroderma by enrolling patients into the new study, "Immunophenotypes in pediatric scleroderma", a combined effort between Dr. Torok, Stevens, Li and the Scleroderma Foundation and CARRA organizations. The plans of this study were discussed and the parents were very enthusiastic.

A total of 125 registrants from California to Missouri to Massachusetts attended, and our goal is to make this an annual event which moves to different locations throughout the United States. One quote from a parent, "My child has had this diagnosis (scleroderma) for 5 years and this was the first opportunity I had to talk face to face with another parent sharing my same concerns".

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