RHEUMATOLOGY RESEARCH
# UPDATE

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DIVISION OF RHEUMATOLOGY AND CLINICAL IMMUNOLOGY

## Inside This Edition



# Rheumatoid Arthritis and Cardiovascular Disease

**Kimberly P. Liang, MD**, assistant professor of medicine in the Division of Rheumatology and Clinical Immunology, has researched numerous aspects of atherosclerotic damage and cardiovascular disease in the presence of rheumatoid arthritis (RA) and vasculitis.

Dr. Liang's primary interests are in the heterogeneity of rheumatic diseases and their pathological link to the development of atherosclerosis and vascular disease. Her current research focus is investigating the evaluation of risks, determinants, and management strategies of premature cardiovascular disease (CVD) in RA. Dr. Liang's studies involve the use of a novel, noninvasive vascular study approach that can provide measures of subclinical atherosclerosis and surrogate markers of future CVD events. Dr. Liang also has an interest in developing expertise in novel vascular techniques and applying these technologies to the diagnosis and follow-up of rheumatic disease patients with vascular diseases. Apart from these research interests, she also is actively engaged in multiple clinical trials and observational studies of patients with systemic lupus erythematosus (SLE), vasculitis, and RA.

Dr. Liang has current NIH funding through an R21 grant that is investigating whether sildenafil (Viagra) use in RA patients can improve endothelial dysfunction (as assessed by brachial artery flow-mediated dilation and peripheral arterial tone), as well as improve serum biomarkers of atherosclerosis and inflammation.

Dr. Liang's recently completed, NIH-funded K23 award investigated whether RA patients were more likely to develop vulnerable, atherosclerotic plaques than non-RA patients. In order to make this determination,

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### What is Microbubble-Contrast-Enhanced Carotid Ultrasound?

This type of ultrasound imaging uses a lipid-covered gas (perflutren) contrast medium that dissolves rapidly in the bloodstream. The contrast produces micrometer-sized bubbles that can be visualized during an ultrasound procedure using a specialized software program to analyze the images.

"The computer analysis takes a considerable amount of time, but what you end up seeing in a real-time moving image is the bubbles traveling through the vessels. The microbubbles, as they move through the vasa vasorum in the adventitia, show up as a scintillating brightness, which is how we know which region of the artery to pick for study. This approach helps us visualize the vasa vasorum of the carotid artery, which cannot be accomplished using traditional contrast mediums," says Dr. Liang.

# Family Planning and Contraception Use by Women With Rheumatic Diseases

**Mehret Birru Talabi, MD, PhD**, is a physician-scientist who studies aspects of family planning and pregnancy in women who have various rheumatic and autoimmune diseases. Dr. Birru Talabi has several long-term research projects ongoing that are focused on the creation of a family planning framework in rheumatology to better guide the care and management of what can be exceptionally complex cases for physicians to navigate.

Dr. Birru Talabi also has been involved with the creation of international guidelines for reproductive health management that were unveiled in the latter part of 2018 by the American College of Rheumatology.

Dr. Birru Talabi's background is in internal medicine and rheumatology, and she has a particular interest in issues related to women's health, having published numerous papers on the subject.

"During my residency training, I concentrated on family planning and women's health. When I started my fellowship in rheumatology, I had a good deal of experience in supporting women as they made reproductive decisions. Whether it was preparing for pregnancy, optimizing their preconception health, or helping them to avoid an unwanted pregnancy, I received intensive training in how to initiate and hold these types of conversations with patients," says Dr. Birru Talabi.

Upon entering her rheumatology fellowship, Dr. Birru Talabi felt that there was less conversation in the field of rheumatology regarding family planning, pregnancy, and potential complications for women dealing with rheumatic diseases. Many, if not all, rheumatic diseases are associated with an increased risk of complications during pregnancy if they are not well-controlled on pregnancy-compatible medications at the time of conception.

"While we may think of lupus and antiphospholipid antibody syndrome as diseases in which pregnancy complications are relatively common, past studies have shown that almost every rheumatic disease, when not controlled at baseline, is associated with suboptimal pregnancy outcomes. Furthermore, women whose diseases are well-controlled tend to do relatively well during pregnancy. When I first started training, some investigators were promoting an international conversation in our field about how to improve pregnancy outcomes among these patients. My area of interest has been to explore how we can better provide and optimize family planning care for these patients," says Dr. Birru Talabi.

## Family Planning in Cases of Rheumatic Disease Is Vitally Important

While women with rheumatic diseases are at a much higher risk for pregnancy complications and adverse maternal, fetal, and pregnancy outcomes, if their diseases are well-managed, and if patients are well-educated and plans are in place to navigate a pregnancy, most women with a rheumatic disease can do so safely. There are risks, of course, but comprehensive women-focused preconception care and peripartum management can make a vitally important difference in outcomes, and not just for those individuals desiring to start a family. While the current literature is limited, what is known is suggestive that women with autoimmune diseases who plan their pregnancies tend to have better outcomes. They have better outcomes from a pregnancy perspective and a fetal perspective.

## Contraception Use: Findings From a New Study

As a fellow, Dr. Birru Talabi conceived of a project to learn more about contraception use among women with rheumatic disease. Would rates of contraception use by these women be higher than the general population because of the known pregnancy risks for women with these conditions? Alternatively, would the findings point to a different outcome?

Past studies have indicated that nearly two-thirds of reproductive-age women who are sexually active in the United States use some form of contraception on a regular basis.

At any given time in the United States, approximately eight to 10 percent of women are actively trying to become pregnant. This statistic points to an immediate discrepancy between the number of women who are sexually active and who are using contraception, and the number of women who want to get pregnant. There's a gap between women who are not using contraception but who are sexually active and don't want to get pregnant. Dr. Birru Talabi was curious to see if this gap was smaller or more significant for women with rheumatic diseases.

"In other words, are women of reproductive age who have rheumatic diseases using contraception? With this study, I wanted to obtain a bird's eye view of what is happening with contraception use in the patient population I help to treat. Contraception use has clear benefits in this population of women. Obviously, it helps to prevent pregnancy among any women who do not wish to become pregnant. It also can help women who wish to become pregnant but who have an active disease state to delay pregnancy until their disease becomes quiescent. We know this probably helps pregnancy outcomes. Contraception also affords time as women transition off of fetotoxic medications in preparation for pregnancy. This is a much better scenario than having to tell a woman who is on a fetotoxic medication that she is pregnant. That is a very tough conversation that no one wants to have with a patient," says Dr. Birru Talabi.

### Study Design

Dr. Birru Talabi and her research team analyzed administrative data from the UPMC electronic medical record between 2013 and 2014 to ascertain how many reproductive-age women with rheumatic diseases treated within UPMC were using contraception over a two-year study timeframe. The study also examined patient medication use with the hypothesis being that women who were using potentially fetotoxic medications might be more likely to use contraception.

"We hypothesized that those who had more visits with primary care providers, gynecologists, or rheumatologists also would be more likely to use contraception than other women who appeared to be less engaged with the health system," says Dr. Birru Talabi.

Dr. Birru Talabi's analysis identified women who saw a rheumatologist at least twice, and who were between the ages of 18 and 50. Knowing the number of rheumatology visits was vital because the researchers wanted to include only women who were receiving some degree of longitudinal care for their rheumatic condition.

The analysis next looked at contraceptive methods used by the women and categorized them as either highly effective or less effective. Highly effective methods were those deemed comparable to sterilization in their efficacy, for example, an intrauterine device (IUD) or subdermal implant.

Medications were categorized by the former FDA risk category, which ascribes most medications a letter designation corresponding to the degree of fetal risk posed by the drug; this was the national medical risk classification system used at the time of the study (2013-2014). This was done to stratify the degree of risk by medication type for pregnancy complications.

## Findings and Outcomes

Close to 2,500 individuals met the inclusion criteria for the study. The average age was 39.4 years. Over the two-year period of the study, almost two-thirds of women used at least one type of fetotoxic medication.

"In our cohort, about one-third of women were using some form of prescription contraception. This tells us that in a high-risk population of women, nearly two-thirds do not have a prescribed form of contraception, putting them at risk for unintended pregnancy. Some of those women, of course, may be getting their contraception needs fulfilled elsewhere. This number uncovered by our analysis shows there is potentially a large group of high-risk individuals who may be at risk for unintended pregnancy," says Dr. Birru Talabi.

What this study ultimately tells Dr. Birru Talabi is that we may need to do a better job with contraception management in this patient population.

"An important finding from our study is that women who were prescribed medications considered unsafe during pregnancy were no more likely to be prescribed contraception. In other words, women who were using high-risk medications were no more likely than women who were using safer medications to obtain contraception. We would have hoped that women using high-risk medications also would be using contraception, but our analysis showed otherwise," says Dr. Birru Talabi. "While this is the largest study on this topic to date, the available research on this subject suggests that these data are also very representative for women with rheumatic diseases outside of our health care system and as a whole. This underscores the need for a national conversation about how we meet the contraceptive and family-planning needs of this vulnerable, high-risk group of women."

## References

Birru Talabi M, Clowse MEB, Bialock SJ, Moreland L, Siripong N, Borrero S. Contraception Use Among Reproductive-Age Women With Rheumatic Diseases. *Arthritis Care Res.* 2018 Aug 14. Epub ahead of print.



# UPMC Physician Resources

Visit **UPMCPhysicianResources.com/Rheumatology** for the latest in free CME courses, videos, news, and events available for physicians.

### Current CME Offerings Include:

**Understanding the Role of Inflammation in Rheumatic Diseases**

*Presented by Terence W. Starz, MD*

Dr. Starz gives a presentation on the mechanisms of inflammation on rheumatic diseases, such as initiation, stopping, and persistence.

**Rheumatoid Arthritis: From the Clinic Back to the Bench**

*Presented by Larry W. Moreland, MD*

Dr. Moreland speaks on rheumatoid arthritis, a systemic immune-mediated inflammatory disease, and recent major breakthroughs in targeted immunotherapies.

**A Year in Review: Rheumatology**

*Presented by Ghaith Noaiseh, MD*

Dr. Noaiseh presents on new trends and predictors of disease progression. His lecture includes a discussion of MRI and ultrasound for predicting synovitis, outcomes from several high-impact randomized trials, and recently approved biosimilars to manage rheumatoid arthritis.

**Sjögren's Syndrome: Key Concepts for Internists**

*Presented by Ghaith Noaiseh, MD*

Dr. Noaiseh discusses this complex syndrome, its complications, and the clinical spectrum on which it presents.

**Spondyloarthropathies**

*Presented by Thaddeus Osial, MD*

Dr. Osial presents on spondyloarthropathies and reviews the history, spectrum of diseases, distinguishing characteristics, pathogenesis, and treatment. This course teaches the varied manifestations as they relate to peripheral arthritis and inflammatory back disease, which extra-articular findings are associated with the spondyloarthropathies, and symptomatology.

**Polymyalgia Rheumatica and Giant Cell Arteritis: From Etymology to a Clinical Understanding**

*Presented by Terence W. Starz, MD*

Dr. Starz reviews the clinical manifestations, approach to diagnosis, pathophysiology, and management of polymyalgia rheumatica and giant cell arteritis.

# Rheumatoid Arthritis and Cardiovascular Disease *Continued from Page 1*

Dr. Liang used a novel microbubble-contrast-enhanced carotid ultrasound (CU) imaging technique. Dr. Liang is currently analyzing all of the data from the K23 studies for future publication and has presented some of the findings at the last several Annual Scientific Meetings of the American College of Rheumatology.

## Cardiovascular Disease and RA: Risks and Likely Mechanisms

Regarding relative risk, patients with RA are approximately twice as likely as non-RA patients to develop cardiovascular disease during their lifetime.

"There is a general understanding that systemic inflammation is important to the rise of CVD, and the systemic inflammation seen in RA is likely contributing to or magnifying any existing inflammation in the body. The presence of antinuclear antibodies (ANA) and rheumatoid factor also are associated with CVD. Presumably, immune dysfunction — the autoimmunity itself — likely is a contributing factor. For sure, there are many factors in individuals with RA that increase their CVD risk," says Dr. Liang.

## RA and CVD: Clinical Trials to Test Primary CVD Prevention Strategies Using Novel Agents

Because the increased risk of CVD in RA patients appears not to be wholly explained by traditional CVD risk factors such as diet, obesity, exercise, and genetics, the auto-immunity and systemic inflammatory response may be causative to some degree. Specifically, inflammation mediates premature endothelial dysfunction, which is one of the early stages of atherosclerosis and is strongly associated with a risk of future CVD events.

Managing or mitigating endothelial dysfunction, then, may decrease the CVD risk in RA. Dr. Liang's R21 grant is designed to test this exact scenario using the medication sildenafil, which functions as a PDE5 inhibitor as well as supporting endothelial function.

"This is a crossover trial that we suspect will shed light on whether sildenafil can prevent endothelial dysfunction in the presence of RA. We have designed a six-month trial in which participants are randomized into either a three-month, 50 mg per day cohort or a placebo group. This is followed by a two-week washout phase, at which point the cohorts will crossover and receive the opposite therapy for an additional three months," says Dr. Liang.

Dr. Liang's study has two specific aims. The first is to determine whether sildenafil has beneficial effects on endothelial function in patients with RA. The study also seeks to determine whether sildenafil use improves biomarker levels of atherosclerosis and inflammation during treatment. Further, if successful, this trial will provide the necessary evidence for expansion into larger trials exploring the use of sildenafil as a CVD preventive measure in other rheumatic diseases that also are characterized by high CVD risk, such as systemic lupus erythematosus.

## K23 Award: Identifying Vulnerable Plaque in Rheumatoid Arthritis

Dr. Liang received K23 funding in 2011 to study the use of microbubble-contrast-enhanced-carotid ultrasound (CU) in rheumatoid arthritis in relation to atherosclerotic plaque vulnerability. Dr. Liang concluded these studies in 2017 and is currently in the process of data analysis and manuscript preparations to publish the findings.

### Dr. Liang's K23 grant had three specific aims:

1. Determine whether patients with RA have an increased density of carotid artery adventitial vasa vasorum compared to control patients without RA, after controlling for traditional CV risk factors. Hypothesis: The density of carotid artery adventitial vasa vasorum as assessed by CU will be higher in RA patients than controls after adjusting for traditional CV risk factors.
2. Determine whether both traditional CV risk factors and inflammatory modulators of plaque vulnerability are associated with increased density of carotid artery adventitial vasa vasorum, as assessed by CU, in RA patients. Hypothesis: Traditional CV risk factors and inflammatory modulators of plaque vulnerability are associated with increased density of carotid artery adventitial vasa vasorum in RA patients.
3. Determine whether increased disease activity measures in RA are associated with increased density of carotid artery adventitial vasa vasorum, as assessed by CU. Hypothesis: Increased density of carotid artery adventitial vasa vasorum is associated with increased RA disease activity measures, even after controlling for traditional CV risk factors.

"Our study was designed to determine whether patients with RA have an increased density of carotid artery adventitial vasa vasorum compared to non-RA controls. We also sought to determine whether both traditional CV risk factors and inflammatory or RA-related modulators of plaque vulnerability were associated with increased density of carotid artery adventitial vasa vasorum as seen using microbubble-contrast-enhanced carotid ultrasound imaging. Finally, we wanted to know whether an increase in disease activity measures in RA was associated with an increased density of the carotid artery adventitial vasa vasorum," says Dr. Liang.

Preliminary results from the study found that the adventitial vasa vasorum density was higher in the RA group than the controls.

"These findings are in line with our hypothesis that rheumatoid arthritis patients develop these early findings of subclinical vulnerable plaque in their carotid arteries more so than non-RA patients. I am looking forward to publishing our findings in full in the coming months, and I recently presented aspects of this research during the 2018 American College of Rheumatology Annual Meeting."

## Large Vessel Vasculitis Pilot Study

Dr. Liang currently has a pilot study in progress (funded by the Vasculitis Foundation) that uses microbubble-contrast-enhanced carotid ultrasound as a way of differentiating between disease activity and damage in cases of active and inactive giant cell arteritis or Takayasu arteritis.

"This study will allow us to compare the densities of the adventitial vasa vasorum in cases of active or inactive vasculitis, using microbubble contrast-enhanced carotid ultrasound. Because it appears that in large vessel vasculitis the earliest signs of inflammation and disease activity present in the adventitial vasa vasorum (i.e., vasa vasoritis), you would expect to see an increased density indicative of active disease. By making comparisons between control groups, it may turn out that this type of noninvasive diagnostic test can be helpful in monitoring disease activity, thereby allowing clinicians a better opportunity to intervene and manage possible disease flares in these patients over time," says Dr. Liang.

## References

Does Sildenafil Improve Endothelial Dysfunction in Rheumatoid Arthritis? NIH Project Number: 5R21AR069174-02. ClinicalTrials.gov Identifier: NCT02908490. Principal Investigator: Kimberly Liang, MD. Status: Currently recruiting participants.

# Sjögren's Syndrome: An Autoimmunity Underdog

Sjögren's Syndrome is a frequently misunderstood and misdiagnosed illness. Relatively speaking, and compared to other autoimmune rheumatic diseases such as rheumatoid arthritis and lupus, Sjögren's Syndrome lacks in research funding and specialized centers adept at diagnosing, managing, and studying the condition, particularly in the United States.

"I typically refer to Sjögren's as the underdog of autoimmune rheumatic diseases," says **Ghaith Noaiseh, MD**, assistant professor of medicine and director of the UPMC Sjögren's Syndrome clinic.

Dr. Noaiseh specializes in the treatment and research of Sjögren's Syndrome, with a particular interest in caring for complex patients who have the disorder and exhibit severe, systemic (extraglandular) manifestations.

Dr. Noaiseh arrived at UPMC in 2012 after completing a fellowship in rheumatology at the University of Pennsylvania where he developed an interest in studying Sjögren's.

"There are very few centers in the United States that have dedicated clinics and research programs for Sjögren's Syndrome, even though the disorder is more common in occurrence than lupus, and much more common in occurrence than scleroderma," says Dr. Noaiseh.

Since arriving at UPMC, Dr. Noaiseh has established and expanded the Sjögren's Syndrome clinic, which resides within the UPMC Lupus Center of Excellence. In 2014, Dr. Noaiseh began the UPMC Sjögren's Registry, which is a biorepository that collects tissue and blood-based data samples from patients in order to facilitate research and promote collaborative investigations with researchers at other institutions with similar interest.

## Sjögren's Syndrome: Beyond Dry Eyes and Mouth

Sjögren's Syndrome is a frequently misdiagnosed disorder. Somewhat similar to lupus, the hallmarks of the disorder are dry eyes and dry mouth, as well as other complications such as fatigue and chronic pain. In some patients, the disease can lead to serious and potentially life-threatening manifestations such as nerve, lung, and kidney inflammation.

"Additionally, about five percent of Sjogren's patients develop non-Hodgkin's Lymphoma, a risk profile that is higher than any other autoimmune disease," says Dr. Noaiseh.

"This is a very important point to make and a reason why these patients need to be regularly evaluated in the rheumatology clinic. There are certain predictors of lymphoma development with which the clinician has to be familiar. Patients who have several of these predictors have the highest risk."

One of the most severe complications in the disease is the development of interstitial lung disease (ILD). For this reason, one of Dr. Noaiseh's frequent collaborators in patient care is the Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease at UPMC.

"Symptoms, as well as laboratory testing of Sjögren's, frequently overlap with other autoimmune disorders. For example, most Sjogren's patients have a positive ANA and symptoms of joint pain and rashes, which is a similar presentation at lupus. This can sometimes account for its misdiagnosis and classification. Additionally, objective testing for dry eyes and mouth, an important step in establishing the diagnosis, is seldom done in the rheumatology clinic, which may delay the diagnosis. We need to have a more heightened awareness of the disease, both in primary care clinics and within rheumatology," says Dr. Noaiseh.

## Sjögren's: Moving Away From Primary and Secondary Designations

Sjögren's Syndrome used to be designated as being either a primary or secondary disorder, but as Dr. Noaiseh explains, the secondary designation is no longer a favorable scientific term to use. The field has migrated away from classifying it as such for several reasons.

"This older, secondary designation implies that, for example, in a case or presence of lupus and Sjogren's in the same patient, that Sjögren's is a secondary phenomenon — that lupus led to the Sjögren's. However, this is not really how autoimmunity works. What is really happening is much more of an overlap type of scenario. It is much more appropriate to view Sjögren's as a distinct disorder that overlaps at times with other rheumatic diseases. The idea here is to reinforce that Sjögren's Syndrome can and does co-occur with other autoimmune diseases," says Dr. Noaiseh.

## Developing New Clinical Guidelines for Sjögren's Syndrome

Dr. Noaiseh was recently invited to chair a panel of experts through the Sjögren's Syndrome Foundation (SSF) to develop new clinical practice guidelines for the diagnosis and management of vasculitis in Sjögren's Syndrome. The clinical guidelines project began several years ago and has since progressed through several phases of development.

## Research and Clinical Trials

Dr. Noaiseh is the site principal investigator for numerous phase 2 and 3 randomized clinical trials assessing the efficacy of different novel biological therapies in the management of Sjögren's Syndrome and SLE. "Since there are virtually no FDA-approved therapies for Sjögren's, we are essentially left with empirical treatment options, experience, and intuition to try to help the patient in front of us manage their disease. There is a significant amount of unmet need in the care of these patients. These kinds of trials are vitally important to our goals of expanding our treatment armamentarium and developing classes of effective, potent medication therapies," says Dr. Noaiseh.

## Further Reading

St Clair EW, Baer AN, Wei C, Noaiseh G, Parke A,Coca A, Utset TO, Genovese MC, Wallace DJ, McNamara J, Boyle K, Keyes-Elstein L, Browning JL, Franchimont N, Smith K, Guthridge JM, et al. The Clinical Efficacy and Safety of Baminercept, a Lymphotoxin-ß Receptor Fusion Protein, in Primary Sjögren's Syndrome: Results from a Randomized, Double-Blind, Placebo-Controlled Phase II Trial. *Arthritis Rheumatol.* 2018.

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## ABOUT THE DIVISION

The Division of Rheumatology and Clinical Immunology has a tradition of excellence in patient care, education, and research for more than 50 years. Our clinical activities emphasize care of both common and rare rheumatic diseases. We have outpatient clinics devoted to all types of autoimmune diseases and musculoskeletal disorders. Our faculty have a clinical and research interest in rheumatoid arthritis, systemic lupus erythematosus, myositis, vasculitis, and scleroderma.

We are committed to a mission of providing the highest quality care for patients with arthritis and autoimmune diseases, and mentoring and training medical students, residents, fellows, and young faculty. Our research mission is to better understand arthritis, autoimmune, and other connective tissue diseases in order to improve diagnosis and therapies, with the ultimate goal of finding a cure or preventing these disorders. Faculty members are involved in both clinical and laboratory research. Our research programs are centered in the clinical areas noted above and include the disciplines of clinical epidemiology, health services, and laboratory research. Our research includes collaborative efforts with other programs in the University of Pittsburgh School of Medicine and the Graduate School of Public Health.

Remarkable advances in drug discovery, mechanisms of disease, epidemiology, outcome research, and other related fields make a career in academic rheumatology an exciting opportunity. The University of Pittsburgh and UPMC have a long tradition of multidisciplinary collaboration. The faculty in the Division of Rheumatology, combined with cutting-edge clinical, educational, and patient care resources, provide for ongoing success of rheumatology at the University of Pittsburgh.

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**Larry W. Moreland, MD**
*Division Chief*

ADDRESS CORRESPONDENCE TO:
**Division of Rheumatology and Clinical Immunology**
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2500 Terrace St.
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412-383-8000

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