University of Pittsburgh & UPMC Scleroderma Center

COLLAGEN CONNECTION

Winter 2013

IMMUNIZATIONS IN PATIENTS WITH SYSTEMIC SCLEROSIS

by Thomas A. Medsger, Jr., MD

There is a recognized increased risk of infections in patients with systemic sclerosis (SSc) even when they are not receiving treatment. This statement applies to both bacterial and viral infections and to both usual (common) and unusual (rare) infections. The reason for this susceptibility is that SSc patients have an abnormal immune system which may not be able to respond in a coordinated and effective way when the patient is exposed to infectious agents. The risk is magnified when SSc patients are taking medications that suppresss the immune response, such as corticosteroids or immuno-suppressive agents (mycophenolate mofetil, cyclophosphamide, metho-trexate).

Several studies have concluded that less that 40% of persons with various types of arthritis (rheumatoid arthritis and psoriatic arthritis) receive the most common immunizations, such as the influenza (flu) vaccine or Pneumovax, which is directed against "pneumococcus", the most frequent bacterial cause of pneumonia. Similar results have been found for scleroderma. A French group published in 2010 that <40% of 177 SSc patients received flu vaccine during one calendar year.

The reasons for low immunization rates are several, including (1) patients' fear of side effects; (2) patients not having adequate information such as reminders from the physicians and (3) physicians' prejudices. Patients are concerned that they may get the disease for which they are being vaccinated (flu, pneumonia) from the vaccine, that their SSc may worsen, or that they might infect others (family members, friends). Physicians sometimes believe that vaccines are ineffective in SSc and other connective tissue disease (CTD) patients or that "live" viruses may be dangerous.

There are 2 important aspects to consider about vaccines. First, to distinguish between "recall" and "neo-" immunizations. Recall refers to a "booster" vaccine. The person has previously had the infection and developed immunity at that time. The goal of recall vaccination is to "boost" or increase existing antibody levels. A "neovaccination" is given to persons who have never had the infection in question and therefore have no immunity. The goal in this instance is to develop antibodies to prevent further infection.

Another important consideration is whether the vaccine contains "live" or "killed" organisms. Live organisms are

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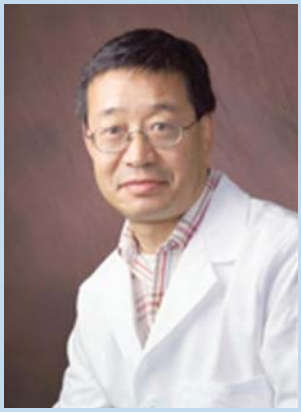

Dr. Zengbiao Qi is a graduate of the University of Oklahoma in Biochemistry in 2001. After graduation, he joined Immunobiology and Cancer programs in Oklahoma Medical Research Foundation to study the effect of E proteins on the development and signaling of thymocytes, the precursors of white blood cells. He joined the University of Pittsburgh Division of Pulmonary, Allergy and Critical Care Medicine as a Research Associate in 2004 and was promoted to Research Assistant Professor in 2007. During that period, his main focus was investigating the mechanism of immune dysregulation, the cause of autoimmune diseases. He joined the Scleroderma Center in June 2011 as a senior research specialist and is responsible for identifying scleroderma-related blood autoantibodies. Also, he provides support for physicians with their research relating to immunology, molecular biology and biochemistry.

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Table 1. Vaccines Available

Entirely Safe (Killed or synthetic)	Most often but not always safe (Live or attenuated)
1. DPT (diptheria, pertussis, tetanus) – childhood	1. Herpes zoster (shingles)
2. Flu and H1N1 flu by injection	2. Nasal flu
3. Hepatis A/B	3. Measles, mumps, rubella (MMR)
4. Human Papilloma Virus (to prevent cervical cancer)	4. Yellow fever
5. Anthrax	5. Oral polio
6. Pneumovax	
7. Mennigococcus (to prevent a type of meningitis)	
8. Hemophilus influenza - childhood	
9. Typhoid	

capable of reproducing and causing infection. "Attenuated" is a term used for a living organisms which are inactivated and thus not capable of producing or causing infection. In contrast "killed" organisms are components of organisms which are made synthetically (in a test tube) which can mimic the organism and cause the human body to make appropriate antibodies.

There is a long list of vaccines which are considered by experts to be "entirely safe" (Table 1). They include the common vaccines that primary care physicians urge all persons to receive, including flu, Pneumovax, and hepatitis A and B vaccines. There is a group of live/attenuated viruses used in vaccinations which could conceivably cause disease in the recipient if that individual is immunosuppressed. They include the shingles virus, nasal flu virus, measles/mumps/German measles and oral polio (Table 1). A theoretical problem with live virus vaccines is that viral particles can be "shed" to other persons in close contact with the vaccine recipient. One study suggested that this type of viral spread to another individual with resulting disease is very low (<1%) and occurs almost exclusively if the "other" person is himself/herself an autoimmune disease or CTD patient on immunosuppressive treatment or otherwise severely immunocompromised, for example having HIV/aids or a transplant recipient on anti-rejection drugs.

A vaccine recently available about which there has been considerable discussion is the shingles vaccine. Shingles is the result of reactivation of the chicken pox virus which can remain dormant for many years in nerve tissue. Activation leads to a rash consisting of fluid filled "blisters" and severe pain along the course of the nerve. Pain may persist long after the rash subsides. The dormant virus can become activated under certain conditions such as older age, CTD, immunosuppressive drugs or other "trigger".

The purpose of the vaccine is recall-to boost immunity. A concern has been the possible development of shingles in the recipient after vaccination. In a Medicare study, 633 patients were vaccinated and there were no cases of shingles identified during a 7 week follow up period. Another study suggested that the shingles vaccine is safe in patients receiving immune suppressive drugs in "standard" doses, including prednisone <20mg/day, methotrexate doses used for treatment of rheumatoid arthritis and Imuran. There are limited data for other drugs such as CellCept. Rheumatologists do not advise receiving the shingles vaccine if a patient is taking "biologic" agents such as Cytoxan, Rituxan, Enbrel, Remicade, Orencia, etc.

Some immunizations are recommended for persons traveling to areas of the world where certain infections are extremely common in the population. An example is the yellow fever vaccine (neo-, live virus). The advice of a foreign travel infectious disease specialist may be necessary regarding receiving this vaccine if a patient is immunosuppressed. One possibility to maximize the likelihood of a successful vaccination is to stop the immunosuppressive drug(s), wait 4 weeks, immunize, then wait an additional 4-6 weeks for proper antibody production to occur. This time period is an estimate - there are no available guidelines. You and your rheumatologist will have to discuss whether or not you will be able to be off your immunosuppressive medications for 8-10 weeks without a disease "flare up".

As noted above, there has been concern that CTD patients may not develop adequate immunity after vaccinations. This is probably correct, as most studies show lower that ideal post-vaccination antibody levels in CTD patients. For example good antibody levels may result in 75-90% of normal persons, 60-80% in CTD patients and 50-70%

in CTD patients on prednisone and/or immunosuppressive drugs. Even with lower antibody levels, immunity to infections may be improved because other parts of the immune system may be "strengthened" by immunization. Thus the standard recommendation is "If it is safe, immunize." There are 3 published studies which focus specifically on SSc patients receiving the flu vaccine or Pneumovax (Table 2). The bottom line is that they are both safe and reasonably effective vaccines.

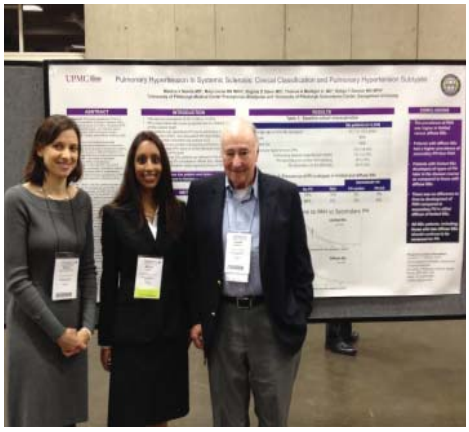
I draw the following conclusions from my reading and my personal experiences.
(1) Vaccines are important in preventing bacterial and viral diseases.
(2) Vaccines in CTD patients are under-prescribed by physicians.
(3) In general, vaccines are extremely safe.
(4) Immunizations are somewhat less effective in stimulating antibody production in CTD patients but also may be protective by stimulating other parts of the immune system.
(5) Regardless, vaccinations should be given to CTD patients, particularly those at increased risk for bacterial or viral infections.
(6) All patients on immuno-suppressive drugs with scleroderma should recieve the flu and pneumonia vaccine. The shingles vaccine should be discussed with their doctor.

AMERICAN COLLEGE OF RHEUMATOLOGY MEETING

The annual meeting of the American College of Rheumatology (ACR) was held in San Diego, CA in October 2013. Investigators from around the world presented results on recent basic and clinical research of systemic sclerosis and localized scleroderma, as well as other rheumatic diseases.

Dr. Robyn Domsic presented two Meet the Professor sessions discussing scleroderma clinical subsets and disease staging for rheumatologists in practice.

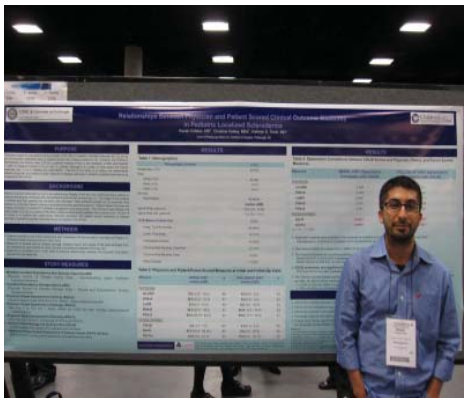
Dr. Monica Mohile, a third year internal medicine resident at UPMC, presented her poster demonstrating that pulmonary hypertension was a long-term complication in both limited and diffuse scleroderma patients.



Drs. Domsic, Mohile and Medsger

Dr. Kathryn Torok was co-author on an abstract regarding Relationships between Physician and Patient Scored Clinical Outcome Measures in Pediatric Localized Scleroderma. Kaveh Ardalan, MD who presented the poster is a pediatric rheumatology fellow at UPMC-Children's Hospital. Christina Kelsey, MSEd, Center staff member, was a co-author.

A collaboration between Keio University (Tokyo, Japan) and the Pittsburgh Scleroderma Center has resulted in the identification of a new scleroderma-associated blood antibody (anti-RuvBL1/2). Dr. Kaji from Keio described our findings at a podium presention. The antibody is uncommon (only 1% of scleroderma patients) and is found most frequently in older men with diffuse (widespread) skin thickening who also have muscle weekness and inflammation (myositis).



Dr. Ardalan at the poster on Pediatric Localized Scleroderma

Table 2. Vaccination Studies in Systemic Sclerosis

Author (Year)	Vaccine	Number of Patients	Summary of Results
Setti (2009)	flu	46	Antibody protection increased from 50% before to 90% after; no patients had worsening of SSc
Litinsky (2012)	flu	26	Antibody levels increased in most patients; lower response in SSc patients with lung disease; no change in measures of disease activity
Mescado (2009)	Pneumovax	16	80+% developed protective antibody levels; same results in SSc subtypes (diffuse, limited) and in patients taking or not taking immunosuppressive drugs

Walk With Tori 2013

On September 8, 2013, nearly 500 people came to the third annual "Walk with Tori" scleroderma walk in Doubs Woods Park, Hagerstown, Maryland. The weather was beautiful and so was the outpouring of support. Not only did people walk to show their support, but many also volunteered to donate blood for our research.

Tori Anderson was diagnosed with scleroderma on Valentine's Day 2008. Along with friends and family, she organizes the walk to bring awareness about the disease and to raise money to support research which hopefully will lead to finding the cause and cure. All monies raised at the event are used for scleroderma research.

Tori and Dr. Thomas Medsger talk before the walk. Photo by Joe Crocetta (reproduced with permission of the Hagerstown Herald-Mail).

To date, Tori and her team have raised over $100,000!

Dana Ivanco and Dr. Robyn Domsic collect blood for scleroderma research. Dr. Qi is in the background.

HONORING HIS MOTHER

Bryant Davis lost his mother to scleroderma 50 years ago. At that time he was the oldest of 4 children, Bryant 9, Debbie 8, Lurline 2 and Emily less than a year old.

On August 17th he held a Scavenger Hunt/Trivia Contest to raise money for our Center's research. The theme was "Remembering 50 Years Ago". With the help of family and friends he raised $1600.00 and presented the money to Tori at the walk.

Bryant Davis presents a check to Tori

Faculty and Staff from the Pittsburgh Scleroderma Center pose with Tori. From left...Zengbiao Qi, Honggui Jia, Dr. Medsger, Tori, Mary Lucas, Maureen Laffoon and Dana Ivanco

"It's not how much we give
but how much love we
put into giving."

Mother Teresa


Nancy McDonald in Egypt, 2011

ADVISORY GROUP MEMBER, NANCY McDONALD, A LIFE OF WORLDWIDE ADVENTURE

"No matter where I go, I'm interested in everything." Pittsburgh native Nancy Hill Eaton Arthurs McDonald is a woman of unmatched curiosity and gumption who leads a life of adventure traveling around the world by boat, plane, dingy – you name it. She has climbed the cliffs in the Galapagos, explored the Mediterranean in Jordan, and made a part-time home in Hawaii. But Nancy has also been living with scleroderma for nearly three decades – and she hasn't let it slow her down. With a spirited laugh, she says, "You know, I have all these problems, but I'm still going."

Nancy's scleroderma diagnosis came in the mid-1980s while she was living in Pittsburgh, before many doctors knew much about the disease. When her dermatologist, Dr. John McSorley, told her that he suspected that she had CREST Syndrome, a form of scleroderma, Nancy's first reaction was, "What? I don't even use Crest toothpaste!" He sent her to see UPMC rheumatologist Dr. Thomas Medsger, who confirmed that she had scleroderma and began a care regimen.

But when Nancy married and moved to San Francisco shortly following her diagnosis, she was forced to find a new care provider for a disease that was still widely unknown. After visiting the top specialists in San Francisco without any success, she decided to do her own research. What Nancy found was striking: the only published research on scleroderma at the Stanford Medical Library had been written by none other than Dr. Medsger. "Without Dr. Medsger and the research staff, I'm not sure where I'd be today!" Nancy exclaims, recalling her discovery years ago, "In short, all I can say is thank you, thank you, thank you."

Her secret? Trust her doctors, support research for a cure, and retain her indomitable, optimistic spirit to never, ever give up.

Nancy speaks earnestly about how important it is to support Dr. Medsger and the Pittsburgh Scleroderma Center's research, noting that there cannot be a cure or improved treatment for those living with scleroderma without purposeful and aggressive research goals; and these must be backed by continuous contributions. "I feel passionately for the human being who has a problem," she says, speaking of how scleroderma is often overlooked by funding groups as an orphan disease.

Dr. Medsger has managed Nancy's care since her original diagnosis, eventually giving her the happy outlook that she will be able to continue living her life on her terms, rather than succumbing to the scleroderma that has threatened her health.

Though she's holding out for a green light from her doctors, Nancy excitedly describes her next big adventure: "I think I want to fly Emirates Airlines to Dubai, spend a few days there, and then hop a ship that goes down toward India, Sri Lanka, Burma, and Thailand, and ends up in Singapore. Then I'll fly over to Hawaii and eventually San Francisco to visit friends…I think I might be worn out at the end of that trip."

Dr. Medsger and the team at the Scleroderma Center work hard to manage symptoms so that their patients can continue living productive lives. But Nancy's life has been filled with worldwide adventure that is far beyond the norm. Her secret? Trust her doctors, support research for a cure, and retain her indomitable, optimistic spirit to never, ever give up.

Thank You

We would like to thank the following donors for their support of scleroderma research

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