The Official Newsletter of the
NIH/NHLBI Severe Asthma Research Program

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A Breath of Fresh Air

SARP Continues!
We Appreciate Your Continued Involvement!

SARP
THE SEVERE ASTHMA RESEARCH PROGRAM
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From the Editor

Greetings to all our loyal SARP participants! It has been almost five years for many of you (and six for some) since you began your participation in this program, designed from the outset to help understand why patients with severe asthma are so different from patients with milder asthma and to lead to development of new and effective treatments. We know this has been a long-involved commitment on your part, and we are enormously grateful for your continued participation—thank you! Since we are at the five-year point, we thought it was important to update you on where we've been, where we are, and where we are hopefully going.

In the last year, built on your continued participation, many new papers have been written about possible mechanisms for severe asthma. Our SARP network has published several papers highlighted in this edition of the newsletter. These papers reveal evidence that a certain biologic process, not previously recognized, could play an important role in asthma symptoms and attacks in about 1 in 10 severe asthma patients. Similarly, another recognized a high level of "Type-2" inflammation was present in some of you, and that corticosteroids (like prednisone, that many of you are familiar with) did little to shut it down. Another study combined lots of different aspects of your asthma, including your lung function testing (spirometry), results from the sputum samples that most of you have given several times, your symptoms, allergy testing, and your response to the steroid shot you got in the beginning, as well as many other factors associated with asthma. All these asthma characteristics were fed into a computer, and with some help from computer-based scientists, 4 different groupings of asthma patients in SARP were identified. These four groups of patients each had different responses to that steroid shot. Using what is known as "machine learning," the same sort of processes that are being used to develop self-driving cars and other computer-based solutions, we were able to identify 11 asthma characteristics which could be used to "predict" how you and other asthma patients would respond to a steroid shot. We are hopeful that these computer-based processes could be developed and utilized in the clinic by doctors, such that they are better able to effectively use prednisone and other steroid treatments.

Inside This Issue

Editor

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At the age of five, SARP is still a young study. Some studies of different diseases (like heart disease) have been going on for over 70 years. The longer we are able to keep going with SARP, the more information we will have on the natural progression of asthma and severe asthma. I am often asked by patients what their asthma will look like five to ten years from when I first see them. Because there are no long-term studies of asthma, I am unable to give them much if any information. SARP should help to change that, such that doctors will be able to have at least some "crystal ball" allowing them see into the future much better than they can today. Every year we go forward, we are closer to achieving that goal. Our goal is to continue the SARP program for another five years.

But to do that end, we need money to help support your visits to the asthma centers where you are followed. We are in the process of applying for additional money from the National Institutes of Health (NIH), the original sponsors of SARP, to continue the program. In the interim, we have been very grateful for some additional financial support from several pharmaceutical companies, listed in this newsletter. Part of our goals for the future is to be able to compare all the information we have collected over the last five years to understand how and if you respond to some of the new medications for severe asthma—many of which those of you with severe asthma are now taking. While these drugs have had an extremely positive impact on some of you, many additional patients continue to struggle with asthma. To this end, many of you may be contacted by your site to participate in clinical trials of new asthma treatments in a program called "PrecISE." Some of these treatments arose out of the first five years of SARP.

Our goal is and always has been to improve the lives of all severe asthma patients. We are so grateful for the last five years of your help with SARP and we are hopeful we will be able to partner with you for many more years to understand and treat asthma better.

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CT Imaging Reveals Mucus Plugs in Asthma Airways

Although many patients with asthma complain of chest congestion and difficulty coughing up sticky mucus, it has been hard to quantify the relationship between mucus and asthma severity.

Thanks to the fact that the SARP protocol included CT chest scans, SARP investigators have been able to examine these scans for the presence of mucus plugs in the airways. The findings show that nearly half of patients in the SARP study have evidence of mucus plugs in their airway and may have plugs in multiple regions of their lungs.

These plugs corresponded with low lung function, but they did not correspond well with symptoms of cough and phlegm. The reason may have to do with the locations of the mucus plugs which tended to be in medium and smaller sized airways that don't have many cough receptors.

The importance of this work is that it suggests that mucus could be targeted to improve lung function and that CT scans could be used to predict which patients might benefit the most from mucus-thinning treatment.

Extracellular DNA in Sputum from Patients with Asthma

The most common form of asthma involves airway inflammation that is characterized by too many eosinophils, a type of white blood cell, in blood and in airway secretions. "Eosinophilic asthma" tends to be responsive to treatment with steroids and these cells have also been targeted specifically with drugs like mepolizumab ("Nucala"), reslizumab ("Cinqair") and benralizumab ("Fasenra").

Many patients with asthma don't have too many eosinophils in their airways, however, and it is less clear what pathology is operating in these patients. In studies of sputum from SARP participants, SARP investigators found an excess of DNA in about 15% of patients. This "extracellular DNA" was found to originate from neutrophils, a type of white blood cell often found in tissue with infection or inflammation. The "DNA-high" patients in SARP had other abnormalities in their sputum as well, including too many proteins. That suggests activation of the "inflammasome," a cellular process that produces cytokines, or signaling proteins, such as interleukin 1 (IL1).

The importance of this research is that it provides data to support targeting DNA, inflammasome activation, or IL1 as strategies to treat asthma. Although more information will be needed to support these approaches, the SARP study has value in pointing to treatment approaches that might rationally be pursued in patients who do not have eosinophilic asthma.

Racial Disparities in Asthma Related to Social and Environmental Factors

National asthma surveillance data highlights disturbing trends in asthma disparities, or imbalance. Self-reported black patients have a higher prevalence of current asthma and substantially greater asthma morbidity than other racial groups.

In a research article recently published in The Journal of Allergy and Clinical Immunology (JACI), Fitzpatrick and colleagues in the National Heart, Lung and Blood Institute's (NHLBI) Severe Asthma Research Program (SARP) looked at differences in healthcare use between self-reported black and white patients with asthma. The study included 579 participants, six years and older, each observed for one year. Data was analyzed according to a theoretical structure after using statistical risk scoring methods to balance the patient groups for other factors linked to healthcare usage.

Self-reported black patients with asthma were more than twice as likely to visit the emergency department for asthma over one year. However, when the statistics were adjusted based on socioeconomic factors and environmental exposures, the racial differences evened out. Furthermore, after statistical adjustment, self-reported black patients with asthma were 43 percent less likely to see a physician or healthcare provider in an outpatient setting for asthma care.

These results highlight the complex nature of asthma disparities and highlight the need for social and environmental policies and interventions to reduce asthma disparities in self-reported black populations. Further examination of healthcare access, mistrust with the medical system, differences in the lived asthma experience including symptom perception are also needed.

Data Analysis Finds Different Corticosteroid Response Phenotypes in Severe Asthma

Despite the importance of corticosteroids (CSs) for asthma management, CSs are also known for their numerous harmful side effects and range of success among patients with asthma. To better understand the CS responsive patterns, we utilized machine learning to characterize different CS responses among subjects with asthma. We separated 346 adult participants with asthma in the Severe Asthma Research Program with similar data (before and 2–3 weeks after triamcinolone administration), based on 100 clinical, physiological, inflammatory, and demographic variables.

Four clusters of individuals with asthma and different CS responses were identified. Clusters 1 and 2 consisted of young patients with allergic asthma and relatively normal lung function who were modestly responsive to CSs. Patients in cluster 3 developed asthma later in life and had low lung function, high baseline eosinophils, and the greatest CS responsiveness. Cluster 4 patients were primarily of young, obese women with severe airway obstruction, little eosinophilic inflammation, and poor response to CS. Twelve selective baseline features were then identified that accurately predicted the patient's cluster assignment (and response to CSs). In summary, machine learning can provide new insights into the factors which influence CS responsiveness and could ultimately lead to improved asthma management.

New Understanding of Severe Asthma Inflammation Caused by Neutrophils May Help Inform New Therapies

Most asthmatic patients present with a type of inflammation called "eosinophilic inflammation", yet there is a subset of patients with a "neutrophilic inflammation" who show a more severe disease that is resistant to treatment with corticosteroids. There is a limited understanding of the cause(s) of this neutrophilic airway inflammation and neutrophil mechanisms that may worsen asthma symptoms. Recently, SARP investigators discovered exciting new and unexpected insights into the causal link between neutrophils and severe asthma that could fuel development of new therapies.

To model allergic lung inflammation in a dusty indoor environment, mice were exposed to a common environmental indoor allergen – house dust mite – as well as to bacterial endotoxin. Exposure to both irritants triggered complex lung inflammation, including a phenomenon known as lung NETosis. Neutrophils form "neutrophil extracellular traps" (NETs) in response to inflammatory triggers. NETosis is the process by which NETs get activated and released. NETs can play roles in helping defend a host from invading bacteria, but they can also cause lung injury and inflammation. Vital NETosis is a process in which neutrophils force out their nuclear material, including DNA, to form NETs and then reseal their outer layers to create cytoplasts – cells that lack a nucleus.

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Every Participant Counts!

Medical research would not succeed without dedicated participants like you. Perhaps what we as researchers appreciate most is your continued participation, or as we refer to it—retention. Retention is the number of participants who remain in the study until it is completed. Occasionally, well-meaning participants do drop out early, which they have a right to do.

The fundamental goal of any research study, but especially a long study like SARP, is to learn as much as possible from our participants that enroll. This is an important motivation for researchers to understand every participant's journey through a study. Each individual teaches us something. Every visit, test, and survey plays a role in the final results of the study, and we value every contribution, with the goal to pay it forward to others living with severe asthma.

The SARP team found that these cytoplasts appeared to play a key role in triggering and amplifying an allergen-initiated neutrophilic immune response in lung inflammation.

In addition to studying mice, the team also examined samples of bronchoalveolar lavage fluid from the lungs of human severe asthma patients, finding that a subset of patients had high neutrophil counts and detectable NETs and cytoplasts. The abundance of the cytoplasts correlated with neutrophil counts and levels of neutrophil-activating cytokines – important implications for how to design more precise clinical trials for the treatment of patients with severe asthma and neutrophilic inflammation. Currently, clinical trials for new drugs to treat moderate and severe asthma do not classify patients by neutrophil count. These findings supported by our SARP patients indicate that markers of NETosis – including NETs and cytoplasts – may provide an opportunity to better tailor future research trials and clinical treatments specifically to asthma patients that have neutrophilic inflammation that doesn't respond effectively to corticosteroids.

For those interested in more information, this study's findings were published in Science Immunology earlier this year and were the subject of a Facebook Live event on August 9, 2018.

Publications: New Knowledge of Severe Asthma from SARP

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3: Fitzpatrick AM, Gillespie SE, Mauger DT, Phillips BR, Bleecker ER, Israel E, Meyers DA, Moore WC, Sorkness RL, Wenzel SE, Bacharier LB, Castro M, Denlinger LC, Erzurum SC, Fahy JV, Gaston BM, Jarjour NN, Larkin A, Levy BD, Ly NP, Ortega VE, Peters SP, Phipatanakul W, Ramratnam S, Teague WG. Racial disparities in asthma-related health care use in the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol. 2019 Jan 8. pii: S0091-6749(18)31732-9. doi: 10.1016/j.jaci.2018.11.022. [Epub ahead of print] PubMed PMID: 30635198.

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