Interviews

AMJ had the privilege of interviewing John H Stone, Roy Fleischmann, and Daniel Wallace, who shared their expertise and experiences in advancing rheumatology care. Stone discussed his pioneering work on IgG4-related disease and his efforts to address steroid toxicity, while Fleischmann reflected on the evolution of rheumatoid arthritis treatments and the impact of JAK inhibitors. Wallace discussed recent advancements in lupus research and the importance of patient advocacy through initiatives like the Wallace Rheumatic Diseases Foundation. Together, they emphasized innovation, education, and collaboration to shape the future of rheumatology.

John H Stone

Director of Clinical Rheumatology at Massachusetts General Hospital and Professor of Medicine at Harvard Medical School

Citation: AMJ Rheumatol. 2024;1[1]:43-46. https://doi.org/10.33590/rheumatolamj/YQDI6418.

Q1 What inspired you to pursue a career in medicine, and how did you eventually find your way into the field of rheumatology and vasculitis?

Growing up I played football, but it quickly became clear that I probably would not become a professional player, so I began to consider other paths. My father was a cardiologist, and I was drawn to medicine because I was attracted to the idea of synthesizing science to help patients. As a young person, while thinking about my career I always envisioned that I would be taking science and bringing that to patients, though I wasn't sure how at first. Later, when I started my first clinical trial, I realized I was doing exactly that; applying novel therapies to patients with diseases. This has been a theme for my entire career.

Initially, I thought I'd specialize in infectious diseases. During my medical training, AIDS was a major focus, and I even considered becoming an AIDS physician in Africa. However, during a rheumatology rotation in my second year of residency, I encountered a 22-year-old drummer with hearing loss, pulmonary nodules, and a positive test for a newly described antibody. My preceptor was running late, and so I got to looking in textbooks to try to figure out what my patient had. I came upon the chapter on granulomatosis with polyangiitis. That experience hooked me on rheumatology.

The diagnostic journey that both the patient and the physician face has always been very intriguing to me, the fact that rheumatic diseases are typically multi-organ diseases, and then the fact that we can treat them. Unlike some

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specialties, we could treat these conditions, though often with suboptimal results, but we've been able to exert positive effects very quickly with steroids. The real promise of going into rheumatology in the early 1990s when I did was that we would be able to develop better therapies that would use a lot less steroids or replace them altogether. Ultimately, over the last few decades we've been doing just that; through the development of better medications, we've been able to develop better therapies and have better patient outcomes. We still use too many steroids, and that is a major interest of mine, glucuronide toxicity.

Q2 You've been at the forefront of research on IgG4-related disease (IgG4-RD), a disease that was virtually unknown in the USA before your work. What was it like to define and develop understanding around a completely new disease?

It has been a dream to participate in the description of this disease. All of my interests have been driven from experiences with individual patients, like the 22-year-old drummer that made me a rheumatologist.

One of the very first patients I saw when I came to the Massachusetts General Hospital, Boston, USA, in 2007 was a 26-year-old woman from Casablanca, Morocco, who was referred to me to rule out Sjogren's syndrome. She had significant swelling under her chin and enlarged submandibular glands. I have never seen anything like that, and I was transfixed by her case. I really struggled while trying to figure out what her diagnosis was. It turned out to be IgG4-RD,

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which didn't even really have a name at the time. It had only been recognized as a unique disease in 2003, and almost no one in the USA knew about that condition. That really caused my career to veer off on to what has been an incredibly exciting 17 years studying IgG4-RD. I've seen hundreds of patients with the condition at the Massachusetts General Hospital Center for IgG4-RD. Like my work with antineutrophil cytoplasmic antibody-associated vasculitis and giant cell arteritis, I've been involved in the development of new therapies for IgG4-RD. It's been incredibly rewarding to not only contribute to the description of a new disease but also to help discover treatments for it.

Q3 How has the research landscape changed for IgG4-RD over the years?

IgG4-RD has been a series of eureka moments. In the early years of recognition of the disease, it was simply recognizing the extent of the disease, recognizing the different organs that it can involve, and the resolution of medical mysteries that had persisted for over a century. For instance, conditions like Riedel's thyroiditis, once thought to be an isolated inflammatory disorder of the thyroid gland, were able to be seen as part of the broader IgG4-RD spectrum. Similarly, autoimmune pancreatitis, Kuttner's tumor, and idiopathic orbital inflammation were also identified as manifestations of IgG4-RD.

Those first few years were about defining the disease's extent. Then, by observing the effects of B cell depletion therapy on the immune system, sometimes just through evaluating peripheral blood samples, we began to understand the disease's pathophysiology in significant ways. Although there are still gaps in our knowledge, we've made tremendous progress in a short time. Now, based on this understanding, we're conducting worldwide, multicenter, randomized, double-blind, placebo-controlled trials, and we are on the verge of having the first approved therapy for IgG4-RD.

Q4 Your research group has made some important discoveries related to IgG4-RD. Can you talk about one or two of these discoveries and their significance for the field?

In the early understanding of IgG4-RD, much of the focus was on recognizing its presence in different organs. Our group was the first to identify that the disease could involve the aorta and the thyroid gland. These were special moments, where we kept realizing that the disease could manifest in yet another area. However, the most significant contribution so far has been recognizing that B cell depletion is a highly effective treatment for this disease.

Traditionally, and still in many parts of the world, steroids have been the cornerstone therapy for this disease, but they are far from ideal

because the disease very often targets the pancreas, making the patients at risk for diabetes and other complications of steroid use. The ability to treat them far more safely and easily with B cell depletion has been really a big step forward therapeutically. By observing what happens to patients' immune systems after B cell depletion, we've been able to tease apart a lot of the different elements that make the disease tick. Ultimately, this understanding is going to lead to even better therapies.

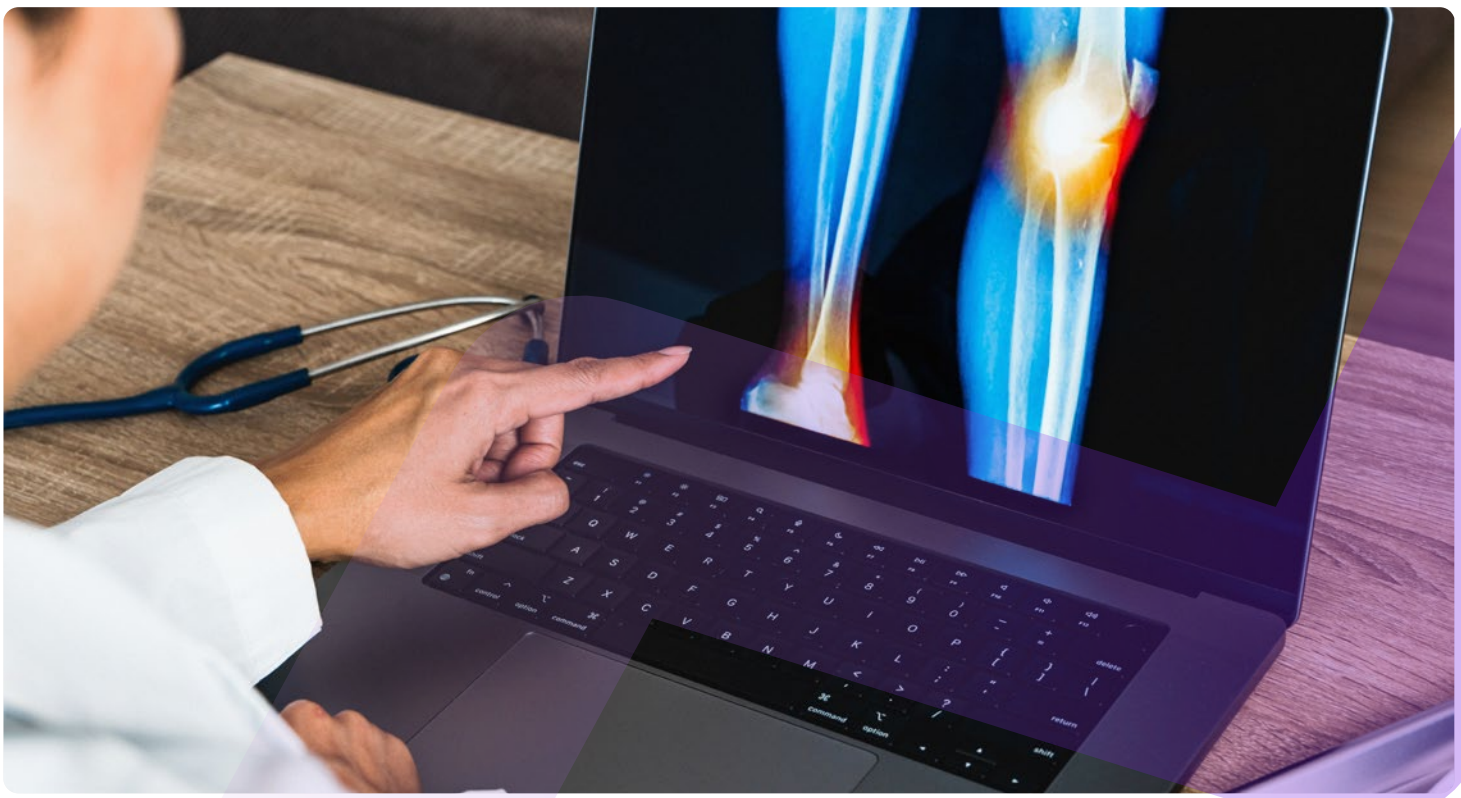
> **We'll have even more elegant ways of shutting this disease off and hopefully curing it in the next decade**

This progress has been incredibly rewarding, especially as we collaborate with investigators from all over the world. We've established wonderful collaborations with investigators in Japan, China, and Europe, and it's a revelation to understand that we're all seeing the same thing, all making the same observations, and finding great satisfaction in the impact we can make together.

Q5 With the continuous development of new therapies, what advancements do you anticipate in the treatment of autoimmune and inflammatory diseases? Are there any emerging therapies that particularly excite you?

I think in the next several years, treatment strategies for IgG4-RD will continue to center around the inhibition or the depletion of B cells. Approaches like mepolizumab, which is similar to rituximab, and new therapies that may not deplete B cells but inhibit them reversibly, such as obeximab that is now in Phase III trials, are showing promise. Cell-based therapies, including CAR-T cell approaches, are also on the horizon and could have a significant impact in the next few years.

We are currently researching the role of complement proteins in IgG4-RD, and complement-based therapies may also play a role in its treatment. Ultimately, I think we're going to understand the mechanisms of the disease far better than we do now, and we'll have even more elegant ways of shutting this disease off and hopefully curing it in the next decade or so, or at least have therapies that are far more imaginative than now.



Q6 What do you see as the most pressing challenges in rheumatology over the next decade? How do you think the field will need to evolve to address these?

We need to educate patients about IgG4-RD because the disease is so insidious and progresses slowly. Many patients have the disease for months or even years before being diagnosed, during which time the affected organs can sustain permanent damage. It's crucial to improve the education of medical practitioners, as awareness and understanding of this disease are still limited.

Moreover, there isn't much accessible information for patients because there has been very little that has been written about the disease that is accessible at the patient level. There is a lot of misinformation on the internet, so we really need to educate practitioners and patients better than we do now.

It's also going to be important to make sure that patients have access to the new therapies that are developed. Oftentimes, these are quite expensive. Without proper measures, people worldwide, including those in Africa, South America, and even North America may not have access to these therapies if we don't take the proper actions to ensure that they do.

Q7 What led you to find the IgG4ward! foundation, and can you share some of the main objectives the foundation aims to achieve?

Educating patients is crucial. For many years, I was focused on diagnosing, treating, and writing about this fascinating new condition. However, I began to notice that the patients kept coming to me with the same questions, and the new patients did not seem to be any farther along in their understanding of the disease than the patients I had managed 5 or 10 years earlier. It became clear that we weren't doing enough to educate patients.

So the first priority for the foundation is to be a trusted source of truth for patients and for people living with IgG4-RD. We aim to do this through our website, fireside chats, and our first patient-focused gathering, the IgG4ward! Jamboree, which will be held this November. This event will bring the IgG4-RD community together and help unify our efforts to educate and support patients.

Educating physicians is equally important. The IgG4ward! foundation has established a physician's network to connect knowledgeable doctors with patients seeking physicians specializing in IgG4-RD and to provide a forum for physicians to exchange ideas. We are also committed to facilitating research, learning continuously, and sharing the latest information with both patients and healthcare providers.

Q8 Looking ahead, what are your long-term goals for your research? Are there any specific areas you are particularly eager to explore in the coming years?

I have really focused my career now on two major areas. First is IgG4-RD, and increasingly those efforts center around the IgG4ward! foundation. I still love to practice medicine and to see patients with IgG4-RD, and I'm going to continue doing that. It's really the lifeblood of everything else that I do. The other major interest of mine within medicine is steroid toxicity, which is a major problem in the world. Again, it gets back to patient education and physician education, the development of new therapies, and inequalities with access to potential steroid therapies. I am the chairman of the Scientific Advisory Board for a company called STERITAS, which is focused on targeting steroid toxicity in a variety of ways: developing instruments to measure toxicity, helping to get new drugs improved reducing the use of steroids in clinical practice, studying steroid toxicity in health economics and outcome research, and developing tools to help patients optimize their own stereo. I think for the rest of my career my focus will be on IgG4-RD and steroid toxicity.