From clinical markers to community support: the future of lupus treatment

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease in which the immune system, for unknown reasons, becomes hyperactive and attacks normal tissue. SLE can affect any part of the body, but most often harms the joints, skin, lungs, blood vessels, kidneys cardiovascular and nervous systems. Dr Michael Madaio is a lead researcher in this area, seeking to improve the diagnosis and treatment of kidney disease in lupus patients. Dr Madaio was recently appointed the Section Chief of Nephrology and Kidney Transplantation in the Department of Medicine at Temple University School of Medicine, PA, USA. Previous to this he was a Professor at the University of Pennsylvania School of Medicine. Dr Madaio's main research area is the immunology of nephritis, in particular lupus nephritis and glomerular diseases. Here he discusses future directions in lupus diagnosis and treatment and the importance of providing support for lupus patients in the community.

You specialize in the study of the immunology of nephritis, in particular, lupus nephritis and glomerular disease. What led you to focus your research in this area?

Whilst doing a nephrology fellowship I became involved in this area through the influence of two mentors, William Couser and David Salant, at Boston University, MA, USA. I was fascinated by the immunological processes involved in the development of nephritis and how to treat patients suffering from these diseases. As I was interested in immunological research, a nephrologist from Tufts University, Jordan Cohen, introduced me to Dr Robert Schwartz, who was then chief of hematology and oncology. I was interested not only in localized immunity in the kidney but also in systemic autoimmunity, particularly lupus, which Dr Schwartz was studying. This gave me a good opportunity to blend the two areas. I consequently extended my fellowship and that led to a junior faculty position at Tufts where I was initially able to work in Dr Schwartz's group and then start up my own lab.

Although Dr Schwartz and I continued to collaborate on the systemic side of the disease, I was particularly interested in how lupus affected the kidney, and my research grew from this interest. I was also able to subspecialize in immunologic renal diseases in clinical practice and developed a special interest in patients with lupus.

What particular areas has your recent research been concentrating on?

Specifically, my recent research has focused on the pathogenesis of lupus; why patients get lupus and the mechanisms behind this. Although my research began by looking at the kidney, I have realized, through my research and that of others, that future treatment will need to be directed more proximally in the immune system, not just what is going on in the kidney, but at the events that precede the development of nephritis. Consequently, I have become more interested in those events as a way to understand the immunobiology of lupus, as the means to help design better, more effective, less toxic therapies for patients.

There is evidence that some communities are at a higher risk of renal-related conditions and autoimmune diseases, including lupus. Which communities have been observed to be at greater risk of lupus?

The fact that certain communities are at a higher risk of lupus has been well known for a long time. For example, it appears that African–Americans are both particularly sensitive to lupus and are prone to more aggressive forms of the disease. This has led researchers to think not only about the factors that lead to the development of lupus, but the factors that lead to disease progression, and we have indeed discovered that multiple genes are involved in this process.

We are trying to understand these pathways, how they contribute to lupus, and then use the information to design better therapies for individual patients. Researchers have learnt over the years that the immune system is fairly redundant, such that targeting pathways late in the immune and inflammatory response is less likely to be successful, since redundancy would allow the system to take over. Conventional therapies

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that affect the immune system as a whole are effective, however they have various toxicities leading to unwanted side-effects.

Therefore, the current goal is to devise therapies that are more specific, but that balance these two extremes; that is target a substantial part of the autoimmune response but have less toxicity.

Do you believe this will lead to personalized medicine for lupus patients?

Therapy will be personalized in a number of ways in the future; it will be personalized in terms of identifying those patients at greatest risk for flares of disease activity, and it will be personalized in identifying patients who are likely to progress to organ failure. All of these processes can be targeted. We are also learning that immunosuppressive and anti-inflammatory drugs are more or less effective in different clinical situations, and we have a lot to learn in this area. For example, a drug may be very effective in reducing inflammation but might not be effective in maintaining immune tolerance, so timing, dosing, and duration of therapy will be relatively important.

In your new position as Chief of Nephrology in the Department of Medicine at Temple University School of Medicine you have stated that an important part of your work is building up basic research as well as providing additional avenues for translational research. Do you believe that barriers between basic and clinical research exist and if so, what is the best way to remove these?

Translating animal models to human disease is difficult; animal models give us a start and a direction but people are more complicated. The animals that we tend to work on are inbred, and we can time when they develop disease and when to intervene, whereas the spontaneous disease in people is more unpredictable and complex.

In patients you don't have this opportunity, you are often dealing with someone after they have established disease and then working backwards. The goals are put out the fire and prevent it from starting up again, without causing too much damage in the process.

There is, however, information emerging in this area from studies that have observed family members of those who have lupus, as it is known that they are more prone to develop autoimmunity. Disease activity in those family members that develop lupus can therefore be monitored, and this information is important for learning what initiates disease.

Data are also emerging from long-term observations of female military recruits in which blood and urine samples have been taken over prolonged periods and then individuals who develop lupus identified. Researchers have consequently gone back and analyzed the catalogued samples and have made some interesting observations. They found that some of these people actually have markers of lupus years before they develop overt disease. This could prove important in diagnosis and in understanding the sequence of events that occurs from these early serological markers of disease activity to full-blown disease.

Another key area of focus is identification of biomarkers of disease activity. Once established, a systemic autoimmune disease, such as lupus, is characterized by disease flares, and disease activity waxes and wanes over months and years. In general, the earlier treatment occurs for flares, the better the prognosis, and that if you can treat disease flares with aggressive therapies, you can prevent the disease from progressing to scarring. This approach should also allow drug toxicity to be reduced as the duration of treatment is minimized. Therefore, looking for biomarkers has substantial merit. A potential advantage in monitoring nephritis is that urinary, as well as hematological, biomarkers can be used, and there is an emerging interest in identifying urinary proteins that may signify lupus activity. There is substantial research in this area and funding agencies, including the lupus foundation and the NIH, have requests for proposals looking for innovative methods of identifying biomarkers of disease activity.

Do you think that the field of biomarkers in lupus will become more important in upcoming years?

I do. Biomarkers for lupus will be developed, along with other biomarkers for inflammation in joints, the kidney and other organs, in general, that will also be applied to lupus. Some of these markers will be lupus specific and some will not, but patients with lupus will benefit. We will also begin to identify patients at risk for lupus, and therapy will become tailored, not only to disease stage but also to how likely you are to respond to different drugs, given your genotype or genetic make up.

It is 40 years since the US FDA approved a new drug for lupus. What do you believe are the reasons behind this?

This is very disappointing. Until recently, lupus has not been a priority for pharmaceutical companies. Nevertheless, although a drug has not been specifically approved for lupus, immunosuppressive agents approved for other purposes have been used to treat lupus. Pharmaceutical companies have not funded controlled trials for these drugs specifically for lupus. However, they are often tested in other settings, such as transplantation. A problem is that as some of these drugs are evaluated for lupus, they go off-patent, and generic forms of the drug are released. The pharmaceutical companies then become less interested in formally testing them in lupus.

An example of this phenomonon is mycophenolate mofetil, a drug that has received a lot of attention for lupus nephritis but that was originally approved for transplantation. After initial interest with promising results, clinical trial funding for this drug is waning as a generic form is now available. This may limit what we can learn about optimizing its use for lupus patients.

What scientific advances are occurring to improve the management of lupus?

The management of lupus is being approached systematically from a number of different directions. A lot of researchers, including myself, have become interested in making sure that lupus is correctly diagnosed and properly categorized, both in terms of what the level of disease activity is and how you can define when a disease worsens or improves.

In the area of nephritis it is a little easier than with some of the clinical other manifestations of lupus as there are more objective data; for example, if kidney function is normal and the patient then goes on to develop end-stage renal disease requiring dialysis or transplantation, that is a hard end point.

Nevertheless, flares of disease activity in between those two extremes are more difficult to define, although again nephritis is one of the easier manifestations of lupus to categorize as there are quantitative assessments of kidney function that can be measured. By contrast, in other areas, such as joint disease, disease activity is defined by functional activity, which is a little more subjective.

Therefore it is very important that these intermediate levels of activity are defined and used as parameters for study. Biomarkers of disease activity have great promise and appeal, since they should help to identify parameters that predict disease activity, severity and progression.

Biomarkers are not a substitute for long-term, more objective markers, but if they reflect those long-term objectives they would be very helpful in monitoring whether a particular drug or therapeutic approach may work.

You are currently Chairman of the Medical Advisory Board of the Delaware Valley Chapter of the Lupus Foundation of America. What are the main aims of this organization?

The main aims have changed, in my opinion for the better. The parent organization, The Lupus Organization of America, has become stronger, more organized and structured over the past 5 years, such that the funds that they generate are being distributed both for patient care and for research, in useful and strategic ways. This has allowed the local foundations to serve their local communities, to educate patients and make the public aware of lupus. It allows for the provision of services that patients wouldn't ordinarily have access to and provides an opportunity for patients to interact with each other and share their experiences, which is often therapeutic for them.

How important do you think it is to provide the public with a comprehensive educational resource regarding this condition?

It is very important as lupus is still relatively poorly understood in the community. As a patient you are often left in a situation where you're not really sure whether you're going to feel well today, tomorrow or next year; how long you're going to live; whether you're going to have major organs involved, such as, for example, kidney disease, and all of these issues can be very frightening.

Another major benefit of these organizations is that they can put people in touch with one another, and other medical personnel, including physicians, social workers and other group leaders who can help them. This is important both for obtaining practical information regarding daily life, for obtaining advice regarding what therapies are available, among many other benefits.

An important initiative in which I have been involved is being carried out by The Office of Women's Health along with funding from

pharmaceutical companies. This involves a group of physicians traveling the country and giving presentations about lupus. The format consists of a series of four presentations, beginning with a general introduction to lupus followed by talks on nephrology, rheumatology and dermatology. In the morning sessions these presentations are aimed at physicians, whereas in the afternoon the talks are supposed to be slightly simplified and more practical for patients, although patients often know as much about their disease as physicians. I think that this forum has been very productive and has educated the public and medical communities. In my experience, both patients who are very well educated about their disease and ask very sophisticated questions, and those who are just learning about lupus attend these forums, and distributing information and reassuring patients at both these levels is equally important.

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Finally, where do you think your research efforts will be focused over the next few years?

Mainly in two areas; optimizing therapy for lupus patients, based on their probability of disease progression and drug responsiveness, and identification of factors that promote the generic disease progression in lupus.

From a nephritis point of view I am interested in developing less toxic and more effective therapies for nephritis that could be applied to lupus nephritis and other forms of nephritis.

I am also interested in working more with patients, as much of my previous work has been with experimental lupus models.

We, the medical community, must make the public aware of lupus and reassure them that it is a disease that can be treated effectively as long as it is recognized early. I am very optimistic that what we have learned in the laboratory will be applied to optimize therapies for lupus patients.