Controlling Lupus

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Today I speak about new treatments for lupus and what we and you, can do about it. For most of you who live with lupus, you know our options for treatment are very limited. For people with mild to moderate disease (in terms of the seriousness of their organ involvement) there are anti-inflammatory drugs, antimalarials and low to moderate doses of glucocorticoids or steroids. For really serious forms of lupus involving major organs (i.e. brain, heart, kidneys) we treat with industrial strength high doses of steroids with short and long term side effects. When this is necessary, we always try to minimize the patient's exposure to steroids by adding various immunosuppressive agents. These suppress the immune system which leads to many possible problems such as infection of malignancies but allow us to lower steroid dose. There are no easy choices for patients.

There has not been a new treatment for lupus in almost 50 years. There are many reasons for this. One is that lupus is, relatively speaking, a rare and unusual condition. From the pharmaceutical industry's view - the people who support drug development - there is no potential market. Lupus is very complex and involves multiple organ systems. There is no model for the industry to follow for successful drug development. And importantly, there is totally inadequate support for research and development of new agents and the capacity to evaluate them.

Every lupus patient has their own finger print … no two lupus patients are alike.

Lupus is diagnosed clinically, there are no magic tests. The standardized classification criteria for lupus set out in 1982 by the American College of Rheumatology (ACR) is an important reference point but imperfect. There are 11 criteria and "a person shall be said to have SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation." Half of the lupus patients that we follow don't meet the ACR criteria. This is one of the major problems when people try to find a group of like patients to study them in more detail or to evaluate a drug.

Lupus is relatively uncommon disease. The best data, and the only data I am aware of that is adjusted for age distribution and ethnicity in the population says that we (United States) have between 184-253 women per 100,000 population with lupus. The estimated incidence per 100,000 is 164-203 for Caucasians, 406-694 for African Americans, 139-245 for Hispanics and 93-103 for Asians. Between 4-35 new people per 100,000 are diagnosed with SLE each year.

Lupus is now a chronic illness. When I first started seeing patients more than 30 years ago, patients with lupus would be admitted to the hospital and sometimes die in the hospital. Now patients survive decades with all the attended problems that occur with people aging, with exposure to powerful medications and the damage to their systems from recurrent lupus.

To summarize, the major challenges to the understanding of its cause and cure include: that it is a rare condition, it involves multiple systems where every patient is different from every other, it is a chronic condition by and large, it is dangerous, recurrent, and unfortunately it is a woman's disease that disproportionately affects women of colour.

What is the hope in our lifetime for lupus?

The first is built on the deeper understanding of the molecular events that cause inflammation in lupus. It is very complicated. We believe that lupus is caused by autoantibodies called high-affinity pathogenic IgG anti-DNA antibodies from B cells. For reasons unknown other cells activate T-cells and these involve certain molecules such as CTLA4, CD40, T-cell antigen receptor, HLA (which may be an immunogenic marker). These are all critical pathways or targets for drug development in that if we can identify something to block them, we might be able to stop the series of events that lead to the production of the pathogenic antibodies.

We have now a number of compounds that may lead to new treatments. There is industry interest in developing these compounds and testing them to see if they can interfere with these basic mechanisms.

By 2010 when Vancouver hosts Lupus 2010, the International Lupus Conference, there may be 20 or so new drugs tested for lupus. How many will pass the test, and be something that you in the audience will benefit from is unknown, but we are at an incredible period of increased understanding and testing of these agents. However, we face enormous challenges to get this job done.

First, human research is very expensive. Compared to 30 years ago when I began my career, the effort, the time, and the cost needed to do human research feels like it has increased 5-20 fold. In the United States, the 1966 Health Insurance Portability and Accountability Act (HIPPAA) has increased the amount of bureaucracy and impediments to getting research done and have not made things better for patients. For clinical investigators, the amount of oversight and documentation has been astronomical and slowed down our ability to respond to new opportunities. Much of these have been in response to highly visible instances of scientific misconduct, conflict of interest and personal injury claims, isolated aberrations, which have undermined the public's trust and have created an unhappy circumstance for the majority of the conscientious and honest scientific community.

Second, industry-funded studies usually trump investigator-initiated studies for resources, patients and institutional support. Industry-funded studies are the critical studies funded by the pharmaceutical industry to test out new agents in patients but investigator-initiated studies are equally important and woefully under-funded. We must find ways to protect and enhance the study of important questions whose answers do not profit companies but patients.

Third, in the rush to test new drugs the informed consent process must not be compromised and quality of usual care must not be less.

Fourth, we must be certain that the lessons learned even in unsuccessful trials be incorporated in the design of future evaluations in SLE so that the field as a whole learns how to evaluate drugs in the most efficient manner and limiting exposure of toxic or ineffective agents. Some of the companies involved in lupus drugs are startup enterprises not fully capitalized and with no corporate memory of experiences from other trials or other trials in lupus. The fact that drugs are proprietary means that investigators may not be free to share the results of their individual experiences with others.

Finally, there is always the first time for a new target and not all new agents will work and some may cause more problems than they fix. Although agents are well tested for safety, one can never know what it will do in humans. In 2006 during a Phase 1 Trial for an anti-CD28 monocolonal antibody – not for lupus, but targeting molecules in the inflammation chain of events – patients receiving this had severe side effects that resulted in hospitalization and near-death. This may be the situation for some new drugs and we won't know until we get there.

What will it take for us to test the new agents that are coming down the road? From the beginning of lupus time, basically 1949 when Hargreaves described the LE cell phenomena, until 2006 there have been less than 1000 SLE participants in trials of experimental therapies. To evaluate the next generation of therapies in the pipeline we will need 2000 participants.

Keep in mind that testing new drugs are done with very strict protocols and patients volunteering for them must meet strict criteria. Generally speaking, it takes 10-20 eligible people with lupus screened to enroll 1 subject. A subject who is enrolled in one experimental drug trial is automatically excluded from another study. If you look around at who is available from the usual sources, i.e. at academic centres that study lupus, there are not enough lupus patients being followed by these groups to test all the new drugs we have.

Participants in drug trials are largely Caucasian. The enrollment of the most at-risk populations, African-Americans, lags and is getting worse. High profile cases of fraud, scientific misconduct, conflicts of interest have undermined the public trust and dampened the normal altruism for participating in drug trials. I ran an NIH funded trial that was stopped within a year because there were not enough SLE patients who wanted to participate in a study of a prevention therapy for cardiovascular disease. The patients said they were too sick, or too well, or their lupus was too complicated, or they had too much on their plate or were too worried about a flare. Together, these include every possible reason for not participating.

Next year, neither the Arthritis Foundation of America nor the Arthritis Society in Canada will be funding new research. In the vacuum people are stepping up and they are stepping up big. Some examples are:

- Woody Johnson, owner of NY Jets, who started the Alliance for Lupus Research with $23 million. He has a daughter with lupus and wants to find a target for new therapy. Nothing less.

- The SLE Foundation and the Lupus Research Institute are funding innovative studies and new investigators in SLE.

- Katherine and Arnold Snider have contributed millions to help lupus patients and to support lupus investigators. Their Kirkland Scholar Program provides senior investigators resources to support their mentees, the next generation of lupus investigators. When they heard that drugs were not being developed because of insufficient infrastructure for lupus research in medical centers they founded and supported the Lupus Clinical Trials Consortium. They also supported ASSIST (Center for Advanced Methodological Support for Innovative SLE Trials) to develop more efficient means to evaluate new therapies for as disease where multiple organs can be affected.

The field is also undergoing a change in thinking bigger and in forming collaborative networks. No one centre follows enough people with lupus to do all the studies that are necessary to improve outcomes and these groups are the future;

- SLICC (Systemic Lupus International Collaborating Clinics)
- CaNIOS (Canadian Network for Improved Outcomes in SLE)
- LCTC (Lupus Clinical Trials Consortium)

I've given you some cause for concern and the realities of our mission but I hope a lot more cause for optimism. "Just when the caterpillar thought the world was over, it became a butterfly."

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