Research Update

Welcome to our latest issue of the Lupus Outcomes Study (LOS) newsletter. Since 2002, we have completed more than 6,800 interviews among 1,204 participants. In that time, the 15 LOS researchers have published 25 papers in medical journals and presented at more than a dozen rheumatology conferences.

This issue highlights a few of the topics that LOS researchers have been working on recently, including: quality of care, depression, disability and childhood lupus. We also include a summary of two recent papers on the genetics of lupus. Most of the articles here are based on papers published in medical journals. If you are interested in seeing the full articles for any of these topics, please contact our office, or go to the UCSF Lupus website to download a copy:

Quality of Care in Lupus

In 1998, the Institute of Medicine published a landmark study, *To Err is Human*, which caused quite a stir. The book pointed out that the quality of medical care was often not as good as we had assumed and that lapses in quality can result in injuries or death. *To Err is Human* resulted in a major push by health care providers and both government and private health insurance companies to improve the quality of care. The initial efforts focused on very common medical conditions such as diabetes and hypertension. However, in the last few years, these efforts have been extended to other medical conditions. Lupus researchers saw an opportunity to improve outcomes among patients by identifying gaps in quality for the condition.

One of the rheumatologists associated with the LOS, Dr. Jinoos Yazdany, has
Quality of Care in Lupus continued

(Continued from page 1)

devoted a lot of effort to developing quality indicators for lupus. Quality indicators are the minimum standards of good care for a specific health condition. To develop quality indicators for lupus, Dr. Yazdany and colleagues reviewed the medical research on key parts of lupus care and then asked an expert panel to set priorities based on the research. A second panel of experts reviewed the work, and settled on the final set of quality indicators. The indicators cover the following topics: diagnosis, preventive health (e.g., vaccinations, sun avoidance, and screening for cardiovascular disease), prevention and treatment of osteoporosis, medication monitoring, kidney disease, and reproductive health. In 2009, the journal *Arthritis Care and Research* published a manuscript describing the development of the lupus quality indicators.

After the publication of the quality indicators, Dr. Yazdany and her colleagues wanted to use the indicators to assess the quality of care people with lupus are receiving. In 2009, we started including a version of the quality indicators in the annual LOS interviews. Dr. Yazdany presented results from the first wave of these interviews at the American College of Rheumatology meeting. We found that for some aspects of care, such as counseling patients to avoid sun exposure, most patients received care in line with the recommendation. For other indicators, such as checking risk factors for heart disease, a relatively small percentage met the recommendation. The results are not all that surprising: the danger of sun exposure in lupus is well known, while the increased risk of heart disease among people with lupus has only recently been uncovered. This research has been helpful in identifying important gaps in care for lupus, and identifying which groups of patients are less likely to receive recommended care. The findings can be used to target quality improvement to where it is needed most.

Since *To Err is Human* was published, health care for certain conditions has improved dramatically in the U.S. We hope that our work on quality indicators for lupus will lead to improvements in the quality of care for this condition, too.

Lupus Genetics Update

Lupus is a complex disease – it shows up in different ways in different patients. Genetics researchers now believe that these different variations of lupus may have different underlying causes. Two studies on this topic from the UCSF Autoimmune Genetics Studies Project, led by Dr. Lindsey Criswell, were recently published in *PLoS Genetics*. One study, headed up by Dr. Sharon Chung, looked at the relationships between genetic markers for lupus and a specific autoantibody, called anti-dsDNA*, often found in lupus patients with kidney disease. They looked at more than 400,000 gene variations and found that many

(Continued on page 6)

* Lupus is an autoimmune disease, which means that people with lupus produce antibodies against their own cells and proteins. Anti-dsDNA is an autoantibody that binds to double-stranded DNA.
Good News for Lupus Patients

On March 9, 2011, the FDA approved Benlysta (belimumab), the first new lupus drug available in more than 50 years. The drug is a “monoclonal antibody,” which is a type of protein made in the laboratory that is designed to attach to only one type of substance in the body. It is given through an IV once per month. Like older drugs for lupus, it suppresses the immune system, but by a new pathway – it inhibits a protein in the body called B lymphocyte stimulator protein. The company that developed Benlysta, Human Genome Sciences, Inc., discovered this protein by sorting through a huge collection of human genes. Benlysta reduced symptoms of lupus in two clinical trials. According to these trials, about 11 patients would have to be treated with Benlysta in order for one to benefit. Study patients had few side effects and the infection rate was similar in the drug and placebo groups. One limitation of the trials was that patients with significant kidney disease and neurologic problems were excluded, so it is not clear yet if Benlysta would be useful for patients with these symptoms.

“Benlysta will probably be used as a second-line treatment in patients who cannot tolerate current first-line treatments for lupus such as mycophenolate mofetil (Cellcept) or azathioprine (Imuran). It is very exciting to have a new option to treat our patients with lupus. Importantly, the experience with belimumab demonstrates that successful clinical trials of new therapeutic agents in lupus are possible. Dr. Yazdany, a rheumatology professor at UCSF, said “We are hoping that this paves the way for additional effective therapies for lupus in the coming decade.”

O

On March 9, 2011, the FDA approved Benlysta (belimumab), the first new lupus drug available in more than 50 years. The drug is a “monoclonal antibody,” which is a type of protein made in the laboratory that is designed to attach to only one type of substance in the body. It is given through an IV once per month. Like older drugs for lupus, it suppresses the immune system, but by a new pathway – it inhibits a protein in the body called B lymphocyte stimulator protein. The company that developed Benlysta, Human Genome Sciences, Inc., discovered this protein by sorting through a huge collection of human genes. Benlysta reduced symptoms of lupus in two clinical trials. According to these trials, about 11 patients would have to be treated with Benlysta in order for one to benefit. Study patients had few side effects and the infection rate was similar in the drug and placebo groups. One limitation of the trials was that patients with significant kidney disease and neurologic problems were excluded, so it is not clear yet if Benlysta would be useful for patients with these symptoms.

“Benlysta will probably be used as a second-line treatment in patients who cannot tolerate current first-line treatments for lupus such as mycophenolate mofetil (Cellcept) or azathioprine (Imuran). It is very exciting to have a new option to treat our patients with lupus. Importantly, the experience with belimumab demonstrates that successful clinical trials of new therapeutic agents in lupus are possible. Dr. Yazdany, a rheumatology professor at UCSF, said “We are hoping that this paves the way for additional effective therapies for lupus in the coming decade.”

For more information about the approval of Benlysta, go to the Lupus Foundation (LFA) website: www.lupus.org

Kids Get Lupus Too

Many people are surprised to learn that lupus is not just an adult disease. In fact, lupus is the second most common chronic rheumatic disease in childhood: it is estimated that 10,000-15,000 children in the United States are currently being treated for lupus.

The symptoms of childhood lupus are very similar to those of adult lupus, and as a result, the same criteria are used to make a diagnosis of lupus in children and adults. In addition, similar medications are used to treat both childhood and adult lupus. Despite the similarities, there are some important differences between lupus in children and adults. Data from the Lupus Outcomes Study (LOS) has helped increase our understanding of these differences, and given us a unique opportunity to describe the long-term health outcomes of patients diagnosed with lupus in childhood. Approximately 100 patients in the LOS have had lupus since childhood. On average, they were diagnosed at age 14, and have now had disease for at least 16 years. We know from the LOS and other studies that children with lupus tend to have more severe disease than adults with lupus, but the reasons for this difference are not known. Kidney disease, for example, occurs much more frequently in childhood lupus. In turn, children are more likely to need immunosuppressive medications, such as steroids, to treat their lupus.

Pediatric rheumatologists have become more aware of the importance of close monitoring of lupus disease activity, response to treatment, and treatment side effects over time. We
Lupus can affect any organ system in the human body, including the brain. Increasingly, researchers are beginning to appreciate that neuropsychiatric symptoms, which include depression and other behavioral and mood related problems, are also common complications of lupus. In a recent study published by members of our research team, about 50% of people with lupus develop depression at some time in their lifetime.

Researchers here at UCSF and elsewhere are recognizing the importance of depression among people with lupus. Patients with lupus who also have depression are at a greater risk for poor health, increased pain, and greater disability. In fact, a recent study from our group suggested that lupus patients with depression had problems taking care of their medical needs (e.g., remembering to take medications), leading to increases in doctor visits and emergency room visits. In the general population, depression is now the leading cause of lifetime disability. Add this burden of depression to another chronic medical condition such as lupus, and we potentially have a population at serious risk for poor health and reduced quality of life.

What is Depression? Is it Different than “Stress”?

Life these days is full of hassles, frustrations, deadlines, and demands. Stress is a normal physical and mental response that lets your body know its usual balance is upset in some way. Stress can be a good thing: it can help you rise to meet challenges and be brave enough to try new activities. But when stress is too severe or too chronic, it stops being helpful and can be damaging. In these cases, stress becomes our enemy and can leave us vulnerable to developing clinical depression.

Everyone occasionally feels sad or blue. People commonly use the term “depression” to refer to a variety of emotional states including brief periods of feeling down (hours) to prolonged periods of severe depression that may last for months or years. The clinical term for depression is a “major depressive episode,” a condition that is diagnosed by a psychologist or a physician. It is characterized by a cluster of symptoms (see Table 1), that last at least two weeks and cause some difficulty in social or physical functioning.

<table>
<thead>
<tr>
<th>Symptoms of a Major Depressive Episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least two weeks or more of several of the following:</td>
</tr>
<tr>
<td>• Sadness, depressed mood, hopelessness</td>
</tr>
<tr>
<td>• Loss of interest or pleasure in activities</td>
</tr>
<tr>
<td>• Loss of appetite OR Increase in appetite</td>
</tr>
<tr>
<td>• Sleep disturbance (either trouble sleeping or sleeping too much)</td>
</tr>
<tr>
<td>• Agitation or slowed behavior</td>
</tr>
<tr>
<td>• Low energy</td>
</tr>
<tr>
<td>• Feeling worthless or guilty, feeling that you are always letting others down</td>
</tr>
<tr>
<td>• Problems with concentration or thinking</td>
</tr>
<tr>
<td>• Persistent thoughts of death or suicide</td>
</tr>
</tbody>
</table>
Can Lupus Cause Depression?

While we do not fully understand the nature of depression in lupus, we have learned a tremendous amount about depression in recent years. Clinical depression probably results from a combination of genetic, biochemical, psychological, and social factors. Depression is a disorder of the brain that begins when certain brain chemicals, called neurotransmitters, are out of balance. Trauma, loss of a loved one, a difficult relationship, or a stressful situation can also trigger depression. Usually depression is first triggered by a "stressor," but later episodes of depression can occur without any obvious trigger.

Lupus patients may be at increased risk for depression for several reasons. First, in some lupus patients, depression may be a reaction to difficult life situations. These can include situations that arise because of one’s lupus, including the initial diagnosis, the onset of disability, losing the ability to enjoy normal activities, or other life stresses. Second, pain and depression often occur together. Research suggests that pain can make depression worse and vice versa. Finally, there is increasing evidence to support a relationship between systemic inflammation and depression. Given that lupus is a chronic inflammatory disease, persons with lupus may be at increased risk. Recently, we studied lupus patients over five years and found that patients with lupus who have other medical complications (e.g., diabetes) and higher levels of systemic disease activity, were more likely to develop depression.

Our team is currently hard at work studying all of these factors in relation to depression in lupus. Identifying early risk factors for the development of lupus will help prevent depression in patients diagnosed with lupus and help determine the most effective treatments for depression in this disease.

How is Depression Treated?

The good news is that depression is a highly treatable disorder. We recommend that people who have several of the mood symptoms described above talk to their doctor. Like many illnesses, the earlier the condition is detected and treated, the more effective the treatment is. Many people suffer in silence; they try to find ways to cope with these feelings themselves. We often hear patients tell us they felt that depression was their “punishment”, that they had some weakness, or that they just had to “snap out of it” or “just think positively.” Or patients tell us that they are depressed “because of their lupus,” so they feel resigned to having mood symptoms in the long term. Remember, depression is a real medical condition, just like asthma, diabetes, arthritis, or lupus. Once a person is properly diagnosed, there are a number of treatment options. The two most common treatment options are medication and psychotherapy (or sometimes both):

(1) Medication therapy, usually called “anti-depressants.” These medications work to normalize the brain chemicals that are already interacting in your brain (neurotransmitters involved in depression include serotonin, norepinephrine, and sometimes dopamine). Each medication is chosen careful in consultation with the doctor and the patient but there are a few facts that everyone should know:
   a. Usually people have to take regular doses (daily) for at least 3-4 weeks before they experience the benefits. These are not medications to take just when you are feeling bad.
   b. Medication should be not started or stopped except under the supervision of a doctor. Some medicines need to be gradually stopped in order to prevent side effects.

(Continued on page 6)
Lupus and Depression continued

(Continued from page 5)

c. If one medication does not work, patients should talk with their doctors about trying another. One size does not fit all with these medications and sometimes a patient must try a few medications before arriving at the correct medication and dosage.

d. Anti-depressant medications do not change your personality. You will still be “yourself” — just hopefully with fewer symptoms of depression. It is very important to talk to your doctor if you feel like you are not your normal self, feel more agitated or worse than before.

(2) Psychotherapy – or “talk therapy” can also be effective. Two kinds of therapy – cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT) – have been studied and shown to be effective. Sometimes therapy can work in as few as 10 weeks. The goal of these methods is to teach new ways of thinking, behaving, coping with stress, and managing your mood symptoms. In therapy, patients can also learn strategies to cope with disease, stresses, and challenges so they are not as overwhelming. Psychiatrists, psychologists and other mental health professionals (e.g., licensed clinical social workers) can administer psychotherapy.

Summary:
Depression is a serious problem worldwide, and lupus patients may be particularly at risk for depression. Lupus patients may be vulnerable to developing depression due to factors related to their disease (e.g., inflammation, brain involvement, or pain) and related to coping with this chronic condition. But, regardless of how it develops, depression is a treatable condition. The toll of depression is substantial, leading to poorer overall health, reduced overall well-being, and poor quality of life. We are working to better understand both the causes of depression in lupus, and the impacts of depression on the lives of people with lupus. We hope to develop ways to identify people with lupus most likely to develop depression and to develop targeted treatments that best prevent and treat depression in lupus.

Lupus Genetics Update continued

(Continued from page 2)

variations known to be associated with lupus were more common in people with anti-dsDNA. Thus, these genetic markers may increase a lupus patient’s tendency to make autoantibodies. There were no genetic markers strongly associated with lupus without anti-dsDNA. Non-genetic factors may play a bigger role in this type of lupus. Further studies of the genetic markers associated with anti-dsDNA autoantibodies may lead to understanding what causes autoantibody production and kidney damage in lupus.

The second study, headed by Dr. Kimberly Taylor, sought to understand how genetic susceptibility for lupus relates to its different features in different patients. They created a “genetic risk score” using 22 gene variations known to increase risk for lupus -- the more risk, the higher the score. Then, they looked at the scores for patients with different features of lupus, such as age of diagnosis, kidney disease, autoantibody production, malar rash, and arthritis. Some of the features, including anti-dsDNA and age at diagnosis, were associated with higher genetic risk scores. Some of them were associated only with a single genetic variation, but not the whole score. Other features were not associated with any of the susceptibility genes or the score. This showed that some lupus clinical features are more related to genetics than others. By examining relationships between genetics, lupus risk, and clinical features of the disease, we hope to better understand how lupus is triggered and how it manifests in patients.
One Health: Get Screened for Osteoporosis and Prevent Bone Thinning

People with lupus are more likely to have a bone fracture, especially of the hip and spine, after minor trauma. Almost 10% of lupus patients will have a bone fracture at some point after their diagnosis. This is because of osteoporosis, or thinning of the bones. Osteoporosis can occur as people grow older, especially in post-menopausal women. Lupus patients are at higher risk for osteoporosis because of chronic inflammation and frequent steroid use, possible early menopause, and because of low vitamin D levels that can occur from avoiding the sun.

Kids Get Lupus Too continued

(Continued from page 3)

learned from the LOS that children with lupus seem to be susceptible to developing heart disease in early adulthood; studies are ongoing to determine if particular interventions can help prevent heart disease in children with lupus. The pediatric rheumatologists at UCSF recently participated in a multicenter clinical trial called the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) study. This trial studied whether a common cholesterol-lowering drug, atorvastatin (Lipitor), prevents fat build-up in the major arteries of the heart among childhood lupus patients. These types of studies are important for identifying strategies to improve long-term health outcomes for patients with childhood lupus.

In collaboration with the University of Utah, and with sponsorship from the American College of Rheumatology, the LOS will soon begin annual surveys of adolescents with lupus, in order to improve our understanding of outcomes of childhood lupus.

Many young people with lupus are sharing their experiences on the web, via blogs. You can check some of them out at the Lupus Foundation’s blog, http://lfa-inc.blogspot.com/

Body Composition and Disability Study Update

In 2007, we began a study looking at the relationship between body composition (the amount of fat and muscle in the body), disease activity, and functioning in lupus. Since then, 172 members of the LOS came into UCSF Hospital to participate in this study, by having a DEXA scan and other testing. In the first results from this study, we found that starting at BMI of 25, functional problems became more common as BMI increased. This was somewhat surprising, because in the general population, functional problems do not show up until BMI reaches the level of obesity, a BMI of 30 or more. At every level of BMI, LOS participants had a higher ratio of fat to muscle than the general population. It’s possible that people who are sicker are less able to participate in physical activity, which may lead to muscle loss. LOS participants with higher BMIs (or more body fat) also had higher cardiovascular risk scores. These findings highlight the importance of maintaining physical activity, both to prevent muscle loss and to reduce the risk of cardiovascular disease. We are in the process of conducting 2-year follow-up DEXA studies to look at changes in body composition and how disease activity may affect those changes. Thanks to all of you who participated in this study!

Find your BMI: (Body Mass Index)

Weight (lbs) / Height (in.)^2 X 703
Or go to: www.nhlbisupport.com/bmi/

Interpretation:
<18.5 = underweight
18.5 - 24.9 = normal
25-29.9 = overweight
30+ = obese

Many young people with lupus are sharing their experiences on the web, via blogs. You can check some of them out at the Lupus Foundation’s blog, http://lfa-inc.blogspot.com/
My name is Christine Bolton. I was diagnosed with Lupus (SLE) in 1978. I was 18 years old and just out of high school. I woke up one morning and my legs were in a lot of pain and I could not straighten them out. I had bald spots in my head where my hair fell off. [The skin] around my eyes was very dark and my cheeks were puffy and red. I had herpes zoster around my left eye and the blisters were very painful. I was very frightened and I didn’t know how I got lupus or how I was going to live with it and the pain.

In 1990 I was hospitalized with fluid in my lungs and around my heart. My right knee was filled with fluid and infection had set in and I had to have knee surgery to correct this problem. All this was due to my lupus (SLE).

I have been off and on many medications. I have been depressed and even suicidal at times. Through the grace of God and prayer I was able to stay strong.

In 2009, I started to feel a lot of pain and shortness of breath. I was in and out of the emergency room and the hospital. I began to break out with blisters on my back, arms, legs, buttocks, face, neck and stomach. I was diagnosed with bullous lupus in April of 2010. I was in some indescribable pain and I felt as thought I was burnt by hot grease. I was in the hospital for weeks and weeks. I had severe anemia and I had Type II diabetes due to the very high doses of prednisone (80 mg). I was on insulin 3x day and metformin 2x day and a host of many medications and pain killers.

I thought I would never get out of the hospital and be well again.

Today, I am doing great! My blood pressure is normal and I am not anemic any more. I do not take insulin any more and my diabetes is doing well. My legs are getting strong again and I breathe very well. My hair has grown back and I am down to 17.5 mg of prednisone.

I thank the Lord Jesus Christ for giving me the strength and I thank Him for His grace and mercy. My last blood test was good and my blood sugar was down. In short, I feel good.

I am seen at San Francisco General Hospital in Ward 92 Rheumatology and my doctor is Dr. A.M. and I am very blessed to have her.

-Christine Bolton,
Richmond, CA

If you would like to send in the story of your experiences with lupus for possible inclusion in a future issue, please contact the LOS office (see box below).