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NEW STUDY PUBLISHED IN THE *NEW ENGLAND JOURNAL OF MEDICINE* OFFERS HOPE TO LUPUS PATIENTS WITH KIDNEY DISEASE

Transplant drugs seen as better alternatives to “gold standard” therapy

Miami (March 4, 2004) – Drugs used to prevent rejection in transplant patients are proving equally valuable in the fight against lupus nephritis (lupus kidney disease), according to researchers at the University of Miami in a study published this week in the *New England Journal of Medicine (NEJM)*.

Lupus nephritis is the most common severe complication of the autoimmune disease systemic lupus erythematosus (SLE). Approximately 1.5 million Americans have SLE and half of those will develop lupus kidney disease. Lupus nephritis increases the risk for premature death and chronic kidney failure, a condition that may require chronic dialysis or transplantation.

In the study, “Sequential Therapies for Proliferative Lupus Nephritis,” researchers showed that maintenance with daily oral treatment with one of the most widely prescribed transplant medications, mycophenolate mofetil (MMF, also known as CellCept®) or the older anti-rejection drug azathioprine (AZA) was more effective and safer than the current “gold standard” therapy, intravenous quarterly pulses of the chemotherapy drug cyclophosphamide (IVCY, also known as Cytoxan®) in the long term treatment of lupus nephritis.

“We’re very excited about our study results that demonstrate that new maintenance treatment regimens with MMF or AZA are more effective and offer a much lower incidence of significant adverse events than

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long-term IVCY,” said Gabriel Contreras, M.D., MPH, lead author of the *NEJM* study, Associate Professor of Medicine at the University of Miami School of Medicine and Director of the Dialysis Unit at the Veterans Affairs Medical Center in Miami.

The most important highlights of the study include the findings that:

- Long-term IVCY was associated with a greater risk of death or chronic renal failure than maintenance therapy with MMF or AZA
- Maintenance therapy with MMF or AZA was safer than long-term IVCY, with fewer hospitalizations, severe infections, amenorrhea and gastrointestinal side effects

Lupus patients with kidney involvement undergo periods of intense disease activity known as flaring. Induction therapy is used to try to induce periods of remission. “During flares, patients usually require higher doses of corticosteroids and additional pulses of IVCY, which increase the risk for more adverse events,” added Dr. Contreras. “Avoidance of renal flares is important as flaring is known to cause damage to the kidneys, which can lead to kidney failure. Once a patient is in remission the aim of maintenance treatment is to keep patients relapse-free.”

Lower Relapse Rates Seen

Another highlight of the study included lower relapse rates. In the study, the rate of relapse was statistically significantly lower in the MMF group versus IVCY. Relapse rates in the AZA group were not significantly better than in the IVCY group. During maintenance therapy 40 percent relapsed in the IVCY group, 32 percent in the AZA group and 15 percent in the MMF group.

“These study results are likely to shift the treatment paradigm away from long-term chemotherapy drugs,” said Dr. Contreras.

This study was funded by a research grant from Roche, manufacturers of MMF under the brand name CellCept®.

Study Design

The open-label, randomized clinical trial of 59 patients with lupus nephritis included 27 African-Americans, 29 Hispanic-Americans and 3 Caucasians. African-Americans and Hispanic-Americans are populations known to be at high risk for lupus nephritis. All patients received the same induction therapy with monthly short-term IVCY and corticosteroids. The patients were then randomized to one of three maintenance therapies: quarterly boluses of IVCY, oral AZA (1-3 mg/kg/day); or MMF (500-3000 mg/day) for one to three years. Each group also received oral corticosteroids.

The 72-months event-free cumulative probability of the composite end-point (death or chronic renal failure) was higher in the MMF (P=0.05) and AZA (P=0.009) groups compared to the IVCY group. Five patients died (4-IVCY, 1-MMF) and five patients developed chronic renal failure (3-IVCY, 1-AZA, 1 MMF).

Thirty-one percent of the patients who achieved remission had a relapse (IVCY=8, AZA=6, MMF=3). The relapse-free cumulative probability was higher in the MMF group compared to the IVCY group (P=0.024). Hospitalizations, amenorrhea, infections, and gastrointestinal side effects were significantly lower in the MMF and the AZA groups compared to the IVCY group.

“I am really encouraged by these study results, which add to the growing body of evidence that CellCept® may be an effective treatment for lupus nephritis,” said Sandra Raymond, President and CEO of the Lupus Foundation of America. “Last October, in a study presented at the American College of Rheumatology’s Annual Meeting, we saw that CellCept® as induction therapy was at least equivalent and better tolerated than IVCY. Now we’re seeing that CellCept® may prove equally valuable as long-term maintenance therapy. I’m very excited that there are now less toxic and more effective treatment options emerging for the millions of people worldwide with lupus kidney disease.”

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About CellCept® (mycophenolate mofetil)

CellCept® (mycophenolate mofetil) is an immunosuppressant or “anti-rejection” drug to be used in combination with other immunosuppressive drugs (cyclosporine and corticosteroids) for the prevention of rejection in patients receiving heart, kidney and liver transplants. CellCept® received FDA approval for the prevention of organ rejection in kidney (May 1995), heart (February 1998), and liver (July 2000). The recommended dosages for CellCept® follow: for adult kidney transplants, 2 g daily; for pediatric kidney transplants, oral suspension 600 mg/m²; for adult heart and liver, 3 g daily.

The principal adverse events associated with the administration of CellCept® (in combination with cyclosporine and corticosteroids in transplant patients) include diarrhea, leukopenia, sepsis and vomiting, and there is evidence of a higher frequency of certain types of infections. A higher proportion of renal transplant patients in the active treatment groups experienced one or more opportunistic infections compared with patients receiving placebo. Cytomegalovirus tissue invasive disease was more common in patients receiving 3 g/day.

Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should use CellCept®. Patients receiving the drug should be managed in facilities equipped and staffed with

adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

There are no adequate and well-controlled studies in pregnant women. However, CellCept® has been shown to have teratogenic effects in animals; it may cause fetal harm when administered to a pregnant woman. Therefore, CellCept® should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus. For full prescribing information, visit www.rocheusa.com/products/cellcept/pi.html.

About the University of Miami School of Medicine

Founded in 1952 as Florida's first accredited medical school, the University of Miami School of Medicine provides the medical staff for the nationally renowned University of Miami/Jackson Memorial Medical Center. Research is a top priority, with more than 1,200 ongoing projects funded by \$188.6 million in external grants and contracts to UM faculty. The school ranks in the top third among U.S. medical schools in terms of research funding awards.

About the Lupus Foundation of America

The Lupus Foundation of America, based in Washington, DC, has a nationwide network of more than 200 chapters, branches and support groups. The LFA mission is to improve the diagnosis and treatment of lupus, support individuals and families affected by the disease, increase awareness of lupus among health professionals and the public, and find the cause and cure. Currently, the LFA is initiating a Five-Year Research Support Program, which seeks to advance biomedical, clinical, epidemiological, behavioral and translational research that will lead to safe and more effective treatments for lupus and a cure for the disease.