CellCept, Rituxan Said to Show Promise for Lupus

The two medications are expected to be particularly useful in the treatment of refractory lupus nephritis.

BY TIMOTHY F. KIRN
Sacramento Bureau

SNOWMASS, COLO. — Mycophenolate mofetil and rituximab are expected to join the lupus armamentarium, promising to be particularly useful for lupus nephritis, Dr. Susan M. Manzi predicted at a symposium sponsored by the American College of Rheumatology.

"Those are two we are putting our money on," said Dr. Manzi, codirector of the Lupus Center of Excellence at the University of Pittsburgh.

Advancement in lupus treatment has not kept pace with breakthroughs in rheumatoid arthritis (RA) therapy, in general, Dr. Manzi said. The tumor necrosis factor inhibitors that are so effective in RA do not appear to have much benefit in lupus, although ongoing experiments continue to assess the effectiveness of very short-term use of these biologic agents in lupus.

And because of the failure of some promising novel agents—notably the still-controversial anti-CD40 ligand—physicians have gotten the impression that advances in lupus treatment have been few and far between.

But that would be a misperception, Dr. Manzi said.

A recently published study compared mycophenolate mofetil (CellCept) with an IV cyclophosphamide regimen in a total of 140 patients, Dr. Manzi said.

Full remissions were more common in patients treated with mycophenolate mofetil, an inosine monophosphate dehydrogenase inhibitor with anti-inflammatory action that is approved for prevention of transplant rejection. Specifically, 22% of the patients on mycophenolate mofetil versus 6% of those on IV cyclophosphamide met the American College of Rheumatology criteria for complete remission (N. Eng. J. Med. 2005;353:2219-28). Patients in both treatment groups showed a significant lessening of their lupus nephritis, and all the patients benefited.

The main advantage seen with mycophenolate mofetil was that it was much better tolerated than IV cyclophosphamide, Dr. Manzi said. Diarrhea was more common in patients on mycophenolate mofetil; all other minor side effects occurred more frequently with cyclophosphamide therapy. Severe infections, such as pneumonia and sepsis, occurred in 1 of 71 patients treated with mycophenolate mofetil, but in 6 of 69 patients treated with cyclophosphamide.

Two patients died during cyclophosphamide therapy, and two others developed irreversible amenorrhea.

One question unanswered by the study was what happens later, Dr. Manzi said. The study drugs were given for 24 weeks, and the patients were assessed at 12 and 24 weeks. It has been suggested that the full beneficial effect of cyclophosphamide occurs after 24 weeks.

The major advantages of the two drugs are tolerability and safety.

DR. MANZI

However, findings from a previous study that also compared the two agents in lupus nephritis and followed the patients for a full year showed that similar percentages of patients (about 80%) on each agent had achieved full remission of their nephritis at the end of the study. That study was considered somewhat less definitive than the new one, at least in this country, because it used oral cyclophosphamide, a practice not common in the United States.

Based on the new study, Dr. Manzi suggested that appropriate patients for mycophenolate mofetil treatment are going to be those without rapidly progressing glomerulonephritis, who were excluded from the study, for whom there might be a risk of infection during the treatment, and, maybe more importantly, women of childbearing age.

At Dr. Manzi's center, mycophenolate mofetil is already being used as a maintenance treatment after short courses of cyclophosphamide.

Rituximab (Rituxan) has been used to treat lupus nephritis in a handful of open-label trials, in a total of about 100 patients. The results are "impressive," Dr. Manzi said. The agent's sole indication is for cancer, specifically B-cell non-Hodgkin's lymphoma.

Two different regimens have been used with the B-cell–depleting agent, one in which treatment is given every 4 weeks, as for non-Hodgkin's lymphoma, and another in which rituximab is given the first day, followed by intravenous cyclophosphamide, followed by tapering prednisone. And, overall 80% of patients treated have had partial remission at 4-6 months, with over 50% achieving long-term remission lasting longer than 12 months.

As with the mycophenolate mofetil, the major advantages of rituximab are tolerability and safety, Dr. Manzi said. Bcause of its widespread use in cancer therapy, safety data are plentiful.

"This drug has a lot of potential," she said. "We certainly are using it off-label now in patients with refractory nephritis—it's just a matter of wrestling with insurance companies to get [the reimbursement] approved." ■

Methotrexate May Help Patients With Resistant Cutaneous Lupus

BY NANCY WALSH
New York Bureau

ABANO TERME, ITALY — Intravenous methotrexate proved to be an effective steroid-sparing treatment for recalcitrant cutaneous lupus, Dr. Joerg Wenzel reported at a congress on skin, rheumatism, and autoimmunity.

Dr. Wenzel and his associates in the department of dermatology at the University of Bonn (Germany) retrospectively analyzed patients who underwent treatment with methotrexate and whose skin lesions had not responded to antimalarials, azathioprine, mycophenolate mofetil, or dapsone.

Initially, the drug was given intravenously to 43 patients in doses of 15-25 mg/week. The dose was titrated down to a final range of 7.5-15 mg/week in eight patients. The oral route in doses of 10-20 mg/week was substituted in seven patients because of lack of compliance.

Disease activity was rated using a cutaneous lupus activation index (CLAI) that provided a single score reflecting the degree of skin involvement, grade of inflammation, and clinical course. At baseline, the mean CLAI was 5.13; this decreased to 1.73, with clinical response being observed after 2-8 weeks, Dr. Wenzel said. This was a "highly significant" decline in disease activity, and all but one patient experienced improvement, he said.

The greatest improvement was seen among 16 patients with the subacute cutaneous subtype of lupus erythematosus. Among these patients, the mean CLAI fell from 5.5 to 1.2, he said. Seven patients (16%) discontinued treatment because of significant side effects, including elevations of liver enzymes and pancytopenia. These quickly resolved when treatment was discontinued.

In 15 patients, administration was switched to the subcutaneous route, using a methotrexate formulation. Efficacy was equivalent to that seen with intravenous administration, and side effects were similar. There were significant differences in adverse effects, however, with parenteral administration, compared with oral delivery, probably because of individual differences in gastrointestinal resorption.

"My personal view is that the subcutaneous route opens the door to patient self-administration," Dr. Wenzel said.

One curious finding in the study was that patients who had extensive lymphocytopenia before treatment experienced a significant increase in lymphocyte counts. This finding following methotrexate administration was strange, he said, as methotrexate itself is an immunosuppressive drug that can cause pancytopenia.

"I believe methotrexate blocks the recruitment of circulating autoreactive, cytotoxic lymphocytes from the blood into the skin," he said. This hypothesis is supported by recent findings in psoriasis, where methotrexate reduced the expression of the skin-homing molecule cutaneous lymphocyte-associated antigen (Exp. Dermatol. 2004;13:426-34). ■

Nonmyeloablative Stem Cell Transplant Promising for SLE

An autologous hematopoietic stem cell transplantation technique that achieves lymphoablation without myeloablation proved effective against severe refractory systemic lupus erythematosus in a preliminary study.

Serology, complement, immunomediated hemolysis and thrombocytopenia, thrombotic events, and pulmonary function all improved while preserving renal function in a single-center study of 48 patients. Nonmyeloablative hematopoietic stem cell transplantation (HSCT) significantly improved SLE symptoms and gave patients a 50% probability of 5-year remission, reported Dr. Richard K. Burt of Northwestern University, Chicago, and associates.

These results justify a randomized clinical trial comparing autologous HSCT with standard care, Dr. Burt and his associates said (JAMA 2006;295:527-35).

Fifty "very ill" patients underwent the two-step procedure involving a lupus-specific conditioning regimen to eliminate self-reactive lymphocytes followed by stem cell infusion. All had glomerulonephritis, lung involvement, CNS involvement, vasculitis, myositis, cytopenias, serositis, ulcerative mucocutaneous disease, and/or antiphospholipid syndrome refractory to optimal therapy.

One patient died from pulmonary and cerebral mucormycosis after stem cell mobilization but before transplantation (treatment-related mortality of 2%). A second patient died from active SLE after postponing transplantation.

The remaining 48 patients were followed for a mean of 29 months. Their probability of 5-year survival was 84%, and of disease-free 5-year survival 50%. Measures of serology, complement, and disease activity all remained improved throughout follow-up. Pulmonary function improved; five patients who had been dependent on supplemental oxygen were able to discontinue it.

Of 22 patients, 18 were able to discontinue anticoagulation without subsequent thrombotic events. Renal function remained stable or improved; 16 patients who had nephritis before HSCT were able to discontinue dialysis afterward. Idiopathic thrombocytopenic purpura cleared in five of seven patients. Autoimmune hemolytic anemia cleared in three of five patients.

—Mary Ann Moon