

Prognosis Positive After Renal Transplants in SLE

BY NANCY WALSH
New York Bureau

LONDON — The prognosis for patients with lupus nephritis who undergo renal transplantation today is good, with a low risk of recurrent renal flare and a decrease in lupus disease activity, Jo H. Berden, M.D., said at the Sixth European Lupus Meeting.

Uncertainty has existed as to whether outcomes among patients with systemic lupus erythematosus (SLE) would be equivalent to those seen among patients whose end-stage renal disease derives from another cause; studies have shown conflicting results and have been limited by confounding factors.

But a more comprehensive review of the European and U.S. experience has found no differences in graft or patient survival between lupus and nonlupus transplant recipients, said Dr. Berden of Radboud University, Nijmegen, the Netherlands.

An analysis based on European data for the years 1984 through 1992 provided by the Eurotransplant International Foundation, Leiden, the Netherlands, found no differences in either patient or graft survival when 165 lupus patients were compared with 20,000 nonlupus controls, Dr. Berden said at the meeting sponsored by the British Society for Rheumatology.

A larger analysis of data from the United States Renal Data System included 772 cadaveric transplants for lupus nephritis and 32,644 cadaveric transplants for other causes. This review also analyzed data from 390 lupus patients whose transplants had been from living donors and from 10,512 nonlupus patients whose transplants had been from living donors.

In an unadjusted analysis, patient survival was better in the lupus group, but graft survival was worse. Once adjustments were made for important confounding factors such as age and gender, however, there were no differences (Kidney Int. 2000;57:2136-43).

Nonlupus patients requiring renal transplantation tend to be male and older than the predominantly female lupus patients with this requirement.

Following transplantation, the incidence of renal flare in lupus patients is reported to be 2%-4% if clinical criteria are used and slightly higher if histologic criteria are used. This is a rather low incidence of recurrence, compared with that for other diseases, the nephrologist said.

Renal transplantation also confers non-

renal benefits to SLE patients. "In the Dutch Working Party on SLE, we found that most patients had severe disease before dialysis, intermediate disease during dialysis, and no extrarenal disease at all after transplantation. Apparently immune suppression that failed to control the disease initially was able to do so post transplantation," he said.

The immunosuppressive regimen used for lupus patients after transplantation should take into account the heightened risk for cardiovascular disease in these patients, Dr. Berden cautioned. Among the immunosuppressant drugs, some, particularly cyclosporine, increase blood pressure. Sirolimus and

cyclosporine raise cholesterol levels; tacrolimus and prednisone can induce or aggravate diabetes. In contrast, mycophenolate mofetil and azathioprine have little if any effect on blood pressure, cholesterol, or glucose levels. The long-term maintenance phase of immune suppression should therefore include one of these two less atherogenic agents, he said.

Experience also has taught that a careful evaluation before transplantation is es-

essential for achieving the best outcome. "We screen all our candidates ... for the presence of coronary abnormalities, even if there are no clinical symptoms," he said. Because the exercise electrocardiogram is not sufficiently sensitive, a thallium scan or stress echocardiogram is recommended. "Until recently, we also did coronary angiography and if abnormalities were seen, revascularization was done," he said. But recently a randomized clinical trial found no benefit for elective revascularization in asymptomatic patients awaiting major vascular surgery (N. Engl. J. Med. 2004;351:2795-804). "Therefore, there now is a question mark as to whether we should always advise revascularization," he said.

Antiphospholipid antibodies, which are present in approximately one-third of lupus patients, present another unresolved issue. These antibodies signal an increased risk for acute graft thrombosis, so it remains unclear whether prolonged anticoagulation is needed following transplantation because there have been no randomized trials addressing this issue.

As with any patient approaching end-stage renal failure, "we should always consider preemptive living transplantation because the results are much better," he said. ■

An analysis of European data found no differences in patient or graft survival when 165 lupus patients were compared with 20,000 nonlupus controls.

MMF Favored by Expert for Treatment of SLE Nephritis

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — Mycophenolate mofetil may be eclipsing cyclophosphamide as the standard-of-care induction therapy for lupus nephritis, Jill P. Buyon, M.D., reported at a symposium sponsored by the American College of Rheumatology.

Although the role of mycophenolate mofetil (MMF) in maintenance therapy still needs to be defined, the immunosuppressive agent has generated a lot of excitement, she said.

"In patients who don't have rapidly escalating renal insufficiency and whose creatinines are less than 2, there is little question at this point in time that I would suggest MMF over IV Cytoxan [cyclophosphamide]," she said. "I think it's better tolerated."

She cited results from the largest open-label, controlled study, led by Ellen M. Ginzler, M.D., of the State University of New York Downstate Medical Center, Brooklyn. In that investigation, Dr. Ginzler and colleagues randomly assigned 140 patients with class III, VI, or V lupus nephritis to MMF, starting at 1 g/day and escalating to 3 g, as tolerated, or to intravenous cyclophosphamide, dosed according to National Institutes of Health protocols. The treatment period was 24 weeks.

In all, 16 of the 71 patients initially assigned to the MMF group achieved complete remission of their nephritis, defined as normal serum creatinine level, inactive urine sediment, and proteinuria less than or equal to 500 mg/24 hours. By comparison, 4 of the 69 patients initially assigned to the cyclophosphamide group achieved this primary end point (Arthritis Rheum. 2003;48[9 suppl.]:S647[abstract 1690]).

MMF was well tolerated and appeared better accepted by participants than cyclophosphamide.

"This study has really changed the way I manage patients," said Dr. Buyon, of the Hospital for Joint Diseases and professor of medicine at New York University. "I certainly call this to my patients' attention, and many, many patients prefer using MMF."

Dr. Buyon starts patients on MMF 500 mg twice daily, titrating to a target dose of 3 g/day. Some patients may not be able to achieve the target dose because of GI intolerance.

All patients started on MMF also receive prednisone at approximately 60 mg daily, which is reduced over the course of 2-3 months to between 5 mg/day and 10 mg/day.

Dr. Buyon added that she also switches patients induced with cyclophosphamide to MMF if they are doing well at 6 months. ■

Thalidomide Proposed to Shut Off Scleroderma, Candidates Sought

BY NANCY WALSH
New York Bureau

NEW YORK — New revelations about the complex cellular processes underlying scleroderma suggest that manipulating the immune system with thalidomide may offer a new means of targeting the disease, Stephen J. Oliver, M.D., said at a rheumatology meeting sponsored by New York University.

Scleroderma begins with inflammation and the production of cytokines, including transforming growth factor (TGF)- β and interleukin (IL)-4, both of which are profibrogenic and activate the fibroblast.

Once the fibroblast becomes activated, it produces its own TGF- β and other cytokines, such as connective tissue growth factor. This leads to further proliferation of fibroblasts and the production of collagen, Dr. Oliver explained.

"At this point, immunosuppression could theoretically act to shut off the production of cytokines and other exogenous activators of the fibroblast. But immune suppression has not been as effective in scleroderma as we would have liked it to be and, in fact, in many cases it hasn't been effective at all." Early studies targeted TGF- β . However, this cytokine has multiple functions aside from its profibrogenic actions, "so blocking TGF- β systemically might not be such a great idea," said Dr. Oliver of New York University, New York.

An alternative approach now being studied involves immune manipulation with thalidomide. In scleroderma, the T helper (Th)2 type of immune response is predominant, and lab-

oratory investigations have revealed that thalidomide stimulates a Th1-type cellular response, causing increased production of interferon (IFN)- γ , IL-2, and IL-12 and enhancing the T-cell expression of the CD40 ligand.

Its potential applicability in scleroderma was suggested by the observation that this autoimmune disease shares many clinical features with graft-versus-host disease—a condition that sometimes responds to thalidomide.

In the first open-label study of the drug in scleroderma, 8 of 11 patients completed 12 weeks of treatment. The initial dosage was 50 mg/day; this was gradually increased to 400 mg/day, which is the maximum dosage used for the treatment of erythema nodosum leprosum.

Pruritus and dry skin were reported by seven of the eight patients, but there were no serious adverse events, such as the induction of renal disease, Dr. Oliver said.

Among the changes seen in patients in this preliminary study were increases in CD8 cells within the skin; this could offset the increased levels of CD4 cells that are associated with fibrosis of the skin, he said. Increases also were seen in tumor necrosis factor- α and IL-12. Moreover, there was a "striking clinical effect" in the healing of digital ulcers in four of five patients (Clin. Immunol. 2000;97:109-20).

Recruitment for a double-blind, placebo-controlled trial is under way. Dr. Oliver noted that he had no potential conflicts of interest. ■

Clinicians with patients who may be candidates for the New York University Scleroderma Trial can contact Dr. Oliver at 212-263-3874.