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RAPAMUNE® (SIROLIMUS) THERAPY ALLOWS FOR EFFECTIVE WITHDRAWAL OF CYCLOSPORINE IN KIDNEY TRANSPLANT PATIENTS

-- International Study Confirms Rapamune-treated Patients Fare Well and Avoid Exposure to the Long-term Dangerous Side Effects of Cyclosporine --

ROME, 31 August, 2000 -- Kidney transplant patients can be effectively treated with the new anti-rejection medication Rapamune (sirolimus) as the long-term primary therapy, permitting the withdrawal of the conventional immunosuppressant cyclosporine, a drug associated with a number of serious adverse effects such as kidney damage, hypertension, hirsuitism and gum overgrowth. An international clinical study, presented here today at the XVIII International Congress of the Transplantation Society, was conducted at 57 transplant centers in Europe, Australia and Canada and included 525 kidney transplant patients.

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"These findings confirm that Sirolimus is an effective alternative to cyclosporine for long-term immunosuppression. It has the major advantage of not causing kidney damage and it is free from a number of other unpleasant side effects associated with cyclosporine" said lead investigator Robert Johnson, M.D., Director of Transplantation at the Manchester Royal Infirmary, Manchester, United Kingdom. "The array of adverse effects caused by calcineurin inhibitors point to the clear imperative for an alternative therapy to be fully integrated into the immunsuppressive regimen."

The kidney transplant study patients were randomly assigned to two treatment groups: one group was maintained on triple therapy of cyclosporine, corticosteroids and 2mg Rapamune; in the other group, patients had their cyclosporine dosing stopped after three months of treatment. The aim of the study was to determine whether cyclosporine, which is part of the standard immunosuppressive drug regimen, could be safely eliminated while maintaining patients on sirolimus and steroids.

No grafts were lost in the study and kidney function in the cyclosporine-free patients was significantly improved. Graft survival at one year in the sirolimus-alone group was 97.3%, compared with 95% in the controlled group. There was a small increase of 6% in episodes of acute rejection in the sirolimus-alone group, but this difference did not reach statistical significance. All of the episodes of rejection were categorized as mild.

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Cyclosporine has long been the therapeutic mainstay for preventing organ rejection after transplantation. However, it can cause progressive damage to the patient's kidneys -- the very organs that patients and their doctors are trying to save through transplantation. Cyclosporine's role in causing kidney damage is attributed to reducing the blood supply to the kidney by causing vascular spasm. It achieves its immunosuppressive effects by inhibiting calcineurin, an important enzyme in the body's normal immune response.

Calcineurin inhibitors such as cyclosporine and tacrolimus produce well-documented adverse events such as kidney damage (nephrotoxicity), tremor (neurotoxicity) and high blood pressure (hypertension). Rapamune has a unique mechanism of action that does not involve calcineurin inhibition and therefore the kidneys are not exposed to the vascular spasm and other chronic toxicities observed with traditional drug regimens.

The findings announced today confirm and complement an earlier study that evaluated cyclosporine withdrawal. The previous study, led by Thomas Gonwa, M.D., of Baylor University Medical Center in Dallas, Texas, USA, demonstrated that discontinuation of cyclosporine at an early treatment stage resulted in significantly improved kidney function and no increase in the rate of acute rejection. Dr. Gonwa's findings were presented at the Transplant 2000 meeting in May in Chicago, and were updated during a symposium at the ICTS meeting in Rome led by Dr. Donald E. Hricik of Case Western Reserve School of Medicine, Cleveland, Ohio, USA.

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This study in the United States and Europe included 247 patients who underwent kidney transplantation. Patients were randomly assigned to receive the standard full-dose of cyclosporine plus 2 mg/day of Rapamune (Group A patients) or a reduced-dose of cyclosporine plus Rapamune (Group B patients). All patients were administered corticosteroids. During the third month after transplantation, those patients in Group B who had not experienced an episode of acute rejection had their cyclosporine dosage tapered and then eliminated.

Dr. Gonwa's primary endpoint was to assess kidney function after six months. Measuring creatinine, a metabolic waste product normally filtered and excreted by the kidney into the urine, is a standard method of assessing kidney function. Higher levels of serum creatinine in the blood mean the kidney is not properly filtering the creatinine and this correlates with impaired kidney function. The findings demonstrated that creatinine was significantly lower in Rapamune-treated patients who started treatment with low dose cyclosporine and then underwent cyclosporine elimination (Group B), compared with patients who continued to receive full-dose cyclosporine (Group A).
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Rapamune (sirolimus) oral solution received marketing approval from the United States Food and Drug Administration (FDA) in September 1999 for the prevention of acute kidney transplant rejection. It has also been approved in Argentina, Brazil, Columbia, Mexico, and Venezuela, and registration is pending in Canada, Switzerland, Australia, Chile and South Africa. Rapamune's application with the European Medicines Evaluation Agency (EMEA) recently received a negative opinion from the Committee for Proprietary Medicinal Products (CPMP), but is under appeal. A tablet formulation was approved by the FDA 25 August, 2000.

Manchester Royal Infirmary is part of Central Manchester Healthcare NHS Trust and is based in the North West of England. Every year we treat approximately 500,000 patients. Last year we carried out over 30,000 operations, including 145 renal transplants and delivered nearly 4,000 babies. To find out more about the organisation visit www.cmht.nwest.nhs.uk.

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