NATIONAL KIDNEY FOUNDATION (NKF) ANNUAL SCIENTIFIC MEETING

The Annual Scientific Meeting of the National Kidney Foundation will be held November 1-3, 1996, at the Ernest N. Memorial Convention Center in New Orleans, LA. This meeting will offer participants a better understanding of the pathogenesis, diagnosis, cure, and prevention of kidney diseases. The presentations will provide the most current information to help participants formulate decisions in the direct care of their patients. Program highlights include Are You Ready for Xenotransplantation?; Vexing Programs in Dialysis Patients; Glomerular Disease Progression? A Debate of the Issue; Dialyist Outcomes Quality Initiative (DOQI) Recommendations. The meeting is a multidisciplinary program offering four separate tracks targeted toward nephrologists, renal dieticians, nephrology social workers, and nephrology nurses and technicians. The National Kidney Foundation, Inc. is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians, and designates this continuing medical education activity for 16.0 credit hours in Category 1 of the Physician’s Recognition Award of the American Medical Association. For registration information, call 800-622-9010 or write to The National Kidney Foundation, 30 East 33rd Street, New York, NY 10016.

SIXTH ALEXIS CARREL CONFERENCE ON CHRONIC REJECTION AND GRAFT ATHERCOSCLEROSIS

The Sixth Alexis Carrel Conference will be held in Banff, Canada on December 4–7, 1996. The meeting is aimed at transplant physicians, surgeons, pathologists, and immunologists, as well as health care professionals with an interest in transplantation. For information regarding registration and abstracts, please contact the conference organizer: Dr. Leendert C. Paul, St. Michael’s Hospital, 30 Bond Street, Toronto, Ontario M5B 1W8. Canada. Telephone: 416-867-3701; fax: 416-867-3709; e-mail: lpaul@utoronto.ca.

ADVANCED NEPHROLOGY: NEPHROLOGY FOR THE CONSULTANT

Advanced Nephrology: Nephrology for the Consultant, sponsored by the Division of Nephrology, Department of Medicine, University of California, San Diego, CA, will be held February 6-8, 1997, at The Hotel del Coronado, Coronado (San Diego), CA. The registration fee: is $395 for physicians in practice, and 8175 for residents/fellows. This course is designated for 17 hours of AMA Category I Accreditation. For information, contact Shirley Kolkey, Course Coordinator, at 1660 Hotel Circle North, #220, San Diego, CA 92108. Telephone: 619-299-6673; fax: 619-299-6675.
INFORMATION FOR SUBSCRIBERS

JASN
The Journal of the American Society of Nephrology

Frequency: One volume per year, beginning in January.

Correspondence concerning business matters should be addressed to: Customer Service, Subscriptions, Williams & Wilkins, 351 West Camden Street, Baltimore, MD 21201-2436. Telephone: (800) 638-6423 from anywhere in the United States and Canada. From other countries, call (410) 428-8555. Fax: (410) 528-8896.

For information on American Society of Nephrology membership, contact: Sherri Mara at (202) 857-1190. Annual dues include $70.00 for journal subscription.

Correspondence regarding editorial matters should be addressed to: Jared J. Grantham, M.D., Editor, JASN, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160-7361.

Instructions to Authors appears in each issue.

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Reprints of individual articles are available only from the authors. If authors need information on their reprint orders, please call (410) 528-4118. Reprints (non-author) in large quantities, for commercial or academic use, may be purchased from the Publisher. For information and prices, call (410) 528-4292.

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Volume index appears in the December issue. Indexing/abstracting services: The Journal is currently included by the following services in print and/or electronic format: Index Medicus, Current Contents (Clinical Medicine), and BIOSIS.

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NEORAL® Soft Gelatin Capsules
(cyclosporine capsules for microemulsion)

NEORAL® Oral Solution
(cyclosporine oral solution for microemulsion)

BRIEF SUMMARY: Please see package insert for full prescribing information.

WARNING: Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe NEORAL®. Patients receiving the drug should be managed in facilities equipped to handle possible medical emergencies. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

NEORAL® may be administered with other immunosuppressive agents. Increased susceptibility to infection may occur. Careful development of lymphoma and other neoplasms may result from the degree of immunosuppression.

NEORAL® Soft Gelatin Capsules (cyclosporine capsules for microemulsion) and NEORAL® Oral Solution (cyclosporine oral solution for microemulsion) have been shown to increase bioavailability in comparison to Sandimmune® Soft Gelatin Capsules and Sandimmune® Oral Solution (cyclosporine oral solution, USP). NEORAL® and Sandimmune® are not bioequivalent and cannot be used interchangeably. When cyclosporine concentrations are monitored in patients taking NEORAL® and that dose adjustments be made in order to achieve target toxicities, the cyclosporine concentrations may initially be lower than those observed with Sandimmune®. For a given trough concentration, cyclosporine exposure will be greater with NEORAL® than with Sandimmune®. In general, the dose adjustments of Sandimmune® to NEORAL®, particular caution should be exercised. Comparison of blood concentrations in the published literature with blood concentrations obtained using current assays must be done with detailed knowledge of the assay methods employed.

INDICATIONS AND USAGE: NEORAL® is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allograft recipients. NEORAL® has been used in combination with azathioprine and corticosteroids.

CONTRAINdications: NEORAL® is contraindicated in patients with a hypersensitivity to cyclosporine or to any of its components.

WARNINGS: (See boxed WARNINGS)

Cyclosporine, the active ingredient of NEORAL®, can cause nephrotoxicity and hepatotoxicity when used at recommended doses. It is not unusual for serum creatinine and BUN levels to be elevated during cyclosporine therapy. These elevations in renal transplant patients do not necessarily indicate rejection, and each patient must be fully evaluated to determine this diagnosis is initiated.

Based on the historical Sandimmune® experience with oral, nephrotoxicity associated with cyclosporine, concentrations of 300 mg/m² or more, 38% of cases of liver dysfunction, and 37% of cases of liver transplant. Mild nephrotoxicity was generally noted 2-3 months after initiation of cyclosporine therapy. In a prospective study of liver transplant patients with serum cyclosporine at a range of 35-45 mg/dL and 2.0-2.5 mg/dl respectively. These elevations were often responsive to therapeutic intervention.

More overt nephrotoxicity was seen early after transplantation and was characterized by a rapidly rising BUN and creatinine. Since these events are similar to renal rejection episodes, care must be taken to differentiate cyclosporine-induced nephrotoxicity from rejection episodes.

A form of a cyclosporine-associated nephrotoxicity is characterized by serial determination in renal function and morphologic changes in the kidneys. From 5% to 15% of transplant recipients who have received cyclosporine therapy develop a renal insufficiency that is associated with a decrease in glomerular filtration rate and histologic evidence of interstitial fibrosis and tubulointerstitial nephropathy, and a stripped form of interstitial fibrosis with tubular atrophy. Though none of these morphologic changes is specific to cyclosporine nephrotoxicity, a diagnosis of cyclosporine-associated structural nephrotoxicity requires evidence of these findings.

When considering the development of cyclosporine-associated nephrotoxicity, it is noteworthy that several authors have reported that cyclosporine nephrotoxicity is associated with antihypertensive drug dose or is significantly high circulating trough levels of cyclosporine. This is particularly true during the first 3 months of cyclosporine therapy when the trough levels vary widely and when, in those cases, the organ appears to be more vulnerable to the toxic effects of cyclosporine. Among other contributing factors to the development of interstitial fibrosis in these patients is the prolonged time period, warm ischemia time, as well as episodes of acute rejection, and acute and chronic rejection. The reversibility of interstitial fibrosis and its correlation to renal function have not yet been determined. Reversibility of arteriopathy has been reported after stopping cyclosporine or lowering the dose.

Baseline renal function at any time requires close monitoring, and frequent dosage adjustment may be indicated.

In the event of severe and unrelenting rejection, when rescue therapy with pulse steroids and mononuclear and monoclonal antibodies to restore renal function to a level acceptable to the recipient to switch to preparative therapy rather than increase the Neoral® dose to toxic levels.

Cyclosporine has been shown to cause hypertriglyceridemia and microangiopathic hemolytic anemia which may result in graft failure. The vasculopathy may occur in the absence of rejection and is accompanied by azotemia. Administration of intravenous fluids, hemodialysis, or peritoneal dialysis may be required. Patients with renal dysfunction due to cyclosporine therapy are being monitored for signs of intravascular volume expansion.

As in patients receiving other immunosuppressants, those patients receiving cyclosporine are at increased risk for infections and should be monitored to prevent infection or malignancy, a treatment regimen containing multiple immunosuppressants should be used with extreme caution.

There have been reports of convulsions in adult and pediatric patients receiving cyclosporine, particularly in combination with high dose methotrexate.

Cyclosporine may cause elevation of serum triglyceride. (See PRECAUTIONS)

Because NEORAL® is not bioequivalent to Sandimmune®, conversion from NEORAL® to Sandimmune® using a 1:1 ratio (mg/kg/day) may result in lower cyclosporine blood concentrations. Conversion from NEORAL® to Sandimmune® should be done with the potential of undertaking dose adjustments in order to achieve target toxicities.

PRECAUTIONS: General: Cyclosporine is the active ingredient of NEORAL®. Hypertension is a common side effect and is relatively often seen during the early period of cyclosporine therapy. The increased hypertension is more frequent than severe hypertension and the incidence decreases over time. Anti-hypertensive agents should be used to control hypertension in those patients who require it.

Drug Interactions: Cyclosporine may reduce the level and bioavailability of oral and intravenous preparations of phenytoin, warfarin, glyburide, and theophylline. In some cases, the effects of these drugs are enhanced. Therefore, careful monitoring of the patients's response to these drugs may be required. Because of the potential for drug interactions, cyclosporine therapy should be initiated in consultation with a nephrologist. Patients should be advised to take the NEORAL® on an empty stomach.

Patients should be informed of the necessity of repeated laboratory tests while they are receiving the drug. Patients should be advised of the potential risks during pregnancy and informed of the increased risk of neoplasms.

Patients should be given careful dosage instructions. NEORAL® Oral Solution (cyclosporine oral solution for microemulsion) should be diluted, preferably with orange or apple juice that has room temperature. Grapefruit and grapefruit juice affect metabolism of cyclosporine and should be avoided. The combination of Neoral® Oral Solution (cyclosporine oral solution for microemulsion) with milk can be incomplete.

Patients should be advised to take NEORAL® on a consistent schedule with regard to time of day and relation to meals.

Laboratory Tests: Renal and liver functions should be assessed repeatedly by measurement of BUN, creatinine, serum bilirubin, albumin, AST, and ALT.

Drug Interactions: All of the individual drugs cited below are well substantiated to interact with cyclosporine.

Drugs That May Potentially Interact with Cyclosporine

Antihypertensives: agents that reduce systemic arterial BP may increase the dose or risk of cyclosporine-induced nephrotoxicity. Alpha-adrenergic blockers, beta-adrenergic blockers, ACE inhibitors, ARB, and diuretics may increase serum cyclosporine levels and toxicity. Concomitant use of these agents should be avoided. Because of the potential for drug interactions, cyclosporine therapy should be initiated in consultation with a nephrologist. Patients should be advised to take the NEORAL® on an empty stomach.

Drug Interactions: All of the individual drugs cited below are well substantiated to interact with cyclosporine.

Drugs That May Potentially Interact with Cyclosporine

Antibiotics: Fluoroquinolones, macrolides, and rifampin have been shown to increase serum cyclosporine levels and toxicity. Concomitant use of these agents should be avoided. Because of the potential for drug interactions, cyclosporine therapy should be initiated in consultation with a nephrologist. Patients should be advised to take the NEORAL® on an empty stomach.

Drug Interactions: All of the individual drugs cited below are well substantiated to interact with cyclosporine.

Drugs That May Potentially Interact with Cyclosporine

Drugs That Affect Cyclosporine Levels: Cyclosporine is extensively metabolized. Cyclosporine concentrations may be reduced by drugs that inhibit drug metabolism.
INNOVATION
Through Microemulsion

- Neoral® demonstrates intrasubject variability of drug exposure (%CV) [measured by the area under the concentration-vs.-time curve] in renal transplant recipients of 9% to 21% compared to 19% to 26% for Sandimmune® (cyclosporine)

- Neoral provides increased bioavailability with adverse events comparable to those of Sandimmune when the dosage of the two drugs is adjusted to achieve the same cyclosporine blood trough concentrations

- Routine monitoring is required and dosage adjustments may be necessary in both de novo patients and maintenance patients converted from Sandimmune to Neoral†

- Neoral and Sandimmune are not bioequivalent and cannot be used interchangeably without physician supervision

- Neoral offers an important option for the prevention of organ rejection in renal, liver, and heart allogeneic transplant recipients

NEORAL®
cyclosporine capsules and oral solution for microemulsion

*The principal adverse reactions of cyclosporine therapy are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia.
†For de novo patients, start with the same Neoral dosage you would use with Sandimmune. For maintenance patients, conversion to Neoral is generally safe and well tolerated. Start with a simple 1:1 dosage conversion to Neoral (see boxed warning). Adjust the Neoral dosage to attain preconversion blood trough concentrations. The daily dose of Neoral should always be given in two divided doses (b.i.d.).

Reference

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