



# SPNSG SPECTRUM

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## Protocol Changes for the MMF/IgAN Clinical Trial

As many of you know, we have run into considerable difficulty in terms of the entry criteria for patients wishing to enroll in this clinical trial. Most of the problems have resulted from patients having a urine protein/creatinine ratio level less than 1.0 on a first morning urine specimen. Following discussions among members of the patient safety committee and planning committee we have adopted a number of changes that will maintain the same requirement that patients have significant proteinuria (plus histologic changes suggestive of progressive disease) but at the same time avoid some of the losses from enrollment that we have encountered on a consistent basis (i.e.: 70–80% of the patients). Note that I have already discussed these with Dr. Norman Stockbridge who is director of the cardio/renal division at the FDA. The modifications to the protocol are listed below. Centers who have already obtained their local IRB approval (n=28) for this trial will be receiving amended protocols over the next week.

### A. Entry Criteria

1. **PROTEINURIA:** Patients will be eligible if they demonstrate a centrally determined protein excretion rate of  $\geq 1\text{g}$  per day **OR** a UPr/Cr  $\geq 1.0$  on an aliquot from a 24-hour urine collection. Patients who are receiving an ACE inhibitor will qualify for entry if their UPr/Cr ratio is  $\geq 0.8$  (females) or  $\geq 0.6$  (males).
2. **GFR:** The minimum acceptable GFR level at entry should be a)  $\geq 50\text{ml}/\text{min}/1.73\text{m}^2$  in patients who are not on an ACEi or b)  $\geq 40\text{ml}/\text{min}/1.73\text{m}^2$  in patients who are are on an ACEi.

### B. Laboratory criteria to be satisfied prior to randomization

1. The UPr/Cr ratio obtained on a 24-hour urine should be  $\geq 0.6$  in males and  $\geq 0.8$  in females.
2. The GFR must be  $\geq 40\text{ml}/\text{min}/1.73\text{m}^2$  prior to randomization.

### C. Patients who have previously failed the entry criteria may be reconsidered for the study

Patients who have already been consented, but failed the original entry criteria will be allowed to be re-evaluated using the new entry criteria, if they still want to join the study.

### D. Additional safety requirement

A basic metabolic profile will be added to the series of lab studies— 1-2 weeks after starting Phase 2 (i.e., ACE inhibitor/ OMACOR<sup>®</sup> phase) because of the inclusion of patients with GFR 40-60ml/min/1.73m<sup>2</sup>.

### E. Documentation of proteinuria prior to entry

Centers will be asked to document a urine protein excretion  $\geq 1\text{g}$  per day or UPr/Cr ratio  $\geq 1.0$  in potential study patients no more than 6 months before the pre-entry study visit.

The SPNSG will not hold a Fall Meeting this year. This is because we will be attending a meeting to discuss the NIH- sponsored multicenter trial of treatment options in patients less than 35 years of age with steroid-resistant FSGS. The meeting will be held during the ASN at the time and location noted below.

**SATURDAY, NOVEMBER 15th FROM 6-8 PM AT THE MANCHESTER GRAND HYATT, REGENCY BALLROOM A–C.**

This meeting is open TO ALL who are interested. Please try to attend if your schedule permits.





## Newsflash: ASN Announces a Clinical Trials Symposium

**MONDAY, NOVEMBER 17, 2003 10:00 a.m. - Noon Symposium on Clinical Trials Room 31**

We are pleased to report that the ASN has selected our two abstracts for inclusion in this symposium which will feature late breaking exciting data of clinical significance in four areas of nephrology. These studies emphasize the emerging emphasis on clinical studies in nephrology to translate basic science knowledge into clinical therapies.

**Note that this symposium was not listed in the ASN Preliminary Program (but is on the meeting website)**

*Moderators: Josephine P. Briggs, MD (NIH, Bethesda)*

*Paul L. Kimmel, MD, FACP (G. Washington University)*

### **The National Analgesic Nephropathy Study: An Update**

*William L. Henrich, MD*

*University of Maryland School of Medicine, Baltimore*

### **Dopamine Receptor 1 Agonists in Early Acute Tubular Necrosis: A Prospective, Randomized, Double Blind, Placebo-Controlled Trial of Fenoldopam Mesylate**

*James A. Tumlin, MD*

*Emory University, Atlanta, GA*

### **Results from the Southwest Pediatric Nephrology Study Group in IgA Nephropathy and Steroid Dependent Nephrotic Syndrome**

*Ronald J. Hogg, MD*

*Medical City Dallas Hospital, Dallas, Texas*

*(from Abstracts #SU-PO978 & #SU-PO979—shown below)*

### **Lipid Lowering and Cardiovascular Outcomes in Type-Two Diabetics on Dialysis: The 4D Trial**

*Christoph Wanner, MD*

*University Hospital, Wuerzburg, Germany*

*Multicenter, Placebo-Controlled Trial of Alternate-Day Prednisone (QOD-PRED) or Daily Omega-3 Fatty Acids (OM-3 FA) in Children and Young Adults With IgAN. R J Hogg, J Lee, N A Nardelli, D Cattran, G Hirschman and B A Julian*

**Abstract:** This randomized, placebo-controlled, double-blind study assessed if a 24 mo course of QOD-PRED (gp A), or daily therapy with purified OM-3 FA (gp B) slows the progression of renal disease when compared to placebo (gp C), in IgAN pts  $\leq 40$  yrs old. Entry criteria included estimated glomerular filtration rate ( $GFR_{est}$ )  $\geq 50$  ml/min/1.73 m<sup>2</sup> and moderate to severe proteinuria - defined as  $UPr/Cr \geq 0.5$  on a first morning specimen. Gp A pts received PRED 60mg/m<sup>2</sup> QOD x 3 mo; 40mg/m<sup>2</sup> QOD x 9 mos; then 30mg/m<sup>2</sup> QOD x 12 mo. Gp B pts received OM-3 FA 4g/day x 2 yrs (1.88g EPA, 1.48g DHA) with lower dose in pts with BSA  $< 1m^2$ . Gp C pts received placebo tablets or capsules simulating PRED or OM-3 FA. All pts were followed for at least 12 mo post-Rx. Hypertension was treated with enalapril 2.5 - 40mg qday for the entire study to maintain Blood pressure (BP)  $< 95$ th percentile. The primary endpoint was time to failure defined as  $GFR_{est} < 60\%$  of baseline, calculated using serum creatinine (SCr) levels measured by HPLC. An overall significance level of 0.10 was used. Ninety-six pts were randomized from 37 centers in the USA and Canada: 33 to gp A, 32 to gp B and 31 to gp C. Gps were comparable at baseline with respect to demographics, SCr, GFR and BP, but gp B pts had significantly higher  $UPr/Cr$  at entry than gp C ( $P=0.003$ ). Most pts (73%) completed 24 mo of Rx. Neither gp A nor B showed benefit over gp C with respect to time to failure with 14 pt failures overall (2 in gp A, 8 in gp B, 4 in gp C). The primary factor associated with treatment failure was baseline  $UPr/Cr$ ; with higher levels correlated with failure rate ( $P=0.005$ ) and time to failure ( $P=0.009$ ). During treatment,  $UPr/Cr$  fell significantly over time in both gps A and B. However, superiority of QOD-PRED or OM-3 FA over placebo in slowing progression of renal disease, based on change in  $GFR_{est}$ , was not demonstrated in this study of IgAN pts.

*Multicenter Trial of Mycophenolate Mofetil (MMF) in Children With Steroid Dependent or Frequent Relapsing Nephrotic Syndrome. R J Hogg, L Fitzgibbons, J Bruick, M Bunke, B Ault, N Baqi, H Trachtman and R Swinford*

**Abstract:** In this multicenter, prospective study, MMF was evaluated in 33 children with SDNS or FRNS in 14 pediatric nephrology centers. All pts were in remission at the time of entry. They received MMF in a liquid formulation (provided by Roche Labs) at an initial dose of 600mg/m<sup>2</sup> BID for 24 weeks, then a tapering dose for 4 weeks. Alternate day prednisone was also given during the first 16 weeks of MMF therapy. Urine protein was monitored at home by the parents using a dipstick. Treatment failure was defined as a relapse of NS, i.e., presence of edema, or 2+ proteinuria for 3 days, **plus** central lab urine protein/creatinine ratio 1.0 on first morning urine **or** serum albumin  $< 3.0$  g/dl. The pts had the following features at the time of study entry: Age: 6.8  $\pm$  2.7 years; Range: 2-15 years; 56% Male; 50% White; 25% African American; 25% Other. Entry Classification: 81% FR; 19% SD. Number of Pre-Entry Relapses: 4.3  $\pm$  2.3 per year. Eight pts (25%) relapsed while on MMF (5 relapsed while on both prednisone and MMF during the first 3 months of study, the other 3 relapsed while on MMF alone). Twenty-four of the pts (75%) stayed in remission throughout the 6 months of MMF therapy. Eight of these pts have stayed in remission during the entire post-MMF period (mean 12 months; range 7-21 months), whereas 16 relapsed 1-14 months after stopping MMF. Thirteen of these 16 pts were re-started on MMF by their primary physician post-study: 4 have subsequently stayed in remission, 5 have had infrequent relapses and 4 have had frequent relapses. We conclude from this study that MMF is an effective agent for maintaining remission in NS patients who receive treatment for at least 6 months and can effectively decrease the adverse events that occur with prednisone in such patients. Long-term controlled studies of MMF in pts with SDNS are warranted.