Vesicoureteral Reflux (VUR) Task Force Meeting
May 18, 2003

Participants

Anthony Atala, M.D.

Jack Elder, M.D.

Saul Greenfield, M.D.

Steven Koff, M.D.

Barry Kogan, M.D.

Michael Mitchell, M.D.

H. Gil Rushton, M.D.

Linda Shortliffe, M.D.

Craig Peters, M.D.

Claus G. Roehrborn, M.D.

Robert Mak, M.D., Ph.D.

Uri Alon, M.D.

Robert A. Weiss, M.D.

Monica Liebert, Ph.D.

Alejandro Hoberman, M.D.

Avital Cnaan, Ph.D.

Meeting Summary

On May 18, 2003, the NIDDK sponsored a strategic planning workshop on the potential for conducting a randomized controlled clinical trial in children diagnosed with vesicoureteral reflux (VUR). The meeting started with overviews of the two big issues facing physicians who take care of this group of patients. Dr. Linda Shortliffe presented an overview of when surgical interventions are indicated for VUR and what type should be used, and Dr. Alejandro Hoberman discussed if and when antibiotic use is indicated.

In her discussion of the surgical issue, Dr. Shortliffe addressed and discussed some important questions that could potentially be answered in a randomized, controlled trial. These questions included an assessment of whether or not surgical interventions improve outcomes and whether or not a delay abrogates potential benefit from intervention. Dr. Shortliffe outlined the pros and cons of the two surgical options—open repair and transurethral injection of bulking agents. The difficulties of choosing appropriate outcome measures that are of clinical importance and that could be assessed in a five-year clinical trial were clearly delineated. Potential candidates include end of reflux, episodes of pyelonephritis, impact on bladder function, renal growth, renal scarring, hypertension, and proteinuria. The difficulty in children is the need for long-term outcome measures.

Dr. Hoberman addressed the antibiotic issue and comprehensively reviewed the literature showing the lack of consistent correlation of VUR and renal scarring, as well as the lack of correlation of antibiotic use, urinary tract infection, and renal scarring. Therefore, he

made the argument that prophylactic antibiotics may not be necessary and may in fact be harmful with the development of antibiotic resistant organisms infecting the upper respiratory tract and ears of children treated long-term in this way.

After these opening overviews, potential protocols for clinical trials in children with VUR were presented.

- Dr. Greenfield presented a protocol that would compare observation (placebo), antibiotic prophylaxis, and transurethral injection of a bulking agent in 350 to 400 girls, ages 0 to 7 years, with grades I to III VUR. The rationale for excluding boys was that the incidence of VUR in boys is so much lower than in girls. The girls would be followed for five years and would be stratified by the presence or absence of dysfunctional elimination syndrome (DES). Assessments would include VCUG and DMSA scans at three and five years. Patients would also have a DMSA scan three months after a urinary tract infection. Outcome measures would include comparing the development of new renal scarring and the incidence of pyelonephritis and cystitis in the three treatment groups. In addition, the influence of voiding dysfunction and durability of the bulking agent would be assessed.

- Dr. Kogan presented a protocol that would compare immediate transurethral injection with a bulking agent to traditional management. The study would include patients ages 3 months to 16 years with grades I to IV VUR. All patients would be treated for DES. Primary outcomes would be rates of pyelonephritis, cystitis, and renal scarring. Dr. Kogan felt that the use of bulking agents would soon become widely practiced, so the window of opportunity to determine the true benefit of this therapy in this patient population was likely to be narrow.

- Dr. Atala presented a third protocol and pointed out some of the shortcomings of the only two major studies that have looked at VUR—the International Reflux Study (IRS) and the Birmingham Study. Both studies showed no difference in scarring when comparing medical and surgical treatment. However, IVPs were used for this assessment and not SPECT DMSA scans. His protocol would include patients with grades IV to V reflux and grade III with scars on SPECT DMSA scan. He considered these the surgical candidates and proposed comparing antibiotic prophylaxis and open surgery. DES would also be assessed in this group. The primary outcome measure would be scarring assessed by annual SPECT DMSA scans. Secondary outcomes would include renal growth, incidence of UTI, creatinine measures, and proteinuria. He also suggested studies to look at gene sequence changes associated with VUR.

- Dr. Hoberman presented a protocol to compare patients, ages 2 months to 36 months, randomized to prophylactic antibiotics or placebo. The protocol would include a dipstick check at home within 24 hours of a fever. The primary outcome measure would be renal scarring, assessed after 24 months. Secondary outcomes

would include incidence of re-infections, time to first re-infection, colonization with resistant bacteria, and direct and indirect resource utilization.

After input from Dr. Roehrborn on clinical trial design and Dr. Cnaan on statistical design, there was much spirited discussion. The meeting ended with a summary of possible areas to study:

1) There are conflicting data on the impact of prophylactic antibiotic treatment. Therefore, it was felt that a placebo-controlled trial in patients with grades I to III VUR is warranted. The cohort could be followed for DES. The outcome measures could be incidence of pyelonephritis and development of renal scars.
2) A comparison of surgical interventions: endoscopic injection of a bulking agent versus open repair. Patients with grades I to III VUR who fail trial #1 above, as well as all grade IV patients, could be randomized to these two treatment arms.
3) Comparison of preemptive surgical treatment and prophylactic antibiotics for patients with grade III VUR.