Addition Clinical Details

Two patients designated as having "primary ITP" also had neutropenia at entry. One of these patients had no previous history of neutropenia which resolved by week 3. Another patient with autoimmune, CTC grade 4 neutropenia at baseline had normal neutrophil counts by week 12. We elected to categorize this patient as primary ITP, since there was no evidence of other autoimmune disease, Evans or SLE. A third patient had grade 3 neutropenia at weeks 2 and 3 that resolved.

Two patients with Evans Syndrome who had grade 3-4 neutropenia (autoimmune pancytopenia) at study entry had stable neutrophil counts through week 12. Another patient with Evans Syndrome had grade 3 neutropenia at week 3 that improved to grade 1 at week 12. One patient with primary ITP had CTC grade 2 anemia at study entry secondary to prior bleeding, but by week 12, the hemoglobin was normal. No renal or hepatic toxicity was observed.

Pharmacokinetics

Pharmacokinetic measurements were collected from 14 subjects at week one and from 11 subjects at week four, divided arbitrarily into two age cohorts (above and below age 10 years). We had usable PK data from 15 subjects. Ten were measured at both time points; four at week 1 only; and one at week 4 only. All of those curves (14 total at week 1, 11 total at week 4) were included in the analysis. Within-subject correlation was accounted for, by including a subject random effect in the analysis of variance. The parameters from a two-compartment model are shown in supplemental Table A. The initial volume of distribution (V_1) for all patients, calculated by back extrapolation to t_0, approximated plasma volume at 53 mL/kg. While the number of data points obtained was not large,

rituximab clearance approximated a two-component process. Kinetics fit a two-component model, with relatively rapid initial half-time (exit) reflecting distribution out of plasma space, and equilibration representing slow return into the vascular pool. The drug elimination half-time was too slow to observe in these 7-day periods. Apparent half-time for initial redistribution from the plasma space was significantly longer for younger subjects at week 4 than at week 1 and was longer for younger subjects at week 4 than for older subjects at week 4 (Supplemental Table A). By comparison, in studies of 14 adults with lymphoma treated with rituximab at the same dosage regimen, the manufacturer reports mean serum half-time of 76 hours (range, 31-153) at week 1 and 205 hrs (range, 84-407) at week 4. There were no significant differences in kinetic parameters between the responders and non-responders. The reason for the difference in pharmacokinetic parameters between the two age cohorts is not readily apparent, but the shorter exit half-time in younger patients at week 1 compared to week 4 may correspond to a higher number of initially accessible B cells in young children.