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ORIGINAL ARTICLE

Pediatric Dosing of Rituximab Revisited: Serum Concentrations in Opsoclonus-myoclonus Syndrome

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Summary: To longitudinally assess serum concentrations of rituximab, it was administered intravenously to 25 children with opsoclonus-myoclonus syndrome at 375 mg/m^2 on each of 4 consecutive weeks with (Group I and II) or without (Group III) conventional immunotherapy. Serum rituximab levels, drawn before and after each infusion and at later intervals, were analyzed by enzyme-linked immunosorbent assay. Rituximab concentration increased stepwise with each infusion, dropping by the next infusion, thereby forming 4 discrete peaks (C_{max}) and troughs (C_{min}). It then fell precipitously to trace levels at 4 months. However, C_{max} and C_{min} curves differed significantly between groups. Compared with the youngest children (Group I), the oldest (Group III) had a 34% lower rituximab concentration at the fourth infusion, 45% less IgM depletion 1 month later, and received 20% less rituximab when the dose was recalculated as mg/kg. Serum IgM and rituximab levels were negatively correlated. Peak rituximab concentration did not correlate with adrenocorticotropic hormone dose. These results indicate that the degree of serum IgM depletion is a useful indicator for rituximab dose equivalency in children of different ages. They also suggest that pediatric rituximab dosing should be based on body weight, not surface area. (ClinicalTrials.gov NCT00244361).

Key Words: anti-B-cell agent, dancing eyes, IgM depletion, Kinsbourne syndrome, neuroblastoma, paraneoplastic syndrome, rituximab pharmacokinetics

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Rituximab, an anti-CD20 monoclonal antibody, has found a niche as B-cell depletion therapy for a growing variety of autoimmune diseases and malignancies involving B-cells.[1] Many of these disorders affect children.[2] Paraneoplastic opsoclonus-myoclonus syndrome (OMS), characterized by B-cell expansion in cerebrospinal fluid (CSF)[3,4] and B-cell infiltration of neuroblastoma,[5] is 1 such example. There have been several reports of clinical efficacy in OMS.[6–9]

However, the dosing of children with rituximab is based on guidelines and practices derived from adults. It is customarily calculated based on body surface area and given in weekly doses of 375 mg/m^2.[1] In addition, rituximab is frequently administered with conventional immunotherapy in autoimmune diseases, but the compatibilities and effects on rituximab levels have not been evaluated. Serum rituximab concentrations have not been studied systematically in children or in OMS.

This study involved the serial measurement of serum rituximab levels in the presence or absence of conventional immunotherapy with adrenocorticotropic hormone (ACTH) and intravenous immunoglobulins (IVIg).[10] It was part of an open-label, prospective, phase I/II clinical trial, the clinical aspects of which were reported.[11] As we noted earlier that serum IgM is the only immunoglobulin to be reduced by rituximab,[6] we tested its relation to rituximab concentration as a possible immunologic correlate.

PATIENTS AND METHODS

Group Designation

The National Pediatric Myoclonus Center recruited children with OMS from the USA and abroad. Parents of 25 meeting inclusion and exclusion criteria signed informed consent for this Institutional Review Board approved study (SCRIHS protocol #04-112) that was conducted from 2004 to 2007 and registered with the Food and Drug Administration (IND no. 11,771) and ClinicalTrials.gov (NCT00244361).

Three groups were designated to capture discrete OMS subpopulations based on OMS duration (Table 1). Group I (n = 12) was acute and started on rituximab and conventional immunotherapy (IVIg and ACTH) together, the agents delivered sequentially. In Group II (n = 8), rituximab was adjunctive to ongoing conventional agents. Group III, chronic and off all conventional agents, received rituximab alone. Group III patients were older because their OMS duration was longer. Mean OMS duration was 0.3 ± 0.2 years in Group I, 1.1 ± 1.7 years in Group II, and 8.6 ± 4.9 years in Group III.

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TABLE 1. Group Designation and Clinical Information

	Group I	Group II	Group III	P*
n	12	8	5	—
Age (y)	1.9 ± 0.52	3.1 ± 2.3	9.8 ± 5.1	< 0.0001 (I & II vs. III)
Range	(1.3-3)	(1.1-8.2)	(4.7-17)	—
Boys/girls	6/6	3/5	3/2	—
Etiology				
Tumor found	2	4	3	
No tumor found	10	4	2	
Tumor type				—
Neuroblastoma	1	3	3	
Ganglioneuroblastoma	1	1	0	
Tumor location				—
Thoracic	0	2	1	
Abdominal	0	2	2	
Pelvic	2	0	0	
Neuroblastoma stage				—
I	0	2	2	
II	1	1	1	
Mean baseline OMS score†	21.5 ± 6	14.5 ± 6	12.0 ± 8	0.011 (I vs. II & III)
Height (cm)	85.7 ± 4.4	96.6 ± 24.2	135.8 ± 30.4	0.0003 (I & II vs. III)
Weight (kg)	12.2 ± 2.0	18.8 ± 14.5	32.5 ± 19.9	0.015 (I vs. III)
Surface area (m^2)	0.56 ± 0.06	0.72 ± 0.35	1.10 ± 0.44	0.0056 (I vs. III)
Rituximab dose (mg/m^2)	375	375	375	—
Rituximab dose (mg/kg)	17.3 ± 1.1	16.3 ± 3.0	13.8 ± 2.4	0.016 (I vs. III)
ACTH dose at initial visit (IU/m^2)	0	50 ± 29	0	—
ACTH dose at 6 months (IU/m^2)	33 ± 17	37 ± 21	0	—

Data are means ± SD.

*ANOVA with significant Tukey posthoc comparisons in parentheses.

†Total score on OMS evaluation scale. Each of 12 items was rated 0-3, and the summed score was designated as mild (0-12 points), moderate (13-24 points), or severe (25-36 points).

The overall onset age of OMS, which was 1.6 ± 0.8 years, did not differ by group. A tumor was detected in 9 patients, but several lines of evidence suggest that neuroblastoma is the uniform causation of pediatric OMS within the neuroblastoma age range.[4] Some authors, however, designate the other cases as "viral" (see Ref.10). The motor severity of patients, as scored by a blinded observer from videotapes (see legend of Table 1),[6] was highest in Group I (the most acute). Groups I and II were moderately severe; Group III was mild. As a whole, there were 8 mild, 12 moderate, and 5 severe cases.

Rituximab

Rituximab (Rituxan), supplied by Genentech, Inc. (South San Francisco, CA)/Biogen IDEC (San Diego, CA), was infused IV once weekly for 4 consecutive weeks at a dose of 375 mg/m^2. Lot numbers were M26743, L89389, M37145, M85663, M67835.

ACTH

In Group I, a 52-week protocol for $ACTH_{1-39}$ (Acthar Gel, 80 IU/mL) (Questcor Pharmaceuticals, Union City, CA) was initiated at 75 IU/m^2 IM twice a day for 1 week, daily for 1 week, on alternate days for 2 weeks, then slowly tapering to 40 IU/m^2 over 2 months and more gradually over the next 7 months, until a final dose of 5 IU/m^2 was reached.[12] Prophylactic treatments were administered as described earlier.[6]

IVIG

In Group I, IVIg was induced at 2 g/kg (divided over 2 d) and maintained at 1 g/kg once a month with acetaminophen and diphenhydramine pretreatments. In Group II, patients were on once monthly maintenance. Various IVIg brands were used, depending on availability.

Rituximab Assay

Blood was drawn 15 minutes before rituximab infusion, then 15 minutes after completion of the approximately 6-hour infusion. Serum was aliquoted and frozen. Serum rituximab levels were quantified by a validated proprietary enzyme-linked immunosorbent assay of Genentech, Inc. through Covance Laboratories, Inc. (Chantilly, VA). The assay uses proprietary polyclonal goat antirituximab antibodies developed at Genentech as the capture reagent, and goat antibody to mouse IgG $F(ab')_2$ conjugated to horseradish peroxidase (Jackson Immuno Research Laboratories, Inc., West Grove, PA) as the detection reagent. The assay has a sensitivity of 500 ng/mL. Assays were done on batches of serum that were stored at −80°C and shipped on dry ice. Serum rituximab concentrations in this study compare favorably with those reported by others (μg/mL) using enzyme-linked immunosorbent assays based on polyclonal capture of rituximab.[13,14]

IgM Assay

Serum IgM was quantitated using the Tina-quant assay in the clinical laboratory (Memorial Medical Center, Springfield, IL).

Statistical Procedures

Serum rituximab concentration data were analyzed by 2-factor mixed models analysis of variance (ANOVA), in which 1 factor was repeated measurements, another factor was independent groups, and the interaction of both factors was tested. Each of the 4 postinfusion data points were

compared by 1-way repeated measures on the peaks, and a second 1-way repeated measures on the troughs. A doubly repeated measures design was used to look for an interaction between the slopes. Between groups, serum rituximab concentrations were compared by 1-way ANOVA with the Tukey post hoc test. For evaluating the relation of treatment group and patient age, analysis of covariance (ANCOVA) was considered. However, ANOVA with the addition of the covariate age was significant ($P = 0.0048$), which would make the results of ANCOVA unreliable. Clinical response and serum IgM concentrations were also analyzed by ANOVA with repeated measures.

RESULTS

Rituximab Concentration

After each infusion (Fig. 1), the serum rituximab concentration increased incrementally above the level after the earlier infusion, reaching the highest value by the fourth. In all groups combined (data not shown), the mean peak concentration increased sequentially to 232 ± 12, 326 ± 18, 350 ± 22, and 447 ± 29 μg/mL. Each postinfusion concentration dropped, but not as low as the prior preinfusion level. As peaks went up over time, so did troughs. Serum rituximab concentrations were highest at every infusion time point in Group I, and higher in Group II than in Group III. Interindividual variability can be appreciated from the range of peak levels in Group I, for example: first infusion, 136 to 372 μg/mL; second infusion 305 to 482 μg/mL; third infusion 280 to 591 μg/mL; fourth infusion 281 to 791 μg/mL.

One month after the last infusion, the serum rituximab concentration had dropped by 85% regardless of the group to 63 ± 7 μg/mL in the combined data. This concentration was similar to the trough level preceding infusion 2. Three months later, rituximab was nearly undetectable. At 6 months after the last rituximab infusion, 4 children had trace levels (0.56 to 3.4 μg/mL); none were in Group I.

Statistical analyses were done separately on postinfusion peaks (C_{max}) and preinfusion troughs (C_{min}) values (Fig. 2). The increase in C_{max} values was statistically significant in the Group I ($P < 0.0001$), Group II ($P = 0.0046$), and Group III ($P = 0.0035$). Peaks 2 and 3 did not differ significantly from each other in any of the groups, but peaks 3 and 4 were significantly higher than peak 1 in all groups. Within groups, all C_{min} serum rituximab concentrations differed significantly from each other ($P \leq 0.0002$), but the baseline zero value had to be excluded from the analysis because it lacked statistical variability.

Between-group comparisons revealed the C_{max} was significantly higher in Group I than Group III for infusion

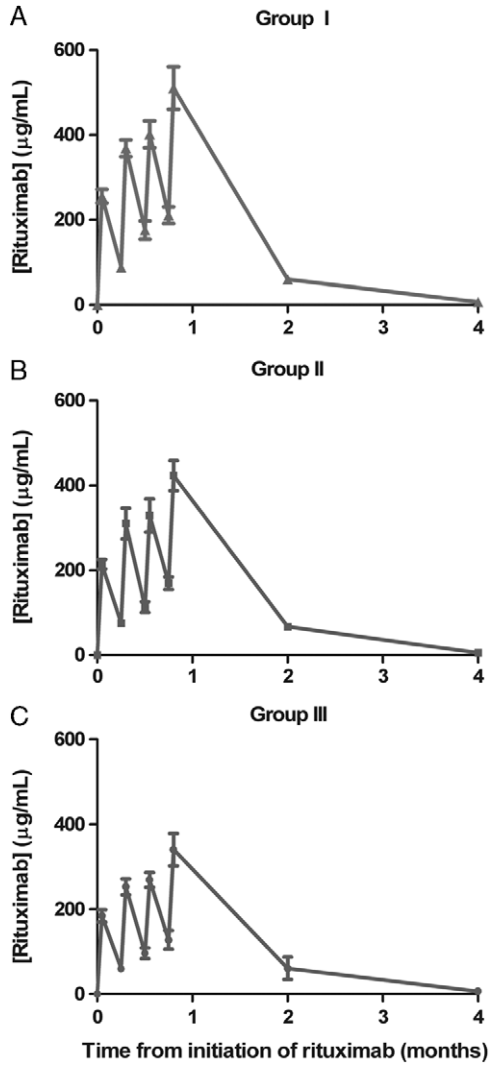

FIGURE 1. Serum rituximab concentrations by group. Data are means ± SEM. Although all patients received the same dose per body surface area, rituximab levels differed by group, as could be accounted for by dose recalculation according to body weight instead.

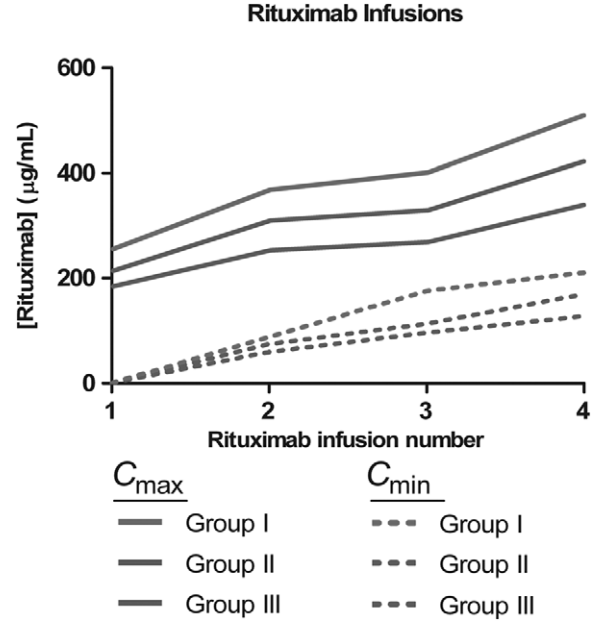

FIGURE 2. Serum rituximab concentration-versus-time profile per infusion with mean infusion C_{max} (peak) and C_{min} (trough) concentrations for each group. Data are means. The relation of C_{max} (solid lines) and C_{min} (dotted lines) concentrations is shown. For each group, all peaks (except 2 vs. 3) and all troughs differed significantly from each other.

TABLE 2. Serial Quantitative Serum IgM Concentrations (mg/dL) Per Treatment Group

		Months After Final Rituximab			
	Baseline	**1**	**3**	**6**	**12**
Group I	94 ± 10	29 ± 4*(−69%)	14 ± 3*(−85%)	32 ± 8*(−66%)	52 ± 6*(−45%)
Group II	98 ± 11	33 ± 5*(−66%)	19 ± 3*(−81%)	32 ± 7*(−67%)	45 ± 16*(−54%)
Group III	109 ± 21	83 ± 23*(−24%)	71 ± 25*(−35%)	72 ± 15*(−34%)	67 ± 35*(−39%)

Means ± SEM.
Laboratory reference ranges for serum IgM were 47-200 mg/dL.
% depletion is given in parentheses.
*Statistically significant by the mixed procedure repeated measures, $P < 0.0001$ for each treatment group.

1 ($P = 0.039$, ANOVA), but not for infusion 2 ($P = 0.055$), 3 ($P = 0.055$), or 4. However, C_{min} values differed between those groups for infusion 2 ($P = 0.0006$), 3 ($P = 0.021$), and 4 ($P = 0.039$).

When the rituximab dose was recalculated based on body weight (mg/kg) instead of surface area (Table 1), there was a significant difference in doses between groups ($P = 0.016$, ANOVA). In Group III, the dose expressed as mg/kg was 20% less than in Group I (Tukey, $P < 0.05$); its serum rituximab concentration at the fourth rituximab infusion was 34% less. Dosage differences paralleled the serum rituximab concentration differences.

To explore whether ACTH affected serum rituximab levels in Group I, 3 children who received rituximab a week before ACTH were compared with 9 others who started ACTH first. Comparisons were made in the peak and trough rituximab concentration after the first rituximab infusion. The peaks (mean ± SEM) did not differ statistically between subgroups: 275 ± 22 μg/mL versus 249 ± 20 μg/mL, respectively. The troughs also were not significantly different: 92 ± 5 versus 87 ± 4, respectively.

Clinical Response

Only Group I and II patients responded clinically to treatment. In Group I, mean total score declined significantly at all time points ($P < 0.0001$): 42% at 1 month, 54% at 3 months, 72% at 6 months, and 78% at 1 year. The net decrease in total score was 16 ± 2 scale points, more than a full severity category. In Group II, total score fell by 45% at 1 month ($P = 0.001$), 53% at 3 months, 56% at 6 months, and 66% at 12 months (all $P < 0.0001$), a net improvement of 11 ± 3 scale points. At the 6 month evaluation, 13 of 23 patients had improved by more than or equal to 6 scale points, 8 by more than or equal to 12 points, 5 by more than or equal to 18 points, and 1 by more than or equal to 24 points. All but 4 of these individuals were in Group I.

ACTH dose was tapered in Group I to 17 ± 3 IU/m^2/d by 6 months, and 9 ± 2 (range 0 to 16) by 1 year, a total decrease of 92% ($P = 0.0013$). In Group II, the respective doses were 38 ± 3 (initial), 19 ± 4 at 6 months, and 11 ± 4 at 1 year (range 0 to 22), a 60% reduction ($P = 0.0007$). By the end of the study, 3 of 11 patients were off ACTH in Group I and 2 of 4 in Group II, which was one-third of all ACTH-treated children.

In Group III, no patient improved even by 6 scale points at 6 months and only 1 did at 12 months. The total scores of the most severe case were 24, 20, 20, and 23 at each respective infusion; 23 at 1 month; 20 at 3 months; 19 at 6 months.

IgM Response

Serum IgM concentration was significantly lower at 1 month in each treatment group (Table 2), but least of all in Group III. The IgM level did not differ significantly between groups, but there was 45% less depletion in Group III. Group I and II IgM concentrations did not differ significantly between each other. The start of IgM recovery was apparent at 3 months, continued through the study period, but was not complete at 12 months (still 39 to 54% depletion). However, differences between groups at 12 months were no longer statistically significant.

Correlations

For each group separately, Pearson correlations were done between patient age and rituximab dose in mg/kg. In Group II ($r = -0.90$, $P = 0.0023$) and Group III ($r = -0.99$, $P = 0.0002$), age and dose were highly correlated. The relationship was less constant in Group I ($r = -0.60$, $P = 0.40$).

There was a trend toward correlation of peak serum rituximab concentration with rituximab dose expressed as mg/kg in the combined groups, but not in individual groups (Table 3). It correlated with patient age, height, weight, and surface area. There was no correlation with ACTH dose.

DISCUSSION

This study shows similarities and differences in serum rituximab levels of children and adults after 4-dose rituximab treatments.[15] In both, the pattern of peaks and troughs[16] is similar, corresponding to a 2-compartment model,[17] although data in children are limited.[18] In adults, the elimination half-life ($T_{1/2}$ *rm*) was 3 weeks, and total systemic clearance ranged from 3.1 to 11.9 mL/h/m^2.[15] We

TABLE 3. Correlations With Peak Serum Rituximab Concentration (C_{max})*

	r	***P***
Cumulative rituximab dose (mg/kg)	0.42	0.047†
Patient age	−0.50	0.011†
Body weight	−0.49	0.013†
Height	−0.42	0.038†
Body surface area	−0.45	0.024†
Serum IgM concentration at 3 months	−0.53	0.015†
% Blood B-cells at 1 months	0.23	0.27
% Blood B-cell at 6 months	0.02	0.92
% CSF B-cells at 6 months	0.15	0.48
ACTH dose	0.24	0.33

*Combined groups.
†Statistically significant Pearson correlations.

have insufficient early data for mathematical modeling as a population pharmacokinetic study to look at body composition and volume of distribution as potential factors.[17] When the study was designed, there was no information to suggest that age and rituximab dose would be confounded; it was an early phase trial to look at different OMS subpopulations. Now that the unexpected age factor has been observed, however, it has to be reconciled. We since located a poster abstract from a small pharmacokinetic study in pediatric chronic immune thrombocytopenic purpura, in which the rituximab half-time was inexplicably longer for younger patients than for older ones at week 4.[18]

As body-weight-based rituximab dosing gave a better indication of serum rituximab and IgM concentrations, it seems reasonable that pediatric rituximab dose be based on body weight, such as IVIg dosing, not body surface area. Chemotherapy for children weighing 10 to 15 kg is usually calculated according to body weight to prevent overdosing, so this approach would be consistent. We do not think the younger children in our study received too much rituximab, rather, the older children were probably underdosed by the surface area-based calculation: they had less IgM depletion and did not respond clinically. A pediatric dose of 17 mg/kg per infusion is supported by our data, which would result in a total dose of about 70 mg/kg. This higher dose would seem to be well tolerated, as we have safely delivered 750 mg/m^2 as a single infusion or given 6 standard dose infusions (unpublished observations). In children, 6 weekly rituximab doses of 375 mg/m^2 have been used to treat refractory autoimmune hemolytic anemia.[19]

There are also other reasons for rethinking the body surface area-based rituximab dosing. Body surface area was introduced to predict a safe starting dose in phase I oncology trials from preclinical animal studies, but its use in oncology became widespread.[20] In the case of rituximab, there are not the serum concentration studies to support it.[14] No rationale for body surface area-based dosing of rituximab was found in rheumatoid arthritis.[17]

A less likely explanation for group differences in rituximab levels is that conventional immunotherapy altered rituximab kinetics. The highest serum rituximab concentrations were in Group I (high-dose ACTH), intermediate levels in Group II (lower-dose ACTH), and lowest in Group III (no ACTH). However, ACTH dose was inextricably linked to OMS acuteness in this study and, hence, age and body weight. In addition, peak and trough rituximab concentrations after the first infusion were not significantly higher in patients who were started on ACTH before rituximab, and rituximab concentration did not correlate with ACTH dose. IVIg dose and dose frequency were a constant between Group I and II. If IVIg saturated FC receptors, theoretically, it could interfere with rituximab binding or B-cell eradication, because the FC part of rituximab and receptors for the FC portion of IgG are needed to accomplish phagocytosis and antibody-dependent cellular cytotoxicity by immune cells.[1] In this study, however, B-cell killing was similar among groups, even with rituximab monotherapy.[21]

Group III alone did not respond clinically, perhaps owing to lower rituximab concentrations. However, OMS was chronic in those patients and had persisted despite earlier conventional immunotherapy, so it may have been untreatable. Only a dose-response study could resolve this issue. Blood B-cell levels were not indicative of rituximab concentration at the dose used.[13] A dose-ranging study that included subtherapeutic doses of rituximab would be necessary to establish a dose-effect on B-cell depletion. However serum IgM depletion did differ significantly between groups, indicating utility as a surrogate marker for rituximab dose comparisons. Although it has been shown by us and others that IgM is the only serum immunoglobulin to change appreciably in concentration after rituximab therapy, little clinical use has been made of this observation.

Rituximab levels are not easily obtained, because detection has depended on proprietary sources of antirituximab antibodies, resulting in in-house assays. Only free rituximab concentrations are measureable currently, whereas most of the antibody is bound. Rituximab also may be released from coated unlysed B-cells or lymph nodes.[15] Higher serum concentrations could reflect more unbound rituximab, but the lower associated IgM levels suggest that was not the case in our study. Low levels have been detected in the CSF of a few adults,[22] but CSF rituximab concentration has not been studied systematically.

Although this study uncovered some unexpected issues, the cause of which lay outside the study design, it serves to inform future trials in this patient group so the same problems are not encountered. Larger studies of more homogeneous patient populations will be needed to confirm these results.

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