WriteClick: *Editor's Choice*

Editors' Note: Commenting on the study on the capacity of patients with Parkinson disease (PD) to consent to research by Karlawish et al., Abe raises important questions and observations on cognitive research in PD. Kim and Kim and Xu et al. critique the Yang et al. study on reduced dosage of rituximab in neuromyelitis optica (NMO). The authors agree with some of their points but also discuss the unclear relationship between clinical effects in NMO and exact numbers of B-cell counts.

—Chafic Karam, MD, and Robert C. Griggs, MD

COGNITIVE IMPAIRMENT AND PD PATIENTS' CAPACITY TO CONSENT TO RESEARCH

Kazuo Abe, Osaka, Japan: As Drs. Marson and Hershey[1] stated in their accompanying editorial, Karlawish et al.[2] provided a welcome and timely scientific contribution to the field of PD clinical research. Ability to consent is crucial in determining effective treatment and research decision making for patients with PD.[3,4] Karlawish et al. investigated research consent capacity (RCC) in patients with PD by using the MacArthur Competence Assessment Tool for Clinical Research (McCAT-CR). The authors found that patients with PD with both borderline impaired and impaired cognition had impairments in RCC, whereas cognitively normal patients with PD did not.

However, the authors did not mention slowing of reaction time or cognitive processing, which are major indicators of cognitive dysfunction. In addition, was there enough time given for the authors' consent process during assessment of the McCAT-CR? Clinicians usually observe patients with PD hesitating or showing no reaction during assessment of cognitive function, yet these reactions do not reflect lack of comprehension. The authors' answers to these questions may be helpful in developing rational processes for research consent in patients with PD.

Author Response: Jason H. Karlawish, Philadelphia: We thank Dr. Abe for his thoughtful comments. People with PD—even those without obvious cognitive impairment—routinely experience psychomotor slowing, including delays in task completion and responses to questions. As a result, we avoided using these measures to determine level of cognitive impairment or to screen cognition for comparison with capacity evaluations. Our evaluators were experts in the assessment and evaluation of PD and thus understood the importance of allowing ample time for responses.

Nevertheless, Dr. Abe raises an intriguing question that we cannot yet answer: How do not only the cognitive but also the motor and affective characteristics of the person being evaluated influence a capacity evaluator's judgment? There are insufficient data to answer this question, especially in PD. In Alzheimer disease, capacity experts have wondered how long information must be retained or how well "the big picture" must be grasped in order to find a person capable of research consent.

In PD, symptoms such as reduced verbal retrieval, blunted affect, and motor slowing may be associated with capacity judgments, but that analysis was beyond our scope. Our focus was on the association between global measures of cognitive performance and capacity evaluation in PD.

1. Marson DC, Hershey LA. Decisional capacity in cognitively impaired patients with Parkinson disease. Neurology 2013;81:1–2.
2. Karlawish J, Cary M, Moelter ST, et al. Cognitive impairment and PD patients' capacity to consent to research. Neurology 2013;81:801–807.
3. Determining Capacity to Consent. Dialogue. Available at: http://www.cpso.on.ca/uploadedFiles/policies/policies/policyitems/capacity_consent_july07dialogue.pdf. Accessed August 30, 2013.
4. Nicholson TR, Cutter W, Hotopf M. Assessing mental capacity: the Mental Capacity Act. BMJ 2008;336:322–325.

RESPONSIVENESS TO REDUCED DOSAGE OF RITUXIMAB IN CHINESE PATIENTS WITH NEUROMYELITIS OPTICA

Ho Jin Kim, Su-Hyun Kim, Goyang-si, Gyeonggi-do, Korea: Yang et al.[1] reported on reduced-dose rituximab treatment in NMO. To demonstrate the efficacy of rituximab, it is critical to show the relationship between the clinical response and B-cell depletion. Low-dose rituximab requires greater vigilance than conventional dosages, and appropriate monitoring is essential. However, the irregular B-cell monitoring (sometimes greater than 15 weeks) in this study is

inadequate for determining the B-cell kinetics following low-dose rituximab. Consequently, the infusions were often administered after the reconstitution of B cells (greater than 3.5%) and exceeded the therapeutic target (greater than 1%). No relapse occurred despite marked reconstitution of B cells. Perhaps the result is not just a treatment effect but largely related to the effect of regression toward the mean, especially considering the low pre-relapse rate (less than 0.5 in 2 patients) and short-term follow-up in this study. More importantly, the reinfusion frequency is unclear (figure 1 is discordant with the table for 3 of 5 patients). Finally, since B-cell reconstitution usually occurs 6 to 8 months after the conventional dosage in other studies,[2,3] the B-cell suppression lasting more than 8 months in 3 of 5 patients following such a low dose of rituximab is very unusual.

Jun Xu, Xin-xin Cheng, Jia-ren Xu, Nanjing, China: Yang et al.[1] reported that a reduced dose of rituximab modified disease progression in NMO. However, the small number of patients, the short follow-up, and the unclear reinfusion frequency reduced the reliability of this study. Even with regular rituximab treatment, 87% (26/30) of patients with NMO spectrum disorder exhibited a marked reduction in annual relapse rate over the 5-year follow-up.[4]

We report a 13-year-old girl with a 4-year NMO history who relapsed twice in less than 8 months after the conventional rituximab treatment (375 mg/m^2 infused once weekly for 4 weeks). The repopulation of reduced total CD19+ B cells (less than 1%) and the memory component of CD19+ CD27+ B cells (less than 0.05%) indicated B-cell depletion. We postulate that the age at onset of 9 years, typical optic neuritis attacks, and longitudinally extensive transverse myelitis lesion segments (C3 to T12) could be negative predictors of rituximab reinfusion. In addition, her positive family history of autoimmune disorders suggests that genetic NMO susceptibility testing could have been helpful before initiating rituximab treatment.

Author Response: Fu-Dong Shi, Chun-Sheng Yang, Li Yang, Ting Li, Wei-Na Jin, Tianjin, China: Kim et al.[1] raised some valid issues. To monitor B-cell repopulation and disease activities more vigorously after rituximab infusions, the patients with NMO enrolled in this study were scheduled to revisit our clinic every 8 weeks to undergo clinical assessments, MRI scans, and determination of peripheral B-cell counts. However, a few patients did not follow these schedules. Rituximab was immediately given when their B-cell count exceeded 1%. For patients with NMO free of relapses during the observational period, it would be inadequate to fully attribute this to natural history because the majority of the patients become progressive over time. In one patient, the B-cell count is still 1.08% 15 months after the last rituximab infusion. Our findings prompt the question whether the dosage used for B-cell malignancy would be appropriate for NMO. Furthermore, the relationship between clinical effects and exact numbers of B-cell counts is unclear. It is possible that beneficial effects achieved by rituximab are not entirely dependent on B-cell count, as antigen presentation, release of multiple cytokines, and production of pathogenic antibodies by B cells[5] are some of the presumed mechanisms.

1. Yang CS, Yang L, Li T, et al. Responsiveness to reduced dosage of rituximab in Chinese patients with neuromyelitis optica. Neurology 2013;81:710–713.
2. Pellkofer HL, Krumbholz M, Berthele A, et al. Long-term follow-up of patients with neuromyelitis optica after repeated therapy with rituximab. Neurology 2011;76:1310–1315.
3. Leandro MJ, Cambridge G, Ehrenstein MR, et al. Reconstitution of peripheral blood B cells after depletion with rituximab in patients with rheumatoid arthritis. Arthritis Rheum 2006;54:613–620.
4. Kim SH, Huh SY, Lee SJ, et al. A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. JAMA Neurol 2013;70:1110–1117.
5. Krumbholz M, Derfuss T, Hohlfeld R, Meini E. B cells and antibodies in multiple sclerosis pathogenesis and therapy. Nat Rev Neurol 2012;8:613–623.

Author disclosures are available upon request (journal@neurology.org).

Responsiveness to reduced dosage of rituximab in Chinese patients with neuromyelitis optica

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