Rituximab Combo Eases Neuropsychiatric SLE

BY KATHRYN DE MOTT Senior Editor

VIENNA — B-cell depletion with rituximab led to significant improvements in patients with CNS neuropsychiatric disability associated with systemic lupus erythematosus, according to a preliminary report presented by C. Michael Neuwelt, M.D., at the annual European Congress of Rheumatology.

In his investigation, Dr. Neuwelt, of the University of California, San Francisco, and Stanford University, Palo Alto, studied 22 patients who met American College of Rheumatology criteria for CNS-NPSLE disability.

In addition, at baseline, patients met at least one of three criteria: abnormal brain MRI, severe progression of cognitive impairment as shown by neuropsychological testing, or cerebrospinal fluid pleocytosis with or without intrathecal elevation of IgG synthesis and/or oligoclonal banding.

Among the participants in the single-center study, 12 were treated with rituximab monotherapy, 7 were treated with a combination of rituximab and IV cyclophosphamide (IV-CYC), and 3 patients received plasmapheresis synchronized with IV-CYC and were maintained on rituximab for prolonged B-cell suppression.

After up to 18 months’ follow up, 72% of the 19 patients treated with either rituximab alone or in combination with IV-CYC showed improved spontaneous behavior. The three patients on triple therapy did not improve and required new therapy regimens.

In addition to monitoring changes on the objective parameters, Dr. Neuwelt emphasized that in at least one case, the patient actually had a disease flare with worsening brain lesions follow-

ing a switch from her prestudy regimen of IV-CYC to rituximab monotherapy.

In the case, combination IV-CYC and rituximab led to significant improvement over baseline. (See MRI images before and after combination therapy, at right.)

Further research is needed to determine the best candidates for rituximab monotherapy and which patients will require combination therapy, said Dr. Neuwelt, who is on the advisory board for Genentech Inc., the manufacturer of rituximab (Rituxan).

However, he did not receive funding from Genentech for his study.

Outcomes from his observational study of 22 patients compared well with earlier, published reports of similar patients treated with IV-CYC with and without plasmapheresis, Dr. Neuwelt explained at the meeting, sponsored by the European League Against Rheumatism.

The previous reports, which defined outcome end points in the same manner as the current study, found a 61% rate of improvement among 31 severe CNS-NPSLE patients treated with IV-CYC (Ann. J. Med. 1995;98:42-41).

Another study, also conducted by Dr. Neuwelt, found a 74% rate of improvement among 26 severe CNS-NPSLE patients who were treated with plasmapheresis either alone or synchronized with cyclophosphamide (Ther. Apher. Dial. 2003;7:173-82).

The lack of head-to-head trials comparing rituximab to other therapies is indicative of the challenges facing lupus therapy investigations.

Clinical trials of lupus patients are notoriously difficult to conduct, given the heterogeneity of the patient population. And CNS is the most difficult aspect of lupus, according to a preliminary indication, Donald Marion, M.D., told this interview.

“We don’t know a lot about the pathogenic mechanisms” that lead to neuropsychiatric manifestations of SLE.

“That’s an area that we know the least about,” and yet it takes a considerable toll on quality of life,” he said.

There are no exact end points with which to measure changes in this manifestation, which makes it a difficult aspect of SLE to study.

He added that better tools to measure patient-centered outcomes in SLE—specifically, ones targeting neuropsychiatric markers—need to be developed.

The justification for trying rituximab in a CNS-NPSLE population is speculative at this time. However, similarities between lupus of the brain and multiple sclerosis exist.

In MS, the importance of B cells and antibody-mediated demyelination comes from histopathologic studies of CNS tissue and analysis of CSF. Similar studies need to be done in the CNS tissue and CSF of CNS-NPSLE patients, Dr. Neuwelt said.

The prevalence of neuropsychiatric disorders in SLE has been found to range from a low of 37% to a high of 95% in various studies.

The most common effects are cognitive dysfunction (55%-80%), headache (24%-72%), mood disorder (14%-57%), cerebrovascular disease (5%-18%), seizures (6%-51%), polymyelopathy (3%-28%), anxiety (7%-24%) and psychosis (0%-8%), according to John Hanly, M.D., head of the rheumatology division at Dalhousie University, Halifax, Nova Scotia.

IV Corticosteroids Increase Deaths From Traumatic Brain Injury

BY JANE SALODOF McNEIL Southwest Bureau

Findings from the Corticosteroid Randomization andEARlier Signiﬁcant Head Injury (CRASH) trial that intravenous corticosteroids increased mortality among patients with traumatic brain injury should put to rest once and for all questions about the role of steroids for this indication, Donald Marion, M.D., told this newspaper.

Current guidelines on the management and prognosis of severe head injury do not recommend use of intravenous corticosteroids, said Dr. Marion, a Boston-based senior research fellow at the Brain Trauma Foundation, New York.

Intravenous steroid use for this indication, Marion noted in his interview with this newspaper that “the question they [the CRASH researchers] really needed to answer was not whether steroids were bad, but whether steroids improve outcome. ‘They not only proved steroids did not improve outcome but also that people who had steroids had worse outcomes... Those people who are following evidence-based medicine are not likely to use steroids.’