Rituximab Combo Eases Neuropsychiatric SLE

BY KATHRYN DEMOTT
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 improvement. 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 measured patient outcomes using several standard SLE disease activity indices.

Dr. Neuwelt emphasized that in at least one case, the patient actually had a disease flare with worsening brain lesions following a switch from her prestudy regimen of IV-CYC to rituximab monotherapy.

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

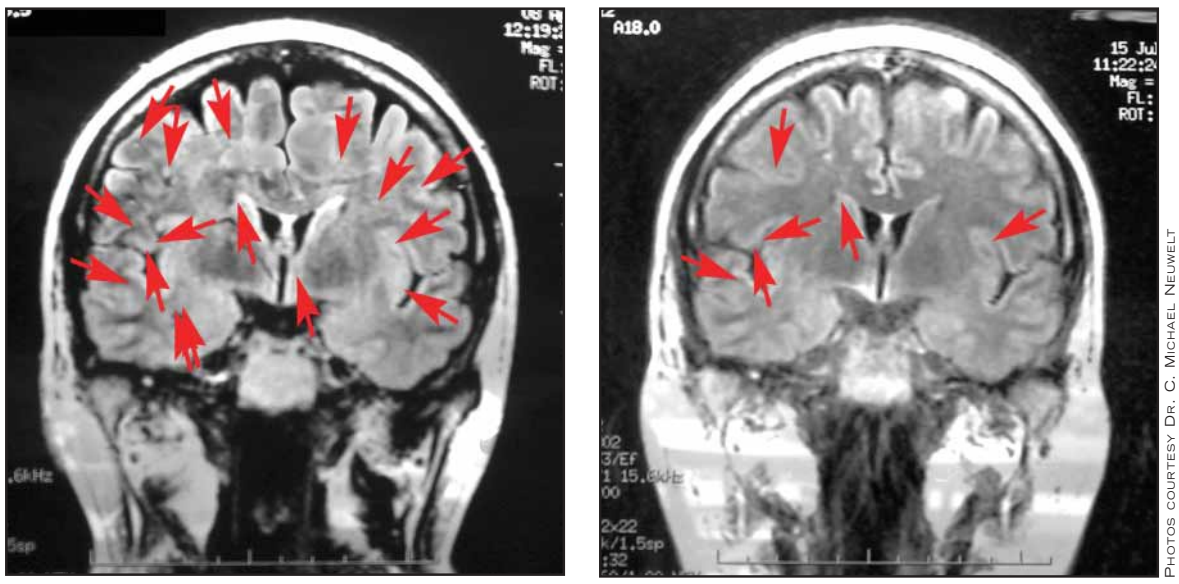
Further research is needed to determine the best candidates for rituximab monotherapy and which patients will require combination therapy, said Dr. Neuwelt, who is on the advisory board for Genentech Inc., the manufacturer of rituximab (Rituxan).

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.

Those 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 (Am. J. Med. 1995;98:32-41).

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).



PHOTOS COURTESY DR. C. MICHAEL NEUWELT

A 45-year-old patient with severe CNS-NPSLE was switched from IV-CYC to rituximab monotherapy. A baseline brain MRI in April (left) showed progression of lesions. After a disease flare, IV-CYC was added. After the combination therapy, an MRI in July (right) showed a reduced number of lesions.

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 to pin down, Dr. Neuwelt said in an 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%), polyneuropathy (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 MACNEIL
Southwest Bureau

Findings from the Corticosteroid Randomization After 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 has been on the decline for at least 10 years in the United States. A decade ago, 60%-70% of physicians used steroids in the treatment of traumatic brain injury (TBI); today that has dropped to about 20%.

Negative findings from the unusually large British CRASH trial of more than 10,000 patients should end debate over use of corticosteroids after head injuries, according to Dr. Marion.

Investigators in the United Kingdom randomized 10,008 adult TBI patients to a 48-hour infusion of methylprednisolone or placebo. They reported 25.7% of the corticosteroid group but only 22.3% of the placebo group died within 6 months of entering the CRASH trial.

'The absence of evidence of any neurologic benefit from corticosteroid treatment might also have implications for [its] use in spinal cord injury.'

Although fewer patients developed severe disability on corticosteroids, the combined outcome of death or severe disability still favored the placebo. In the corticosteroid arm, 38.1% were dead or severely disabled at 6 months, compared with 36.3% of the control group (Lancet 2005;365:1957-9).

"These analyses lend support to the conclusion … that corticosteroids should not routinely be used in the treatment of head injury," the CRASH trial collaborators stated in a research letter.

The results provide "clear evidence that treatment with corticosteroids following head injury affords no material benefit," according to the investigators.

"The absence of evidence of any neurologic benefit from corticosteroid treatment might also have implications for the use of corticosteroids in spinal cord injury, which should remain an area for debate."

The trial randomized patients with a Glasgow Coma Scale score of 14 or less within 8 hours of head injury. All patients received a 48-hour infusion of either placebo or methylprednisolone, which Pfizer provided.

The 6-month analysis was based on follow-up data for 9,673 patients (96.7%): 4,854 on corticosteroids and 4,819 patients on placebo.

At that point, a total of 1,248 corticosteroid patients and 1,075 placebo patients had died.

Conversely, 2,213 placebo patients (45.9%), but only 2,120 corticosteroid patients (43.7%), had made a good recovery. Stratification by severity of head injury and time from injury produced no substantial differences.

Dr. 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." ■

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