B-Cell Depletion Shows Promise in CNS-NPSLE

BY KATHRYN DEMOTT
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 and/or 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.

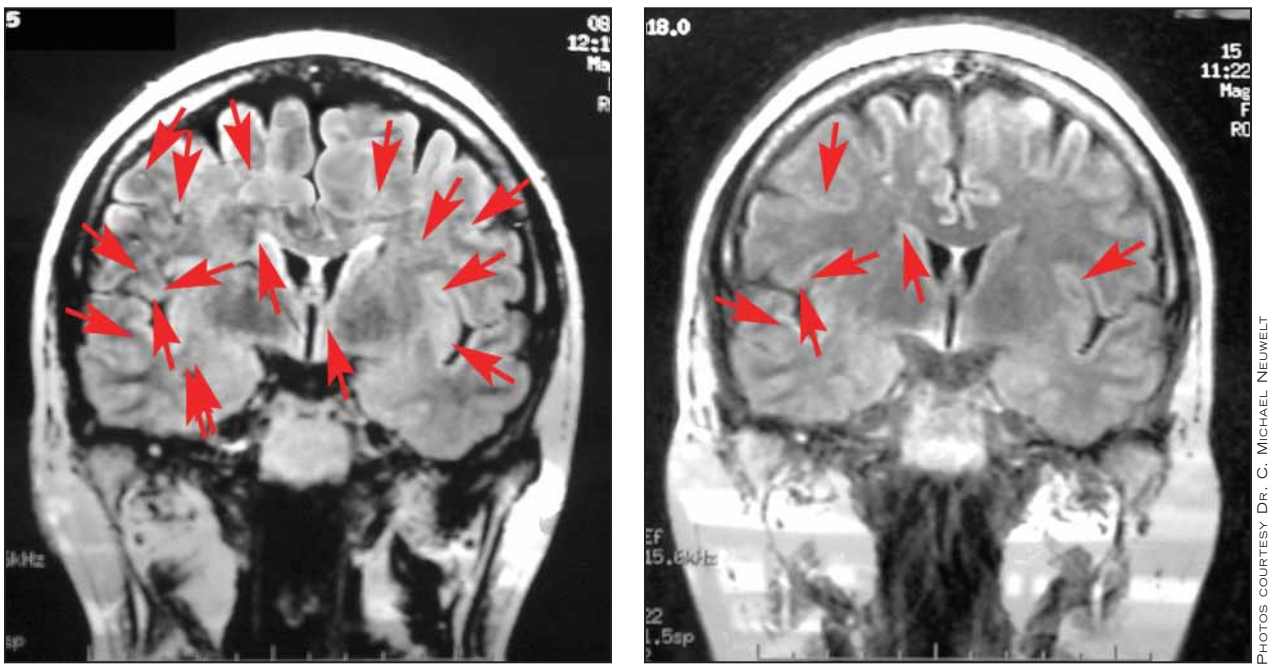
After up to 18 months' follow up, 72% of the 19 patients treated with either rituximab alone or in combination with IV-CYC showed improvement. The three patients on triple therapy did not improve and required new therapy regimens.

In addition to monitoring changes in the objective parameters, patient outcomes were measured 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).

Further research is needed to identify 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 for his study.

Outcomes from his observational study of 22 patients compared well to 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.



Photos courtesy Dr. C. Michael Neuwelt

A 45-year-old woman was switched from IV CYC to rituximab monotherapy. Shortly after the switch, the patient's disease flared and a brain MRI in April (left) showed progression of her lesions. IV CYC was then added back to her regimen. A follow-up MRI in July showed the number of lesions was reduced on the combination.

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 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 effects are 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 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, 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 37% to 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. Dr. Hanly also presented on CNS-NPSLE at the meeting. ■

Initiate Prevention of Steroid-Induced Bone Loss in SLE Early

BY NANCY WALSH
New York Bureau

BIRMINGHAM, ENGLAND — All patients with systemic lupus erythematosus who are taking 7.5 mg prednisone or more daily should be treated to prevent bone loss, Bevra Hahn, M.D., said at the joint meeting of the British Society for Rheumatology and the German Society for Rheumatology.

Almost everyone loses bone mass at that level of steroid treatment, and relatively rapidly. "We know most bone loss occurs in the first 12 months of steroid treatment, so there isn't any point … waiting until the disease goes into remission—and lupus hardly ever goes into true remission—or waiting until they are better or their drug regimen is simpler," she said.

Despite the fact that estrogen therapy is "out," there are still treatment options. Calcium plus vitamin D supplementation is a typical initial approach, and has a small but measurable impact on reducing the degree of bone loss.

Another choice would be to use a vitamin D metabolite such as calcitriol. "These are more effective, but if you use a vitamin D metabolite, don't give supplemental calcium and be sure to monitor for hypercalcemia and maybe even hypercalcuria if you are practicing in an area where there are a lot of renal stones," said Dr. Hahn, professor of medicine and chief of rheumatology, University of California, Los Angeles. Hypercalcemia is particularly hazardous when patients are acutely ill and take to bed. The drug should be stopped at that time, she said.

But there's no question in 2005 that bisphosphonate therapy is the most effective strategy to prevent bone loss in steroid-induced osteoporosis, she said. In fact, calcium plus ordinary vitamin D has been used as the placebo in a lot of the clinical trials of bisphosphonates.

"It doesn't matter which one you choose—whichever one you like. Now that Fosamax comes in a liquid I have a lot more patients who can tolerate bisphosphonate therapy," she said. Liquid alendronate causes less esophageal irritation and gastric distress than the capsules, she said.

Another option for certain patients is treatment with the anabolic hormone PTH 1-34 (teriparatide, Forteo). This drug is useful for patients who have very low bone turnover and are continuing to fracture despite treatment with bisphosphonates, active vitamin D, and calcitonin, she said.

In some patients it isn't enough to turn the osteoclast off, which is how these drugs work. For these patients it's also necessary to turn the osteoblast on, which is what PTH does, she said.

PTH stimulates osteoblast accumulation and bone formation through receptor signals that modulate osteoblast proliferation and maturation. It also increases the lifespan and productivity of the osteoblast by preventing apoptosis (Treat. Endocrinol. 2002:1;175-90).

Unfortunately, patients don't like to take this drug because it's injectable and must be taken every day or every other day. But three other formulations, two injectable and one oral, are now in clinical trials (Expert Opin. Investig. Drugs 2005;14:251-64).

One caution is needed with using PTH in patients with lupus. "This is not recommended by anybody but me, but I think you should screen your patients for hyperparathyroidism before you start PTH. I have found elevated levels of parathyroid hormone in one-third of my lupus patients, and we shouldn't be giving PTH to people who already have primary hyperparathyroidism," she said. ■