RAVE Trial Portends New Era in Vasculitis Tx

**BY BRUCE JANCIN**

**SNOWMASS, Colo.** — The future of therapeutics in at least one form of severe vasculitis appears to lie in the biologic agents, in light of rituximab’s impressive showing in the RAVE trial, Dr. Leonard H. Calabrese observed at a symposium sponsored by the American College of Rheumatology.

RAVE (Rituximab for the Treatment of Wegener’s Granulomatosis and Microscopic Polyangiitis) was an eagerly awaited, randomized trial presented last fall at the annual meeting of the American College of Rheumatology. It demonstrated that rituximab (Rituxan) was as effective as—and safer than—standard-of-care cyclophosphamide at inducing remission in patients with severe antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

Moreover, in a prespecified subgroup analysis, patients who entered RAVE with a severe flare of their vasculitis rather than with new-onset disease had a statistically and clinically greater remission rate with rituximab than with cyclophosphamide. “This is a very important study that marks a major shift in thinking,” said Dr. Merrill.

Indeed, in recent decades the emphasis has been on developing strategies to fine-tune cyclophosphamide therapy for this disease, which is characterized by flares and inconsistent clinical course of the disease. We know from the results of clinical trials that no one drug can be expected to work for more than 60% of patients with lupus. But we can’t yet pick out in advance the subgroup of patients who will respond to a given drug, she said.

The heterogeneity of the disease across patients and the absence of scientific evidence to explain the biological mechanisms underlying the variations have been impediments to fruitful clinical experimentation, and have led to a series of disappointing clinical trial outcomes, said Dr. Merrill, of the University of Oklahoma in Oklahoma City.

“Targeted therapies can only work if you know what you’re targeting, in whom, and why,” she noted. “We have the technology to be able to identify those subsets of patients that we ought to be targeting with each treatment, but we don’t have the will.”

Additional complications include the inconsistent clinical course of the disease, which is characterized by flares and remissions that make it difficult to assess the impact of investigational therapies and also contribute to the selection of meaningful clinical end points, and the need (according to the Food and Drug Administration) to show clinical superiority of the investigational agents over standard treatment, said Dr. Merrill.

“The irony, of course, is that the standard of care in lupus is off-label therapy, because there hasn’t been a new drug approved for the disease in more than 50 years,” she said.

Because the standard treatments are off label, their therapeutic effect has not been established in clinical trials. “Many clinical trials in lupus have to be carried out for a whole year, and they can’t really be performed unless patients are on these background medications, but we don’t know what these background medications are doing biologically to patients, or how they are interfering with our assessment of a study agent,” Dr. Merrill said.

Arguably, the potentially promising agents that have failed to achieve intended levels of improvement in patient outcomes in lupus trials—including mycophenolate mofetil (CellCept), abatacept (Orencia), prasterone (Prexara), abetimus sodium (Riquent), and rituximab (Rituxan)—might have demonstrated treatment effects if patient selection had been optimized based on patient-specific biology, if investigators had a better understanding of the impact that background medications have on patient response and adverse events, and if more specific responder indices were available to assess treatment effect, according to Dr. Merrill.

“I’d say that 90% of patients in the RAVE trial, Dr. Ulrich Specks, who was in the audience for the ACRA Snowmass symposium, rose to emphasize that in the 101 RAVE participants with baseline severe flares, the 6-month remission rate was 67% with rituximab, which was statistically superior to the 42% rate in the cyclophosphamide arm.

“So for the treatment of severe flares of the disease, rituximab is probably going to be the standard of care as we move forward. It will spare patients from prolonged cyclophosphamide exposure,” said Dr. Specks of the Mayo Clinic in Rochester, Minn. Key remaining questions—such as how best to reinfuse rituximab when B cells eventually return—are being addressed in an ongoing follow-up study.

Rituximab may not be the only biologic response modifier with a bright future in ANCA-associated vasculitis.

Dr. Calabrese said that although he, like most rheumatologists, has opted out of the use of anti-tumor necrosis factor–alpha therapies together in light of the negative Wegener’s Granulomatosis Etanercept Trial (N. Engl. J. Med. 2005;352:351-61), he wonders whether etanercept (Enbrel) was the right drug. The anti-TNF agents don’t all act in the same way, and most of the anecdotal reports of treatment success have involved infliximab (Remicade), not etanercept, he noted.

Dr. Peter A. Merkel, director of the vasculitis center at Boston University, conceded that it is possible a different anti-TNF agent would have done better, but these large National Institutes of Health trials take years to complete, and the research momentum has shifted away from the older biologics. Now underway, for example, is a clinical trial in Wegener’s granulomatosis of abatacept (Orencia), a fusion protein that inhibits co-stimulation of T cells and is approved for the treatment of rheumatoid arthritis.

**Disclosures:** Dr. Calabrese disclosed that he serves as a consultant to Amgen Inc., Centocor Inc., Genentech Inc., Sanofi-Aventis, UCB, and Wyeth.

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**Expert Outlines Drug-Development Outlines in Obstacles in Lupus**

**BY DIANA MAHONEY**

**DESTIN, Fla.** — “The problem with drug development in lupus is lupus,” Dr. Joan T. Merrill said at the Congress of Clinical Rheumatology.

“Lupus is an incredibly heterogeneous disease. We know from the results of clinical trials that no one drug can be expected to work for more than 60% of patients with lupus. But we can’t yet pick out in advance the subgroup of patients who will respond to a given drug,” she said.

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