

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. Calabrese of the Cleveland Clinic Foundation.

Indeed, in recent decades the emphasis has been on developing strategies to fine-tune cyclophosphamide therapy to minimize its serious toxicities.

The most popular of these strategies is step-down therapy—specifically, 3 months of cyclophosphamide as induction therapy, followed by maintenance treatment with a nonalkylator (most commonly methotrex-

ate, although azathioprine, mycophenolate mofetil, leflunomide, and intravenous immunoglobulin have also been studied).

For non-life-threatening, early, systemic disease, the NORAM (Non-Renal Vasculitis Alternative Treatment With Methotrexate) trial demonstrated that it was reasonable to do away with cyclophosphamide altogether, and to use methotrexate for induction as an alternative (Arthritis Rheum. 2005;52:2461-9).

However, in severe ANCA-associated vasculitis with impaired vital organ function, cyclophosphamide has remained the workhorse—that is, until RAVE.

RAVE was a National Institute of Allergy and Infectious Diseases-sponsored, 197-patient, randomized trial involving assignment to B-cell depletion via four once-weekly infusions of rituximab (375 mg/m²) or oral cyclophosphamide (2 mg/kg per day). At 6 months, the remission rate was 64% in the rituximab arm and similar (53%) in the cyclophosphamide arm. However, 19% of patients in the rituximab group experienced one or more adverse events, compared with 32% of those on cyclophosphamide.

RAVE study chair Dr. Ulrich Specks, who was in the audience for the ACR 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 pro-

longed 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- α therapies altogether 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's 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 costimulation 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.

Expert Outlines Drug-Development 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.

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 complicate 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



In lupus, 'targeted therapies can only work if you know what you're targeting, in whom, and why.'

DR. MERRILL

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 (Prestara), 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.

In fact, it is the attention paid to some of these factors that likely contributed to the recent success of two separate phase III trials of belimumab (Benlysta), the monoclonal antibody that targets B-lymphocyte stimulator (BLyS), she said.

In the initial phase II, double-blind, placebo-controlled trial of belimumab in patients with active lupus, the drug failed to improve disease activity as measured by the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index), and did not decrease time to first SLE flare (Arthritis Rheum. 2009;61:1168-78).

In a post hoc exploratory analysis of the data, however, the investigators "noticed that if they looked just at the subset of patients who had been either ANA [antinuclear antibody] positive or [anti-double-stranded DNA] positive at study entry, they actually could see more patients with a 4-point reduction in the SLEDAI over time at each visit" than in the placebo group, said Dr. Merrill.

Based on this observation, the investigators used the phase II trial data to develop a new SLE Responder Index (SRI) that incorporated components of the SLEDAI, the BILAG (British Isles Lupus Assessment Group) disease activity instrument, and the PGA (Physician Global Assessment).

They used the new instrument as the primary efficacy end point at week 52 in

the BLISS-52 (Belimumab in Subjects With Systemic Lupus Erythematosus-52) and BLISS-76 phase III trials, said Dr. Merrill.

In both BLISS trials, belimumab met the efficacy end point, which was defined as a reduction from baseline of at least 4 points on the SLEDAI disease activity scale, no worsening of disease as measured by the PGA, no new BILAG grade A organ domain score, and no more than one new BILAG grade B organ domain score, Dr. Merrill noted.

The differences between the treatment and control groups that were observed in both trials were small but statistically significant, and they were historically meaningful because they put the drug on the pathway for FDA approval, she said.

"This is a major development, not because [belimumab] is expected to be a cure-all or the best treatment for every lupus patient, because it is not," said Dr. Merrill. Rather, FDA approval of belimumab, if it happens, will break ground for other studies to follow and, after 50 years, "there will finally be an approved therapy that we can hold other [experimental] therapies up against." ■

Disclosures: Dr. Merrill has served as a consultant and clinical trialist for Genentech/Roche, Bristol-Myers Squibb Co., MedImmune Inc., and Human Genome Sciences; she has been a consultant for Amgen Inc., UCB Pharma Inc., and Serono Inc.; and she has received grants from Aspreva/Vifor and Wyeth/Pfizer for investigator-initiated