Hydroxychloroquine Scores Big in Lupus

BY BRUCE JANCIN

FROM A SYMPOSIUM SPONSORED BY THE AMERICAN COLLEGE OF RHEUMATOLOGY

SNOWMASS, COLO. – The past 12 months have brought a slew of studies making a persuasive case for hydroxychloroquine as a far more important drug in lupus than previously thought. Indeed, the drug could now even be considered essential.

"In 2011, all lupus patients should receive hydroxychloroquine. The indication for hydroxychloroquine in lupus is lupus," declared Dr. David Wofsy, professor of medicine and microbiology/immunology at the University of California, San Francisco.

There is now solid evidence that hydroxychloroquine (Plaquenil) prevents lupus flares, treats the skin manifestations of the disease, protects against thromboembolic events, prevents cardiac neonatal lupus, and prolongs life. "It will be a very long time before we've proven that any biologic therapy can do all those things," said Dr. Wofsy, also chief of rheumatology at the San Francisco Veterans Affairs Medical Center.

He cited several eye-opening hydroxychloroquine studies that were presented at the 2010 annual meeting of the ACR. In one, investigators from the Systemic Lupus International Collaborating Clinics (SLICC) presented findings from an international registry of 1,593 lupus patients followed since 2000. In a multivariate analysis, antimalarial therapy was independently associated with a highly significant 70% reduction in mortality.

It's particularly noteworthy that in this report from 35 of the world's leading lupus centers, only 65% of patients were on antimalarial therapy. Dr. Wofsy urged audience members to pull the records of all their lupus patients and put those who aren't now taking hydroxychloroquine on the drug forthwith.

Also at the 2010 ACR meeting, French investigators presented a prospective study of 300 SLE patients on hydroxychloroquine for cutaneous lupus. The researchers found that serum drug levels were strongly correlated with clinical response. The 114 patients with a complete response had a mean hydroxychloroquine level of 910 ng/mL. The 100 nonresponders had a mean level of 569 ng/mL, while partial responders averaged 692 ng/mL.

The thromboprotective effect of hydroxychloroquine was demonstrated in a University of Toronto case-control study involving newly diagnosed lupus patients prospectively followed long term. Fifty-four patients who experienced thromboembolic events were matched with 108 lupus patients who did not. In a multivariate analysis adjusted for disease severity and duration and calendar year, antimalarial therapy was associated with a 68% reduction in the risk of thromboembolic events.

The protective effect was similar for arterial as well as venous thrombosis (Arthritis Rheum. 2010;62:863-8).

Dr. Wofsy noted the irony that this new appreciation of hydroxychloroquine's abundant benefits in lupus comes on the eve of what is widely anticipated to be regulatory approval of the first drug ever to be approved for lupus: belimumab (Benlysta), the fully human monoclonal antibody directed against the B-lymphocyte stimulator.

Last November, a Food and Drug Administration advisory panel recommended marketing approval for belimumab by a 13-2 margin. The FDA has announced it will issue its decision this month.

Is belimumab a better drug for lupus than hydroxychloroquine?

Many physicians might reflexively assume that a very costly new biologic agent for lupus must be better than an old, cheap antimalarial, but that's far from certain at this point, according to the rheumatologist.

"All of us know that Plaquenil is not the solution to lupus. But it is a reasonable low bar to place when we think of the biologic therapies," he said in urging his colleagues not to underestimate the value of the antimalarial or fall prey to the coming massive marketing hype for belimumab.

Dr. Wofsy declared that he serves as a consultant to Bristol-Myers Squibb and has received research grants from numerous other companies developing new treatments for autoimmune diseases. ■

Azathioprine Effectively Prevents Vasculitis Relapse

BY DENISE NAPOLI

FROM JAMA

Azathioprine was more effective than was mycophenolate mofetil for the prevention of relapse in antineutrophil cytoplasmic antibody–associated vasculitis.

"Although mycophenolate mofetil may be considered in refractory cases, it should not be considered the first-line remission maintenance therapy in AAV," according to Dr. Thomas F. Hiemstra and colleagues (doi:10.1001/jama.2010.1658).

Dr. Hiemstra of the University of Cambridge, England, looked at 156 patients in an open-label, multicenter, randomized controlled trial known as IMPROVE (International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides).

Patients were newly diagnosed with Wegener granulomatosis or microscopic polyangiitis. All had a positive indirect immunofluorescence or enzyme-linked immunosorbent assay for antineutrophil cytoplasmic antibodies, or ANCAs.

Initially, all study participants received cyclophosphamide and glucocorticoids for induction of remission. Once remission was established, patients were divided into two groups, to receive either azathioprine or mycophenolate mofetil.

A total of 80 patients in the azathioprine group were given 2 mg/kg per day of azathioprine, up to 200 mg. The dose was titrated to 1.5 mg/kg per day after 12 months of treatment, down to 1 mg/kg per day after 18 months, and discontinued after 42 months.

The remaining 76 patients received mycophenolate mofetil at 2,000 mg/day. The dose was reduced to 1,500 mg/day after 12 months, to 1,000 mg/day after 18 months and withdrawn after 42 months.

The median follow-up for both groups was 39 months. All participants were counted in an intent-to-treat analysis.

Dr. Hiemstra recorded 42 relapses in the mycophenolate mofetil group, out of 76 patients (55%), compared with the azathioprine group, which had 30 relapses out of 80 patients (38%).

That amounted to an unadjusted hazard ratio for relapse of 1.69 among mycophenolate mofetil users (95% confidence interval, 1.06-2.70; $P = .03$).

After adjustment for age, sex, diagnostic subtype, route of cyclophosphamide administration [during initial treatment], and baseline creatinine level, the HR for relapses associated with mycophenolate mofetil use was 1.80 (95% CI, 1.10-2.93; $P = .02$).

There were no significant adverse event rate differences between the groups. According to Dr. Hiemstra, there were 22 severe adverse events in 13 patients in the azathioprine group, and 8 events in 8 patients in the mycophenolate mofetil group.

These included severe infection (8 in the azathioprine group and 3 in the mycophenolate mofetil group); leukopenia (11 episodes in the azathioprine group and 5 in the mycophenolate mofetil group); and malignancies (2 bladder cancers and 3 skin cancers in the azathioprine group, versus 1 skin malignancy among mycophenolate mofetil users). ■

VITALS

Major Finding: Patients taking mycophenolate mofetil had a 1.80 adjusted hazard ratio for relapse of ANCA-associated vasculitis, compared with azathioprine patients.

Data Source: The International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides (IMPROVE) trial, an open-label, randomized controlled study.

Disclosures: Dr. Hiemstra reported receiving honoraria from Amgen, and several coinvestigators disclosed financial relationships with other drug makers. The study was partially funded by Hoffmann-La Roche Ltd., which markets mycophenolate mofetil as CellCept.

VIEW ON THE NEWS

Study Needed on Classification, Tx

Dr. Gary S. Hoffman of the Cleveland Clinic wrote that while there have been "major contributions" in the field of vasculitis over the last several decades, data on these rare diseases are still lacking.

"The difficulty inherent in the organization of this trial is implied by noting that recruitment of 175 newly diagnosed patients with [antineutrophil cytoplasmic antibody]-positive Wegener's granulomatosis and microscopic polyangiitis required 42 centers from 11 European countries over 7 years," he said.

Indeed, while the current trial "provides important and reliable new knowledge for the clinician," several issues remain unresolved, he added.

For one, "as in other trials involving patients with WG and MPA, severe infections and leukopenia continue to be a major concern," Dr. Hoffman pointed out.

Moreover, the authors only included ANCA-positive patients.

"Approximately 10% of patients with identical clinical phenotypes might be ANCA-negative and also respond to all anti-inflammatory or immunosuppressive therapies shown to be effective for those who are seropositive," he wrote.

Finally, given the side-effect profile, "the risk-benefit formulas of long-term maintenance therapy vs. discontinuation and treatment of relapses require further study."

"Although the therapeutic options have expanded, clinicians face difficult treatment decisions when patients in remission are unable to tolerate or have contraindications to maintenance agents such as methotrexate or azathioprine," he concluded.

DR. HOFFMAN *holds the Harold C. Schott Chair for Rheumatic and Immunologic Diseases at the Cleveland Clinic, and is director of the Center for Vasculitis Care and Research at the Cleveland Clinic Foundation. His comments were taken from an editorial accompanying the study (JAMA 2010 Nov. 8 [doi:10.1001/jama.2010.1676]). He reported having no financial disclosures.*