

New Lupus Drugs Remain Elusive After 50 Years

BY NANCY WALSH

FORT LAUDERDALE, FLA. — The saga of mycophenolate mofetil for lupus exemplifies the difficulties in developing new drugs for a condition with such protean manifestations and inconsistent course, for which there has not been a new drug approved for 50 years.

“An important question is whether the newer drugs don’t work, or whether we’re not testing them and measuring response correctly,” said Dr. Susan Manzi, director of the Lupus Center of Excellence at the University of Pittsburgh.

Only corticosteroids, hydroxychloroquine, and aspirin have FDA approval for systemic lupus erythematosus (SLE). And although current off-label therapy often also includes NSAIDs, cyclophosphamide, azathioprine, and cyclosporine, there has been considerable enthusiasm in the lupus community for the newer immunosuppressants and biologic agents that have revolutionized treatment of other rheumatic diseases. Unfortunately, results thus far have been somewhat disappointing, according to Dr. Manzi.

Mycophenolate mofetil (MMF) is an example, having been compared with cyclophosphamide in three randomized trials. Cyclophosphamide is generally considered to be effective—if toxic—by the lupus community, although randomized data are lacking and the drug is not FDA approved for SLE.

“We all got very excited about MMF when the first study came out in 2000,” she said. That study included 42 patients with diffuse proliferative lupus nephritis who were randomized to receive either oral MMF plus prednisolone for 12 months or oral cyclophosphamide plus prednisolone for 6 months, followed by azathioprine plus prednisolone for an additional 6 months. The investigators found that MMF was as effective as cyclophosphamide but less toxic, with 17 (81%) and 16 (76%) of the MMF and cyclophosphamide patients, respectively, achieving complete remission (*N. Engl. J. Med.* 2000;343:1156-62).

This was followed in 2005 by an open-label noninferiority trial that compared MMF in doses up to 3,000 mg/day with monthly intravenous cyclophosphamide (0.5-1.0 g/m² body surface area) as induction therapy for

6 months in 140 patients with class IV and V nephritis.

In this trial, too, MMF was more effective than cyclophosphamide, with 23% of MMF patients and 6% of cyclophosphamide patients achieving complete remission. More than half of patients in the trial were black, and a subanalysis determined that the nonwhite patients were those who responded best.

The safety profile also was better in the MMF group, with no cases of amenorrhea, compared with three cases in the cyclophosphamide group (*N. Engl. J. Med.* 2005;353:2219-28).

“Most people said MMF might be a good drug for patients without rapidly progressive disease, particularly if you are concerned about infertility or infection,” Dr. Manzi said at a meeting sponsored by RHEUMATOLOGY NEWS and Skin Disease Education Foundation.

But then came the Aspreva Lupus Management Study, the largest industry-sponsored randomized trial, presented as a late-breaking abstract at the American College of Rheumatology (ACR) meeting in 2007. This trial was required by the FDA to be a superiority study, randomizing 370 patients with class III-V lupus nephritis to 24 weeks of MMF in target doses of 3 g/day or intravenous cyclophosphamide at 0.5-1.0 g/m² in monthly pulses. Both groups also received prednisone, and response to treatment was defined as a decrease in proteinuria and improvement or stabilization of serum creatinine.

With 56% of MMF patients and 53% of cyclophosphamide patients responding, the study did not meet its primary efficacy end point of showing superiority for MMF. Moreover, there was no difference between the groups in terms of adverse events, which was “a double whammy,” Dr. Manzi said.

“If they had shown a much better safety profile, the company might have had a chance to go back to the FDA and see if they could move forward, but there was no difference in safety,” she said.

“Even though MMF performed the same as cyclophosphamide in this trial, the FDA’s view is that it isn’t good enough. Because cyclophosphamide is not ap-

proved, it is considered the same as placebo, and you have to do better than placebo, which has been a stumbling block for our trials. So even though three randomized trials have shown that efficacy and safety are equal to or better than cyclophosphamide in lupus nephritis, MMF is not approved,” she said.

Other agents also are being tested, again with mixed results. In a phase II study, belimumab did not meet the primary outcome measure, but a post hoc analysis found that many patients in the trial were not serologically positive. “They may have been enrolling the wrong patients,” she said, noting that a phase III trial is underway.

At the 2008 ACR annual meeting, results for trials of rituximab and abatacept were presented as late-breaking abstracts. In a phase II/III study that included 257 patients with moderate to severe extrarenal lupus, there were no differences between rituximab and placebo on any clinical end points, although a subgroup analysis found significant improvements in black and Hispanic patients.

In an exploratory phase II trial, 175 patients whose primary disease manifestations were discoid rash, polyarthritis, or serositis were randomized to receive prednisone plus abatacept, 10 mg/kg, or placebo by intravenous infusion on days 1, 15, and 29 and then every 4 weeks for 1 year. This again was a negative trial, Dr. Manzi said, with 79% and 82% of patients in the abatacept and placebo groups experiencing flares when the steroids were tapered. Patients whose primary complaint was arthritis seemed to respond the best.

“So lupus is still a complex disease and measuring response remains incredibly challenging. We’re also challenged by the fact that we have to do superiority studies, and we have to be careful about who we enter into trials,” she said.

Dr. Manzi disclosed that she receives grant research support and is on the speakers bureau for multiple companies including Aspreva Pharmaceuticals Corp., the manufacturer of MMF. SDEF and this news organization are owned by Elsevier. ■



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Dyslipidemia Common in Patients With Lupus and RA

BY NANCY WALSH

FORT LAUDERDALE, FLA. — Patients with systemic lupus erythematosus and rheumatoid arthritis should be considered in a cardiovascular risk category equivalent to that of patients with diabetes, with aggressive management of risk factors, particularly dyslipidemia, according to experts.

It is not yet clear whether the increased incidence of coronary artery disease (CAD) in patients with lupus and rheumatoid arthritis (RA) is a result of rheumatic factors that drive the atherosclerotic process, or if risk factors in the milieu of rheumatic disease cause patients to be more vulnerable, Dr. Daniel Edmundowicz said.

“But in any case, the process is driven by dyslipidemia,” he said.

“We are born with LDL cholesterol levels around 35-40 mg/dL, and a lab result that says you are normal at 130 mg/dL is wrong—that’s average but it’s abnormal for homo sapiens, and if you are vulnerable you are in trouble,” he said.

Because of this vulnerability, “many of us feel that patients with rheumatologic diseases should be considered CHD [coronary heart disease] risk equivalents,” said Dr. Edmundowicz, director of preventive cardiology at the University of Pittsburgh Medical Center’s Cardiovascular Institute.

“CHD risk equivalent” is the designation given by the National Cholesterol Education Program (NCEP) to people with diabetes and conditions such as peripheral artery disease who have a high prevalence of CAD events such as fatal and nonfatal myocardial infarction.

Currently, NCEP practice guidelines suggest that patients who are CHD risk equivalents be treated aggressively with regard to their risk factors such as cholesterol.

“In my opinion, patients with rheumatologic diseases should be reaching the same aggressive risk factor goals, which would mean non-HDL cholesterol less than 130 mg/dL or less than 100 mg/dL for patients who already have CAD, and LDL cholesterol of less than 100 mg/dL

or less than 70 mg/dL if they already have CAD,” he said.

For many patients, meeting these goals will require statins, Dr. Edmundowicz said at a meeting sponsored by RHEUMATOLOGY NEWS and Skin Disease Education Foundation.

“Over the past 20 years, we have demonstrated that statin therapy is safe, and there now are effective and inexpensive generic lipid-lowering drugs. With a 40-mg dose of simvastatin you can get almost a 40% reduction in LDL,” he said.

But with aggressive statin therapy it is important to realize that titration of the drugs provides minimal additive benefits and can increase toxicity. “If you start your patient on 40 mg of simvastatin and then raise it to 80 mg you are probably only going to get an additional 5% of lowering of lipoproteins but you are much more likely to get myalgias,” he said.

Additive or combination lipid therapy is now becoming much more popular, utilizing agents that have different mechanisms of action. For example, blocking cholesterol uptake with ezetimibe and

absorbing biliary cholesterol with bile acid sequestrants can provide very effective lowering of LDL, he said.

Attention also must be paid to lowering blood pressure, smoking cessation, and increasing physical activity. Benefits of exercise training in patients with RA and lupus include improvements in aerobic capacity, endurance, and strength, and can help decrease joint swelling and pain, increase social activity, and reduce depression and anxiety.

Of course, these patients have considerable limitations, with restricted joint range of motion and deconditioning, but even small inroads in exercise training can be very beneficial, he said. “You can’t forget these things,” he said. “Atherosclerosis is killing our patients. The charge to a community of physicians who take care of very-high-risk patients like yours is not to leave it to the other guy.”

Dr. Edmundowicz disclosed that he is a consultant to GNC, Merck & Co., Schering Plough, and Takeda. SDEF and this news organization are owned by Elsevier. ■