New Lupus Drugs Remain Elusive After 50 Years

BY NANCY WALSH
New York Bureau

FORT LAUDERDALE, FLA. — The saga of mycophenolate mofetil for lupus exemplifies the difficulties in developing new drugs for the condition, for which there has not been a new approval in half a century.

"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 nonsteroidal anti-inflammatory drugs, cyclophosphamide, azathioprine, and cyclosporine, newer immunosuppressants and biologic agents have had disappointing results in lupus, according to Dr. Manzi.

Mycophenylate mofetil (MMF) is an example, having been compared with cyclophosphamide in three randomized trials. Cyclophosphamide is generally considered effective—if toxic—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/m^2 body surface area) as induction therapy for 6 months in 140 patients with class IV and V nephritis. Patients with rapidly progressive disease were excluded.

In this trial, too, MMF was more effective than cyclophosphamide, with 23% of MMF patients and 6% of cyclophosphamide patients achieving complete remission. The safety profile also was better with MMF, with no cases of amenorrhea, compared with three cases in the cyclophosphamide group (N. Engl. J. Med. 2005;353:2219-28).

'Lupus is still a complex disease, and measuring response remains incredibly challenging.'

DR. MANZI

"I think most people said MMF might be a good drug for patients without rapidly progressive disease," Dr. Manzi said at a meeting sponsored by RHEUMATOLOGY NEWS and the Skin Disease Education Foundation.

But then came the Aspreva Lupus Management Study, a large industry-sponsored randomized trial, presented as a late-breaking abstract at the 2007 American College of Rheumatology (ACR) meeting. This superiority study randomized 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/m^2 in monthly pulses. Both groups also received prednisone. Response 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.

"Even though MMF performed the same as cyclophosphamide in this trial, the FDA's view is: That is not good enough. Because cyclophosphamide is not approved, it is considered the same as placebo, and you have to do better than placebo," she said. "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."

Other agents also are being tested, 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. 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 patients who received rituximab and those who got placebo on any clinical end points.

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 negative, with 79% and 82% of patients in the abatacept and placebo groups flaring when the steroids were tapered.

"So lupus is still a complex disease, and measuring response remains incredibly challenging," said Dr. Manzi.

Dr. Manzi receives grant research support and is on the speakers bureau for multiple companies including Aspreva Pharmaceuticals Corp., maker of MMF.

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Guidelines Aim to Standardize Systemic Sclerosis Research

BY DIANA MAHONEY
New England Bureau

New recommendations for the standardization of research on endothelial precursor cells are expected to optimize future investigations of these cells in systemic sclerosis and to simplify the comparison of different studies, according to the authors.

Endothelial precursor cells (EPCs) play an important role in the homeostasis of the vascular network and are considered potential candidates for novel therapeutic approaches as well as possible biomarkers for vascular repair, new vessel formation, and cardiovascular prognosis. However, methodical and other inconsistencies across research studies complicate data interpretation, wrote Dr. Jörg H.W. Distler of the University of Elrangen-Nuremberg (Germany) and colleagues in the European League Against Rheumatism Scleroderma Trials and Research (EUSTAR) group. Specifically, different protocols for EPC isolation, enrichment, culture, and quantification, as well as insufficient data on potentially confounding risk factors, have led to conflicting results in previous studies (Ann. Rheum. Dis. 2009;68:163-8).

Among the holes in the current pool of research is the absence of studies demonstrating EPCs in vascular lesions of animal models of systemic sclerosis, the authors wrote, noting that, to date, studies have shown EPCs in vascular lesions of ischemia. Additionally, "the mechanisms by which EPCs have contributed to vascular repair and neovascularization have not fully been elucidated," they wrote. "It remains to be determined whether EPCs mediate their effects in humans independently from mature endothelial cells or whether EPCs function more as bystanders of angiogenesis."

Finally, the numbers of EPCs characteristically in the blood of patients with systemic sclerosis is in need of clarification, as the results of existing studies are contradictory. "The initial study suggested a profound decrease of circulating EPCs, whereas subsequent studies found increased numbers of EPCs in patients with systemic sclerosis"—differences that might be a function of different disease durations in the study patients or different cell enrichment techniques prior to fluorescence-activated cell sorting (FACS) analysis, the authors wrote.

The following recommendations should be incorporated in future studies, the authors advised:

► Studies should include a detailed description of methods and materials used.

► Cardiovascular risk factors and drugs should be described in detail. Statins, in particular, impact circulating EPCs.

► Studies with small numbers of patients should be avoided because they are of limited help in light of the heterogeneity of systemic sclerosis and the large number of potential confounding factors that influence the number of EPCs.

► Basic methodological guidelines for the isolation, culture, enrichment, and detection of EPCs should be followed and described in detail.

► For in vitro EPC culture, the contents of endothelium growth medium 2 (EGM-2) are best defined and as such should be the medium of choice for future experiments.

► Culture dishes should be coated with laminin and type IV collagen because of the close resemblance to the vascular basal membrane.

► For all in vitro cultures, the endothelial phenotype should be confirmed at the end of the culture period.

► For the quantification of EPCs in the blood, the expression of CD133, vascular endothelial growth factor type 2 receptor (VEGFR2), and CD34 together with a viability marker should be evaluated in a multiparameter flow cytometer.

► Standard operating procedures for FACS (see box) must be strictly followed.

The various authors reported receiving research grants and/or honoraria from several major pharmaceutical companies. ■

Flow Cytometry for EPC Detection

Strict adherence to the following standard operating procedures for fluorescence-activated cell sorting (FACS) analysis in endothelial cell precursor research is critical, according to the EUSTAR statement authors.

► Clean the flow cytometer rigorously to avoid sample contamination.

► Set and monitor the sensitivity of fluorescence detectors.

► Collect a minimum of 500,000 events to collect an adequate number of endothelial precursor cells.

► Use a real-time viability stain, such as 7AAD or propidium iodide, and identify and exclude dead cells to minimize nonspecific staining and improve assay resolution.

► Use a blocking serum to decrease nonspecific binding via Fc receptors.

► Establish a dump channel in order to exclude from analysis those cells that are not of interest.