Induction Plus Maintenance Effective in Wegener's

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San Diego — Progress is being made in establishing a safe, effective, global treatment strategy for Wegener's granulomatosis and microscopic polyangiitis, but relapses are still common and the optimal maintenance therapy remains to be established, according to Dr. Christian Pagnoux.

Speaking on behalf of the French Vasculitis Study Group at the annual meeting of the American College of Rheumatology, Dr. Pagnoux said that an induction regimen of pulsed intravenous cyclophosphamide plus corticosteroids followed by maintenance therapy with either methotrexate or azathioprine had been effective in a prospective, multicenter trial.

It had been shown previously that pulsed intravenous cyclophosphamide was as effective as daily oral cyclophosphamide for inducing remission in these antineutrophil cytoplasmic antibody–associated vasculitides, and was less toxic. In this trial, 159 patients were given the drug in a dose of 700 mg/m^2 on days 0, 15, and 30, and then every 3 weeks until remission, followed by three additional pulses. They also received oral corticosteroids.

Relapse-free survival at 18 and 30 months after diagnosis was 87% and 73% for the azathioprine group and 90% and 78% for the methotrexate group.

Then they were randomized to receive either oral azathioprine, 2 mg/kg per day, or methotrexate, 0.3 mg/kg per week, for 12 months.

The primary end point was the number of adverse events in each maintenance arm, while secondary end points were survival and relapse-free survival 5 years after enrollment of the first patient.

The induction regimen was effective for 126 (79%) patients. A mean of 10 cyclophosphamide pulses were given before remission was achieved, and the mean cumulative dose was 10.4 g. Corticosteroids were tapered rapidly, but the daily dose remained above 20 mg/day for more than 5 months.

Among patients who did not achieve remission, 32 did not respond to cyclophosphamide and one had an allergic reaction. Twenty of the 33 were switched to oral daily cyclophosphamide, and 15 responded, but 14 of the nonresponders ultimately died, 10 without having time to receive any further therapy, said Dr. Pagnoux of Hôpital Cochin, Paris.

An additional 12 patients were excluded from the analysis because they had remained on maintenance therapy for periods exceeding 12 months for no justified reason, he said. Among the 114 patients who were evaluated, 55 had been randomized to receive azathioprine and 59 to receive methotrexate. Baseline characteristics in the two groups were comparable.

Adverse events occurred in 47% of the azathioprine group and in 56% of the methotrexate group, while serious adverse events requiring withdrawal occurred in 13% and 20%, respectively.

Although there were more adverse events among patients in the methotrexate arm, the differences were not statistically significant.

However, three patients in the methotrexate group died, two from sepsis "directly related" to methotrexate, he said.

"Notably, the one patient who died in the azathioprine group had a pulmonary embolism 7 months after being switched to methotrexate because of an adverse event related to azathioprine," Dr. Pagnoux said.

A total of 40% of patients in the azathioprine group had at least one relapse during the trial, as did 31% of the methotrexate patients. Again, this difference was not statistically significant.

Relapse-free survival rates at 18 and 30 months after diagnosis were 87% and 73% for the azathioprine group and 90% and 78% for the methotrexate group.

"This trial showed the efficacy of intravenous cyclophosphamide as induction, and good outcome with overall mortality of 11.3%," he said.

"Hopefully, ongoing trials will probably tell us whether longer maintenance treatment or other drugs like mycophenolate mofetil can further improve outcome," Dr. Pagnoux said. ■