MAS Treatment Failures Stir Controversy

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SNOWMASS, COLO. – Treatment of macrophage activation syndrome with a combination of high-dose corticosteroids and cyclosporine is quite effective in the majority of cases if started sufficiently early; it's what to do for the others where the controversy arises, according to Dr. Alexei A. Grom.

One reasonable option is to use the International Histiocyte Society treatment protocol for hemophagocytic lymphohistiocytosis, a hematology/oncology disorder bearing clinical similarities to macrophage activation syndrome (MAS). This protocol entails supplementing corticosteroids and cyclosporine with etoposide (VP-16), a mitotic inhibitor and antineoplastic agent used in treating a variety of cancers. Etoposide is employed to induce apoptosis of activated phagocytic macrophages and other immune cells, he said at the symposium.

But while etoposide is a reasonable next step, the drug's numerous short- and long-term side effects – including severe myelosuppression leading to fatal sepsis – have caused many physicians to look for alternatives. Among the more promising are antithymocyte globulin and rituximab, said Dr. Grom, a pediatric rheumatologist at Cincinnati Children's Hospital Medical Center.

Antithymocyte globulin depletes T cells, including CD8 cells, and monocytes. Numerous case reports describe successful use of this agent in treating MAS.

The rationale for using rituximab, a potent depleter of B cells, applies to patients with Epstein-Barr virus–induced MAS. Because of the immune dysfunction present in MAS, these patients develop persistent viral infection harbored chiefly by B cells. Dr. Grom has used rituximab successfully in patients with Epstein-Barr virus–triggered MAS, and he suspects that this approach may also be very effective in the setting of MAS associated with systemic lupus erythematosus.

The increased level of tumor necrosis factor present in MAS has prompted numerous attempts to use etanercept and other anti–tumor necrosis factor biologics. Results have been largely disappointing.

"Personally, I think we should stay away from TNF-alpha antagonists in MAS," the pediatric rheumatologist said.

The efficacy of interleukin-1 and -6 inhibiting agents in systemic juvenile idiopathic arthritis (SJIA) makes them appealing agents for the treatment of MAS, because MAS episodes are often triggered by flares of SJIA. However, case reports involving the interleukin-1 inhibitor anakinra have yielded mixed results, and to date there is very little experience with interleukin-6 inhibition in MAS.

First-line treatment of MAS by Dr. Grom and his Cincinnati colleagues begins with high-dose steroids, typically 3-5 days of intravenous methylprednisolone pulses at 30 mg/kg per day before dropping down to 2-3 mg/kg in two or three divided doses. Cyclosporine is dosed at 2-5 mg/kg in two divided doses, usually given intravenously.

Dr. Grom said he had no relevant financial disclosures. ■

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ness of the syndrome and consequent earlier diagnosis and initiation of treatment.

"I think that in adult rheumatology this condition is still relatively unrecognized. My adult rheumatology colleagues in Cincinnati believe that many of these patients end up with a diagnosis of culture-negative sepsis," he said.

It is crucial to understand that roughly one-third of patients with MAS will experience recurrent episodes.

For this reason, Dr. Grom provides patients with a letter explaining their condition in the event they should have a recurrence while out of town, necessitating a visit to an emergency department where physicians may be MAS inexperienced.

Dr. Grom declared having no relevant financial interests. ■