

Can Bone Marrow Transplants “Reboot”...

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...An Immune System Ravaged by Autoimmune Disease?

A complete immune system “makeover” would be an attractive option for many otherwise refractory neurologic diseases that are primarily or partly caused by autoimmune problems—and such a strategy might be within reach for several disorders, according to Daniel Drachman, MD. At the 129th Annual Meeting of the American Neurological Association, Dr. Drachman proposed that when conventional immunosuppressive regimens fail, patients are more likely to respond to either immunoablation and stem cell transplant, or to “rebooting”; the immune system with high-dose cyclophosphamide immunoablation and restoration from endogenous stem cells; autologous or allogeneic stem cell transplant is also a possibility. “What we really would like to do is eliminate completely the old, autoreactive immune cells and replace them with CD34+ hematopoietic stem cells, which then produce an entirely new immune system,” Dr. Drachman said, “but this is an enormous task.”

FROM ANECDOTE TO ACTION

The goal of replacing all the autoimmune cells with a pristine immune system was inspired by anecdotal reports of a few patients who had bone marrow transplants as part of their cancer treatment and experienced striking improvement in coincidental autoimmune disease.

“Will complete replacement work? Powerful immune suppression during the ablation phase may do the trick. The new immune system may become tolerant to autoantigens, just as the developing immune system does. Alternatively, the treatment may be able to reset the immune system’s thermostat and restore its sensitivity to immunotherapy,” said Dr. Drachman, Professor of Neurology and Neuroscience at Johns Hopkins University in Baltimore.

Dr. Drachman and Alan Pestronk, MD, first tested the effect of treatment with cyclophosphamide and “rescue” with syngeneic bone marrow transplant in an experimental animal model of myasthenia gravis in rodents. This resulted in a striking decrease in the pathologic antibodies, but memory cells persisted even two months later. The investigators then combined cyclophosphamide with total body irradiation, again followed by syngeneic bone marrow transplant. This produced a dramatic reduction in the autoantibodies and completely eliminated the autoreactive “memory” cells of the immune system.

“Since those early experiments, we learned that total immune ablation is not necessary and that an autoimmune individual’s bone marrow cells may not be autoreactive. They may be stem cells that haven’t “learned” yet to be autoreactive. We also learned that the results of treatment may be durable,” Dr. Drachman remarked.

POTENTIAL APPLICATIONS

This approach is being studied in multiple sclerosis (MS), myasthenia gravis, several autoimmune neuropathies, aplastic anemia, and systemic lupus erythematosus. Dr. Drachman said that patient selection includes being certain that the candidate patient has an autoimmune disease, that the problem is truly refractory, that the patient is neurologically salvageable, and that the patient will be able to withstand the rigors of the procedures.

However, Dr. Drachman cautioned that patients who have had immune system replacement require intensive monitoring. “You’ve got to watch them every day in the posttreatment period. You follow the restoration of the hematopoietic system. If there are too few red cells, you give back red cells. If there are too few platelets, you give platelets. If there is neutropenic fever, you treat that. You have to use prophylactic antibiotics and antifungals and monitor for herpes zoster and cytomegalovirus infection. You must follow and manage the patients intensively throughout the immediate posttreatment weeks. Then when the immune system is reconstituted, you reimmunize the patients against polio, tetanus, diphtheria, and measles,” he said.

PROMISING RESULTS

Dr. Drachman reviewed seven studies of immune system replacement in MS. All of the published studies used autologous stem cells to reconstitute the immune system after immunoablative treatment. “Although preliminary, the results were surprisingly uniform and quite encouraging,” he said. “In the largest study, of 85 patients, 74% were stabilized for three years. However, there are significant risks to stem cell replacement. This is not a simple procedure.”

MRI scans showed a decrease in plaques, and responders had few active lesions. However, some patients had further progression of brain atrophy, probably due to preexisting damage that resulted in continuing “degenerative”

changes, rather than additional autoimmune damage. “The results of stem cell transplantation in MS are less promising beyond age 40, in patients with poor functional scores, and in patients with primary progressive MS,” Dr. Drachman noted.

“At Johns Hopkins, we use high-dose cyclophosphamide (Hi Cy) for immune ablation without additional stem cell replacement. Hi Cy eliminates the mature white blood cells but does not kill the bone marrow stem cells, because they have an enzyme—aldehyde dehydrogenase —that inactivates cyclophosphamide. The immune system is then reconstituted from the endogenous stem cells. We call this procedure rebooting the immune system,” he explained.

The results in several of eight myasthenia patients treated so far have been “absolutely spectacular,” according to Dr. Drachman. “One woman had been hospitalized 12 times in the year prior to coming. She is doing kickboxing and running three miles a day. Another was a woman who came in with a walker and was sent straight to the neurologic critical care unit, where she required intubation and plasmapheresis. Four months later she is doing ballet and playing soccer with her kids. Not everybody improves that dramatically—but some results are really impressive.”

Immune system replacement has also been tried in autoimmune neuropathies. “The problem with Hi Cy treatment of the autoimmune neuropathies is that the patients are often referred to us too late,” Dr. Drachman related. “At that point, all we can hope to do is stabilize. The key point is to treat these patients before there is irreversible damage.” Taken from: http://www.neurologyreviews.com/dec04/nr_dec04_bonemarrow.html
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