Multiple Sclerosis Discovery Forum
INSPIRING CONNECTIONS

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Stem Cell Transplants Risky But Effective

Initial results from the HALT-MS trial suggest that autologous hematopoietic stem cell transplantation may be a highly effective treatment for patients with aggressive relapsing-remitting MS. However, some worry that the aggressive therapy is needlessly risky when safer alternatives are available and may be just as effective.

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Cartoon by Cynthia McKelvey.

It appears that a complex series of genetic and environmental factors pile on top of each other over the course of an individual's life to trigger multiple sclerosis. Wouldn't it be great if patients could just hit the "reset" button on their immune system and start again with a clean slate? Results from the HALT-MS clinical trial suggest that idea may be more realistic than it sounds.

Three years ago, 24 patients with highly aggressive relapsing-remitting MS (RRMS) underwent autologous hematopoietic cell transplants (HCT)—a risky procedure that involves harvesting a patient's hematopoietic stem cells from their bone marrow, destroying almost all of the immune system, and then replacing it with the undifferentiated stem cells. The phase 2 trial has so far had excellent results, with most of the patients showing no signs of disease activity.

But not everyone is popping the champagne just yet. While hematopoietic stem cell transplants could theoretically be a one-time treatment that could lead to lifetime remission from MS, only time will tell if the treatment is that durable. And some skeptics aren't holding their breath.

The study

The HALT-MS results reported in *JAMA Neurology* represent the three-year interim report (Nash *et al.*, 2014). The final report will come out in 2 years.

The researchers defined the primary outcome measure as "event-free survival defined as survival without death or disease activity from any one of the following outcomes: (1) confirmed loss of neurologic function, (2) clinical relapse, or (3) new lesions observed on magnetic resonance imaging." This type of outcome measure is increasingly being referred to as "no evidence of disease activity," or NEDA, though it's unclear how feasible of a long-term goal it may be.

Nevertheless, 78.4% of the study participants achieved NEDA at 3 years, compared to 39% of patients receiving alemtuzumab at the 2-year follow-up in the CARE MS1 trial (Rotstein *et al.*, 2014).

"It's dramatically higher efficacy," Michael Racke, M.D., of Ohio State University told MSDF. Racke, who was one of the study's co-authors, pointed out that it could be a potentially cheaper treatment option as well, presuming the effects are long-lasting and patients would only need to undergo the procedure once.

Of course one limitation of the study is a lack of a control group. And with such an intense treatment, there is bound to be a placebo effect, James Bowen, M.D., of the Swedish Neuroscience Institute in Seattle, WA, who was also involved in the study, told MSDF.

"It's a reason to do MRIs and it's also a reason to do a 5-year follow-up. Five years gives us more time for that placebo effect to wear off," Bowen said.

When asked how the treatment works, Racke told MSDF, "Theoretically, if you look at identical twins where one twin has MS, 75% of the time the other twin doesn't have MS. What we're trying to do is make an MS patient their own identical twin that doesn't have MS."

But what does that mean, exactly?

How it works

To perform HCT, physicians must first harvest undifferentiated hematopoietic stem cells from the patient's bone marrow. Then the patient undergoes a conditioning regimen that uses chemotherapy and radiation to destroy part or almost all of their immune system. These

conditioning regimens can be myeloablative or nonmyeloablative; they can eradicate the bone marrow or not. Myeloablative regimens, like the one used in the HALT-MS trial, are more conventional but also riskier and more intense.

After the conditioning regimen, assuming no adverse events such as infections occur, the patient's stem cells are grafted back into the body, where they differentiate and rebuild the immune system from the ground up. Of course, the question remains whether autoreactive cells would reappear, causing a relapse.

"I'm a neurologist, so all of these therapies are pretty aggressive from a neurology perspective. I was thinking 'Oh we're just going to kill off your entire immune system and replace it,' " Bowen said. But it's more complicated than that; the immune system doesn't replace itself so much as it redevelops, similar to how it does in embryogenesis.

"When an immune system is developing during embryogenesis it goes through a stage where it deletes autoclones—you delete the bad guys that are able to attack your own body," Bowen said. "But when you're transplant people, [the immune system] goes through this stage where it deletes autoclones."

The transplant also causes certain shifts in cell populations, such as CD4 and CD8 cells. "In addition to kind of changing out of the immune system, you also get this shift in the immune system in a way that we think is less likely to be autoimmune," Bowen said.

But is it really necessary to obliterate a patient's immune system to accomplish this? Not everyone agrees.

Dialing in the intensity

HCT is more often used in aggressive cancers such as leukemia. These patients would almost certainly die without treatment, so physicians are more willing to take risks. But MS is not considered to be a terminal illness, calling into question the optimal way to balance risk with reward.

Conventional wisdom says that in order to get a true immunological reset, one must remove all traces of the dysfunctional immune system before transplanting the stem cells. The thinking is that autoreactive immunological cells that survive could easily multiply and continue to attack the immune system.

"The whole point of doing this is to wipe out the disease-causing cells," Mark Freedman, HBSc, MSc, MD, CSPQ, FAAN, FRCPC, of the Ottawa Hospital Research Institute told MSDF. "If you can't wipe them out completely, then what's the point of subjecting people to this terrible procedure which can kill people?" Freedman was not involved in the study but is conducting his own HCT trial using a more intense conditioning regimen than the one used in HALT-MS.

Freedman believes it's necessary to wipe out every last disease-causing cell, which would require risking the patient's overall health since the conditioning regimen is nonspecific and will kill the "good guys" along with the "bad guys." He told MSDF he believes that the regimen in HALT-MS was not intense enough, which would explain why only 78.4% of the patients are showing no sign of disease activity instead of 100%.

"It's a matter of time before other individuals have reactivation of their disease, and it's probably because they didn't knock out all the cells," Freedman said.

But such aggressive treatments may come with a hefty price. While they may work in the short term, the chemotherapy will increase the risk of cancer in the long term, and opinions are varied on whether it's worth it. While some researchers, such as Freedman, believe that the conditioning regimen in HALT-MS was not intense enough, others believe that it was too intense.

"Autoreactive cells are normal. Cells that recognize cells are normal. But the disease is pathologic," Richard Burt, M.D., of Northwestern University told MSDF. In other words, there are no good guys or bad guys, so the goal should not be to totally eradicate the bad guys but to change the interaction between the cells. Burt believes that the intense regimens used on cancer patients and in the HALT-MS trial are dangerous and unnecessary for patients with MS (Burt *et al.*, 2010). Instead, he and his team use a nonmyeloablative conditioning regimen. They will be publishing results from their trials later this month.

"What you want to do is knock your immune system down sufficiently, but you don't want to get rid of every last one. You want to stop inflammation," Burt said.

Immune cells react to a number of stimuli, Burt said, and sometimes the cells become confused by stimuli and attack the body, leading to autoimmunity. But if the noise of the stimuli can be removed, then the immune cells can learn tolerance and not attack the body. Burt said removing inflammation, which can be achieved by his nonmyeloablative procedure, is the key to reprogramming the immune system.

Nonetheless, physicians who perform stem cell transplants continue to improve their techniques, ultimately reducing the morbidity and mortality rates resulting from the conditioning regimen (Soldán and Weinshenker, 2014). MS patients also tend to be healthy in every regard except for their disease, and thus seem likely to tolerate the regimens better than cancer patients. But the jury is still out on the ideal risk-benefit ratio for conditioning MS patients.

The gift that keeps on giving

Some evidence also suggests that the stem cells may lead to neuroregeneration, though the researchers were unable to track that outcome in the HALT-MS trial. In animal studies, HCT seems to lead to a restoration of nerve function, Freedman said.

But it's difficult to monitor restoration in humans. "The problem is in the face of ongoing activity or damage, it's very hard to see any kind of repair," Freedman said. "[It's] like you're now the road crew who's going to go out in a country where the war's going on and you're fixing the roads. Hopefully the bombs aren't going off."

The conditioning regimen, followed by the HCT, may be enough to stop the bombs, he added.

At the end of his interview with MSDF, Bowen emphasized that this sort of treatment is a last-ditch effort reserved only for patients whose RRMS is very aggressive and unresponsive to conventional treatments. But for some patients, that may leave a very narrow window of opportunity.

The line between relapsing-remitting and secondary progressive MS (SPMS) is blurry, but it's important to define that line when deciding on stem cell therapy. Since progressive forms of MS are considered neurodegenerative, not inflammatory, stem cell transplantation is highly unlikely to have any meaningful effect on SPMS patients. While it's always difficult to determine when a patient crosses the line from relapsing to progressive MS, patients with particularly aggressive forms of RRMS can be especially hard to treat, Freedman said.

"What you don't want to do is go down a shopping list of 10 to 12 drugs, meanwhile the patient has now advanced to a stage where a bone marrow transplant won't do them any good," Freedman said. "You're dealing with a war."

Key open questions

- What is the best conditioning regimen for patients with MS?
- How can physicians best intervene before patients slip into the progressive phase of the disease?
- What other ways might HCT be made safer and more effective?
- How long will the effects of HCT be sustained in MS patients?

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Freedman and Burt reported no conflicts of interest.

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