Jennifer Molson had severe multiple sclerosis until a stem-cell therapy triggered a recovery, and she now works at the Ottawa hospital where she was treated.

TONY FOUHSE

STEM CELLS

Stemming the tide

Could a high-risk treatment play a part in tackling multiple sclerosis?

BY ASHER MULLARD

When neurologist Mark Freedman and haematologist Harry Atkins started planning a radical multiple sclerosis (MS) experiment in 1999, they set the wheels in motion for a spectacular failure. They learned nothing about how MS develops — but still achieved something remarkable.

The two doctors at the University of Ottawa in Canada wanted to reset a patient's immune system in much the same way that you reboot a computer, hoping to watch the autoimmunity redevelop and thereby pinpoint the elusive origins of MS. The restart button was dangerous: a concoction of potentially fatal toxins that would destroy the aberrant immune cells that drive the neurodegenerative disease, followed by a transplantation of the patient's own haematopoietic stem cells (which give rise to blood cells) to protect against subsequent infection. The researchers hoped that done cautiously, this extreme approach, called autologous haematopoietic stem-cell transplantation (aHSCT), might also buy their patients a little extra time.

Freedman and Atkins have yet to see how immune cells turn against the central nervous system in MS. "We failed, miserably," says Freedman, with a smile. Instead the pair had stumbled across something much more useful: a powerful treatment for the disease. Earlier this year they reported that of the 24 patients who have received aHSCT at the Ottawa Hospital, 23 have not relapsed[1].

"We took patients who were really going downhill fast, and we stopped the disease dead in its tracks," says Freedman. The responses are durable too, having lasted more than 14 years in some patients. Most of the patients stopped getting sicker, but half a dozen have made remarkable neurological recoveries.

Other hospitals have reported similar success using aHSCT to treat MS. A recent meta-analysis of 15 studies since 1995, involving 764 patients, found that 67% of aHSCT recipients had no evidence of disease activity 5 years after treatment[2].

Even so, many neurologists have reservations about the high-risk treatment, which haematologists initially developed as a last resort to treat blood cancers. And trials of aHSCT in MS have all been small and uncontrolled, prompting some neurologists to argue that it is premature to embrace the results.

"We've had many treatments that have appeared promising when used in uncontrolled trials, but that have failed in larger trials," warns Christopher Bever, a neurologist at the University of Maryland Medical Center in Baltimore. Already, he says, exploitative, unlicensed clinics around the world are profiteering from the enthusiasm for stem cells.

RISKY BUSINESS

There is no disputing that the therapy carries great risk. The drugs that knock out the immune system bring patients to the brink of death — and around 2% of aHSCT-treated patients die from transplant-related causes[2]. Although this death rate is falling, reflecting a better understanding of how to deploy the

treatment in the clinic, recovery remains slow and painful, and the side effects can be lifelong. "It's not for everyone," says Freedman.

One person who did benefit, though, is Jennifer Molson. She was diagnosed with MS in 1996, after pins and needles in her left hand made her drop a jug of milk on the floor. Five years later, at the age of 26, her disease was so aggressive that she needed help bathing, getting dressed and eating. She had quit her job, given up her dreams of becoming a police officer, and was confined to a wheelchair.

A grim magnetic resonance imaging (MRI) scan eventually provided a silver lining. "It looked like someone had taken a cheese grater to my brain," she says. Freedman, who was one of her doctors, turned to her and said "Congratulations, you are sick enough now. Now we can try and do something for you," she recalls.

In June 2002, Molson became the fifth MS patient to receive aHSCT at the Ottawa Hospital. Freedman and his colleagues first harvested stem cells from her bone marrow that they would later use to bolster her immune system. For 10 days, they blasted her with chemotherapy to kill off the faulty immune cells that were responsible for her decline; the rest of her immune system was collateral damage. On day 11, the doctors reinjected her with the stem cells to stave off what could otherwise be deadly infections.

"People who are thinking about this really need to talk to their physicians."

She hit rock bottom during the subsequent month in the hospital, and spent more than a year at home recuperating. "I had no idea how sick I was going to be," she says. She still had the neurodegenerative losses of MS, but she also started vomiting on a daily basis and was plagued by 'chemo fog' — thinking and memory problems brought on by the chemotherapy drugs. Her energy was gone, as was her hair. She came down with a painful case of shingles and a blood infection. "I went into a bit of depression," she says. "'What did I do to myself?' I'd wonder."

But Molson was one of the lucky ones. The next patient to enter the trial died 62 days after transplantation from treatment-related sepsis and liver injury.

Eventually, Molson made a remarkable recovery. When she started the trial, she could not stand up on her own. Last summer, she went paddle boarding on the choppy, chilly Ottawa river. She still has to take drugs for heartburn and for chemotherapy-induced menopause, but she has been free from MS relapse for 14 years. "I like to use the word 'cure'. The doctors don't, so we'll stick with 'lasting remission'," says Molson, who now works as a research assistant in the hospital where she was treated.

In total, 35% of the patients in Freedman's trial have enjoyed sustained improvements on an expanded disability status scale, which quantifies MS disability.

No one really knows what is driving these recoveries, although Freedman suspects that remyelination might be occurring. In MS, inflammatory flare-ups strip neurons of their protective myelin sheaths, leaving them vulnerable to degeneration. Cells called oligodendrocytes can remyelinate damaged neurons, but this regenerative ability tends to fade as the disease progresses. Researchers have struggled, and so far failed, to use drugs to induce remyelination[3].

The stem cells used in aHSCT are intended to protect patients from infection, and are not thought to be involved in remyelination. But preliminary imaging data nevertheless suggest that the remyelination pathway might be activated in some aHSCT recipients.

DIVIDED OPINION

Neurologists remain divided over how to roll out aHSCT to patients with MS, however. "The bottom line for me is that aHSCT is unproven," says Bever. He calls the results "striking", but argues that they need to be handled with care until they are replicated in a larger, controlled clinical trial. "I don't bring it up with patients," he adds.

Jeffrey Cohen, a neurologist at the Cleveland Clinic in Ohio, is more optimistic. "The evidence already supports using this approach in patients with very active disease that have failed all the available therapies," he says. But these patients are rare, he adds, and "the available evidence does not support using it more generally."

Freedman, whose team now considers offering aHSCT to 2 or 3 patients per month, counters that there is a case for broader use. Transplantation should be a treatment option for patients who have rapidly developing and uncontrollable disease[4], he says. If neurologists use aHSCT only as an absolute last resort, he adds, they might miss the window of opportunity when it offers the most promise. Once the disease becomes too advanced, or patients lose the ability to cope with immuno-ablation, the risk–benefit analysis for aHSCT can become more complex.

More clinical trials could resolve the debate. In 2012, Freedman and his colleagues planned a 114 patient, controlled phase III trial of aHSCT, in which control patients would be randomized to the best available therapy initially and then crossed over onto aHSCT only when their disease progresses[5]. But funding for the trial has remained elusive, and recruitment might also be problematic because people in the control group might drop out to explore other experimental options. Some researchers want to use safer, less toxic drugs to wipe out the immune system in the first phase of the treatment — a move that Freedman says is a mistake because it could leave behind autoimmune cells as well.

Researchers are also advancing an entirely different approach that uses mesenchymal stem cells. Whereas haematopoietic stem cells are intended only to prevent infection in aHSCT, mesenchymal stem cells are thought to offer regenerative capabilities. Preclinical data suggest that mesenchymal cells secrete proteins that can protect axons, improve neuronal survival and induce repair[6].

A few phase I studies have shown that these cells are safe[7], and researchers are now looking for signs of efficacy in larger phase II trials. Freedman, for example, is collaborating with colleagues to enrol 40 patients with either relapsing–remitting or secondary progressive MS into a Canadian trial called MESCAMS. The results, which are expected in late 2017 or early 2018, will be pooled with data from another 120 patients who are receiving the same stem-cell treatment in other countries.

Cohen is also set to launch a phase II trial using mesenchymal stem cells in 120 patients with MS in 2017. His group is fine-tuning some technical details, such as how many mesenchymal stem cells to inject into patients, and whether the cells should be frozen before use or injected directly from culture. "These seem like pedestrian issues, but are probably very important," he says.

Despite the huge amount of uncertainty that surrounds the experimental use of stem cells, a growing number of clinics with dubious scientific qualifications are already cashing in on the stem-cell hype. Profit-driven clinics around the world are offering experimental treatments — that may or may not actually include stem cells — to any patients with MS who will pay. "It's a big issue," says Cohen. "It's hard to know what's actually going on in these clinics."

Molson empathizes with desperate people who turn to these clinics through frustration with the slow pace of scientific progress. "I was willing to die to get better. I was in their shoes," she says. But even she did not properly appreciate the full risks of a legitimate treatment — in a regulated trial, where she knew exactly what she was getting — until it was too late. "People who are thinking about doing this need to talk to their physicians," she says.

Stem cells may finally be starting to live up to their potential in treating MS — but they are still not ready for prime time. ■

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