Scientists explore new MS therapies

Scientists are exploring pharmaceutical, diet-altering gut bacteria and stem cell work.

by Mary E. King, PhD

Scientists are exploring a variety of approaches to treat MS, including pharmaceutical to diet-altering gut bacteria and stem cell work. Momentum talked to two experts about innovative pharmaceutical and cell therapy approaches: Dr. Daniel Ontaneda, MD, PhD, from the Mellen Center for MS at the Cleveland Clinic in Cleveland, and Dr. Michael D. Kornberg, MD, PhD, from the department of neurology at Johns Hopkins University School of Medicine in Baltimore.

Target MS progression

Evobrutinib is a type of protein that can be given orally instead of by injection or infusion. It targets specific immune cells that play an essential role in the progression of MS. It primarily blocks B cells, reducing their activity and inhibiting other immune cells (myeloid cells), which may have additional roles in MS. Evobrutinib targets immune cells differently from ocrelizumab (Ocrevus), which is already on the market. Blocking B cells is a new approach to treating MS and could help individuals not helped by Ocrevus. Evobrutinib had positive results in a phase 2 trial. Importantly, it reduced the number of active brain lesions in MRI scans of the participants compared to those who received a placebo, and it was fairly well tolerated. Phase 3 trials are underway in participants with relapsing-remitting MS (RRMS).

Michael D. Kornberg, MD, PhD, leads an MS research team at Johns Hopkins University School of Medicine.

"[Evobrutinib] will likely have a place in treating RRMS, due to its fast on/off mechanism of action and its safety profile," Kornberg says. "However, what is most exciting about this new class of drugs is that, unlike those currently available, they target cells that are thought to play a primary role in progressive MS. This creates hope that they may provide benefit in progressive MS."

While the new class of drugs may be available for RRMS within the next few years, data about its effectiveness in progressive MS will take longer, Kornberg says.

According to Ontaneda, phase 2 results are promising, but he adds, "This therapy will need to be tested in larger phase 3 studies to determine efficacy as compared to other MS disease-modifying therapies."

Reboot the immune system

Scientists are also studying a type of stem cell transplant (aHSCT) that "reboots" the immune system using cells taken from an individual's bone marrow.

"aHSCT has the potential to 'cure' MS if given early in the course of the disease, but it carries substantial safety concerns, and whether it's more effective than other highly effective MS therapies remains unknown," says Kornberg.

Ontaneda says that while aHSCT is a promising therapy, it is commonly reserved for the most aggressive forms of RRMS.

The BEAT-MS trial is a large phase 3 trial recruiting 156 people with RRMS at 19 sites across the U.S. to study aHSCT.

“This will be the first trial to directly compare the efficacy and safety of aHSCT to other highly effective therapies and will likely determine whether aHSCT becomes a standard part of MS treatment,” Kornberg says.

“The safety of aHSCT has been improving over time, as experience with different regimens and protocols have been tested, which make the trial results very important. The trial is testing aHSCT against the current best available medical therapy for MS,” Ontaneda says.

Repair existing damage to nerve cells

Researchers also want to find a way to reverse nerve damage. In laboratory studies, another agent, elezanumab, does just that: It helps repair nerve cells and the myelin that coats them. Research is now underway in people with MS.

The first study, a small phase 1 trial, demonstrated that elezanumab is safe in individuals with either secondary progressive MS or RRMS. It is being tested for how well it works in two double-blind studies, one with 123 individuals with primary progressive MS and one with 208 people with RRMS. Participants will receive either this experimental agent or a placebo in addition to their usual MS therapies.

Ontaneda says elezanumab targets a specific protein active in MS that blocks nerve growth and nerve repair. “This is a relatively new approach in MS, and it holds promise as a potential therapy to reverse the damage. It is also being studied in stroke and spinal cord injury,” he says.

“Unlike currently available drugs, the hope is it will repair prior damage and improve disability rather than simply prevent new lesions from forming,” says Kornberg. “Therapies that lead to the recovery of neurologic function are a major unmet need for MS patients.”

Because elezanumab is in such early stages of research, its success is still very uncertain.

In an approach involving stem cells — NurOwn (MSC-NTF) cells — researchers are removing a specific type of cell from an individual’s bone marrow and treating these cells so they will secrete natural chemicals that stimulate nerve growth. The cells are reinfused into the individual. Scientists hope this therapy will protect nerves from further damage and boost myelin repair in damaged nerves. It is being tested in 20 people with progressive MS.

A different tactic to help protect nerves and increase myelin repair involves an experimental therapy using extremely tiny crystals of gold (biocatalytic nanocrystalline gold (CNM-Au8)). In laboratory experiments, these specially designed crystals boost the energy-producing steps that occur naturally inside cells. The therapy helps brain cells, which need a lot of energy to repair myelin. CNM-Au8 also seems to help protect nerve cells against further damage. Scientists are now testing CNM-Au8 in 150 people with MS in a phase 2 trial to determine

whether it is effective in promoting myelin repair and protecting nerve cells.

Targeting viruses linked to MS
Previous infection with Epstein-Barr virus (EBV) has been linked to the risk of developing MS. ATA188 is a therapy that uses immune T cells from healthy donors. When given to people infected with EBV, these cells will specifically attack certain immune cells infected with EBV. Researchers are studying ATA188 in a phase 1 trial in 97 individuals who live with progressive MS.

Kornberg says, “There is a clear, consistent association between EBV infection and risk of MS. One hypothesis is that persistent EBV infection of immune cells continues to drive disease throughout a patient’s life. If this hypothesis is correct, ATA188 could eliminate the ongoing trigger for the disease. However, there is no definitive evidence yet supporting the hypothesis that persistent EBV infection is a cause of MS.”

Temelimab is an agent that targets another class of viruses called human endogenous retroviruses (HERVs). The science is relatively complex, but what’s important is that HERVs produce a protein that researchers have found inside active MS lesions. In lab experiments, the protein seems to promote unwanted inflammation and hinder the repair of myelin. The hope is that by blocking HERVs, temelimab will help repair myelin and slow or stop MS progression. It’s being studied for safety and to see how it acts in humans in a phase 2 study of 40 people with RRMS.

Types of therapies and trials

Two significant approaches underlie most of these new therapies. One is the use of monoclonal antibodies, which are special proteins carefully designed in the laboratory to bind only to certain molecules. A monoclonal antibody gives researchers a way to carefully target and block a specific action or cell type, like the multiplication of a type of immune cell called a B cell that plays a crucial role in MS. The novel antibodies discussed here are evobrutinib, elezanumab and temelimab.

Another hot topic in biomedical research, including in MS, is the use of cell therapy. Stem cells are found in both embryos and adults. Two new therapies use adult stem cells. One is called autologous stem cell transplantation (aHSCT), a complex procedure that “reboots” the immune system. Doctors must destroy a person’s immune system using chemotherapy, then regrow it using the individual’s own stem cells (autologous) taken from bone marrow before administering chemotherapy. This course is risky because the person won’t have a working immune system to fight off infection while new immune cells are being made. Another approach using stem cells — NurOwn (MSC-NTF) cells — removes a specific type of stem cell from bone marrow, treats the cells to stimulate nerve growth and returns them to the patients. The immune system is not “rebooted” in this procedure.

These potential therapies are in various stages of research, from smaller, earlier phase 1 or phase 2 trials that can give early signals of success to larger, later-stage phase 3 studies designed to rigorously test safety and efficacy.

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