Game-Changers

The rapid development of new therapies is giving hope to people with multiple sclerosis—and Rush specialists are among those leading the way

As recently as 40 years ago, people diagnosed with multiple sclerosis (MS) were almost entirely at the mercy of the disease: There were no proven medical interventions that could halt or slow the progression, or even improve symptoms. People with the most severe forms faced certain debility, often in the prime of their lives.

That was the landscape of MS when Dusan Stefoski, MD, completed his residency at what was then Rush-Presbyterian-St Luke's Medical Center and signed on to the Rush Multiple Sclerosis Center. Four decades later, that landscape is unrecognizable—thanks in large part to the pioneering efforts of Stefoski, now the center’s director, and his Rush colleagues, past and present.

One of those colleagues is Michael Ko, MD, who also trained at Rush before joining Stefoski in practice. Ko recently sat down with his mentor to talk about the rapid evolution of MS treatment, and Rush’s vital role in bringing a slew of promising therapies to the market.
Ko: You first started working with MS patients in 1977. How would you describe the state of MS treatment at that time?

Stefoski: It could best be described as underdeveloped. There was only 1 FDA-approved treatment for MS, adrenocorticotropic hormone (ACTH)—which stimulates the adrenal gland cortex to secrete cortisol and aldosterone, among others, in addition to possibly having a direct ameliorating effect on the immune system. ACTH had some efficacy in terms of speeding up the recovery from acute relapses of MS. But it had no proven efficacy over the long run; it didn’t change the course of the disease.

Ko: There wasn’t another option until Betaseron (interferon beta-1b) was approved in 1993. When you started using it, what was the impact of that medicine?

Stefoski: The impact was relatively modest. People were excited because there was finally a new drug for treatment of MS that held a promise of modest benefit over time. But the availability was initially rather limited, so relatively few people received the drug, and even those who received it often did not experience much in the way of benefit.

But 3 years later, the next interferon, Avonex (interferon beta-1a), was approved. Technically speaking, it showed better long-term efficacy than Betaseron, and Avonex actually began to change the way people felt, meaning they improved some over the long run. We were instrumental in collaborative research to develop Avonex.

Ko: You and your colleagues were also involved in the clinical trials for Tysabri (natalizumab). Was that considered a game-changer when it was approved in 2004?

Stefoski: It was a dramatic game-changer, because that treatment really could halt the disease process in a way that we had not seen before. And it could stop further progression in many people—not all of them, but a large majority of people with MS experienced improvements within the first few months of treatment.

Ko: We’ve treated a lot of people with Tysabri at Rush. Do you think that experience—the high volume of patients—has contributed to a better understanding of how it’s used?

Stefoski: Our initial contribution with Tysabri was collaboratively instrumental in demonstrating its efficacy, because we were part of the phase III trial. But since 2012, we have published a series of pioneering reports on the management of one of the major potential complications of treatment with Tysabri: progressive multifocal leukoencephalopathy (PML), a rare infection of the brain caused by the JC virus. The JC virus is not actually related to MS or to Tysabri. Many healthy people harbor the normally rather innocuous JC virus. However, in people with MS who have the JC virus, treatment with Tysabri creates a situation that allows the virus to establish itself in the brain and cause PML, which can be severely incapacitating or even fatal.

We were the first in the world—and you were part of that whole process—to develop a novel protocol for early detection and treatment for MS patients who contracted PML in association with Tysabri. We monitor patients both clinically and with brain MRI at 3-4 month intervals, which enables early detection of PML and allows for better management outcomes. Our groundbreaking approach consists of accelerated elimination of the JC virus by stimulating the person’s own immune system with filgrastim (G-CSF, Neupogen). This reduces the damage and fosters a faster recovery. Furthermore, we were the first to also administer maraviroc (Selzentry), an antiretroviral that modulates immune T-cell recruitment, in PML patients.

As reported, there were no fatalities among the PML patients we treated, which is significant in that PML used to be considered a fatal disease.

Ko: There has been recent interest in high-dose chemotherapy and hematopoietic stem cell transplantation, or bone marrow transplantation, at Rush and other institutions. What has been your experience with this approach?

Stefoski: High-dose chemotherapy is a very powerful treatment for MS. It is considered induction therapy, because it has an immediate effect of completely stopping the disease process, which can last for quite a while. Although this approach was conceived elsewhere some time ago, we were among the first in the world to start using it, and to date we’ve treated more than 30 patients with excellent results.

As for stem cell transplantation in MS, the treatment is very high-dose chemotherapy using a powerful anti-cancer medication such as cyclophosphamide (Cytoxan), though other drugs or combinations of drugs have been used at other institutions. Chemotherapy is effective for MS and other autoimmune diseases because it kills the attacking cells, but unfortunately, it also kills healthy cells. The patient’s immune system is nearly destroyed and has to be reconstituted, which is achieved by giving them back their own saved bone marrow stem cells, either autologous (their own marrow) or allogeneic (donor marrow). So the stem cells do not actually treat MS, they just restore the immune system that has been badly damaged by the chemo.

Ko: Do you consider high-dose chemo a cure?

Stefoski: No. Most of these people do well for an extended period, up to 5 years following the initiation of treatments, but 25-30 percent of patients begin to experience recurrence of MS at that point, albeit often in a milder form. And
because it’s so harsh, it’s generally a once-in-a-lifetime therapy; if additional treatments are needed later, standard therapies are applied.

**Ko:** In March 2017, ocrelizumab (Ocrevus) became the 15th FDA-approved medication for MS, and Rush was the first center in Illinois and one of the first in the country to use it. It’s been receiving a lot of interest in the MS community. What do you expect to see from it?

**Stefoski:** It’s yet another game-changer for people with MS. It’s the first and only disease-modifying therapy for both primary progressive and relapsing forms of MS, and it has the potential to lead to new avenues of treatment for other diseases as well.

One interesting thing about it is that it treats MS in a way that we never considered would work. The approach is called anti B-cell therapy—Ocrevus is a monoclonal antibody that targets the CD20 molecule on the surface of B cells, allowing for their destruction. The traditional concept of the MS disease process is that T cells are the main culprits, but over the past few years the role of B cells has also emerged.

B cells are best known for their involvement in antibody production through plasma cell formation, but they are also involved in other functions of the immune system, including directing the actions of their counterpart T cells. Research has shown that B cells can induce T cells to attack myelin though a process known as antigen presentation; that’s why eliminating B cells can be effective for MS. Ocrevus removes B cells that would have been bound for the nervous system to orchestrate inflammation.

What this means is that B cells are perhaps just as important as or even more important than T cells in MS. That’s a huge paradigm shift. Anti T-cell drugs do work in MS—cladribine is one such drug—but the vital role of B cells has now been established.

One of the most appealing and impressive facts about Ocrevus is that it’s administered to patients only twice a year, intravenously, in our offices. That is a tremendous benefit for patients.

**Ko:** Your research with Floyd Davis, MD, on dalfampridine (originally known as 4-AP) was truly groundbreaking. How did you start pursuing that line of research when there was not a lot of backing?

**Stefoski:** The initial discovery was really a theoretical one. Some of that work was done here at Rush, when it was realized that blocking the potassium channel on nerves damaged by MS could improve nerve signaling.
In MS, normal electrical nerve signaling fails because the stripping of myelin that coats the nerves leads to their short-circuiting, slowing and even completely blocking the signals. That’s why people with MS often develop their problems.

Theoretically, in early computer modeling, it was clear that if we could block the potassium channel, it should improve the signaling. But there were no known potassium channel-blocking drugs, or chemicals for that matter. It turns out that researchers at a physiology laboratory at Duke University had discovered, unrelated to MS, that this chemical known then as 4-aminopyridine (4-AP for short) was a potassium channel blocker on nerve fibers. They cataloged it as such, not anticipating any immediate therapeutic usefulness.

Our team at Rush was able to make the connection between our research and the discovery at Duke, and we began studying 4-AP, initially just in nerves and cells. It worked right away, so we quickly shifted into carefully structured human trials in the early 1980s. There was only one other team of researchers doing similar work, at the National Hospital of Neurology and Neurosurgery (aka Queen Square) in London. Their contemporaneous research looked very good in the laboratory, but their clinical results were unsuccessful, and they never pursued it any further. Ours were successful, and we pressed onward with our efforts that ultimately brought dalfampridine to the market as Ampyra.

Most of our research efforts with this project were funded through private philanthropic donations expressly to the Rush MS Center. Without those generous donations, our work would not have been possible because, as you mentioned, there was no backing from other sources.

**Ko:** What has been the impact of Ampyra in the MS world, and at Rush in general?

**Stefoski:** It’s the first and only drug in the history of neurology and MS that can help people who have MS walk better and faster, so it falls into the category of function-restoring drugs, not just symptom-relief drugs.

I’m emphasizing that distinction because while its effects are often misconstrued as symptom relief, Ampyra actually restores function. The difference is clear when we analyze the loosening of spastic muscles by the symptom-relief drug baclofen. Baclofen diminishes stiffness, which is beneficial; but it does not actually improve function in the damaged nerves. Ampyra enables patients to walk better and faster, because it restores the nerves’ ability to propagate impulses by making the signals longer and stronger.

Ampyra was the first commercially successful drug ever discovered at Rush, a fairly rare occurrence at any academic institution. Because of its international success, Ampyra has brought significant funds to Rush, which are being reinvested into various research projects that could generate important discoveries.

**Ko:** One of the other medications used almost exclusively at Rush for MS is cladribine, a potent chemotherapy drug that’s being investigated as an oral medication. What is your experience with it? Could it eventually get approved in the US for MS?

**Stefoski:** I reckon that it will be. We have been the early proponents and prescribers of cladribine for MS, and it has proven efficacious in halting the destructive processes of MS and lowering the risk of disability progression. The original work was done at Scripps in California, but we may have been the second center in the world to start using it. We were part of the oral cladribine phase III trial, which almost led to its approval, but the company that created it, EMD Serono, did not pursue approval at that time. They are now rekindling their efforts to bring it to market in the US, and it was recently approved in Europe. I think it will be approved fairly quickly in the US because of the efficacy and safety demonstrated in multiple trials worldwide, which included our team at Rush.

**Ko:** Nerve regeneration using stem cell therapy is a very hot topic in the MS community. Do you see that coming to fruition anytime soon?

Bringing Ampyra, a drug that can improve walking for many people with MS, to the market in 2010 was a crowning achievement for Dusan Stefoski, MD, and his mentor Floyd Davis, MD.
Stefoski: I do not. The problem with real stem cells is that we don’t know where they go and what they do once they’re put into people’s bodies, at least as far as MS is concerned. Other alleged “stem cell” treatments marketed for MS are actually high-dose chemotherapies, and with those therapies, stem cells serve only to rescue the immune system. The only systematic approach to the treatment of MS with stem cells was done in Israel, with modest benefit. We’re talking about adult mesenchymal stem cells, incidentally, not fetal stem cells. There has been no work with embryonic stem cells for MS.

Unfortunately, since the FDA has relaxed its regulation of adult stem cell treatment centers in the US, they have popped up all over the place. People are going and paying cash up front, but they don’t know what they’re getting. A person with MS is much better off going to a medical facility with a reputation, where they can be properly evaluated and receive a proven treatment that might actually be of benefit.

Ko: What are the benefits of coming to the Rush MS Center specifically?

Stefoski: I think what differentiates Rush from other MS centers is that we have a tradition of and expertise in being proactive with treatments. It’s not unusual for people with MS to be treated with one drug for life even though they’re getting worse, because some centers don’t escalate treatments or think proactively and start with a high-potency treatment. At Rush, we take a proactive approach that is tailored to each person’s type of MS. And we don’t shy away from using a variety of cutting-edge or exclusively experimental treatments, when appropriate, in addition to some very powerful existing drugs that many other major MS centers in the region hardly ever use.

Ko: We are also comprehensive in the sense that we’re the only institution with an independent MS center. We don’t share space with other specialties, such as epilepsy or movement disorders. Our nurses are dedicated MS nurses, and we have dedicated office staff. We are not sharing resources.

Stefoski: That dedicated specialization is very important. Patients are always seeing the same MS center staff members, all of whom have expertise working with this population—from the first administrative contact to the final decision-making health care provider. We used to have a dedicated psychologist, physical therapist, and occupational therapist on our team. Our patients still have access to PT, OT, and psychology, because those disciplines exist within Rush University Medical Center, but the specialists themselves are not dedicated to MS. We hope to eventually return to that level of multidisciplinary care at our center, because that’s the approach preferred by both patients and our staff.

Ko: The Rush MS Center has been around for several decades and has a reputation as a leader in MS treatment and research. What does the future hold?

Stefoski: The biggest task now is expansion, to be able to accommodate the increasing numbers of patients receiving intravenous medications. There are 6 IV medications for MS that can be administered on an outpatient basis, so we recently began to expand our infusion facility as well our professional staff. As for research, we are embarking on testing of a few brand-new drugs, some of which have the potential to repair tissues damaged by MS.

Ko: Treatments have advanced significantly in a relatively short period of time.

Stefoski: About 25 years.

Ko: When you started out, did you think there would be this much progress so quickly?

Stefoski: I did, and that’s actually why I went into the field of MS—the potential for innovation was palpable. In 1977, when I was finishing my residency in neurology here at Rush, I was offered the opportunity to stay on by 3 sections within the Department of Neurological Sciences. The first was neuromuscular neurology, which was too intensely reliant on electromyography (EMG). The second was epilepsy, but back then EEGs (electroencephalograms) were these endless reams of paper that you had to read for hours on end. With MS, it was almost exclusively patient work, which I found very engaging. I also realized that I could learn a lot from Dr. Floyd Davis, who was the founding director of the Rush MS Center and the only MS specialist in Chicago at that time. He was doing some really interesting MS-directed research, so I joined his team and our work evolved, leading to the development of Ampyra. It turns out I was correct in anticipating such progress.

Ko: Dr. Davis taught you, and you, in turn, have taught me and my peers. When you decide to step away from practicing medicine, what will your legacy be?

Stefoski: I believe a legacy is something best left to objective observers to determine. But from a more subjective point of view, there are several things I’m extremely proud to be cultivating here at Rush and teaching to both current and prospective providers of expert MS care: the strong emphasis on compassionate, comprehensive patient care established by Dr. Davis decades ago; a forward-thinking and decisive approach to treatment of people with MS; and a steadfast commitment to translational research, which has led—and will, I am confident, continue to lead—to the development of meaningful novel therapies for MS.