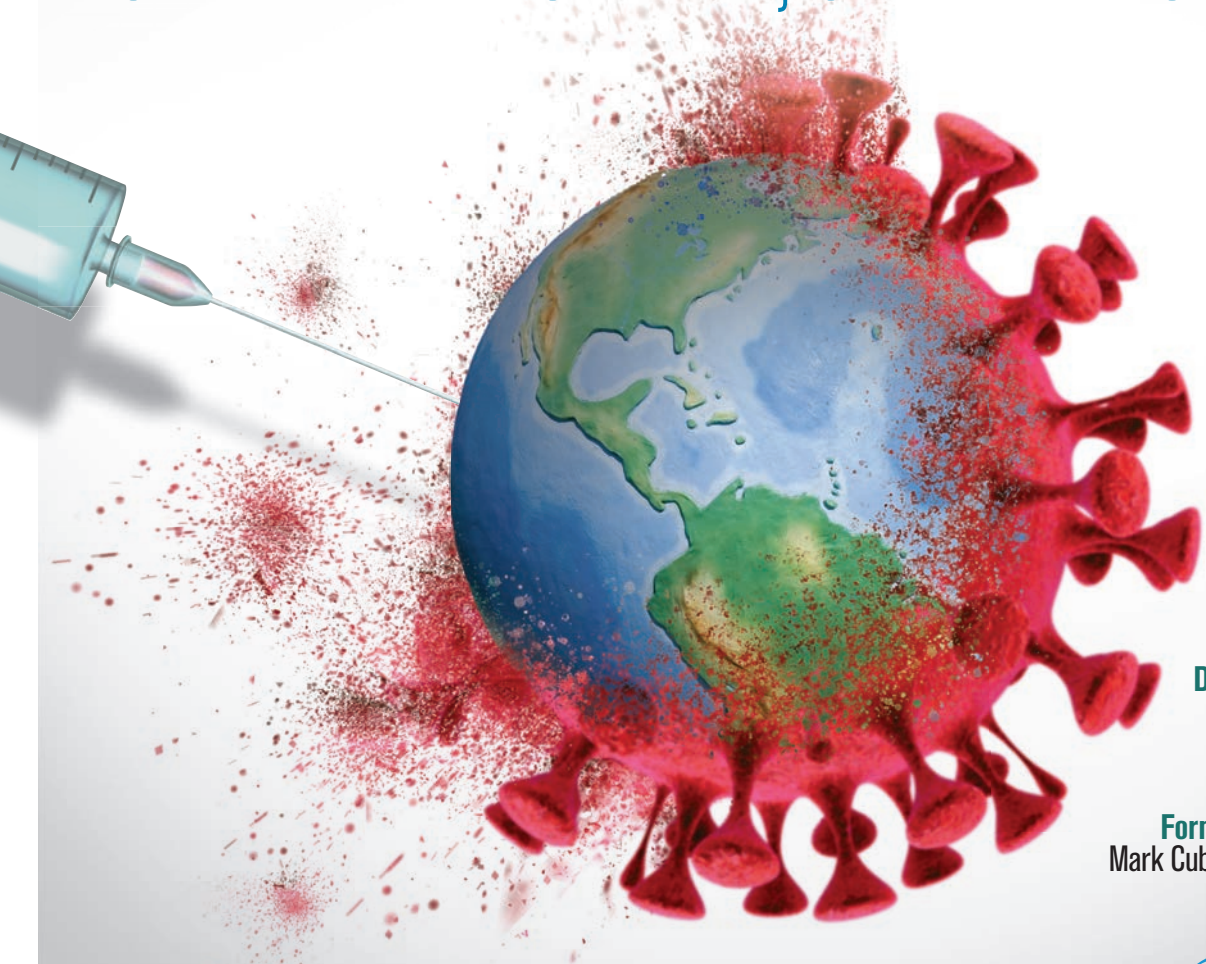
Technology AI for fraud detection | **Chronic Disease** Pediatric insomnia

Managed Healthcare EXECUTIVE®

The C-Suite Advisor

Finding a way forward for PUBLIC HEALTH

GREATER INVESTMENT, GREATER DISTRUST



Industry Analysis
Value-based care

Drugs in the Pipeline
Multiple sclerosis

Formulary Development
Mark Cuban's online pharmacy

April 2022 VOL. 32 NO. 4
Managed Healthcare Executive.com

Medical World News

Deep Dive Into Primary Care Direct Contracting

Multiple sclerosis

Some drugs new, some tried-and-true

The race is on to be the first-approved Bruton tyrosine kinase inhibitor. Meanwhile, trials are underway to test statins and metformin as treatments for multiple sclerosis. *by* **ROSANNA SUTHERBY, PHARM.D.**

Multiple sclerosis (MS) is a progressive autoimmune disease that affects nearly 1 million people in the United States. The debilitating disorder is characterized by lesion formation throughout the central nervous system (CNS), brought on by demyelination and inflammation of different components of the CNS. Wayward B cells, T cells, monocytes, macrophages and microglia are responsible for wreaking this havoc. Several up-and-coming treatments home in on these cells with increasing specificity.

The disease has been grouped into four types that are based on the overall course of the disease and frequency of symptoms. Relapsing-remitting MS (RRMS) is the most common type, accounting for approximately 85% of cases. It is characterized as episodes of new or worsening symptoms (relapse), followed by recovery periods (remittance). Over time, RRMS typically changes into secondary-progressive MS (SPMS). Someone with SPMS experiences steadily worsening MS-associated symptoms and disability. Roughly 15% to 20% of people with MS have the primary-progressive (PPMS) form of the disease in which they experience gradual disease progression from the start without the relapse-recovery cycle of RRMS. Progressive-relapsing MS (PRMS) is the least common form of the disorder. People with PRMS experience gradual deterioration from the start but may also have relapsing periods similar to those seen in patients with RRMS.

Given that RRMS is, by far, the most common type of MS, it is not surprising that currently available drugs primarily target this form of the disease. However, some new agents in development may change that. These drugs include a new class for MS treatment and potential therapies for progressive forms of MS.

Bruton tyrosine kinase inhibitors

Three potential newcomers to the MS armamentarium are racing through the pipeline as they compete to be the first-in-class Bruton tyrosine kinase (BTK) inhibitor. BTK is a nonreceptor kinase that plays a critical role in signal transmission through B cells and myeloid cells, both of which are significantly involved in MS pathology. Drugs that inhibit BTK can block the activation of B cells, thereby inhibiting the release of proinflammatory cytokines that are responsible for MS symptoms and disease progression.

Evobrutinib, developed by Merck, is an oral selective and irreversible BTK inhibitor that interferes with B-cell activation and macrophage activity. It also hinders B cells from acting as antigen-presenting cells, thereby reducing inflammation in the CNS. In phase 2 trials, evobrutinib significantly reduced the number of active lesions in participants with RRMS but had no effect on relapse rate or progression of disability. The drug is currently under investigation in phase 3 trials as a treatment for RRMS.

Competing with evobrutinib is Sanofi's tolebrutinib, which is another BTK inhibitor that is under investigation for the treatment of relapsing forms of MS. In a phase 2 trial, tolebrutinib achieved primary and secondary end points, with at least 85% relative reduction in new or enlarging lesions. Because of this drug's mechanism, it affects B cells and CNS microglial cells, both of which are thought to be involved in neuroinflammation and neurodegeneration. Because it can cross the blood-brain barrier, tolebrutinib may have additional capabilities

THE FOUR TYPES OF MS

- Relapsing-remitting multiple sclerosis (RRMS)
- Primary-progressive multiple sclerosis (PPMS)
- Secondary-progressive multiple sclerosis (SPMS)
- Progressive-relapsing multiple sclerosis (PRMS)

that the company intends to research further. The drug is currently in phase 3 trials, evaluating its efficacy in the treatment of RRMS and disability progression.

Roche's fenebrutinib may potentially address the scarcity of treatments for the progressive forms of MS. The company believes the drug may offer a new mechanism to suppress MS activity and slow disease progression through its ability to inhibit the activation of both B cells and myeloid lineage cells. Additionally, fenebrutinib may be associated with fewer side effects than evobrutinib and tolebrutinib. The drug is currently in phase 3 trials as a treatment for RRMS, PRMS and PPMS.

Masitinib

Masitinib, developed by AB Science, a French biotech company, is an oral tyrosine kinase inhibitor that targets mast cells and microglia. Similar to fenebrutinib, masitinib has been developed to treat the progressive forms of MS. Findings from phase 2b/3 trials indicate masitinib can significantly slow disease progression in adults with PPMS and nonactive SPMS. Another phase 3 trial has been planned to confirm these results in a larger population.

Ublituximab

Ublituximab is a potent glycoengineered anti-CD20 monoclonal antibody that is currently in phase 3 studies for the treatment of RRMS. Ublituximab targets an epitope on B cells that express CD20. By binding to B cells, ublituximab triggers both antibody-dependent cellular cytotoxicity and complement-dependent cellular cytotoxicity, leading to cell death. The hope is that by eradicating B cells responsible for much of MS pathology, ublituximab can slow disease progression and reduce or prevent further damage in the CNS.

TG Therapeutics, a North Carolina biotech company, has submitted an application to the FDA for the approval of ublituximab, and the agency is expected to make a decision in September 2022. If approved, ublituximab would join Roche's Ocrevus (ocrelizumab) and Novartis' Kesimpta (ofatumumab) as the third anti-CD20 monoclonal antibody approved by the FDA as a treatment for relapsing MS. One of ublituximab's possible advantages is that it takes less time to infuse.

Vidofludimus calcium

Vidofludimus calcium, developed by Immunic Therapeutics, a New York biotech company, is designed to repress proinflammatory cytokines produced by T helper cells, thereby reducing inflammation associated with MS. The manufacturer sees several advantages to this drug over existing therapies, including a favorable side effect profile. Vidofludimus calcium is currently in phase 3 trials for potential use in RRMS.

Old drugs, new tricks

Drug repurposing is catching the eye of drug developers, partly because using known entities can shorten the time it takes to put a drug through trials and gain FDA approval. Three established drugs are under investigation as potential MS treatments.

Statins, approved as agents that lower low-density lipoprotein cholesterol levels, are also known to have anti-inflammatory and neuroprotective properties. Simvastatin is being investigated as a potential treatment of PPMS and SPMS. A phase 2 study demonstrated that high doses of simvastatin reduced brain atrophy by 43% compared with placebo, and it slowed the progression of physical disability and cognitive decline in individuals with SPMS. After these encouraging results, Jeremy Chataway of University College London Institute of Neurology, and his colleagues launched a phase 3 trial evaluating the efficacy of simvastatin in slowing disease progression in patients with SPMS.

Metformin has been used in the United States for nearly three decades to lower glucose production and enhance insulin sensitivity in people with Type 2 diabetes. The Multiple Sclerosis Society UK in London is sponsoring a phase 2 trial to evaluate whether metformin combined with clemastine, an antihistamine, can stimulate the brain to generate new myelin.

Clemastine is thought to signal stem cells to begin myelin repair, whereas metformin puts the cells in a position to respond to the signal. If the metformin-clemastine combination proves to be safe and effective, it would become the first treatment to promote neuron remyelination in patients with MS.

Rosanna Sutherby, Pharm.D.,
is a medical writer and community pharmacist in High Point, North Carolina.