March 2021 Newsletter

What's New in MS Research?

MS is a chronic, unpredictable and often disabling disease of the central nervous system that affects nearly one million people in the United States. In recent years, new medications have become available to help slow the progression of the disease and manage its symptoms. Researchers continue to piece together new information as they work toward ultimately finding a cure. Read on about some interesting findings that have been published in the last 6 months.

The causes of MS are still unclear, however researchers are making inroads into this important topic. For example, a Danish study recently concluded that children of diabetic mothers may be at an elevated risk of developing MS. Data showed that MS risk among individuals whose mothers were diagnosed with diabetes before pregnancy was 2.3 times higher than those with nondiabetic mothers. Of note, investigators concluded that MS risk was not significantly affected by having a mother diagnosed with diabetes during pregnancy or having a diabetic father.

Two papers were recently published looking at the role of the microbiome in the development and progression of MS. A team of researchers from Germany, Spain and

Switzerland reported that a protein called "IL-17" (which is generated in the gut to regulate its microbiome) appears to be a critical driver in the likelihood of autoimmune disorders like MS in mice. Another study, also in mice, recently found that a subset of brain cells (astrocytes) can turn off inflammation within the brain, based on signals regulated by the bacteria in the gut. Figuring out how to harness this beneficial activity in humans may lead to new treatment approaches for MS, including probiotics to alter the balance of gut bacteria.

Significant progress has been made in the treatment of MS with a wide variety of oral and injectable disease modifying therapies (DMTs) available for relapsing and progressive forms of the disease. Two studies, published in early February, draw conclusions about the effectiveness of these treatments. The first study suggests that DMTs are effective at improving disability outcomes in relapsing-remitting MS (RRMS) over the long term. The second study identified two factors associated with treatment failure in RRMS. Data showed that DMTs were less effective in subjects who started treatment when they were younger than 26 years old, or if they had two or more relapses in the previous year. Interestingly, results suggest that the presence of enhancing lesions on MRI (which indicate disease activity) did not significantly affect treatment outcome.

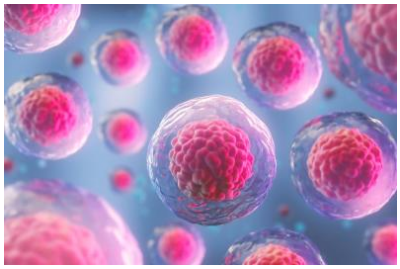
The following research sheds new light on a number of FDA-approved MS treatments. A small study recently found that intravenous cladribine (Mavenclad) may be as safe and effective as oral cladribine at reducing relapses, improving MRI activity, and slowing disease progression in individuals with active MS, with a reasonable safety profile. Further analysis of data from the EXPAND study recently showed Siponimod (Mayzent) had a significant benefit on cognitive function in patients with secondary progressive MS (SPMS). A recent review concluded that treatment with dimethyl fumarate (Tecfidera) was associated with a higher risk of adverse events, such as flushing, gastrointestinal issues and lymphopenia, over the short term. More research is required to determine its long-term safety. Ocrelizumab (Ocrevus), which can be used to treat RRMS, is also the first approved medication for primary progressive MS. A recent study determined that people with MS treated with

ocrelizumab experience lower work and activity impairment than those treated with other DMTs.

Three publications reveal new findings about MS and its treatments in the context of COVID-19. German researchers published a review of 873 published cases of people with MS and COVID-19 infection as of December 2020. Results suggest immunosuppressive therapy itself does not appear to be a substantial risk factor for the virus. With regard to the different DMTs, the most COVID-19 cases were reported in those receiving anti-CD20 treatment (317 cases). There was a 4 percent mortality rate from COVID-19 infection among people with MS and 3 percent required ventilation therapy. Severe and fatal cases of COVID-19 occurred in subjects not taking DMTs, those with previous cardiovascular diseases, or with higher levels of disability. Researchers suggest that DMTs could be protective, either directly or indirectly, by reducing MS disease activity. A second study found that, overall, people with MS have similar incidence, risk factors and outcomes for COVID-19 as the general population. Data also showed that subjects treated with an anti-CD20 therapy for a longer period of time appeared to be at a higher risk of COVID-19 and less than 20 percent developed antibodies to the virus. Only increased age was related to the severity of COVID-19 infection. Researchers in Croatia identified 33 people with MS who had to delay treatment with ocrelizumab by approximately one month due to COVID-19. None of the subjects had a relapse during this period and there were no other clinical consequences from the delay.

Several novel MS treatments are working their way through the research pipeline, with mixed results. A clinical trial done at 90 MS clinics across 13 countries recently showed that high dose biotin did not significantly improve disability or walking speed in subjects with progressive MS. Results also suggest this treatment had a negative safety profile. Researchers at Oregon Health & Science University developed a compound, called sobetirome, that mimics the myelin-generating effect of thyroid hormone by stimulating the maturation of its precursor cells (known as oligodendrocytes). New results show promise for sobetirome's ability to stimulate the repair of myelin in mice. German researchers recently published results from a study looking at the effectiveness of an mRNA vaccine to treat MS in mice. Mice with an MS-like disease were given an mRNA

vaccine containing the code for part of a myelin component. Data revealed that the mice experienced less severe disease than would have been expected and their normal protective immune responses were not compromised. It's important to note that early findings in animal models require considerable study before they can be applied to humans.



Recent advances have also been made in stem cell research. Italian investigators published a paper in January looking at outcomes of 210 people with MS who received autologous hematopoietic stem cell transplantation (HSCT) from 1997 to 2019. Nearly all of them had either RRMS or active SPMS. After ten years, 65 percent of the subjects continued to experience no worsening of disability. This rose to 71 percent among those with RRMS. Researchers from Lithuania conducted a smaller study of 24 subjects with active RRMS that failed conventional MS treatments and underwent HSCT. Results showed information processing speed and verbal learning were significantly improved one year after stem cell therapy. Researchers in Israel and Germany recently published results from a study looking at the optimal route of administration, and the safety and effectiveness of mesenchymal stem cell (MSC) transplantation in 48 subjects with active progressive MS. Results showed treatment with MSCs was well-tolerated and had short-term benefit. Intrathecal administration was more effective than intravenous administration. A larger clinical trial is needed to confirm these findings.

We've covered the general topic of alternative therapies for MS, cannabis and the practice of mindfulness in previous newsletters. Recent studies have shown a number of these unconventional treatments to be beneficial. Danish researchers recently published results from a study that showed treatment with medical cannabis oils was safe and well tolerated, and resulted in a reduction in pain intensity, spasticity and sleep disturbances in subjects with MS. Investigators in Iran found that 8 weeks of group-based cognitive hypnotherapy significantly improved the psychological well-being of subjects with MS. Another study team in Iran looked at the effects of 3 months of cognitive rehabilitation versus donepezil therapy on memory, attention, depression, and quality of life in subjects with MS. Subjects on both treatments showed improvement in all areas, however cognitive rehabilitation was superior altogether. A clinical trial conducted at the Ohio Health

Multiple Sclerosis Center showed that 4 weeks of mindfulness meditation training improved processing speed above and beyond adaptive cognitive training, or no intervention at all.

While there is no specific diet that will prevent or cure MS, scientists continue to find evidence that eating certain foods and nutrients, and avoiding others, may help a person's MS symptoms and disease activity. In November, Yale researchers published a study suggesting the abnormal immune system response that causes MS may be triggered by the lack of a specific fatty acid in fat tissue, called oleic acid. Oleic acid is found in cooking oils, meats, cheese, nuts, sunflower seeds, eggs, pasta, milk, olives, avocados, and other foods. However, it's important to note that further study is needed to determine whether consuming more oleic acid would reduce disease activity in people with MS. Italian researchers conducted a study looking at the life and dietary habits of 435 people with MS. Their findings suggest the Mediterranean diet may have a beneficial effect on MS course and disability, and this effect is likely mediated by a change in the gut microbiome.

It's a well-known fact that exercise and physical fitness are beneficial, regardless of an MS diagnosis. Researchers in Canada recently published a review of evidence from animal models of MS and clinical studies of people with MS that concludes exercise protects and repairs the brain. The reviewers note that while data suggest that exercise improves brain and spinal cord structures and functions, there is still much to learn. Another study looked at physical fitness in youth with MS, and its relationship to disease activity. Data showed that youth subjects with MS had lower levels of physical fitness in general, compared with healthy controls. Those that did moderate or vigorous exercise had less disease activity and disability.

MS is at least two to three times more common in women than men. There is mounting evidence that the female hormones, such as estrogen and progesterone, not only affect the reproductive system, but also the nervous and immune systems. In February, investigators at the University of California, Riverside, reported that treatment with an estrogen-like compound, called indazole chloride, repaired damage to myelin, protected nerve fibers from damage, and partially restored visual function in mice with an MS-like disease. It's important

to note that estrogens impact the reproductive system and have been linked to cancers. Further study is required to determine if such a treatment would be safe and effective for people with MS. Another interesting study of nearly 3,000 women with MS concluded that most of the complications associated with pregnancy (preeclampsia, gestational diabetes, placenta complications, emergency c-section, instrumental delivery, stillbirth, premature birth, infants with congenital malformations or low Apgar score) are not more likely in women with MS. Data suggest that women with MS were more likely to have elective c-sections, induced delivery, and babies that were small for their gestational age, than women without MS. The use of DMTs did not significantly impact birth weight. It's important to note that this study did not collect information on smoking status, which can impact birth weights.

Advancements in research are continually shedding light on what causes MS (or makes it more likely), discovering factors that impact the disease course, and revealing new treatment strategies. This new knowledge helps to improve the health and quality of life for many people who live with the disease and is moving us closer to finding a cure. The core of ACP's mission is to facilitate research efforts like these, that significantly impact the MS community.