Biomarkers and efficacy of vaccine responses among patients treated with new MS drug

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In March 2017, the U.S. Food and Drug Administration approved ocrelizumab as the first treatment for both relapsing (RMS) and progressive forms of multiple sclerosis (MS), a genetic disease that afflicts approximately 400,000 Americans with an estimated 10,000 new cases every year. This week at the 2018 American Academy of Neurology (AAN) Annual Meeting in Los Angeles, Penn Medicine neurologist Amit Bar-Or, MD, FRCPC, chief of the Multiple Sclerosis division and director for the Center for Neuroinflammation and Experimental Therapeutics, presented findings from two studies that look more deeply into the impact of ocrelizumab in these patients.

Ocrelizumab works by targeting and eliminating cells that have the CD20 molecule on their surface, which include a broad range of B cells of the immune system. In previous work looking at blood of patients prior to and following this treatment, Bar-Or and colleagues discovered that treatment decreases the ability of the patient's B cells to overly activate other cells of the immune system, resulting in decreased MS attacks. In particular, the researchers found that MS attacks are driven by interactions between B cells, T cells, and cells known as myeloid cells - an important insight, as MS has long been thought to be primarily mediated by T cells.

While this prior work highlighted how different immune cells can participate in MS relapses through their interactions outside of the central nervous system (CNS), the first new study (Abstract # S24.002) that Bar-Or presented at the AAN annual meeting provides new insights

on biological markers directly assessed within the CNS of patients. By measuring the number and profile of immune cells and injury markers in the spinal fluid before and after therapy, this study provides new insights into MS disease mechanisms and further explains the benefit of this treatment in limiting new MS activity and injury.

The analysis found that treatment reduced the presence of inflammation and injury markers measured within the spinal fluid at 12 and 24 weeks post-treatment. This included decreases in the median numbers of both B cells and T cells, and in the median concentration of neurofilament light chain (which is released when the nerve fibers known as axons, or their neurons, are injured). There was a good correlation between the levels of neurofilament and the numbers of T cells and B cells measured in the spinal fluid of patients. Together these findings suggest that interactions between T cells and B cells within the CNS may be important contributors to the neuronal damage seen in MS.

In a second study, Bar-Or and colleagues examined the role of ocrelizumab on responses of MS patients to a range of vaccines (Abstract #S36.002). The goal was to assess how effective particular immunizations would be in treated MS patients. The team looked at patients who received ocrelizumab and those who did not receive the treatment, and compared their vaccine responses to tetanus, the seasonal flu, and pneumococcus. They also asked about vaccine responses to a completely new antigen that people likely have never been exposed to (referred to as a neoantigen). For this, they chose to assess immune responses to vaccination with the keyhole limpet hemocyanin (KLH) neoantigen. Patients mounted positive response to the vaccines across groups, but the levels of immune responses conferred by the shots were lower across the board in patients treated with ocrelizumab. For example, there was a positive response to the tetanus vaccine at eight weeks in approximately 24 percent of those treated with ocrelizumab versus almost 55 percent of those who were not treated with

ocrelizumab.

"This study shows that while people with MS treated with ocrelizumab can still mount vaccine responses, it's not nearly as strong as prior to treatment," said Bar-Or, the senior author of the study. "While antibody responses were reduced in the ocrelizumab treated patients, they still responded to a certain level. This is valuable information in terms of seasonal vaccines such as the flu - it appears safe for patients taking ocrelizumab to get vaccinated and vaccination is likely to provide them with at least some protection from such infections."

Overall, findings of this study confirm the current prescribing recommendations for ocrelizumab - namely that patients should follow standard guidelines for receiving vaccines prior to treatment. If patients require vaccinations, they should ideally get them six weeks prior to beginning treatment with this drug.

"Translational research like this work with ocrelizumab is an example of what we're trying to do at Penn," Bar-Or added. "Research like this allows us to learn more both about the mechanisms underlying MS activity and injury, as well as the biology of MS treatments, which in turn will help us better individualize treatments for specific patients."

The first study detailed in this release is still underway, with additional results expected in 2019. This work was supported by Genentech, Inc., developers of ocrelizumab. The AAN abstract with more data can be found here. The second study presented by Bar-Or is sponsored by F. Hoffmann-La Roche Ltd, the holding company for Genentech. The AAN abstract is available online.

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