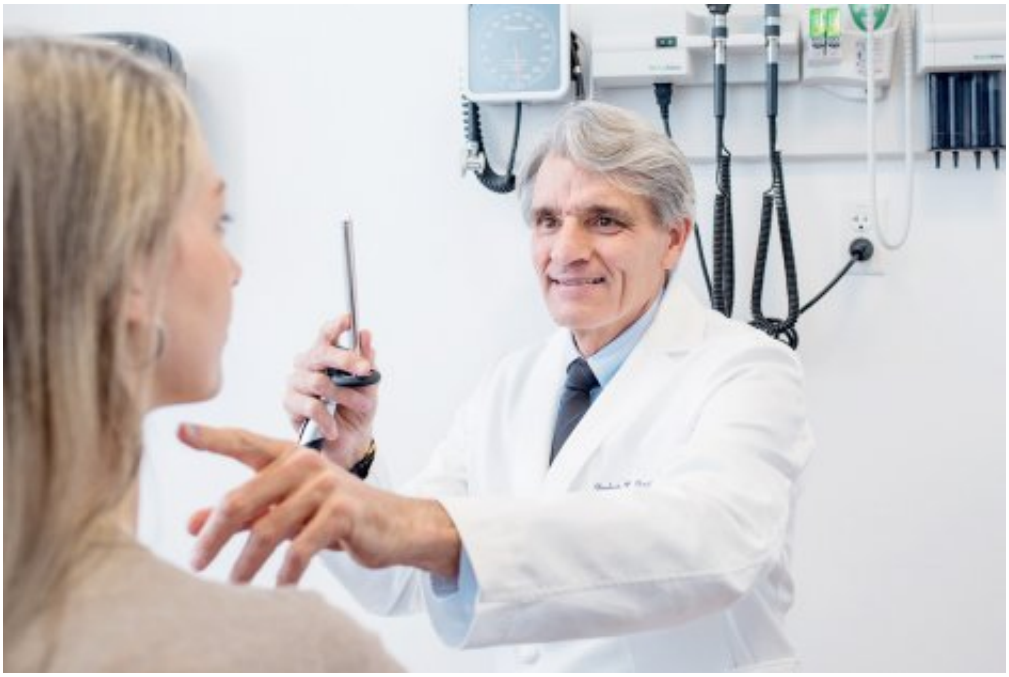
Positive multiple sclerosis clinical trial suggests 'unprecedented' effects in relapsing form of the disease

December 22 2016, by Pete Farley



Stephen Hauser, MD, served as chair of the Scientific Steering Committee for the OPERA trials and is corresponding author on the NEJM paper reporting the results from those trials. Credit: Barbara Ries

In findings that show the effectiveness of a new strategy for treating multiple sclerosis (MS), researchers are reporting positive results from three large, international, multicenter Phase III clinical trials of the investigational drug ocrelizumab (brand name Ocrevus) in both relapsing

multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS).

The trial results are published online on Dec. 21, 2016, in The *New England Journal of Medicine* (*NEJM*), and are discussed in an accompanying editorial.

In multiple sclerosis, the immune system attacks the body, making it a so-called autoimmune disease. To date, all MS drugs have targeted the immune system's T cells. Ocrelizumab, in contrast, depletes populations of the immune system's B cells.

Two companion papers in *NEJM* present data on the drug from two identically designed studies in RMS, known as the OPERA I and OPERA II trials, and from a trial involving patients with PPMS, called the ORATORIO study. All three trials, which involved hundreds of patients and dozens of researchers in several countries, were sponsored by F. Hoffman-La Roche (Roche), which holds the patent on ocrelizumab.

The OPERA trials compared the effectiveness and safety of ocrelizumab to that of interferon beta-1a (Rebif), a current standard-of-care medication for RMS. Magnetic resonance imaging conducted during the trial showed that inflammatory lesions in the brain in the ocrelizumab-treated group were reduced by 95 percent, compared with those receiving interferon, and reduced by about 99 percent from baseline levels at the beginning of the trials. These imaging results were accompanied by up to a 47 percent reduction in relapses of symptoms, and up to a 43 percent reduction in disability, compared to interferon.

'Unprecedented' Results from Trials

The reduction in inflammatory brain lesions seen in the OPERA trials is

"unprecedented," said UC San Francisco's Stephen Hauser, MD, who served as chair of the Scientific Steering Committee for the OPERA trials and is corresponding author on the *NEJM* paper reporting the results from those trials. Hauser, professor and chair of UCSF's Department of Neurology, and colleagues have long championed the idea that B cells play a central role in MS, and their research over many decades was instrumental in bringing ocrelizumab into clinical trials.

As there are no existing treatments for PPMS, the ORATORIO trials compared ocrelizumab with a placebo, and "clinically meaningful" reductions in disability progression and in other markers of worsening disease were seen, results that have never been observed in PPMS.

In all three trials, the most common adverse events associated with ocrelizumab were infusion-related reactions and infections, which were mostly mild to moderate in severity.

"This work, which we hope will have great benefits for the millions of people with MS, is the result of a longstanding collaboration between the global scientific community and industry," said Hauser, also director of the UCSF Weill Institute for Neurosciences.

MS is a chronic disease that affects an estimated 2.3 million people around the world, including an estimated 400,000 people in the United States, and while there are many approved drugs aimed at keeping RMS in check, approximately 10 percent to 15 percent of people with MS are diagnosed with PPMS, for which there are no approved treatments. There currently is no cure for either condition.

MS occurs when the immune system abnormally attacks the myelin sheath, a fatty substance that insulates and supports the axons radiating from nerve cells in the brain, spinal cord, and optic nerves, causing inflammation and consequent damage that interrupts the normal flow of

communication in the nervous system. This damage can cause a wide range of symptoms, including muscle weakness, fatigue, and difficulty seeing, and may eventually lead to permanent disability. Most people with MS experience their first symptoms between 20 and 40 years of age, making the disease a leading cause of non-traumatic disability in younger adults.

RMS is the most common form of the disease and is characterized by episodes of new or worsening signs or symptoms (relapses) followed by periods of full or partial recovery. PPMS is a debilitating form of the disease marked by steadily worsening symptoms but typically without distinct relapses or periods of remission.

Drug is Under Review by FDA

Marketing applications for ocrelizumab, under the brand name Ocrevus, have been submitted for both RMS and PPMS by Genentech, a member of the Roche Group, and are currently under review by the U.S. Food and Drug Administration (FDA) and European Medicines Agency. Ocrevus was granted Priority Review Designation by the FDA with an initial targeted action date of Dec. 28, 2016, that has been extended to March 28, 2017. This extension is the result of the submission of additional data by Genentech regarding the commercial manufacturing process of Ocrevus, which requires additional time for FDA to review. The extension is not related to the drug's efficacy or safety.

"These new publications indicate that B cells play a central role in MS," Hauser said. "In the OPERA I and OPERA II RMS studies, ocrelizumab consistently and significantly reduced disease activity and disability progression compared with a standard-of-care high-dose interferon while demonstrating a favorable safety profile. The consistency of these data, the effect seen in these clinical studies, and the favorable safety profile may support treating MS earlier with a high-efficacy, disease-modifying

medicine."

More information: Xavier Montalban et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis, *New England Journal of Medicine* (2016). DOI: 10.1056/NEJMoa1606468

Stephen L. Hauser et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis, *New England Journal of Medicine* (2016). DOI: 10.1056/NEJMoa1601277

Provided by University of California, San Francisco