Ocrelizumab: hope for patients with primary progressive multiple sclerosis?

Recently approved by the FDA, ocrelizumab (Ocrevus®) is the first indicated disease modifying drug for primary progressive multiple sclerosis (PPMS). This followed results from a major two year clinical trial in which ocrelizumab-treated subjects with primary progressive multiple sclerosis experienced a 24% reduction in disability progression compared to placebo. The drug also showed significant benefit in relapse reduction by 46% in two clinical trials compared to interferon beta 1a (Rebif®) treatment, thereby, also earning the indication for relapsing-remitting multiple sclerosis (RRMS).

Ocrelizumab opens a new front in the battle against both progressive and relapsing forms of multiple sclerosis (MS) by means of a different immune action than existing disease modifying drugs. MS specialists have long used a similar, older drug called rituximab (Rituxan®) for MS, and a special variant called neuromyelitis optica (NMO), but because the FDA never approved rituximab for the treatment of MS, it’s off label status meant that many insurers refused to cover the drug, and many physicians would not prescribe it for MS.

Both ocrelizumab and rituximab work by blocking a key receptor on B lymphocytes called CD20. They are a class of drugs called monoclonal antibodies, which are manufactured precision molecules made from human or mouse genes that target specific cell proteins. The difference between ocrelizumab and rituximab is that the latter is made from one human and one mouse gene, and the former is made from two human genes. The CD20 binding causes depletion of circulating B lymphocytes for up to six months (approximately 99% of B lymphocytes are unaffected because they reside in tissues or immune organs and are not exposed to the drug).

Why makes these B lymphocyte depleting agents different? The thrust of much research and drug development in MS has focused on T lymphocytes, another variety of immune cells. T lymphocytes are the colonels of the immune response, recognizing the infectious enemy and leading other immune cells into battle. MS results from mistaken identity. T lymphocytes misdirect the attack towards myelinated nerve fibers in the central nervous system. B lymphocytes were believed to have a subordinate role, presenting fragments of the enemy to T lymphocyte recognition receptors, producing antibodies under the direction of T lymphocytes and releasing proteins that aid in inflammation. However, in PPMS, B lymphocytes may have a more direct role. In progressive MS, follicles of B lymphocytes are found in meninges, the tissue lining of the brain. Indeed, the most characteristic finding in the cerebrospinal fluid of individuals with multiple sclerosis is the presence of antibodies manufactured in the central nervous system (oligoclonal bands). Although, it should be noted that antibodies are not directly affected by anti-CD20 therapies because they are made by plasma cells, which come later in B lymphocyte development.

Another factor that makes ocrelizumab and rituximab attractive to patients is the infrequency of administration. Both drugs are given initially as two intravenous infusions, followed by one infusion every six months in the case of ocrelizumab and two infusions biannually in the case of rituximab. Infusion reactions, generally easily treated, are seen in 30-40% of instances. The other most common complication of ocrelizumab therapy was infection of the upper and lower respiratory tracts. Although the FDA did not raise it as a special concern, there were a total of 20 cases of cancer in ocrelizumab exposed subjects (double-blinded and extension phase) compared with four malignancies in the
interferon beta 1a and placebo treated groups. Eight cases of breast cancer occurred in ocrelizumab-exposed subjects compared to none in the interferon 1a or placebo groups. Seven skin cancers occurred in ocrelizumab subjects (5 basal cell, 2 melanoma) compared with 1 in the placebo or interferon beta 1a group (squamous cell). It should be noted that more subjects were exposed to ocrelizumab during the trials than placebo or interferon beta 1a treatments, but caution might be raised in patients with a history of cancer or genetic predisposition to cancer.

What is the benefit of having an approved B-lymphocyte depleting therapy for MS? Healthcare providers now have an approved treatment for their patients with PPMS to delay their neurological disability. Ocrelizumab may also be more effective in patients who have not responded to other therapies, and it might be a switch option for patients on natalizumab (Tysabri®) who are JV virus positive. However, caution in this respect is warranted. Recently, a JC virus positive patient developed progressive multifocal leukoencephalopathy (PML) after one dose of ocrelizumab, having been previously treated with Tysabri.

REFERENCES


Ocrelizumab FDA Package Insert