Full trial results released for new progressive MS treatment ocrelizumab

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The full clinical trial results have been published for ocrelizumab (Ocrevus®), a new treatment option for primary progressive MS and relapsing MS. The early promising results of the clinical trials were first released in September 2015 (see previous article here).

Ocrelizumab was the subject of three Phase III clinical trials, one where it was tested against placebo (dummy infusion) in people with primary progressive MS and two where it was tested against interferon beta 1a in people with relapsing MS.

The first clinical trial, known as 'ORATORIO' and published in the *New England Journal of Medicine*, included 732 people with primary progressive MS. 488 people were given ocrelizumab every 24 weeks for 120 weeks, while 244 people received the placebo. 600mg of ocrelizumab was given as two equal infusions into the vein 14 days apart. The research team then analysed the number of people who had confirmed disability progression at a range of time points.
At all time points, ocrelizumab showed slowing of disability accumulation in comparison to placebo for people with primary progressive MS. At 12 weeks, the percentage of people with confirmed disability progression on ocrelizumab was 32.9% compared to 39.3% in the placebo group. At 24 weeks, 29.6% of people in the ocrelizumab group had confirmed disability progression vs. 35.7% in the placebo group.

At the end of the study, participants taking ocrelizumab also showed less decline in their timed 25-foot walk (a measure of mobility and leg function) compared to those on placebo, but there was no difference seen on a different measurement of physical function. Those treated with ocrelizumab also showed on average lower numbers of active lesions, lower numbers of new lesions and lower overall brain volume loss on magnetic resonance imaging (MRI) compared to those on placebo.

Ocrelizumab had some side effects in this trial including reactions to the infusion, respiratory infections and oral herpes infections. Reactions to the infusion were often reduced after the first dose by changing the way the infusion was given in later doses. A slightly higher cancer rate was observed in the people given ocrelizumab, although overall rates remained extremely low. This will continue to be monitored by the pharmaceutical company and study team.

In the second study, two clinical trials, known as 'OPERA I' and 'OPERA II', of ocrelizumab in people with relapsing MS were combined and also published in the *New England Journal of Medicine*. These trials compared ocrelizumab to interferon beta, a currently available therapy for relapsing MS. 827 patients were treated with ocrelizumab infusions every 24 weeks and also received subcutaneous injections of placebo (saline solutions) three times per week. 829 people received interferon beta 1a (Rebif®) subcutaneous injections three times per week, with a placebo infusion every 24 weeks. The ocrelizumab dosage was the same as for the primary progressive MS trial above.
Treatment with ocrelizumab reduced the annualised relapse rate by 46% and 47% compared to interferon beta1a across the two trials for relapsing MS. People receiving ocrelizumab also showed

a 40% lower risk of disability progression compared to interferon beta 1a at 12 weeks and 24 weeks in both trials. There was a 33% higher level of disability improvement in people receiving ocrelizumab compared to interferon beta 1a. On MRI, ocrelizumab reduced the number of active lesions by 94% and 95% compared to interferon beta 1a in the two trials. New or newly enlarged lesions were also reduced.

The same side effects were seen in these trials as seen in the primary progressive MS trial. However, serious side infections were more commonly seen in the people taking interferon beta.

Ocrelizumab works by depleting B cells, a specific type of immune cell, via a molecule present on their surface known as CD20. It represents the first treatment that has shown effectiveness in slowing progressive MS and provides the first hope for a treatment option for this group of people. It also provides another treatment option for people with relapsing forms of MS.

Ocrelizumab has been submitted to regulatory authorities for approval for use as a treatment for primary progressive MS and relapsing MS in the USA, Europe and Australia (more information here). In December 2016, the U.S. Food and Drug Administration extended its review timeframe of ocrelizumab and it is expected that they will come to a decision by March 28, 2017. We do not yet have an expected decision date for the Australian Therapeutic Goods Administration.
Identifying and fast-tracking further treatment options for the progressive forms of MS is a key objective of the International Progressive MS Alliance.