FAIRPARK-II : Statement from the clinical trial team

Parkinson's disease (PD) affects over 6 million people worldwide. It is characterized by the loss of brain cells (neurons) that produce dopamine - a neurotransmitter essential for controlling movement. Drug treatments that replace dopamine improve symptoms but do not slow the loss of nerve cells or the progressive worsening of the disease.

Iron accumulates in the brains of people with PD and excessive levels of iron have been implicated in the loss of dopamine-producing neurons. It has been shown in experimental models that reducing excess iron with chelating drugs prevents its toxic effects and limits this neuronal death. However, iron is also important for the proper functioning of many biological processes, including the production of dopamine itself. Iron can therefore have both beneficial and detrimental effects.

Deferiprone is an iron chelator that has the ability to remove iron from overloaded areas while redistributing it to areas that need it. It has been used to treat iron overload in a rare red blood cell disease (called "thalassemia") for many years. Two earlier clinical trials in a small number of Parkinson's patients suggested that treatment with deferiprone given in addition to the usual dopamine replacement drugs, such as L-DOPA, reduced the accumulation of iron in the brain and improved motor disability.

The objective of the European multicenter FAIRPARK-II study was to investigate the effect of deferiprone on the progression of PD. The study, funded by the European H2020 program, promoted by the Lille University Hospital, was coordinated by Prof. Devos with the strategic support of the NS-PARK network, which brings together all the French expert centers on Parkinson's disease accredited by the National Clinical Research Infrastructure F-CRIN, the European Clinical Research Organization ECRIN, and Inserm Transfer. Its results have just been published in the New England Journal of Medicine.

The FAIRPARK-II study enrolled 372 people with PD at 23 European centers to determine whether deferiprone could slow disease progression when given at the very beginning of the disease, before dopamine replacement drugs are started, at a stage when more dopaminergic neurons remain.

People in the study received either oral deferiprone (30 mg/kg/day) or placebo for 9 months. Patients and physicians were blinded to the treatments administered throughout the study.

Analysis of the results showed that deferiprone reduced iron levels in areas of the brain important for movement control. Using the standard clinical assessment scales for PD, there was a deterioration in movement and quality of life in patients taking placebo over the 9 months. Surprisingly, and contrary to the study hypothesis, those treated with deferiprone experienced a small but significant greater deterioration than the placebo group over the 9 months. In contrast, markers of dopamine neuron loss were not different between the two groups, showing that deferiprone did not precipitate neuron loss, but likely had a deleterious effect on motor symptoms without altering neuron loss.

These results are in stark contrast to the other 4 independent trials involving about 240 people with PD, where no worsening of symptoms was observed. The major difference between these trials and the FAIRPARK study is that in the other 4 studies all participants were already receiving dopamine replacement drugs, such as L-DOPA, in addition to deferiprone. This is probably where the explanation for these conflicting results lies.

By the time a person is diagnosed with PD, they have already lost about 50% of the dopamine-producing neurons in their brain. The remaining neurons must therefore be more active to maintain dopamine production and facilitate movement. As mentioned above, iron facilitates dopamine synthesis by serving as an important cofactor for the key enzyme, tyrosine hydroxylase, which catalyzes the first step in dopamine synthesis. Therefore, in the early stages of PD, iron accumulation may help neurons compensate for dopamine synthesis even though, over time, iron accumulation becomes toxic. Iron removal in the early stages may therefore be at the expense of dopamine synthesis, resulting in a slight deterioration in movement control in patients taking deferiprone, but without accentuating neuronal loss. On the contrary, previous trials have shown that deferiprone could slow it down. In these trials, the effects of deferiprone on dopamine synthesis were offset by treatment with L-DOPA, the precursor of dopamine, and it therefore had no deleterious effect on symptoms.

The FAIRPARK II study has led to a better understanding of the complex role of iron in Parkinson's disease: a positive role in compensatory phenomena by increasing dopamine synthesis at the very beginning of the disease, and a deleterious role, accelerating neuronal loss due to its accumulation at later stages. The possibility of its elimination by iron chelators such as deferiprone has therefore not been abandoned, quite the contrary! However, in the future, its efficacy will have to be tested in conjunction with dopaminergic treatment (with L-DOPA) in Parkinson's disease. Deferiprone is also currently being tested in other neurodegenerative diseases such as amyotrophic lateral sclerosis, parkinsonian syndromes or Alzheimer's disease.

We are therefore continuing our research because neuroprotective treatments are one of the greatest needs of people suffering from Parkinson's disease or any other neurodegenerative disease.

Footnote

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