ARC 2015 Lay summary Session 7: Clinical trials and trial design

Session 7 was focused on clinical trials to test potential new therapies for Friedreich's ataxia and for cerebellar ataxias. The recent major discoveries which have improved our understanding of the development of Friedreich's ataxia and have lead to new therapeutic approaches can be summarized as: HDAC inhibitors (such as nicotinamide), inducers of frataxin trascription, gene therapy, iron chelators and antioxidant activators.

Oxidative stress, a process responsible for ageing and the degeneration of cells, has been long thought of as the origin and the cause of the progression of FA, resulting in the impairment of antioxidant defence machinery. Numerous studies have identified the nuclear factor erythroid-derived 2-related factor 2 (Nrf2) as a promising target for therapy. In a condition of oxidative stress, the Nrf2 gene moves to the nucleus and activates the antioxidant response of the cell. It is well known that Nrf2 signaling is impaired in FA patients, and Dr Colin Meyer from Reata Pharmaceuticals in the US utilised this knowledge in his trial design. It involves the activation of Nrf2 by RTA 408, a synthetic chemical with highly potent Nrf2 activation properties.

The study is divided into two parts: the first part will be a randomized, placebo-controlled, double-blind study to evaluate the safety of RTA 408 at increasing doses; the second part will evaluate the safety, efficacy and pharmacodynamics (what the drug does to the body) of up to two dose levels of RTA 408 in patients with Friedreich's ataxia.

Another very promising study was conducted by Professor Richard Festenstein at Imperial College in the UK. His work was based on the concept that GAA repeats in FA lead to trascriptional silencing of the frataxin (FXN) gene responsible for the disease. Prof Festenstein's previous work has shown that nicotinamide (a HDAC

inhibitor) can increase frataxin levels by remodeling the structure of the FXN gene. His team have begun an exploratory study to test the epigenetic and neurological effects of nicotinamide in patients with FA. Their first result was an increase in levels of the frataxin protein in a dose-dependent manner, which was probably due to the fact that the FXN gene was no longer silenced. The researchers also found nicotinamide to be safe and well tolerated, but further investigations on the long-term clinical benefits of the drug are still needed.

Dr Robert Molinari representing the company Retrotope Inc (USA) announced the start of a new trial using PUFAs (polyunsaturated fatty acids) as a novel therapeutic approach for people with FA. This approach tries to prevent and reverse mitochondrial membrane lipid peroxidation damage, a key mechanism involved in the pathogenesis of neurodegenerative diseases including FA. This is the first clinical trial using these modified lipids as a potential therapy; it's due to start at the end of 2015.

Another promising trial was announced by Prof Zohar Argov, Chief Medical Officer at BioBlast Pharma (Israel), due to start shortly and testing the effect of a drug called Cabaletta in patients with SCA3. The drug is a high dose of the sugar trehalose that can reduce the toxic effect of ataxin-3 protein aggregates, which are thought to cause the condition, and improve symptoms in animal models of SCA3. Bioblast Pharma is investigating sites for this multi-centre trial, the outcomes of which could benefit not only patiens with SCA3 but also other types of SCAs.

Overall, research into clinical trials for the ataxias has been making real progress and expansion in terms of the number of ongoing trials and also trials that are currently in the pipeline.

By Dr Emanuela Piermarini, Children's Hospital "Bambino Gesù", Rome
and Dr Julie Vallortigara, Research Officer at Ataxia UK