Decreasing iron neurotoxicity in pantothenate kinase-associated neurodegeneration

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Pantothenate kinase-associated neurodegeneration (PKAN) is an ultra-rare disease caused by a mutation in the pantothenate kinase 2 (PANK2) gene, leading to multiple progressive impairments until the patient cannot function independently, typically in early adolescence.[1] No drug has been shown to slow this decline. PKAN causes a conspicuous increase of brain iron, particularly in the globus pallidus by disrupting the pantothenate (vitamin B5) anabolic pathways,[2] and it is the most common form of neurodegeneration with brain iron accumulation. Iron is a pro-oxidant and can foster cell death by ferroptosis, which has sparked interest in lowering brain iron as a therapeutic strategy for PKAN, similarly to other neurodegenerative diseases in which iron accumulation occurs.[3]

Thomas Klopstock and colleagues[4] report the findings of the TIRCON trial of deferiprone (30 mg/kg per day) to slow progression of PKAN. Deferiprone is a moderate-affinity iron chelator that permeates cell membranes, crosses the blood–brain barrier (unlike other iron chelators), and has a well-known safety profile, since it is used clinically for treating transfusion-induced iron overload in beta-thalassemia.[5] Deferiprone has been shown to reduce brain iron in a clinical trial of Parkinson's disease,[6] and it is currently being tested in a phase 2 randomised controlled trial for Alzheimer's disease (NCT03234686). The TIRCON study of 88 patients consisted of an 18-month randomised, placebo-controlled phase (2:1 drug to placebo; TIRCON2012V1), followed by an 18-month open-label extension study (TIRCON2012V1-EXT). Deferiprone was well tolerated, and target engagement was confirmed with the marked lowering of iron in the globus pallidus, as measured by MRI-R2*.

The clinical efficacy of deferiprone in the study was somewhat unclear. Deferiprone led to a non-significant reduction in the primary outcome measure (p=0·07), the Barry-Albright Dystonia (BAD) scale, during the placebo-controlled phase. Further evidence during the open-label phase, during which the patients who had received placebo acted as their own controls when subsequently treated with deferiprone, supported a slowing in disease progression with deferiprone (p=0·021). In a prespecified subgroup analysis, deferiprone delayed decline in patients with atypical PKAN (those with a later presentation and slower decline than patients with classic PKAN; p=0·019) in the placebo-controlled phase of the study. There was no evidence to support a similar treatment effect in the classic PKAN subgroup.

A caveat of the study was the inclusion of patients with, or approaching, the maximum score on the BAD scale, which is not sensitive to detect changes at this advanced stage. Indeed, patients with more advanced disease seemed to deteriorate less on the BAD scale, which might be problematic, given that a larger proportion of patients with high (>24 points) were randomly assigned to the deferiprone group than to receive placebo. This limitation was especially relevant in the patients who had already reached the maximum score at baseline and who therefore could not measurably deteriorate further on this scale. However, subsequent sensitivity analyses showed the same trend toward slowing of disease progression with deferiprone across different stages of the disease (although there were non-significant differences in subgroups with few participants), which might signify that the drug was somehow beneficial across all stages of disease.

These caveats must be considered in the context of the fact that PKAN is an ultra-rare disease. TIRCON is the first randomised controlled trial for PKAN, and the investigators estimate that they enrolled 10% of all patients with PKAN in the USA and Europe, which is a major achievement. Apart from the outcomes of the clinical trial, this study is important because of its longitudinal follow-up of so many people with PKAN, which will be invaluable for preparing future clinical trials and understanding the disease trajectory at different stages.

The results provide further insight into the role of iron in PKAN. Although the treatment lowered brain iron, all patients still declined, suggesting that there are other primary drivers of toxicity in this disease. One might speculate that the optimal benefit of deferiprone would occur when it is administered as early as possible (ie, before neurodegeneration manifests), and the trial provides evidence to support this hypothesis.

Iron is thought to accumulate in the brains of patients with PKAN because of build-up of the amino acid

cysteine, which chelates and deposits iron in the cells of the globus pallidus.[7] Cysteine is ordinarily metabolised in the biosynthetic pathway of coenzyme A; however, the first step of this pathway, the phosphorylation of dietary pantothenate to 4-phosphopantothenate, is prevented in PKAN by a mutation in PANK2.[2] Cysteine concentrations rise as a result and coenzyme A is depleted, and both are major regulators of the iron-dependent cell death pathway (eg, ferroptosis). Cysteine is the rate-limiting substrate for glutathione synthesis, which is the necessary cofactor for glutathione peroxidase 4, the master regulator of ferroptosis.[8] Coenzyme A is required to produce phosphatidylethanolamine, which is the main target for iron-induced peroxidation in ferroptosis.[9] Although it could be hypothesised that neuronal death in this disorder of neurodegeneration with brain iron accumulation is caused by ferroptotic cell death, patients with PKAN should be protected from ferroptosis because of these biochemical changes.

Given the challenges in implementing clinical trials in this population, we must glean as much information as possible from this trial about the efficacy of deferiprone. The uncertain role of iron in causing toxicity and the limitations of the primary outcome measure used in this study notwithstanding, there are certainly hints that deferiprone was beneficial: the treatment seemed to slow deterioration in patients with atypical PKAN; the extension phase showed evidence of slowed disease progression; and secondary analyses of the placebo-controlled phase provided evidence that deferiprone might reduce the use of dystonia medication, freezing of gait, and cognitive impairment. Therefore, these results support the possibility that brain iron accumulation is indeed at least a component of pathogenesis. The tolerability of deferiprone in this study supports conservative iron chelation as a therapy in patients with PKAN, given that there are no other treatment options. However, other potential biochemical consequences of the mutation also warrant investigation.

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SA and AIB report research grants from the Australian National Health and Medical Research Council and the **US** National Institutes of Health, relevant to this work. AIB is a shareholder in Alterity Ltd, Cogstate Ltd, Brighton Biotech LLC, Grunbiotics Pty Ltd, Eucalyptus Pty Ltd, and Mesoblast Ltd. He is a paid consultant for, and has a profit share interest in, Collaborative Medicinal Development Pty Ltd.

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Antiplatelets after intracerebral haemorrhage: treat the patient, not the brain imaging

Clinicians underestimate harms and overestimate benefits from medical interventions.[1] However, according to a report by Rustam Al-Shahi Salman and colleagues[2] published in *The Lancet Neurology*, the perceived risk from restarting antiplatelet therapy after intracerebral haemorrhage in patients with cerebral microbleeds has been substantially overestimated on the basis of observational data. Use of antiplatelet therapy in patients with intracerebral haemorrhage is common,[3] a conservative estimate is one in four patients, so more certainty in making decisions regarding restarting such therapy is highly relevant.

The RESTART trial,[4] which is published in *The Lancet*, randomly assigned 537 survivors of intracerebral haemorrhage that occurred while taking antithrombotic therapy to start or avoid antiplatelet therapy. The investigators

Published **Online** May 22, 2019 http://dx.doi.org/10.1016/S1474-4422(19)30189-9

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