## THE HUNT FOR BETTER TREATMENTS FOR HUNTINGTON'S DISEASE CONTINUES

Huntington's Disease (HD) is an autosomal dominant condition that typically presents in midlife with a combination of motor, cognitive and psychiatric problems along with sleep and metabolic abnormalities. It runs a clinical course over 15-20 years leading to death as patients become demented and bed bound. There are currently no proven disease modifying therapies for HD. While the recent work with anti-sense therapies (ASO) against huntingtin has generated much excitement they are yet to demonstrate a measurable change in disease progression. Furthermore, given they promise to "modify" and not "cure" HD patients we will still require adjunct symptomatic treatments, potentially for longer periods of time. Symptomatic therapies for HD do exist and are widely used for treating the chorea and some of the psychiatric aspects of the condition although the extent to which they work is variable<sup>1</sup> and many experience significant side effects with them. Therefore, there is still a need to develop better symptomatic therapies, ideally with single drugs that can help treat more than one sign and symptom of this condition.

One such potential agent is pridopidine (TV-7820; formerly known as ACR16 and Huntexil), a dopamine stabiliser with additional high affinity to the sigma-1 receptor chaperone protein (S1R) which was previously trialled in HD<sup>2-4</sup> and for which the results of third large scale, randomised trial, the PRIDE-HD study, are now reported (REF). In the two earlier studies, HART<sup>3,4</sup> and MermaiHD<sup>2</sup>, pridopidine was well tolerated but in neither trial did it meet its primary endpoint of a significant improvement on the modified motor score (mMS) [a subset of the UHDRS-Total Motor Score (UHDRS-TMS) that reflects voluntary motor function] in the treated HD patients. However, in both trials there was evidence that the drug may be having more global motor benefits not detected by the mMS but better reflected through changes in the UHDRS-TMS. This provided the rationale for continued development of the drug under a revised protocol in the new PRIDE-HD study in which nearly 400 patients with early stage HD received one of 4 doses of pridopidine (45mg, 67.5mg, 90mg or 112.5mg twice a day) or placebo in a double-blind fashion. The primary endpoint was change to the UHDRS-total motor score (TMS) at 26 weeks – a score that captures all the motor features of HD including abnormalities of eye movement, speech, dexterity, motor sequencing as well as degrees of bradykinesia, chorea, dystonia and the ability to walk and balance. The results of PRIDE-HD now show no significant benefit of pridopidine, at any dose, on UHDRS-TMS in early stage HD patients. So why is this?

The dopamine stabilizing function of pridopidine, allowing it to treat both hyperactive and hypoactive dopaminergic states<sup>5</sup> make it in some ways a logical choice as a potential HD therapeutic given the clinical features of the condition. It has long been known that the dopamine system is abnormal in HD with early loss of dopamine receptors in the brain, possibly secondary to increased

dopamine release, with the most effective agents for treating HD being those that reduce dopamine release or block dopamine receptors<sup>1</sup>. However, this is yet to be confirmed empirically; it may be that these changes relate to primary transcriptional abnormalities across the dopaminergic synapse. Furthermore, HD pathology is not limited to the dopaminergic network<sup>6</sup> and the contribution of this wider pathology to the clinical features of the disease is not known. Therefore, stabilising dopaminergic function in the brain of patients with HD may be of limited value, as this trial would lead us to conclude.

Of course, it may be that PRIDE-HD failed as a consequence of selecting the wrong primary endpoint, dose of medication or duration of treatment but this seems unlikely given the substantial background to the trial. Some favourable signal was seen at the 52 week timepoint but it is hard to rationalise why it would take so long to emerge if it was due to dopamine stabilisation. Of course, it may relate more to the drugs newly described putative nondopaminergic chaperone protein actions, but regardless, the size of effect is small and curiously is only seen at selective doses. Furthermore, it is only apparent on the exploratory endpoints such as the Q-Motor scores (a more objective motor assessment) and the relevance and clinical significance of these findings is unknown.

Finally, the value of this whole therapeutic approach could be debated, given that therapies already exist which targeting the motoric aspects of HD. There is greater need for symptomatic therapies that can help those features for which we currently have nothing to offer e.g. cognitive deficits. All of which would argue against proceeding to further trials of pridopidine for HD.

## 771 words

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