New hope for rare disease drug development

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Using combinations of well-known approved drugs has for the first time been shown to be potentially safe in treating a rare disease, according to the results of a clinical trial published in the open access *Orphanet Journal of Rare Diseases*. The study also shows some promising preliminary results for the efficacy of the drug combination.

Drug development can take decades to bring safe and effective treatments to patients. Re-use of existing drugs for new purposes is of considerable interest due to its potential to save time and resources, and help circumvent the low amount of funding that goes into rare disease drug development.

Presently incurable, Charcot-Marie-Tooth type 1A disease (CMT1A) is a rare genetic condition that affects around one in 5,000. The disease leads to loss of nerve fibers, muscle wasting and weakness, and causes slowly progressive sensory defects and loss of fine motor skills.

Principal Investigator of the trial, Shahram Attarian of Marseilles University Hospital, Hôpital de la Timone, Marseilles, France, said: "Considering the debilitating nature of the disease and the absence of treatment, there remains a pressing unmet need for an efficacious and safe treatment for CMT1A. The study shows that we now have a potential treatment that is safe to use, but also shows some initial promise in being effective. This invaluable insight will be key in designing the next stages of the international Phase 3 clinical trial which is set to begin in 2015."

The researchers tested the potential of PXT3003, a low-dose combination of three well-known compounds already approved for other conditions. Baclofen is used to treat spasticity, naltrexone for opiate and alcohol addiction, while sorbitol is prescribed for intestinal disorders. Combination treatments are based on the idea that diseases can be more efficiently treated using multiple disease-relevant targets.

The Phase 2 randomized clinical trial involved 80 adult patients with mild-to-moderate CMT1A at six hospital sites in France. The participants received twice-daily placebos or one of the three increasing doses of PXT3003 over one year.

The safety and tolerability of PXT3003 was found to be good. Results showed no indication of the drug negatively influencing vital signs (blood pressure, heart rate and weight), electrocardiogram measurements or blood tests. The percentage of patients with treatment-emergent adverse events was similar across all treatment groups including the placebo, and most of those were mild, transient and benign.

In addition, there were some promising preliminary results for the drug's efficacy, including an improvement in measurements that took account of everyday activities, sensory and motor symptoms, and arm and leg strength. Among the three increasing doses tested, the highest one showed consistent improvement after 12 months. These preliminary results in adults, where symptoms have evolved since childhood, strongly suggest there could be benefits in testing PXT-3003 in children as a preventative treatment.

Because of the difficulty of arranging large scale clinical studies of rare diseases like CMT1A, the authors say that the effects of PXT3003 described are preliminary indications of drug activity, rather than definitive conclusions on drug efficacy. However, they say the results act as a helpful exploratory analysis of the efficacy of PXT3003 for

designing the next phase of clinical trials.

The combination treatment is thought to act by controlling the overexpression of the PMP22 gene, involved in the structural protein component of myelin, a protective substance that covers nerves. In a companion study2, published in the same journal, the researchers show that in rats with CMT1A, the drug successfully lowered PMP22 expression and improved impaired myelination and nerve fiber performances.

More information: An Exploratory Randomised Double-Blind and Placebo-Controlled Phase 2 Study of a Combination of Baclofen, Naltrexone and Sorbitol (PXT3003) in Patients with Charcot-Marie-Tooth Disease Type 1A. *Orphanet Journal of Rare Diseases* 2014, 9:199. www.ojrd.com/content/9/1/199

Chumakov et al. Polytherapy with a combination of three repurposed drugs (PXT3003) down-regulates Pmp22 over-expression and improves myelination, axonal and functional parameters in models of CMT1A neuropathy. *Orphanet Journal of Rare Diseases* 2014, 9:201. www.ojrd.com/content/9/1/201

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