

Neurturin and Parkinson's Disease – the latest chapter

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Parkinson's disease (PD) is characterised by the loss of dopamine cells in the substantia nigra and as such many restorative therapies have been developed to try and repair this network. This has involved using cellular transplants as well as growth factors – administered either as direct infusions or via viral delivery systems. One such approach has involved the GDNF like factor – Neurturin (NTN) – delivered using an AAV2 system in patients with advancing PD. This, in open label studies, showed promise but in a double blind placebo controlled trial failed at its primary end point at 12 months – although at the unblinded 18 month time point there was some signal of efficacy.

As a result a new study was set up that sought to deliver NTN into the nigra and putamen of slightly earlier stage PD patients. This new study has now been reported to have also failed as was indicated by a press release two years ago. This new paper detailing the trial results has just been published along with another one reporting on four cases from the trial that came to post mortem.

The clinical trial involved 48 patients of whom 23 received the active treatment with a primary end point at 15 months of change in UPDRS in a practically defined off state. Several secondary measures were also looked at along with safety. The main finding was that the active treatment showed no efficacy and there were no significant adverse effects.

The second study looked at four patients who died from unrelated causes – two of these deaths happened soon into their treatment with this agent and two many years later, one of whom turned out to have

MSA. In all cases the volume of distribution of the NTN was the same at about 20% with little evidence for a major effect on the TH system either at the level of cell bodies or fibre sprouting – paralleling the clinical response which was seen in the trial.

So what does all this mean – Is this approach not useful? I think before one concludes that this is the case, there are three major issues that need to be considered;

1. Were the patients given this therapy the correct group of patients, given that the dopaminergic system is already majorly affected at the time of diagnosis?

It is well known that by the time a patient with PD presents with motor deficits about 50% of the dopaminergic neurons and 80% of their fibres are already lost. Furthermore, within a few years of diagnosis there is a near complete loss of dopaminergic fibres within the striatum of PD patients and thus it may be that only those individuals early in the disease course may be amenable to treatment. This is addressed in Figure 3 of the paper, where those closest to disease onset have a greater response to the NTN – as such there may be merit in doing a new trial in newly diagnosed de novo PD cases.

2. Does NTN work as you would expect in the alpha synuclein diseased human adult PD brain compared to rodent and non human primate animal models of PD?

Recently there has been work from the Bjorklund lab suggesting that GDNF does not work in the presence of alpha synuclein pathology because of changes in the GDNF receptor signalling pathway, which can be rescued using Nurr 1. If true in the PD brain, then it implies that GDNF like factors such as NTN may have a muted response compared to that seen in animal models of PD that use non alpha synuclein approaches such as neurotoxins. As such new trials may want to employ agents that upregulate Nurr 1 expression.

3. Was the right dose given over the right volume of distribution to allow meaningful effects to be seen? Looking at the histology in patients in receipt of NTN, there is a question as to whether the volume of distribution would be sufficient to generate the necessary extent of putamenal innervation required to see an effect. As only 20% of the putamen received the agent presumably at different concentrations, this seems likely. Thus higher doses using convection enhanced delivery systems may have improved on this, and may be a way to consider taking this agent forward.

Overall this paper shows that NTN has no significant benefit in PD patients when given at this dose in this way at this stage of the disease – although new trials to look at this further can clearly be designed given some of the issues that this trial has thrown up. Indeed whether this means that all similar growth factors will be equally ineffective is unclear, but in the next 12 months or so we should know at least what effects GDNF has when given either as a direct infusion into the brain or delivered via a different viral vector system to the PD striatum.

Olanow CW et al (2015) Gene delivery of neurturin to putamen and substantia nigra in Parkinson Disease: A double-blind, randomized controlled trial. *Ann Neurol*. Epub.

Bartus RT et al (2015) Post-mortem assessment of the short and long term effects of the trophic factor neurturin in patients with α -synucleinopathies. *Neurobiol.Dis.* 78:162-171.

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