OPEN LABEL STUDIES IN PD ARE A WASTE OF TIME AND MONEY- NO

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Parkinson's Disease (PD) is a common disorder that has as part of its core pathology the loss of the dopaminergic nigrostriatal neurons and the formation of alpha synuclein positive Lewy bodies. Whilst it is now recognised that PD has a much more complex pathology than this, most patients respond well to dopaminergic drug therapies in the early stages of disease but with time this efficacy wears off and side effects develop. Thus there is a need for a better, more biological, way to deliver dopamine to the parkinsonian brain which whilst not curing the patient should substantially improve their dopaminergic symptoms and signs.

One approach has been to use dopamine producing cells grafted into the striatum, of which the most successful have been those derived from the developing human fetal ventral mesencephalon (hfVM). The use of this tissue was the subject of many successful open label trials in the late 1980s and 1990s, but at the turn of the century two "double blind placebo group" trials showed that this therapy was ineffective and produced side effects in the form of graft induced dyskinesias (GIDs). The outcome of these two trials essentially brought the field of cell based therapies in PD to a halt at a time when stem cell based approaches were still being actively pursued and developed.

The question therefore arises as to which of these trials is giving us the right answer- the open label studies showing efficacy or the double blind placebo controls trials showing no benefits?

Those brought up on the power of the double blind placebo control trial will say that the true answer lies here but reasons for doubting this are;

(i) The long term follow up of patients in the open label study has shown benefits over 10 years post grafting, with improvements that are out of keeping with natural history studies of this condition. In some cases transplanted patients have normal dopamine levels in their grafted striatum based on PET scans with a clinical state equivalent or better to that seen when they first presented to their neurologist 25 years earlier often in the absence of any anti-PD drug therapies;

(ii) The placebo effect, that is often cited as being a major confound in trials of this nature, was not seen in the sham grafted group in the second NIH funded study, and in the first "double blind placebo controlled trial" the control group was lost after 1 year as the majority were then grafted.

(iii) The end point of both the double blind placebo control trials was 1 and 2 years respectively and cellular based grafts may take longer to have maximal benefit as has been seen in some of the longer term follow up of patients in open label studies.

(iv) The trials used techniques that had not been optimized and thus the trials may have failed for this reason alone. In the first trial less tissue was grafted than in the open label studies and no immunosuppression was used despite it being known that such tissue induces a host immune response, albeit much less than that with peripherally placed grafts of tissue. In the second trial immunotherapy was only given for 6 months and on cessation of that treatment, the course of the patients in the grafted arms got worse suggesting they may have been subject to an immune response. In the gene and growth factor trials in PD, the ability to judge dose and optimal delivery of the agent were not known prior to the double blind trials commencing. Indeed in the gene therapy trials the use of low doses initially is mandatory (as is necessary in the translation to the clinic) which will mean that the patients are unlikely to respond optimally. Thus dose finding studies need to be done until that optimal dose is found and its delivery to the target area maximized- a problem that also applies to the GDNF studies;

(v) The power of the studies to see benefits is limited by the very small sample sizes, and this can only be circumvented by using smaller groups followed for longer;

(vi) Finally it is now clear that PD is heterogeneous and that different types of patients behave differently over time and in response to dopaminergic medications, and as such treating all patients in the same way opens up trials to the risk of failure because of inadequate patient stratification. A problem that is now well recognized and being used in other experimental trials of therapy in other conditions such as oncology;

To illustrate the dangers of premature double blind placebo control trials imagine that if in the 1950s we had conducted a double blind placebo controlled trial of 40 patients with a chest infection given either placebo or 100mg penicillin bd for 3 days, with an end point at 5 days of an improvement on

their CXR. The result would have been a negative one (i.e. failed primary end point). The conclusion would therefore be that antibiotics are of NO use in microbial infections in man! Of course the study would have failed because (a) the sample size was too small; (b) the dose of drug was wrong; (c) the end point was wrong; (d) and the patients were all assumed to have the same chest infection. Similarly look at the evolution of heart transplantation. No double blind placebo control trials have been done but most people would accept that the open label studies have shown it works with prolonged follow up of grafted patients!

So are open label studies in PD a waste of time. No, but ultimately any therapy needs to be shown to have an advantage over its competitors in the treatment of PD and that will necessitate studies that are not just open label. However until such times as we know how to optimally give any of these new types of experimental therapy to patients with PD, the open label study with long follow up remains the best and only way to move the field forward.