J R Coll Physicians Edinb 2008; 38:322–3

CLINICAL

What is the optimal treatment for early Parkinson's disease?

R Davenport
Consultant Neurologist, Department of Clinical Neurosciences, Western General Hospital, Edinburgh, UK

TITLE Fourteen-year final report of the randomized PDRG-UK trial comparing three initial treatments in PD

AUTHORS Katzenschlager R, Head J, Schrag A, Ben-Shlomo Y, Evans A, Lees AJ on behalf of the Parkinson's Disease Research Group of the United Kingdom.

JOURNAL *Neurology* 2008; 71:474–80.

DECLARATION OF INTERESTS The author has received educational financial support and consulting fees from the makers of several dopaminergic drugs within the past five years.

Published online ***November 2008***

Correspondence to ***R Davenport, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK***

tel. ***+44 (0)131 537 2072***
fax. ***+44 (0)131 537 1132***
e-mail ***rjd@skull.dcn.ed.ac.uk***

SUMMARY

This paper is the final chapter of the long-running UK Parkinson's Disease Research Group (PDRG) trial, which randomised 782 patients with early Parkinson's disease (PD) between 1985 and 1990 to one of three treatment arms: levo-dopa (LD) alone, selegiline plus LD, or bromocriptine alone. The primary outcome measures were mortality and motor disability, and for this final assessment, mini mental state examination (MMSE) and a quality of life analysis (Short Form-36) were included. In 1995, a statistically higher death rate in the selegiline plus LD versus the LD alone arms was reported,[1] leading to the termination of this arm of the trial. This final follow-up paper analysed the follow-up of all patients at a median of 11.4 years.

Although the mean age at randomisation was about 63 years, 480 (61.4%) were dead at final follow-up, a standardised mortality ratio of 1.88 (95% CI 1.72–2.06); there were no significant mortality differences between the groups. Of the 302 survivors (38.6% of study population), only 166 (21%) were available for analysis in this report, with a median follow-up of 14 years for this group.

A small but significant advantage in motor scores favouring the LD arm persisted, and this was reflected by significant differences in the physical summary sections of SF-36 scores, with a trend in favour of LD for vitality and general health perceptions. The prevalence of motor complications was similar for the LD and bromocriptine arms. The prevalence of dementia was less in the LD arm (18%), compared with bromocriptine (29%), although this was not statistically significant.

OPINION

The debate over the optimal treatment for early PD has been running for decades, and the fear over LD motor complications among patients and doctors has resulted in 'LD phobia', leading to various LD-avoiding strategies, most commonly the early introduction of dopamine agonists (DAs).[2] Numerous trials have shown that DAs are associated with fewer early motor complications but at the cost of less effective relief of the motor symptoms and higher rates of adverse effects, some of which are very harmful (e.g. fibrotic complications of the ergot DAs and impulse control disorders). Where do the PDRG results fit in?

Firstly, it confirms the clinical impression that PD is a miserable, progressive disease, with an increased death rate. The average age at randomisation was a few years lower than the average age of PD onset, yet 60% were dead after just over a decade, with up to a third of survivors demented. Regarding choice of initial treatment, there were no differences in mortality or motor complications between the groups, but the advantage of LD in terms of better motor scores and improved quality of life was evident, and no clinically meaningful advantage of early treatment with bromocriptine was demonstrated.

There are some methodological problems. The trial was unblinded, but the biggest problem was the loss of surviving participants for the final analysis, accounting for 17% of the study total. Critics will also claim that bromocriptine is an outdated DA, but the results in terms of motor scores and complications are similar to the newer DAs and there is no evidence to suggest newer DAs are better than bromocriptine.[3]

Despite these criticisms, and while we await data from other trials investigating early PD treatment (PD MED,

ADAGIO), these results are important for several reasons. They allow us to have a more informed discussion with patients regarding treatment, and should be helpful in breaking down LD phobia. They also provide important prognostic information which, as clinicians, we should not ignore and be prepared to discuss with our patients. But perhaps most importantly, they demonstrate the absolute need for long-term follow-up in trials of chronic conditions, and the UK PDRG should be congratulated for its tenacity in this regard.

REFERENCES

1 Lees AJ, on behalf of the Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995; 311:1602–7.

2 Weiner WJ, Reich SG. Agonist or levodopa for Parkinson disease? Ultimately, it doesn't matter; neither is good enough. *Neurology* 2008; 71:470–1.

3 Clarke CE, Deane KHO. Ropinirole versus bromocriptine for levodopa-induced complications in Parkinson's Disease. *Cochrane Database of Systematic Reviews* 2001, Issue 1.