Disease-modifying Therapies in PD

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PD progression ultimately leads in most patients to disability, handicap and death. Despite current best standard of care, disability and mortality among PD patients are still higher than in the general population. There is therefore a great interest in developing interventions that can change disease progression for the better.

Attempts to understand PD progression have mainly focused on the mechanisms leading to the death of dopaminergic neurons. Based on this approach, many pathophysiological mechanisms have been explored (oxidative stress, mitochondrial dysfunction, inflammation, excitotoxicity, growth factors deficit, apoptosis, protein handling dysfunction, autophagy...). Accordingly, many drugs have been considered as candidates feeding the pipeline for drugs that could improve PD progression.

Up to now, within the past 15 years, up to 20 drugs have been tested for this purpose in large, long and expensive prospective randomised trials using various designs (wash-out, delayed start...) and outcome measurements (biomarkers, disability progression, time to milestones...). Unfortunately, in most instances, the results of these studies did not show any benefit or remained inconclusive, due to methodological limitations. However, in the recent delayed start ADAGIO trial, we could demonstrate that a drug like rasagiline at the dose of 1 mg/d had a disease modifying effect and reduced the progression of disability over the first 18 months of treatment. This is the first positive signal based on clinical outcomes in the field.

Better understanding of PD causes, development of better predictive animal models, new designs of clinical trials, development of better outcome measures and endpoints are necessary to further improve our search for efficacious agents on the course of PD.

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