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Human Medicines Development and Evaluation

Questions and answers on additional clarification for inclusion criteria in the "Guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease" rev. 2

Question 1

May subjects with recently diagnosed early Parkinson's disease but who have previously been treated with short courses of dopaminergic therapy be considered "the NOVO" patients and as a consequence be included in studies in early Parkinson's Disease?

Answer question 1

The definitions used in the guideline on Parkinson's disease e.g. 'de novo Parkinson's disease', 'early Parkinson's disease', 'advanced Parkinson's disease patient' are considered working definitions based on clinical practice and are not intended to define exact and mutually exclusive patient populations.

The current definition of 'de novo patients' in the Parkinson's disease guideline refers to either newly diagnosed patients with Parkinson's disease or patients not receiving L-dopa. This was based on the earlier clinical practice when newly diagnosed Parkinson's patients usually received first dopamine agonists and later when motor responses become insufficient L-dopa was added or patients were switched to L-dopa monotherapy. Hence the addition of or switch to L-dopa indicated a landmark in disease progression. From a pragmatic viewpoint it indicated an early form of more advanced Parkinson´s disease.

Further, the rationale behind including newly diagnosed Parkinson's disease patients naïve for L-dopa or dopamine agonists was that response to treatment, both reversible and irreversible, was not affected by pharmaco-dynamic changes that previous dopaminergic therapy might have induced.

However, this practice no longer holds as the rationale for the delay of introduction of L-dopa treatment, e.g. preventing L-dopa associated motor complications, is challenged. Hence dopaminergic therapy is started earlier. In addition, as the effect on motor symptoms of L-dopa in general is larger as compared to dopamine agonists, L-dopa is more and more often given as initial treatment. Hence the demarcation criterion of early versus more advanced Parkinson's disease, i.e. start of L-dopa therapy is no more optimal.

In general it is not expected that patients with recently diagnosed Parkinson's disease either naïve /non-naïve to short term dopaminergic treatment in a clinical trial will have different motor response.

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This is in contrast to chronic long term use which may induce long lasting if not irreversible pharmaco-dynamic effects. Unfortunately, there are limited data to substantiate these expectations, or demarcate the transition of short-term or long-term pharmacodynamics effect induced by treatment.

Hence, whether newly diagnosed patients who received previous dopaminergic treatment are not different from those naïve for dopaminergic treatment in a study will require further justification by data. This could be done by including patients with newly diagnosed Parkinson's disease within a short time interval since diagnosis i.e. 3-6 months, short-term use of dopaminergic treatment before study entry i.e. at most 30 days, a sufficient washout of previous medication and a separate analysis of the results for patients naïve / not-naïve for dopaminergic treatment.

Unfortunately as the duration of the pharmaco-dynamic effect of previous dopaminergic treatment is unknown, it is difficult to determine which length of the washout period would be sufficient. It is recommended to evaluate the effect of stopping previous dopaminergic treatment by monitoring motor scores during the washout; a worsening would indicate loss of pharmacodynamic effect and/or rebound, stabilisation might discriminate between initial rebound and return to baseline values. Further, a separate analysis of the results for patients naïve / not-naïve to previous dopaminergic treatment allows an evaluation whether the two patients are /are not different in response i.e. previous treatment had / had no priming effects.

Hence there is no principal objection against inclusion of newly diagnosed patients receiving dopaminergic monotherapy for a short period provided the suggested safeguards are taken care of.