HOW TO START PD TREATMENT: WITH A DOPAMINE AGONIST

Spiros Konitsiotis
Greece

The precursor of dopamine levodopa, 50 years after its introduction remains the gold standard for treating motor symptoms in Parkinson's disease. Unfortunately, its clinical use is seriously limited by the development of motor complications after a certain time of treatment. The comprehension and handling of those complications and especially dyskinesia became the most challenging goal for movement disorder experts.

Dopamine agonists (DAs) were primarily introduced as adjunct therapy to levodopa in advanced PD and their use was considered an opportunity to allow the lowering of levodopa dose and improve continuous dopaminergic delivery. Since then, multiple studies have established the efficacy of these agents in improving motor symptoms in early stages of the disease, rendering DAs an attractive option as first-line monotherapy treatment in PD.

There is a substantial body of evidence indicating that the more continuous dopaminergic stimulation provided by dopamine agonists may not only improve motor complications but also prevent the mechanisms leading to their development and progression. In the last decade, several studies have been carried out to compare the risk of developing motor complications in patients treated with levodopa versus patients treated with DAs. Long term follow up of these studies became now available confirming that patients initially treated with DAs have a reduced risk of developing motor complications (both dyskinesias and fluctuations) even after the inevitable addition of levodopa at some point later.

At least three such long term studies, with the three major DAs currently in use, pramipexole[1], ropinirole[2] and rotigotine[3], versus levodopa, all unanimously showed that DAs induce far less dyskinesia than levodopa when used as unitial monotherapy in early untreated PD patients.

A recently published meta analysis gathered all randomized controlled trials (RCTs) comparing a DA as initial treatment monotherapy for early PD versus levodopa[4]. Ten RCTs were finally considered as eligible to be included in the analysis, involving in total 2223 patients (1171 in the DA group and 1052 in the levodopa group). The overall analysis showed that patients in the DA group had 87% lower odds to develop dyskinesia than patients in the levodopa group ($P < 0.01$), clearly confirming the low dyskinetogenic potential of DAs. A most important finding was that the odds for dyskinesia in the DA group even after the introduction of levodopa were observed to be constantly lower than in the levodopa group. Regarding the association between dyskinesia and dose of DAs, our meta regression analysis showed that the relationship between the dose of DAs and the occurrence of dyskinesia is insignificant, a result that indicates the DA dose, inside the range of those clinically recommended, is an improbable culprit for dyskinesia. In agreement with our findings for DA dose, the duration of treatment with DAs had no significant effect on the incidence of dyskinesia, a result supporting as well the safety of the cumulative dose of this drug class. In contrast to levodopa for which longer use has been linked to dyskinesia, long-term treatment with DAs seems not to increase the risk for dyskinesia. In addition, the odds for dyskinesia in the DA group compared with the odds for dyskinesia in the levodopa group were not related with disease duration. Finally, the ergoline derivation of Das also had no significant effect on dyskinesia OR.

In conclusion, the advantage of the early use of DAs seems to be indisputable. The above findings provide evidence for the safety of DAs as far as dyskinesia is concerned, a property independent of their dose, the treatment duration and the duration of disease. Additionally, the benefits of DAs seem to extend beyond the period when these drugs are received as initial monotherapy, to the stage when the addition of levodopa is unavoidable, by reducing the risk of levodopa-induced dyskinesia and consequently meeting the challenge for a longer 'honeymoon' period.

References

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