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A Clinical Trial of Isradipine: What Went Wrong?

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Parkinson disease (PD) is the second most common progressive neurodegenerative disorder, marked by the relentless progression of a mélange of motor and nonmotor symptoms. Treatment with levodopa or related medications provides substantial relief for most motor symptoms, especially early in the disease, whereas treatment for most nonmotor symptoms remains utterly inadequate. Moreover, no current agents stall or even delay PD progression. The projected increase in PD prevalence (1), with the daunting socioeconomic burden that accompanies it, pushes investigators and the public to develop a disease-modifying therapy. Industry and the federal government have supported clinical investigators in testing many drugs during the past 25 years, yet no trial has found an effective means to slow PD progression. What lessons can we learn from yet another large clinical trial, this time testing whether isradipine can slow PD progression?

The Parkinson Study Group STEADY-PD III Investigators report the results from a randomized, parallel-group, double-blind, placebo-controlled trial evaluating the effect of immediate-release isradipine, a dihydropyridine calcium-channel blocker, on clinical progression of PD (2). Fifty-seven Parkinson Study Group sites in North America recruited 336 patients with early-stage PD (within 3 years of diagnosis) who did not have any prior exposure to dopaminergic drugs. They were randomly assigned to receive either 5 mg of isradipine twice daily ($n = 170$) or placebo ($n = 166$) for 36 months. Demographic characteristics, including age, sex, disease duration, and baseline severity, as well as the overall use of antiparkinsonian agents (including dopaminergics during the study) were well matched across groups. The primary outcome measure of mean change in the total Unified Parkinson's Disease Rating Scale (UPDRS) parts I to III score in the "ON" state (while receiving drugs for symptomatic relief) did not statistically significantly differ between the isradipine (2.99 points) and placebo (3.26 points) groups even after adjustment for dopaminergic treatment. None of the secondary outcome measures statistically significantly differed between groups, including change in UPDRS part III (motor ratings) score in the "OFF" state, number of participants requiring dopaminergics, and time to initiation of this symptomatic treatment. Thus, in this carefully designed and meticulously executed study, isradipine at the current dosage failed to slow progression in early-stage PD.

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Negative results often spark a closer scrutiny of the scientific premises prompting the trial in the first place. Isradipine blocks L-type $Ca_v1.3$ calcium channels located in a select group of pigmented brainstem nuclei, including the substantia nigra of the midbrain containing nigrostriatal dopaminergic neurons (3). Parkinson disease pathophysiology seems to selectively target these neurons, and L-type $Ca_v1.3$ calcium-channel antagonists provide neuroprotective effects in toxindriven animal models of parkinsonism (4). Furthermore, retrospective studies suggest that persons receiving dihydropyridine antagonist antihypertensive agents that penetrate the blood-brain barrier have a lower risk for subsequent development of PD (5). Together, these points justify pursuit of this clinical trial.

What went wrong, then? One possibility is that the primary outcome measure—change in UPDRS ON score—was inadequate. Ideally, one would prefer a more direct, objective measure of disease progression, such as change in brain deposition of synuclein pathology (6); however, a reliable in vivo biomarker of α-synuclein remains to be developed. Furthermore, that may not translate into direct clinical benefit, as identified by a quality-of-life measure or change in UPDRS score (preferably an OFF score to reduce symptomatic treatment confounding, which apparently did not obscure the findings, as demonstrated by the investigators). Isradipine does not directly modulate dopaminergic neurotransmission; hence, the primary outcome measure of longitudinal change in UPDRS score seems logical. However, the limited decline in UPDRS score in the placebo group over a 3-year period, especially in the setting of concurrent dopaminergic intake, highlights its limitations as a marker of progression. An in vivo positron emission tomography or single-photon emission computed tomography measure of striatal uptake of a radiotracer selective for presynaptic sites may provide a potential candidate outcome measure because isradipine seems unlikely to directly affect the binding or metabolism of such a radioligand. However, even this approach harbors potential danger because studies have shown that motor parkinsonism correlates with nigral dopaminergic cell counts but not with striatal dopamine once the nigral cell loss exceeds 50% and the severity of parkinsonism correlates with nigral cell counts rather than terminal field measures in the striatum (7–9). Molecular imaging targeting nigral dopaminergic cells may provide a better measure of PD progression (10).

Despite the lack of an ideal outcome measure, a larger problem may be a lack of target engagement in the brain, which limits this study and all previous studies of potential disease-modifying agents. Did the administered dose of isradipine engage the L-type calcium channel in the brain in these participants? Trying a higher dose may help to address this limitation, but this may not be tolerated because orthostasis commonly occurs in PD and may be exacerbated by isradipine, an antihypertensive agent. Rather, a direct measure of target engagement should be developed before any additional studies of isradipine are considered. We need to know whether and to what degree an agent hits its target in the brain to provide a less ambiguous test of efficacy. A target engagement measurement is particularly important in studying a prodromal population that may require long-term treatment to identify whether this changes the rate or time to progression to PD.

This isradipine trial and others have continued to hone our clinical trial skills, but we still need more reliable in vivo biomarkers of disease progression and measures of specific target engagement for future clinical trials. Pressures from our patients and families afflicted with

PD push us to move faster, and we have to balance that with degree of scientific rigor. If we do not, then we may continue to fail.

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