Parkinson’s disease (PD) is the second most common neurodegenerative disease affecting older adults and its prevalence is expected to increase substantially over the next 20 years. The economic burden of PD is estimated to be $23 billion annually in US and projected to increase to $50 billion by year 2040. Despite an increasing understanding of the genetics and pathophysiology of PD, therapy remains limited to symptomatic treatments and our ability to slow the progression of this common neurodegenerative disease remains elusive. Recent failures of creatine and coenzyme Q10 have added to the frustration of patients, physicians and researchers. Disease modifying therapy remains a critical unmet therapeutic need that would likely have a significant impact on the global burden associated with PD.

EVIDENCE FOR CALCIUM CHANNEL BLOCKERS IN PARKINSON’S DISEASE

PD is characterized by motor symptoms that include slowness of movement, stiffness, tremor at rest and gait and postural dysfunction. These motor symptoms are secondary to preferential and selective loss of dopaminergic neurons in the substantia nigra pars compacta that project to the striatum. The reason for the selective vulnerability of this neuronal population in PD may lead to important insights into PD pathogenesis and therefore treatment. A recent hypothesis from the Surmeier laboratory proposes that the selective vulnerability of these neurons is due to the reliance of these neurons on L-type calcium channels (Cav1.3) that act as autonomous pacemakers. Autonomous pacemaking means that the cells fire at a preset rate all the time similar to selected cells in the heart. Such pacemaking properties are highly energy demanding and as such can make cells vulnerable to PD pathology.

Indeed, the reliance of these neurons on these particular calcium channels increases with age, as does PD incidence, and parallels the increasing sensitivity of these neurons to toxins associated with parkinsonism (e.g. MPTP). In addition, a number of other neuronal populations known to be affected to varying degrees in PD are also similarly reliant on this sub-type of calcium channels.

Calcium channel blockers are frequently used for treatment of hypertension. Use of already approved drugs for alternative indications is called “repurposing” and can substantially facilitate the process of drug development and reduce the cost. Isradipine, one of the FDA approved dihydropyridine calcium channel blockers, was chosen to explore the hypothesis that blocking these calcium channel blockers may be neuroprotective in PD models because, of available calcium channel blockers, it is the most potent inhibitor of this subtype of calcium channels and its chemical structure suggests that it has excellent penetration of the blood brain barrier. Pretreatment with isradipine demonstrates neuroprotective effects in in vitro and in vivo toxin models of PD importantly, without causing any negative effect on cells function or on animals’ behavior. Essential for the future studies, the levels of isradipine achieved in these models are consistent with levels achieved in humans treated within the normal dosing range for hypertension.

Recent epidemiological data also supports potential neuroprotective effect of calcium channel blockers in PD. Ritz et al. assessed risk of the new diagnosis of PD in a cohort of 1,931 patients with new diagnosis of PD versus 9,651 matched controls. The study demonstrated a 27 percent risk reduction (OR= 0.73) of a new diagnosis of PD in subjects treated with centrally acting calcium channel blockers compared with non-centrally acting calcium channel...
blockers or other antihypertensive agents. These findings are consistent with those of multiple investigators that demonstrate between a 23 to 29 percent risk reduction of incident PD in current users of calcium channel blockers and this finding was most consistent in patients treated with dihydropyridine calcium channel blockers and those that were preferentially centrally acting. Pasternak et al. also demonstrated a reduced mortality in patients with PD treated with dihydropyridine calcium channel blockers potentially suggesting a protective effect. In an attempt to explore the role of dihydropyridine calcium channel blockers on PD progression, Marras et al. set explored current use of these agents in patients with PD. They found a significant reduction in the time to requiring drug treatment for PD disability, nursing home admission and death. Despite this they did not find a difference between more centrally acting and non-centrally acting agents leading the authors to question the veracity of the findings.

THE EXPERIENCE OF ISRADIPINE IN PD

We have conducted two trials of isradipine in PD populations. The first study was an open label dose escalation safety and tolerability study of isradipine CR in patients with early PD. The study enrolled 31 subjects and demonstrated dose dependent tolerability of isradipine CR; with tolerabilities of 94 percent for the 5mg dosage, 87 percent for the 10mg dosage, 68 percent for the 15mg dosage, and 52 percent for the 20mg dosage. Isradipine had no significant effect on blood pressure or PD motor disability. The two most common reasons for intolerability were leg edema (n=7) and dizziness (n=3). Importantly there was no difference in isradipine tolerability between individuals being treated with dopaminergic therapy and those who were not.

The second study was a Phase II double-blind, randomized, placebo-controlled, tolerability and dosage finding study of isradipine CR in patients with early Parkinson Disease (STEADY-PD) funded by the Michael J Fox Foundation (MJFF) and Northwestern Memorial Foundation (Dixon fund). The objective of the study was to establish safety and tolerability of isradipine CR across the FDA approved dosing range (5-20mg) in a larger cohort of patients with early PD and to evaluate comparative efficacy of three dosages of isradipine CR provided that each dose was tolerable. The study recruited subjects with early PD not requiring dopaminergic therapy (stable dose of amantadine, anticholinergics and MAO-B inhibitors were allowed). The study was a multicenter 52 week, randomized, 4-arm double-blind parallel group trial with 100 subjects randomized to 5, 10 or 20mg of isradipine CR or matching placebo daily. The dosage that was tolerable and demonstrated preliminary efficacy was to be used in the future pivotal (Phase III) efficacy study. Tolerability of each active dosage was compared with the tolerability of placebo, while efficacy comparisons were made between three active treatment arms. Similar to the open label study, there was a dose-dependent tolerability with both the 5mg and 10mg dosages meeting the tolerability threshold but with clear intolerability of the 20mg dosage. Again edema (n=30) and dizziness (n=24) were the most common side effects, with only edema showing a clear dose dependent effect. Despite the frequency of dizziness, no significant effects on blood pressure were identified in the Phase II study. There was no statistically significant efficacy difference as measured by the Unified Parkinson Disease Rating Scale (UPDRS) or other variables between the active treatment groups. While the study was not powered to detect differences between treatment and placebo, there was a trend towards less disability on higher doses of isradipine.

STEADY-PDIII

Based on convergent data from in-vivo, in-vitro, epidemiological studies and pilot trials in PD, we have initiated a Phase III trial of isradipine 10mg daily will slow the progression of PD—STEADY-PDIII. The study is a multi-center randomized, double-blind, placebo-controlled, parallel group study of isradipine 10mg daily in 336 participants with early PD at 56 Parkinson Study Group sites in North America (see http://steadypd3.com for complete list of sites). The study was funded by the National Institute of Neurological Diseases and Stroke (NINDS) and is currently the only Phase III neuroprotective study in PD funded by NINDS. The primary outcome is the change in total UPDRS from baseline to 36 months in the practically defined “ON” state. Figure 1 summarizes the design.

The study aims to recruit participants with recently diagnosed PD (de novo) not yet taking any major classes of PD medication. The reason for targeting de novo PD
participants is to allow intervention to be tested early in the course of the disease and to make data comparable to previously completed studies for the similar indication. While the participants are recruited into the study prior to initiation of dopaminergic therapy, they will be allowed to start such treatment in the course of the study as their symptoms warrant. It is anticipated that majority of them will require dopaminergic therapy by study completion. Change in UPDRS has been the standard outcome measure used in both symptomatic and disease modifying trials and is the most well validated measure of PD disability currently available. The novelty of the current study design is its 36 month duration. Previous disease modifying studies have been of relatively short duration (12-18 months) assuming that if benefit is shown it will persist long term. However, even if the intervention is effective early in the course of the disease, it remains to be proven that the benefit will persist longer term. For example, studies evaluating the impact of initiating therapy with dopamine agonists versus levodopa have found that early differences do not necessarily result in longer duration benefits. Studies of the impact of urate levels on PD progression have shown benefits in early untreated patients but not in early patients treated with dopaminergic therapy. The interpretation of prior disease modifying therapies has therefore been obscured by the lack of long term follow up. STEADY-PDIII will therefore be the first disease modifying study in de novo population to assess the impact of an intervention over a longer time period and after most individuals have already initiated dopaminergic therapy. This will allow us to gain important insights into the impact of isradipine on various secondary outcome measures that are meaningful to patients and clinicians.

In this context, STEADY-PDIII will look at important secondary outcomes that evaluate the impact on clinically relevant outcomes that are only testable with longer duration follow up, notably dopaminergic therapy use, development of dopaminergic motor complications, and non-motor disability. The current study is explicitly designed to evaluate whether a benefit in UPDRS with isradipine occurs in the setting of differential dopaminergic therapy use, reduced rate of dopaminergic motor complications, and a reduction in non-motor disability. In addition, the 36 month time point may give us some insight into the impact of isradipine treatment on cognition, a domain where even small benefits are likely to have a clinically significant effect.

These major secondary outcomes include:

1) Time to initiation of dopaminergic therapy. This outcome has been used as a primary measure in a number of previously completed studies of putative disease modifying agents including the landmark DATATOP trial of selegi- line in early PD. It reflects progression early in disease not obscured by symptomatic treatment and may give some insight into the impact of isradipine during this early period.

2) Time to and severity of dopaminergic motor complications. Prior studies of initial dopaminergic therapy and risk of motor complications (40) demonstrate that 30-50 percent of subjects will develop dopaminergic motor complications after two years of dopaminergic treatment (roughly equivalent to the 36 month time point for our cohort) and that most of these complications will be accounted for by wearing OFF, followed by dyskinesias. Dopaminergic motor complications are influenced by type of initial therapy (dopamine agonist or levodopa) and disease progression. Therefore, dopaminergic motor complications may reflect a secondary measure of progression once type of initial treatment is accounted for.

3) Non-motor disability. Non-motor symptoms will be assessed utilizing the MDS-UPDRS Part 1 score. The MDS-UPDRS is a valid and reliable scale (45) that unlike the original UPDRS assesses a whole range of non-motor symptoms relevant to PD including cognitive impairment, hallucinations, depressed mood, anxiety, apathy, dopamine dysregulation, sleep disruption, daytime sleepiness and urinary symptoms. Non-motor symptoms can be challenging to treat and have a disproportionate impact on quality of life. Therefore therapy that influences these outcomes will likely have a significant impact on PD quality of life.

We have also chosen a number of exploratory measures that take advantage of the longer duration of follow up in the current study compared to previous de-novo studies and represent clinically valuable and complementary outcomes in PD. Finally, we will model the trajectory of UPDRS change before and after initiation of dopaminergic therapy as an exploratory analysis. If isradipine provides a benefit on UPDRS progression we would anticipate detecting a difference in the trajectory of the UPDRS change between isradipine and placebo as dopaminergic therapy would not be expected to differentially influence the rate of progression of UPDRS; therefore any difference in slopes would be accounted for by isradipine. A special emphasis will be made on the impact of the intervention on the quality of life measures including a novel NEURO QOL tool developed by the National Institute of Health.

SUMMARY

Treatment that slows the progression of PD is a major unmet therapeutic need that has the potential to dramatically impact the millions of individuals worldwide affected by this condition. Due to a convergence of strong preclinical, epidemiological and trial data; isradipine represents a currently available treatment that holds substantial promise
to address this need. Our preliminary data in PD supports the tolerability of 10mg daily and is a dosage that achieves levels consistent with the neuroprotective effects in the pre-clinical models. STEADYP-PDIII is designed to assess whether isradipine has a clinically meaningful impact on disease progression as well as a variety of secondary measures with intrinsic value to patients. The fact that isradipine is commercially available in a generic form and thus is inexpensive will facilitate rapid translation of the study results, if positive, into clinical practice. Recruitment in this pivotal trial will begin in the summer/fall of 2014 with results expected in 2019. Additional data about the study can be found on the study website (http://steadypd3.com).

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