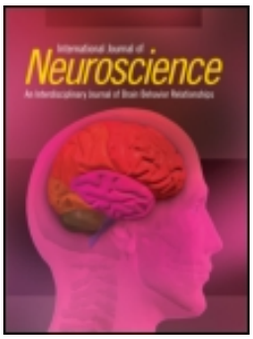

International Journal of Neuroscience

ISSN: 0020-7454 (Print) 1543-5245 (Online) Journal homepage: informahealthcare.com/journals/ines20

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To cite this article: Robert A. Hauser (2011) Future Treatments for Parkinson's Disease: Surfing the PD Pipeline, International Journal of Neuroscience, 121:sup2, 53-62, DOI: 10.3109/00207454.2011.620195

To link to this article: https://doi.org/10.3109/00207454.2011.620195

International Journal of Neuroscience, 121, 53–62, 2011

ISSN: 0020-7454 print / 1543-5245 online
DOI: 10.3109/00207454.2011.620195

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Future Treatments for Parkinson's Disease: Surfing the PD Pipeline

Robert A. Hauser

Departments of Neurology, Molecular Pharmacology and Physiology, College of Medicine, University of South Florida, Tampa, Florida, USA

ABSTRACT

Our current wish list for the treatment of Parkinson's disease (PD) includes therapies that will provide robust and sustained antiparkinsonian benefit through the day, ameliorate or prevent dyskinesia, and slow or prevent the progression of the disease. In this article, I review selected new therapies in clinical development for motor features or treatment complications of PD, and some that may slow disease progression. These include adenosine 2a (A2a) antagonists (istradefylline, preladenant, and SYN115), levodopa/carbidopa intestinal gel (LCIG), IPX066—an extended-release formulation of carbidopa/levodopa, XP21279—a sustained-release levodopa prodrug, ND0611—a carbidopa subcutaneous patch, safinamide—a mixed mechanism of action medication that may provide both MAO-B and glutamate inhibition, PMY50028—an oral neurotrophic factor inducer, antidyskinesia medications (AFQ056 and fipamezole), and gene therapies (AAV2-neurturin and glutamic acid decarboxylase gene transfer). Some of these therapies will never be proven efficacious and will not come to market while others may play a key role in the future treatment of PD.

KEYWORDS: Parkinson's disease, treatment, adenosine antagonists, disease modification, dyskinesia, gene therapy, levodopa, neurotrophic factors, surgery

INTRODUCTION

Future treatments are born of today's unmet needs. Over the long term, many patients with Parkinson's disease (PD) experience substantial disability due to cognitive dysfunction or balance impairment [1]. It seems likely that it will be difficult to develop highly effective symptomatic therapies to treat these problems once they are well established. Therefore, there is a critical need for therapies to slow or stop the progression of the disease from an early stage. In addition, most patients with PD will experience motor fluctuations and dyskinesias over time despite currently available therapies [1]. Many would benefit from a highly effective medication that provides a robust and sustained antiparkinsonian effect through the day. There is also a need for a highly effective treatment for dyskinesia. Such a treatment could reduce disability and discomfort from dyskinesia and free physicians to use dopaminergic therapies more liberally.

In this article, I review selected new therapies in clinical development that may alleviate motor features or slow disease progression. Some will no doubt never be proven effective or achieve regulatory approval, while others may provide the basis for the future treatment of PD.

A2a ANTAGONISTS

Adenosine 2a (A2a) receptor antagonists are a new class of nondopaminergic medications currently under evaluation for their ability to improve signs and symptoms of PD. Theoretically, they offer the potential to provide benefits that are not delivered by traditional dopaminergic medications and might avoid dopaminergic side effects. A2a receptors within the striatum colocalize with dopamine D2 receptors on GABAergic striatopallidal output neurons of the indirect pathway and to GABAergic recurrent collaterals [2]. A2a antagonists are thought to provide antiparkinsonian benefit by reducing the overactivity of the striatopallidal

Received 23 April 2011.

Address correspondence to Dr. Robert A. Hauser, M.D., M.B.A., USF Parkinson's Disease and Movement Disorders Center, NPF Center of Excellence, Department of Neurology, College of Medicine, University of South Florida, 5 Tampa General Circle, Suite 410, Tampa, FL 33606, USA. E-mail: rhauser@health.usf.edu

pathway [3]. In nonhuman N-methyl-4-phenyl-1,2,3,6-tetrahydropyidine (MPTP)-lesioned primates, A2a antagonists provide motor benefit with little or no development of dyskinesia, and in levodopa-primed animals, improve motor function without worsening dyskinesia [4–7]. In rodent models, there is also evidence of improvement in some nonmotor functions including memory, olfaction, and mood [8]. Neuroprotective effects have been demonstrated in a variety of models [9, 10].

Istradefylline

Istradefylline was evaluated in a proof-of-concept, placebo-controlled study that employed intravenous levodopa infusions in 15 PD patients with motor complications [11]. Istradefylline potentiated the antiparkinsonian response to a low-dose, suboptimal levodopa infusion, and the antiparkinsonian response to 80 mg istradefylline plus a low-dose levodopa infusion was similar to an optimal-dose levodopa infusion but with 45% less dyskinesia. In addition, the clinical benefit observed after stopping levodopa infusion lasted 76% longer. In a 12-week exploratory trial of 83 PD subjects with both motor fluctuations and dyskinesias, istradefylline 20 or 40 mg once daily reduced OFF time compared with placebo by 1.7 hours ($p = .004$) [12].

Two phase 2 clinical trials were then conducted in patients with motor fluctuations. In one, istradefylline 40 mg/day reduced OFF time compared with placebo by 1.2 hours ($p = .005$) [13]. In the other, istradefylline 20 mg/day reduced OFF time by 0.64 hours (4.35%, $p = .026$) and istradefylline 60 mg/day reduced OFF time by 0.77 hours (4.49%, $p = .024$) [14]. Nonsignificant increases in ON time with dyskinesia were observed in both studies, but this was predominantly an increase in nontroublesome dyskinesia.

In a phase 3 trial, istradefylline 20 mg/day reduced OFF time compared with placebo by 0.7 hours ($p = .03$) [15]. However, another phase 3 trial of istradefylline (10, 20, and 40 mg/day) did not demonstrate significant reductions in OFF time compared with placebo [16]. Why this trial failed is not known but could possibly be due to chance or a problem with trial execution.

In 2008, the *Food and Drug Administration* (FDA) issued a not approvable letter regarding istradefylline [17] and expressed concern as to whether the efficacy results sufficiently supported its clinical utility. This concern may have arisen from a lack of two positive phase 3 trials and the observed reduction in OFF time, as a 1-hour reduction may represent the minimum clinically important difference [18]. Kyowa elected to suspend the development of istradefylline in North America [19] but to continue development with a phase 3 trial in Japan. Results of this trial demonstrated that compared with placebo, istradefylline 20 mg/day reduced OFF time by 0.65 hours and 40 mg/day reduced OFF time by 0.92 hours [20].

Istradefylline was also evaluated as monotherapy in early PD. In a 12-week double-blind study of 176 patients, istradefylline 40 mg/day did not provide a significant improvement in Unified Parkinson's Disease Rating Scale (UPDRS) motor scores compared with placebo (–1.11, $p = .228$) [21].

Overall, it appears that istradefylline is well tolerated and has mild efficacy in reducing OFF time in PD patients with motor fluctuations. In contrast to results from animal studies, istradefylline does not appear to have significant efficacy as monotherapy. These results raise several important questions about A2a antagonists as a class. Most importantly, can other A2a antagonists provide greater efficacy to reduce OFF time in patients with motor fluctuations and can they provide efficacy as monotherapy? Istradefylline's future is currently uncertain.

Preladenant

Preladenant was evaluated in a phase 2, dose-finding trial that randomized 253 PD patients experiencing at least 2 hours of OFF time per day [22]. Subjects were treated by the addition of preladenant 1, 2, 5, or 10 mg BID or matching placebo for 12 weeks. The preladenant 5 mg BID group experienced a mean reduction in OFF time compared with placebo of 1.0 hour ($p = .0486$), and the preladenant 10 mg BID group experienced a mean reduction in OFF time compared with placebo of 1.2 hours ($p = .019$). ON time with troublesome dyskinesia was not significantly increased (5 mg BID: –0.1 hour, $p = .812$; 10 mg BID: 0.2 hours, $p = .540$). Preladenant was well tolerated, especially at the 5 mg BID dosage. The most commonly reported adverse events (AEs) were worsening parkinsonism (placebo, 5 mg BID, 10 mg BID = 9%, 11%, and 15%, respectively), somnolence (6%, 9%, and 13%,), dyskinesia (13%, 9%, and 13%), nausea (11%, 13%, and 4%), constipation (2%, 13%, and 4%), and insomnia (9%, 9%, and 9%).

Phase 3 studies of preladenant as an adjunct to levodopa and as monotherapy are now underway. Results from the monotherapy trial may indicate whether A2a antagonists can provide symptomatic benefit in early PD, given the negative results from the istradefylline monotherapy trial. In addition, future studies will assess effects on nonmotor symptoms including motivation, initiative, and fatigue.

SYN115

SYN115 was evaluated in a phase 2a randomized, placebo-controlled, double-blind crossover study [23]. Patients with mild PD received SYN115 for 1 week (20 mg BID, $n = 12$; 60 mg BID, $n = 14$) followed by a 1-week washout and then placebo for 1 week, or the reverse order, and were evaluated before and during an intravenous (IV) levodopa infusion. With SYN115 60 mg BID, tapping speed was faster than with placebo, both before (5%, $p = .03$) and during (6%, $p = 0.02$) levodopa infusion. A phase 2 trial in patients with motor fluctuations is now underway.

Future of A2a Antagonists

The efficacy and safety of A2a antagonists is still being defined. It seems likely that they can provide at least mild benefit to reduce OFF time in patients with motor fluctuations. Animal studies suggested that by adding an A2a antagonist and lowering the levodopa dose, antiparkinsonian benefit could be maintained with less dyskinesia. This has not yet been evaluated in PD patients. In addition, it is unclear whether A2a antagonists can provide symptomatic benefit as monotherapy in early PD. An intriguing observation from animal studies is that coadministration of an A2a antagonists from the time dopaminergic therapy is begun might prevent the development of dyskinesia [24]. This too needs to be evaluated in future clinical trials. Additional areas of investigation include nonmotor symptoms such as fatigue, mood, and motivation.

LEVODOPA FORMULATIONS

Levodopa/Carbidopa Intestinal Gel (LCIG; Duodopa)

Levodopa/carbidopa intestinal gel (LCIG; Duodopa) is an aqueous gel that contains 20 mg/ml levodopa and 5 mg/ml carbidopa [25]. It is supplied in 100 ml cassettes containing 2000 mg of levodopa, enough for a full day's treatment for most patients. The cassette attaches to a portable infusion pump that pumps the gel through a transabdominal tube connected to a percutaneous endoscopic gastrostomy (PEG) tube with the tip positioned in the proximal jejunum or duodenum. The pump can be carried in a harness that can be worn over the shoulder or around the waist. Most commonly, the gel is infused during waking hours, although some patients may benefit from around-the-clock infusion.

LCIG is effective to reduce motor fluctuations and dyskinesia in advanced PD [25–27]. It is currently approved for clinical use in more than 30 countries and has been used by more than 3,000 patients. It is currently in phase 3 testing in the United States.

Multiple small, open-label trials have been published and are reviewed in detail elsewhere [25–27]. Nyholm et al. [28] conducted a randomized, crossover trial comparing nasoduodenal infusion of LCIG for 3 weeks to carbidopa/levodopa CR (controlled release; 50/200 mg) with carbidopa/levodopa IR (immediate release; 12.5/50 mg) as needed for 3 weeks. Pharmacokinetic evaluation demonstrated that the average intraindividual variation for plasma levodopa concentration was 34% with oral medication compared with 14% with LCIG infusion ($p < .01$). Motor assessments using hourly video scoring demonstrated a significantly increased number of near-normal state observations (80% vs. 61%, $p < .01$) with LCIG compared with oral medication. Observations of bradykinesia (OFF) and dyskinesia were both also decreased with LCIG.

Another study [29] (DIREQT; Duodopa Infusion: Randomized Efficacy and Quality of Life Trial) compared nasoduodenal infusion of LCIG to individually optimized combinations of pharmacotherapy in a randomized crossover trial using two 3-week treatment periods for 25 patients. Clinical assessments were undertaken using blinded rater assessments of half-hourly video recordings. Results showed that the median percentage of ratings in the functional ON state was significantly increased with LCIG compared with standard pharmacotherapy (100% vs. 81%, $p < .01$). Dyskinesia was uncommon and not different during the two treatment periods. Quality of life scores were significantly better with LCIG.

Multiple longer duration open-label studies have also demonstrated benefit with LCIG delivered via PEG. One study evaluated 9 patients [30]; two withdrew from the study, one due to hallucinations and confusion and one due to acute peripheral neuropathy after 7 months. For the remaining 7 patients, at 12 months, daily OFF time was reduced from a mean of 384 to 30 minutes ($p < .01$) and daily time with disabling dyskinesia was reduced from 156 to 40 minutes ($p < .01$). In another study of 13 patients [31], after 6 months of LCIG treatment, mean OFF time was reduced from 50% to 11% ($p = .001$) and mean ON time with disabling dyskinesia was reduced from 17% to 3% ($p = .007$). Benefit for fluctuations and dyskinesias has been reported for up to 7 years [32]. Improvements have also been noted in nonmotor symptoms [33], including cardiovascular, sleep, attention/memory, gastrointestinal (GI), urinary, and total Nonmotor Symptoms Scale (NMSS) score.

The French DUODOPA Study Group performed a questionnaire-based retrospective study of 102 patients treated with duodenal LCIG infusion from 2003 to 2007 [34]. Efficacy was rated in 75 patients who

received long-term intraduodenal infusion. Neurologists reported improvement for motor fluctuations in 96%, dyskinesia in 95%, dystonia in 91%, gait in 61%, and dysphagia in 60%. Ninety-two percent of patients reported improvement in quality of life. Safety was assessed in 91 patients. Eighteen (18%) had AEs related to gastrostomy including 4 (4.3%) who experienced peritonitis, and 2 patients (2.2%) had severe psychosis within a week of starting treatment. Notably, technical problems occurred in 57 cases (63%), including inner tube disconnected with leakage (20%), inner tube pulled out (18%), inner tube obstructed (17%), and inner tube dislocated with migration in the intestine (21%). Technical problems led to discontinuation in 6 cases.

An open-label, international, 54-week study of LCIG is underway, and interim results were recently reported in abstract form. In this study, an individualized regimen of LCIG is infused for 16 hours/day and other PD medications are permitted after the first 28 days. The interim analysis included 192 patients, of whom 69 (35.9%) completed long-term treatment, 24 (12.5%) withdrew, and 99 (51.6%) are ongoing. Mean OFF time at baseline was 6.7 hours. OFF time was reduced by 4.2 hours at 24 weeks ($n = 144$) and by 4.6 hours at 54 weeks ($n = 61$; both, $p < .001$) [35]. ON time without troublesome dyskinesia, UPDRS scores, and quality of life assessments [36] were also significantly improved. Most AEs were mild to moderate but serious AEs occurred in 60 patients (31.3%) [37]. AEs led to discontinuation of therapy in 14 (7.3%). The most common AEs were abdominal pain (30.7%), complication of device insertion (21.4%), and procedural pain (17.7%). In addition, excessive granulation tissue was noted in 13.5%, postoperative wound infection occurred in 10.4%, and peritonitis/pneumoperitoneum occurred in 10.4%.

A phase 3, 12-week, randomized, double-dummy study to compare LCIG with oral levodopa/carbidopa IR is now underway [38]. In this study, patients are randomized to receive either LCIG infusion via PEG plus placebo tablets or placebo gel infusion via PEG plus levodopa/carbidopa IR tablets. The primary outcome variable is the change in OFF time from baseline to week 12 as assessed by home diaries [39, 40].

Current information suggests that LCIG infusion is highly effective to treat motor fluctuations and dyskinesias, and results from the phase 3 trial are awaited. The population in which LCIG infusion can be considered is basically similar to the deep brain stimulation (DBS) population, that is, patients whose fluctuations and dyskinesias cannot be adequately managed with available oral medications. However, LCIG may be considered in patients with mild dementia and those with some hallucinations, a group that would not normally be acceptable for DBS. The main drawbacks are the invasiveness of the procedure, the inconvenience of carrying the pump, and the problems associated with managing device malfunctions, including tube dislocations and obstructions. At this time, LCIG appears to be a reasonable alternative to DBS in appropriate patients.

IPX066

IPX066 is an extended-release oral formulation of carbidopa/levodopa. IPX066 was initially compared with carbidopa/levodopa IR in an open-label crossover study [41]. Twenty-seven patients with fluctuations on carbidopa/levodopa IR were randomized to a week of IPX066 followed by a week of carbidopa/levodopa IR, or the reverse order. On the first day of each week, patients were evaluated after single-dose administration. Following a single dose, time to ON was similar for both medications. However, UPDRS motor scores were significantly better with IPX066 from hours 3 to 6 ($p < .05$), reflecting a considerably longer duration of action. During maintenance therapy through the week, the mean daily dosing frequency for IPX066 was 3.5 compared with 5.4 for carbidopa/levodopa IR. Patient diaries indicated that subjects experienced 2 hours less OFF time per day with IPX066 ($p < .0001$) despite less frequent administration.

Three hundred ninety-three subjects with fluctuations on carbidopa/levodopa IR were randomized in a phase 3, double-blind trial [42]. Subjects entered the study and underwent a 3-week dose adjustment period of carbidopa/levodopa IR. They were then switched to IPX066 and underwent a 6-week adjustment phase. For the final 13 weeks, they were randomized to their adjusted IPX066 or carbidopa/levodopa IR regimen using a double-dummy design. The mean daily dosing frequency was 3.6 for IPX066 compared with 5.1 for carbidopa/levodopa IR. Results demonstrated that IPX066 provided a 1.1-hour improvement in ON time without troublesome dyskinesia compared with carbidopa/levodopa IR ($p < .001$). Thirty-nine percent of patients rated themselves as much or very much improved with IPX066 compared with 17% with carbidopa/levodopa IR ($p < .0001$). A similar proportion of subjects experienced AEs with either medication.

IPX066 was also evaluated in early PD. In a large, double-blind, 30-week study, 381 levodopa naïve patients were randomized to placebo or IPX066 at a daily levodopa equivalent dose of 300, 500, or 800 mg divided TID (q6h) [43]. The mean improvement in UPDRS II (ADL) + III (motor) scores was 11.7, 12.9, and 14.9 for the three IPX066 doses compared with 0.6 units for placebo ($p < .0001$ for all doses). The most commonly reported AEs with IPX066 compared with placebo were nausea (18.0% vs. 8.7%), dizziness (14.2% vs. 5.4%), and headache (12.5% vs. 10.9%).

Evidence indicates that IPX066 maintains therapeutic levodopa concentrations significantly longer than carbidopa/levodopa IR. Patients with fluctuations on carbidopa/levodopa IR, 5 (or more) times per day, can likely be switched to IPX066 TID and experience a reduction in OFF time. In clinical practice, IPX066 may be particularly useful for patients when they first develop wearing off on carbidopa/levodopa IR administered TID or QID. Although clearly efficacious in early PD, the ultimate value of IPX066 in early disease may depend on whether more continuous dopamine stimulation can reduce the development of dyskinesia [44]. This is an important issue to examine in future trials.

OTHER ANTIPARKINSONIAN MEDICATIONS

XP21279

XP21279 is a sustained-release formulation of a levodopa prodrug that is actively transported by high capacity nutrient pathways located throughout the lower GI tract. This allows more time for absorption than occurs with levodopa, as levodopa can only be transported across a short segment of the small intestine distal to the stomach.

A phase 1 trial demonstrated that XP21279 provided more sustained blood concentrations of levodopa than carbidopa/levodopa IR [45]. In this double-blind, single-dose study, for carbidopa/levodopa IR (fed), the ratio of maximum concentration (*C*max) to the mean concentration at 12 hours (*C*12) was 39.7, whereas the *C*max/*C*12 for XP21279 (fed) administered with carbidopa was 4.2.

Results of a phase 1b study in PD patients with motor fluctuations were recently reported [46]. This was an open-label, two-period trial. Subjects received carbidopa/levodopa IR 25–100 TID or QID for 2 weeks followed by XP21279 (190 mg, comparable with 104 mg levodopa) TID with carbidopa 25 mg TID. Fourteen subjects entered and 10 completed the study. Pharmacokinetic evaluations demonstrated that XP21279 provided significantly less variability in levodopa concentration than carbidopa/levodopa IR ($p < .05$). Compared with carbidopa/levodopa at baseline, 6 of 10 XP21279-treated subjects had ≥30% reduction in mean daily OFF time. Mean time to ON after the first morning dose was similar for XP21279 (0.93 hours) and carbidopa/levodopa IR (0.98 hours).

XP21279 cleverly takes advantage of nutrient transporters located throughout the lower GI tract, thereby providing the potential for much more sustained levodopa blood concentrations than occurs with carbidopa/levodopa IR. It holds great promise but further trials are required to determine if it can live up to that potential.

ND0611

Neuroderm had been developing a transdermal patch using levodopa ethyl ester. However, skin irritation at the application site was found to be unacceptable and this project was terminated [47]. ND0611 is a continuously delivered carbidopa solution administered subcutaneously by a patch. In preclinical studies, levodopa half-life, area under the curve, and trough concentrations of levodopa were greatly increased when ND0611 was administered with standard oral levodopa products. In a phase 1 study in healthy volunteers, ND0611 administered with carbidopa/levodopa IR improved levodopa half-life, area under the curve, trough levels, and time with concentrations above 1000 ng/ml.

These preliminary observations suggest that maintenance of adequate peripheral blockade of dopa decarboxylase may improve levodopa pharmacokinetics. It may also be of benefit to combine approaches to prolong levodopa delivery as discussed above with sustained dopa decarboxylase inhibition.

Safinamide

Safinamide may provide benefit in PD through both MAO-B inhibition and inhibition of glutamate release [48]. Safinamide was studied in early PD in a trial of 172 patients either untreated or on a stable dose of a dopamine agonist ($n = 101$) [49]. Subjects were randomized to once daily placebo, 0.5 mg/kg safinamide, or 1.0 mg/kg safinamide. The percentage of responders (≥30% improvement in UPDRS motor score) at 3 months was 21.4% in the placebo group, 30.9% in the low-dose safinamide group (NS), and 37.5% in the higher-dose safinamide group ($p = .016$). In subjects taking a dopamine agonist, responder rates were 20.6% in the placebo group, 36.4% in the low-dose safinamide group (NS), and 47.1% in the higher-dose safinamide group ($p = .024$).

Safinamide was also studied in PD patients with motor fluctuations on levodopa [50]. In a 6-month, placebo-controlled study of 669 subjects, the addition of safinamide, 50 mg/day and 100 mg/day, significantly improved ON time compared with placebo without worsening dyskinesia.

Phase 3 studies of safinamide as an adjunct to a dopamine agonist in relatively early PD and as an adjunct to levodopa in patients with motor fluctuations are underway.

There is also interest as to whether safinamide might provide an antidyskinetic effect. In MPTP-lesioned, levodopa-primed, dyskinetic monkeys, safinamide

reduced both intensity and duration of dyskinesia following levodopa administration [51]. In addition, the beneficial antiparkinsonian response to levodopa was prolonged, indicating that the reduction in dyskinesia was not simply due to an antidopaminergic effect.

Results of phase 3 studies are awaited. Safinamide may be particularly useful if it is able to provide both an antiparkinsonian benefit and a reduction in dyskinesia.

Cogane (PMY50028)

Cogane is an oral neurotrophic factor inducer that readily crosses the blood–brain barrier. In vitro experiments using rat mesencephalic neurons demonstrated that the administration of Cogane, either before or after 1-methyl-4-phenylpyridinium (MPP+) significantly reduced and reversed neuronal atrophy and cell loss to a magnitude similar to that achieved by a combination of brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF) [52]. In MPTP-lesioned mice, oral administration of Cogane for 60 days reduced substantia nigra dopamine neuron loss, attenuated reduction of striatal dopamine transporter (DAT), and significantly increased striatal levels of BDNF (511%) and GDNF (297%) [52]. In MPTP-lesioned parkinsonian monkeys, oral administration of Cogane for 18 weeks was associated with a 27% median reduction in parkinsonian disability at 9 weeks and a 43% reduction at 18 weeks [53]. A phase 2, proof-of-concept and dose-ranging study is now underway in patients with early PD [54].

ANTIDYSKINESIA MEDICATIONS

AFQ056

AFQ056 is a selective antagonist of the metabotropic glutamate receptor 5 (mGluR5). In MPTP-lesioned monkeys, AFQ056 significantly reduced levodopa-induced dyskinesia and did not worsen the antiparkinsonian response [55]. Moreover, when AFQ056 was combined with a low dose of levodopa, the antiparkinsonian response increased and dyskinesia remained mild.

AFQ056 was evaluated in patients with moderate-to-severe levodopa-induced dyskinesia in a 16-day, randomized, placebo-controlled study in which 16 patients received placebo and 15 received AFQ056 titrated to a maximum of 150 mg BID [56]. A significant reduction in dyskinesia was observed as assessed by the Lang-Fahn Activities of Daily Living Dyskinesia Scale ($p = .02$) and the Abnormal Involuntary Movement Scale (AIMS) ($p < .001$). In a second study, AFQ056 was evaluated in patients with severe dyskinesia in a 20-day, randomized, placebo-controlled study [57]. In this study, 14 patients were randomized to placebo and 14 to escalating doses of AFQ056. AFQ056 provided a significant antidyskinetic effect compared with placebo on the AIMS ($p = .032$) and UPDRS part IV, items 32 and 33 ($p = .001$).

In a phase 2 study, patients with moderate-to-severe dyskinesia were randomized to the addition of AFQ056 (10, 25, 50, 75, and 100 mg BID) or placebo for 12 weeks [58]. Significant improvements were seen in the primary outcome (modified AIMS) at the assigned dose of 100 mg BID compared with placebo ($p = .007$). Reductions in dyskinesia were also observed in the 100 mg BID group compared with placebo as assessed by UPDRS IV item 32 ($p = .005$). However, no significant changes were observed in the PD Dyskinesia Scale (PDYS-26) or the Clinician's Global Impression of Change (CGIC).

Fipamezole

Fipamezole is a selective alpha-2 adrenergic antagonist. In MPTP-lesioned monkeys, fipamezole significantly reduced levodopa-induced dyskinesia without worsening antiparkinsonian benefit, and prolonged the benefit of levodopa by 66% [59].

In a small study [60], 21 moderate-to-advanced PD subjects received fipamezole as a buccal spray in single ascending doses of 15, 30, 60, and 90 mg. Fipamezole reduced dyskinesia severity by 23% at 60 mg ($p < .05$) and 31% at 90 mg ($p < .05$); the levodopa response duration was prolonged by 41 minutes with fipamezole 90 mg ($p < .05$). Fipamezole demonstrated no antiparkinsonian benefit as monotherapy.

Fipamezole was then studied in a 4-week, phase 2, double-blind, placebo-controlled, dose-escalating trial that included 115 subjects in the United States and 64 subjects in India [61]. For the total study population, there was no significant difference compared with placebo for the primary end point (Levodopa-Induced Dyskinesia Rating Scale, LIDS). However, the prespecified analysis of the US subjects demonstrated that fipamezole 90 mg significantly reduced dyskinesia ($p = .047$), there was a dose-effect response ($p = .014$), and dyskinesia reduction correlated with improvement in CGI ($p = .035$).

Future of Antidyskinetic Medications

A robust antidyskinetic medication would be very helpful for the management of advanced PD, both to reduce the unwanted effects of dyskinesia and to allow more liberal use of dopaminergic medications. Whether antidyskinetic medications currently in development can provide sufficiently robust efficacy to fulfill this role is currently unclear. Ultimately, it will be important to

demonstrate not only a reduction in a dyskinesia outcome measure but also that the reduction in dyskinesia provides a clinically relevant benefit. Clinical trials that assess the overall benefit when a potential antidyskinetic medication is added and the levodopa dose increased may be required to assess the true value of such therapies.

GENE THERAPY

CERE-120 (AAV2-NRTN)

Neurotrophic factors are compounds that promote development, survival, and function of neurons. Neurturin (NRTN) is a member of the GDNF family of ligands [62]. Neither GDNF nor NRTN crosses the blood–brain barrier, and therefore, alternative delivery methods are required.

CERE-120 is an adeno-associated virus serotype 2 (AAV-2) vector encoding for human NRTN. In aged monkeys, unilateral injections of CERE-120 into the caudate and putamen resulted in robust NRTN expression in the caudate, putamen, and substantia nigra pars compacta (SNc) 8 months after administration [63]. Positron emission tomography (PET) revealed a significant (~20%) increase in 18F-fluorodopa uptake in the injected striatum compared with the uninjected side. In addition, there was a significant increase in tyrosine hydroxylase (TH)-immunoreactive fibers and an increase in the number of TH-immunoreactive cells. In another study [64], CERE-120 was injected unilaterally into the striatum and substantia nigra of monkeys 4 days following a unilateral injection of MPTP. CERE-120-treated monkeys displayed greater preservation of dopamine neurons than control monkeys, and MPTP-induced motor impairments improved 80%–90% over 4 months.

A phase 1, 12-month, open-label study was performed in 12 patients with advanced PD [65]. Subjects were administered a low or high dose of CERE-120 via bilateral injections into the putamen. The treatment was found to be safe and well tolerated. Mean UPDRS motor OFF scores improved by 36% ($p = .000123$) and ON time without troublesome dyskinesia increased by 25% ($p = .025$). However, there were no changes in 18F-fluorodopa uptake on PET, and there were no significant differences between the low- and high-dose groups.

In a randomized, double-blind, controlled trial of 58 advanced PD patients [66], subjects received CERE-120 injected bilaterally into the putamen or sham surgery. Results demonstrated no significant differences across groups in the primary end point, UPDRS motor scores in the practically defined OFF state at 12 months ($p = .91$). However, there were differences observed in practically defined motor OFF scores at 18 months (difference = –7.61, $p = .0213$) and several secondary outcome measures. Histological analysis in 2 patients who received CERE-120 revealed NRTN expression in ~15% of the putamen but very little in the SNc [67]. Moreover, there was scant evidence for TH induction in the putamen and none in the SNc. This is strikingly different from what is seen in MPTP monkey models and suggests that transport deficits in PD neurons may limit and/or delay the response. A phase1/2 clinical trial is now underway to assess a higher dose of CERE-120 injected into both putamen and SNc.

Whether CERE-120 will ultimately prove effective for the treatment of PD is unknown. As currently conceived, CERE-120 is targeted to dopaminergic neurons, and would not be expected to slow disease progression or improve symptoms due to dysfunction elsewhere in the brain.

Glutamic Acid Decarboxylase (GAD) Gene Transfer

In PD, SNc neuronal loss and consequent striatal dopamine reduction lead to excessive inhibitory output from the globus pallidus interna (GPi) and substantia nigra pars reticulata (SNr). This is due to disinhibition of the subthalamic nucleus (STN), which drives the GPi and SNr via release of the excitatory neurotransmitter glutamate.

GAD catalyzes the synthesis of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain. GAD gene transfer in the STN modifies the phenotype of STN neurons from predominantly excitatory to predominantly inhibitory [68], thereby reversing excessive drive on GPi and SNr, and returning their output to a more normal state.

Twelve patients with advanced PD were followed for 12 months in a phase 1, open-label study of various doses of AAV-GAD injected unilaterally into the STN [69]. The procedure was well tolerated and there were no AEs related to the gene therapy. UPDRS OFF motor scores on the side opposite injection were improved by 33% ($p = .0012$) at 6 months and 29% ($p = .0057$) at 12 months. However, changes in ADL scores were not significantly improved and there were no differences observed across dose groups.

In a phase 2, double-blind, randomized trial [70], 45 advanced PD patients received sham surgery or infusion of AAV2-GAD and 37 were included in the statistical analysis. Subjects were excluded from analysis because of infusion failure or infusion outside the predefined target zone. At 6 months, practically defined OFF UPDRS motor scores improved by 8.1 points in the GAD group and 4.7 points in the sham surgery group ($p = .04$).

Ultimately, AAV2-GAD will need to be proven effective and to provide clinically meaningful benefit using intent-to-treat methodology. Unanswered questions include "how long is the duration of benefit?" and "is it possible that some patients might experience 'too great' an effect and experience unwanted dyskinesia?"

CONCLUSION

We still need therapies to provide robust antiparkinsonian benefit through the day, to eliminate or avoid dyskinesia, and to slow or stop the progression of the disease. Review of potential future therapies suggests that we are making progress. More sustained antiparkinsonian benefit is close at hand, antidyskinetic medications are moving forward, and neuroprotective/neurorestorative therapies are on the horizon.

Declaration of interest: Dr. Robert A. Hauser has received honoraria or payments for consulting, advisory services, speaking services, or research as listed below:

Advisory board: Boehringer Ingelheim Pharmaceuticals, Inc., Teva Neuroscience, Impax Pharmaceuticals, UCB, Inc., GE Healthcare, IPSEN Pharmaceuticals, Novartis, Parkinson Study Group, Solvay, Quintiles, and Biogen Idec.

Speakers bureau: Allergan Neuroscience, GlaxoSmithKline, TEVA Neuroscience, Boehringer Ingelheim Pharmaceuticals, Inc., Novartis Pharmaceuticals, and IPSEN Pharmaceuticals.

Consulting: Bial, Lundbeck, Biogen Idec, Boehringer Ingelheim, Chelsea Therapeutics, GE Healthcare, Impax, Santhera Pharmaceuticals, Merck Serono/EMD Serono, Solvay Pharmaceuticals, Synosia Therapeutics, Schering-Plough, Shire Pharmaceuticals, Inc., XenoPort, Inc., and Medivation, Inc.

Research: PICO-Tesla, Schwartz Pharma, Genzyme, Acadia, Solvay Pharmaceuticals, Impax, TEVA Neuroscience, (Merck) Serono, Schering-Plough, Novartis Pharmaceuticals, IPSEN Pharmaceuticals, XenoPort Pharmaceuticals, Chelsea Therapeutics, Allergan Neuroscience, Molecular Biometrics, The Michael J. Fox Foundation for Parkinson's Research, and the National Parkinson Foundation.

Royalties: University of South Florida.

In addition, Dr. Hauser has consulted in litigation with lawyers representing various current and former manufacturers of welding consumables.

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