New and Emerging Therapies in Parkinson’s Disease

As the therapeutic landscape expands, an increasing range of options and a promising horizon will improve management of motor fluctuations for many patients with Parkinson’s disease.

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Parkinson’s disease (PD) impairs motor, sensory, autonomic and cognitive functions. In particular, management of motor fluctuations remains an unmet need in patients with PD. Continuous dopaminergic stimulation (CDS) reduces motor complications in animal models, while motor complication management in advanced PD focuses on extending the duration of levodopa with adjunctive medication.

Ahead, we will review the newest additions to the PD therapeutic landscape, with a particular focus on new levodopa agents. We will also look ahead at emerging therapies and attempt to better grasp how an expanding arsenal may impact care.

2015: THE YEAR OF LEVODOPA

Levodopa, one of the oldest and most potent therapies for PD, underwent two changes in delivery systems last year. One is a longer acting oral formulation and another delivered via a PEG-J tube to smoothen delivery and improve motor fluctuations.

Rytary. Approved in early 2015, Rytary (Carbidopa and Levodopa Extended Release, C/L ER) is the newest oral therapy for PD. It is a true extended-release levodopa with immediate, intermediate, and extended release beads in a 1:4 ratio between carbidopa and levodopa. It is available in a variety of strengths to allow customized dosing.

The maximum total daily dose of C/L ER is 2450mg and can be divided between three to five times a day. A comparison of the pharmacokinetics between C/L ER, Carbidopa / Levodopa Immediate release (C/L IR), Carbidopa / Levodopa controlled release (C/L CR), and Carbidopa / Levodopa / Entacapone (C/L/E) demonstrated that C/L ER achieved peak plasma concentrations in one hour, similar to C/L IR and sustained plasma concentrations for 4.5 hours longer than other extended release formulations including C/L/E.

In clinical trials, C/L ER demonstrated benefit in levodopa naïve patients as well as moderate to advanced patients previously treated with C/L IR and C/L/E. The ADVANCE trial compared C/L ER to C/L IR. C/L ER increased on time without troublesome dyskinesia and reduced off time by two fold as compared to C/L IR. C/L ER reduced dose frequency compared to immediate release. Similarly, the ASCEND trial compared C/L ER to C/L/E, while C/L ER reduced off time and dose frequency and increased on time without troublesome dyskinesia as compared to C/L/E.

The single biggest challenge with dosing C/L ER is dose conversion. With official dose conversion resulting in nearly 75 percent of patients needing a dose adjustment, the great majority will need a dose increase. Another

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pitfall with the official dose conversion is the three-times-a-day dosing schedule; it will not be effective for patients taking C/L IR four or more times a day. An alternate dosing strategy that may quickly bring a patient closer to the final C/LR ER dose would be to double the total daily dose of IR C/L and dose at 2/3 of the frequency. For example: a patient on C/L IR 25/100 1 tab six times per day would covert to 1200mg of C/L ER divided into four doses, approximately two capsules of ER C/L /145mg at each dose.

The dose conversion for patients on C/L/E is higher as entacapone increases central nervous availability of levodopa. The C/L/E to C/L ER dose conversion ratio in the ASCEND trial is 2:5. An additional unique benefit of C/L ER is that the capsules can be opened and the beads taken with apple sauce for patients with dysphagia and maintains the extended release property.

Duopa (CLES). During the course of PD, predictable response to oral medication is lost and alternatives need to be employed. Gastroparesis leads to delayed “on” dose failures, and food interactions. Duopa (Carbidopa / Levodopa Enteral Suspension, CLES) allows for the continuous delivery of levodopa to the jejunum via a PEG-J tube and external pump. The CLES concentration of carbidopa to levodopa is 1:4 ratio, 4.63mg/20mg per 1ml.

The pivotal study was a double blind, double dummy, active control, parallel group study. The study population of 66 was distributed 1:1 between placebo and treatment arms. Patients had a baseline mean “off” time of six to seven hours and baseline mean “on” time without troublesome dyskinesia of eight to nine hours. The treatment group received oral placebo and CLES via PEG-J. The placebo group received oral C/L 25/100 and placebo via PEG-J. Patients were titrated to optimal dose over four weeks and then a fixed dose maintenance phase of eight weeks. The primary end point was change in mean daily “off” time from baseline to week 12 and the secondary end point was change in mean daily “on” time without troublesome dyskinesias between baseline and 12 weeks.

Results showed that the treatment (CLES) group achieved a 1.9 hour reduction in daily “off” time and a 1.9 hour improvement in daily “on” time without troublesome dyskinesias, as compared to oral C/L 25/100 group. CLES reaches peak plasma concentration at 2.5 hours after initiation and stays constant until the pump is turned off at 16 hours. Side effects were primarily related to surgical procedure—57 percent in the CLES group vs. 44 percent for the placebo group. Most of the device related adverse events occurred in the immediate post-operative period, i.e. nausea, constipation, and incision site erythema. Neuropathy was noted due to a B6 deficiency. One potential complication is withdrawal hyperpyrexia and confusion due to the sudden reduction of CLES delivery from pump failure or J-tube migration. It is important to provide patients with a rescue supply of oral levodopa.

CLES is a valuable tool for patients with motor fluctuations (wearing off and or dyskinesias) that cannot be managed with medical therapy. It provides an attractive alternative for some patients to deep brain stimulation (DBS). CLES opens the window for surgical management of PD to patients with mild cognitive impairment or early dementia. At our center, we have three patients that received DBS therapy to reduce the symptoms of PD and, despite programming and reduction of oral medications, have significant motor fluctuations due to disease progression. These patients underwent CLES and currently have improved motor control and almost no “off” time.

EMERGING THERAPIES

Looking ahead, clinicians eagerly await various options advancing CDS with the less invasive apomorphine, improving dyskinesia management and novel delivery of rescue therapy. Here is a brief glimpse at some agents currently under investigation:

Safinimide. An ultra selective reversible monoamine oxidase B (MAO-B) inhibitor, safinimide is a unique molecule that targets the traditional dopaminergic system and also sodium and N-type calcium channels that modulate the glutaminergic system. Safinimide is 1,000-fold more selective for MAO-B than MAO-A, as compared to rasagiline (127 fold) and selegiline (107 fold). Due to the selectivity and reversibility, it does not have any restric-
tions or drug-drug interactions typical of other MAO-B inhibitors.\textsuperscript{15}

In the MOTION trial, safinimide was studied at 50 mg and 100mg dose reduced disability as measured on the Unified Parkinson’s Disease Rating Scale. In the SETTLE and 016 trials, safinimide was added to levodopa resulting in reduced daily “off” time, AM “off” time as well improved “on” time without or non troublesome dyskinesia.\textsuperscript{16,17} In the 018 trial, safinimide reduced moderate to severe dyskinesia, as measured on the dyskinesia rating scale (DRS), when added to levodopa without reduction of levodopa dose.\textsuperscript{18}

In summary, safinimide would reduce “off” time and improve “on” time without worsening dyskinesia. The anti-dyskinesia benefit with a unique mechanism of action is a benefit not seen with other existing MAO-B inhibitors or other dopaminergic therapy.

**Inhaled Levodopa.** Although levodopa remains the most effective medication to improve the motor symptoms of PD, motor complications continue to affect the quality of lives of PD patients.\textsuperscript{19} Pharmacologic interventions bypassing the gastrointestinal system continue to be an active area of research, since constipation and gastroparesis delay gastric emptying and cause “wearing off” or delayed “on” episodes.\textsuperscript{19-21} Transdermal and subcutaneous dopaminergic medications may be tried to lessen or abort these episodes.\textsuperscript{20} Oral levodopa for rescue for an off-period can have a long latency for effect, especially in individuals who are suffering from constipation and gastroparesis.

Clinical trials are focusing on different ways to deliver levodopa by alternate administration in order to abort a “wearing off” episode or morning akinesia.\textsuperscript{19} In the 19th International Congress in Parkinson’s disease and Movement Disorder an abstract was presented evaluating an inhaled levodopa formulation known as CVT-301. In this study, 86 PD patients experiencing wearing off were randomized to placebo or CVT-301. The inhalation formulation can raise levodopa concentrations to therapeutic levels within 10 minutes. Subjects used CVT-301 approximately two times a day and reduced “off” time by approximately 1.6 hours without an increase in “on” time with dyskinesia noted.\textsuperscript{21} Further safety and clinical efficacy trials are still ongoing.

**Apomorphine Infusion.** Apomorphine is a highly potent dopamine agonist (DA) that was created more than a century ago.\textsuperscript{22} In contrast to pramipexole and ropinirole, which are mainly D2 and D3 agonists, Apomorphine has a potent effect at the D1 receptor in addition to the D2-D5 receptors.\textsuperscript{23} It is available in two formulations: intermittent injection and continuous infusion. It is available in the US as an intermittent injection marketed as Apokyn since 2004 useful for managing dose delay and morning akinesia.\textsuperscript{24}

Numerous studies showed the efficacy and safety of apomorphine in patients with advanced PD using either intermittent or continuous subcutaneous injections to treat off symptoms.\textsuperscript{24} Reduction of “off” time (up to 70 percent) was shown in several studies by using apomorphine infusion in the open label and non-controlled fashion.\textsuperscript{25-27} Additionally, dyskinesia reduction and non-motor symptoms such as pain, anxiety, fatigue, and hyperhidrosis have been reported.

**Practical Pointer...**

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Infusion of Apomorphine Long Term Study (INFUS-ON) is an ongoing phase 3 study that’s expected to complete in 2018.\textsuperscript{28} The infusion will provide a non-surgical alternative to manage off time and dyskinesia refractory to oral medications. An infusion pump should be offered to the advanced PD patients when multiple doses of rescue injection are required or in cases of difficult to manage motor complications, impaired gastric absorption, and poor compliance with multiple oral therapies.\textsuperscript{22}
CONCLUSION
There are numerous options that are newly available and on the horizon that are designed to improve management of motor fluctuations of patients with PD. Both C/L ER and CLES are novel delivery systems that are being utilized to overcome the short half-life of levodopa. Emerging therapies such as apomorphine infusion and inhaled levodopa use novel delivery systems of existing compounds that bypass the gastrointestinal system. Novel compounds such as safinamide offer a unique mechanism of action, provide higher degree of selectivity and potentially less drug interaction. The next challenge beyond these novel compounds and delivery systems is to look at medications that potentially modify the course of the disease.

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THE BOTTOM LINE
Two new levodopa agents headline the newest innovations in therapeutic development in Parkinson’s disease treatment. One is a longer acting oral formulation and the other is delivered via a PEG-J tube to smoothen delivery and improve motor fluctuations. Emerging therapies such as apomorphine infusion and inhaled levodopa use novel delivery systems of existing compounds that bypass the gastrointestinal system, while novel compounds, such as safinamide, offer a unique mechanism of action, provide higher degree of selectivity and potentially less drug interaction. Beyond these novel compounds and delivery systems, the next great challenge in Parkinson’s management is the development of medications that potentially modify the course of the disease.