Innovative Therapeutic Options for PD:
Long-acting Levodopa Formulations, Infusion Therapy and Others

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Neurology
Problem #1: The response to each levodopa dose progressively shortens over time.
On-off response: Clinical and biochemical correlations during oral and intravenous levodopa administration in parkinsonian patients

SHOULSON, MD, GLAUBIGER, MD, PhD, & CHASE MD

“A constant intravenous infusion of levodopa resulted in stable plasma dopa concentrations and virtual disappearance of motor fluctuations.”

NEUROLOGY 25: 1144-1148, December 1975
Oral, extended-release forms of levodopa

- Controlled-release carbidopa-levodopa (Sinemet CR®) has unpredictable intestinal absorption and should not be used for daytime use.
- Extended-release carbidopa-levodopa (Rytary®) was FDA approved in January 2015.
Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson’s disease and motor fluctuations: a phase 3 randomised, double-blind trial

Figure 2: Mean daily off-time throughout the study

30% reduction of OFF time
Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson’s disease: a randomised, double-blind, placebo-controlled phase 3 trial
Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson’s disease: a randomised, double-blind, placebo-controlled phase 3 trial.
Levodopa/Carbidopa intestinal gel infusion
Levodopa-Carbidopa Intestinal Gel in Advanced Parkinson’s Disease: Final 12-Month, Open-Label Results

B. PDQ-39 Summary Index Score

Mean ± SD change over time from baseline to last visit.

Long-term PEG-J treatment week

Baseline: 0, 4, 12, 24 weeks; Last visit: 54 weeks.

n = 320, 312, 302, 290, 273, 317
Levodopa/carbidopa intestinal gel infusion in advanced Parkinson’s disease: a 7-year experience

“59 patients - over 90% reported an improvement in their quality of life, autonomy and clinical global status”

<table>
<thead>
<tr>
<th>Patients (n = 39)</th>
<th>Great improvement</th>
<th>Moderate improvement</th>
<th>Slight improvement</th>
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<tbody>
<tr>
<td>Quality of life</td>
<td>17 (44%)</td>
<td>19 (48%)</td>
<td>3 (8%)</td>
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<tr>
<td>Autonomy</td>
<td>12 (30%)</td>
<td>20 (51%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Clinical global improvement</td>
<td>24 (62%)</td>
<td>11 (28%)</td>
<td>4 (10%)</td>
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“The most common adverse events were dislocation and kinking of the intestinal tube”
Intrajejunal Levodopa Infusion in Parkinson’s Disease: A Pilot Multicenter Study of Effects on Nonmotor Symptoms and Quality of Life
Add-ON Medications

- **Safinamide (Xadago)**
  - IMAO-B
  - Improves OFF time without troublesome dyskinesia

- **Gocovri (Amantadine Extended Release)**
  - Improves troublesome dyskinesia
  - Once a day administration with fewer side effects than regular amantadine

- **Apomorphine Injection (Apokyn)**
  - Subcutaneous Injection
  - “Rescue Therapy” from OFF-periods
In the Pipeline

Sublingual Apomorphine (APL-130277) for the Acute Conversion of OFF to ON in Parkinson’s Disease

When Dopamine Agonists Are Used as “Rescue Therapy” from OFF-periods
In the Pipeline

Continuous Subcutaneous Administration of Levodopa/Carbidopa (ND0612) for the Treatment of Parkinson’s Disease
Take Home Messages – Available Therapies

1) Extended Release formulations of carbidopa/levodopa have become available for patients with wearing off in between levodopa doses
2) Inhalator formulations of carbidopa/levodopa have become available for patients requiring “rescue” therapy from unpredictable OFF-periods
3) Enteral infusion of carbidopa/levodopa have become available for patients with severe motor fluctuations that are not good candidates for DBS or that are not willing to undergo brain surgery
4) Additional ADD-ON medications have become available for patients with troublesome dyskinesia
Take Home Messages – In the Pipeline

1) Sublingual formulations of dopamine agonists are under study (Phase-III) as a rescue therapy for patients with unpredictable OFF periods

2) Subcutaneous infusion systems of carbidopa/levodopa are under study (Phase-III) for patients with severe motor fluctuations that are not good candidate for DBS or that are not willing or not ready to undergo brain surgery
Thank You

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