Measurement Issues in Parkinson’s Disease

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Outline

• Problems
  • Symptomatic effect vs. disease modification
  • Potential confounding effects of existing medications

• Solutions
  • Study design
  • Outcome measures
  • Statistical analysis

• Proposed Phase 3 Inosine Trial
Symptomatic effects vs. disease modification

• If patients on a treatment do better, have we treated the disease or just masked its symptoms?

• Does it matter?
  • Symptomatic benefits may diminish with time
  • Neuroprotection should benefit patients long-term

• Two trial design options:
  • Track pathophysiologic markers (e.g., nigrostriatal function by neuroimaging, CALM-PD-CIT, REAL-PET)
  • Differentiate symptomatic effects from disease modification using a two-period design
Two-period designs

- Randomized withdrawal (e.g., DATATOP), or
- Randomized start (e.g., ADAGIO, see below),
- A four-arm cross-over (i.e., A/A, A/P, P/A, P/P; Balaam’s)

[Diagram showing two-period designs with UPDRS on the y-axis and Time on the x-axis. The diagram illustrates the effects of placebo and study intervention on UPDRS scores over two phases.]

[from Olanow et al. Mov Disord 2008]
Confounding by rescue therapy

• Effective therapies are available to treat symptoms of PD
• If a trial participant’s symptoms worsen, they will receive symptomatic treatment
• How can we estimate benefit (or lack thereof) from an experimental treatment if symptoms are masked by an existing therapy?
Example of confounding by rescue therapy

Observed change from baseline

Placebo

Placebo

Active

Active

Placebo

Active

Active

UPDRS

Time

Observed change from baseline

Unobserved change from baseline

Levodopa initiated

Unobserved

UPDRS

Time

Unobserved change from baseline

Placebo

Placebo

Active

Active

Placebo

Active

Active

UPDRS

Time

Observed change from baseline

Unobserved change from baseline

Levodopa initiated

Unobserved

UPDRS

Time

Observed change from baseline

Unobserved change from baseline

Levodopa initiated

Unobserved

UPDRS

Time

Observed change from baseline

Unobserved change from baseline

Levodopa initiated

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Time

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Levodopa initiated

Unobserved

UPDRS

Time

Observed change from baseline

Unobserved change from baseline

Levodopa initiated

Unobserved

UPDRS

Time
Options for avoiding confounding

1. Measure time-to-need-for-rescue-therapy
2. Measure symptoms while participants are temporarily off symptomatic therapy
3. Analyze symptoms conditional on intensity of symptomatic therapy
4. Analyze symptoms irrespective of symptomatic therapy if the proportion using symptomatic therapy is equal to or lower than in the active arm
5. Analyze time-to-rescue-therapy and symptom progression as a combined endpoint
6. Analyze symptoms censored at initiation of symptomatic therapy
1. Measure time-to-need-for-rescue-therapy

• Issues
  • Need for rescue therapy is subjective
  • Different rescue therapies may not be equivalent
  • Clinical relevance has been questioned

• Examples
  • DATATOP, PRECEPT
2. Measure symptoms while off rescue therapy

• Issues
  • Exposes participants to PD symptoms
  • Weaning-off time may vary from person to person

• Examples
  • ELLDOPA, SINDEPAR
3. Analyze conditional on intensity of rescue therapy

• Issues
  • Levodopa equivalents have been defined
  • But they are only approximations and may not apply to newer therapies

• Examples
  • STRIDE-PD (secondary), NSTAPS (secondary)
4. Analyze irrespective of rescue therapy

• Issues
  
  • Only informative if rates of initiating rescue therapy are equal to or lower than in the active arm
  
  • Progressively more conservative as the difference in rates of initiation rescue therapy grows larger

• Examples
  
  • NET-PD, STEADY-PD III, Phase 3 Inosine Trial (secondary)
5. Analyze time-to-event and symptom progression as a combined endpoint

• Issues
  • Assumes greater importance of time-to-rescue-therapy vs. symptom progression
  • Inherits issues related to time-to-rescue-therapy with still greater subjectivity and variability in the decision to initiate rescue therapy

• Examples
  • SURE-PD (secondary)
6. Analyze outcomes censoring at initiation of rescue therapy

• Issues
  • Requires a model for unobserved outcomes
  • Weights differently participants with early vs. late initiation
  • Only appropriate for trials of untreated patients and relatively short follow-up

• Examples
  • SURE-PD, Phase 3 Inosine Trial
Shared-baseline, random-slopes model censoring at initiation of rescue therapy in SURE-PD

Pre-Rx Score = Trt × Wks + Trt × Sex × Wks + Sex|Wk + random(1|Site) + random(1 + Wks|Pt × Site)
Phase 3 Inosine Trial

- Population: untreated PD patients with low serum urate (≤5.7 mg/dL)
- Two-arm: placebo vs. inosine titrated to raise serum urate to 7.1 to 8.0 mg/dL at trough
- Two period: treated for 24 months, plus 3 months off treatment
- Primary outcome: MDS-UPDRS I-III total score censored at initiation of dopaminergic therapy
- Primary analysis: shared-baseline, random-slopes model (at both participant and site levels), adjusting for age, gender, and MAO-B inhibitor use at baseline
- Secondary analyses:
  - Time to need for dopaminergic therapy
  - All observations at 24 months irrespective of dopaminergic therapy
  - All observations adjusting for time-dependent levodopa equivalents
  - Combined time-to-dopaminergic-therapy and UPDRS progression
Conclusions

• Best practices include:
  • Two-period designs to test for disease modification
  • Short-term functional outcomes for efficiency
  • Censoring at initiation of rescue therapy to avoid confounding
  • Sensitivity analyses using alternative measures of treatment benefit