Applying LGM and GMM Analyses in Clinical Trials

Working Example

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Stull et al., 2011

- Three clinical trials conducted to assess safety and efficacy of indacaterol
  - A novel, once-daily, inhaled, long-acting, β2-agonist for the treatment of chronic obstructive pulmonary disease
- Initial data analysis was conducted using ordinary least-squares regressions
  - Indacaterol was found to increase lung function and improve patient-reported symptoms and health status

Purpose

- The three trials were analysed using mixture modeling techniques to answer the following questions
  - Are there groups of individuals within treatment groups who respond differently but who are hidden when whole treatment group means are analysed using traditional techniques?
  - In what ways do individuals show a differential response? That is, are there hyperresponders? nonresponders? decliners?
  - In what ways are groups of differential responders different? That is, are there differences in characteristics of individuals who are responding versus those who are not responding?

Clinical Trial Descriptions

- INHANCE
  - Indacaterol 150 μg and 300 μg vs. placebo and open-label tiotropium 18 μg for 6 months, randomizing patients at 1:1:1:1
- INLIGHT-2
  - Indacaterol 150 μg vs. placebo and blinded salmeterol 50 μg for 6 months, randomizing patients at 1:1:1
- INVOLVE
  - Indacaterol 300 μg and 600 μg vs. placebo and blinded formoterol 12 μg for 12 months, randomizing patients at 1:1:1:1
  - Only data from the first 6 months of INVOLVE were used to keep the analyses comparable across the 3 trials
Assessments

- Primary analyses
  - St. George’s Respiratory Questionnaire (SGRQ)
    - Validated measure of health status in diseases of chronic airflow limitation
    - Contains 3 subscales: Symptoms, Activity, Impacts
    - Symptoms subscale was used for the present analyses
    - Scored 0-100; higher scores indicate worse health status
  - Modified Medical Research Council (mMRC) dyspnea scale
    - Clinician-rated degree of participants’ dyspnea (breathlessness)
    - 5-point scale based on the degree of physical activities that may lead to dyspnea

Statistical Analyses: Latent-Growth Models

- Latent-growth models (LGMs) were used to explore responses on the SGRQ symptom subscale from baseline to 6 months across the 3 assessment points, controlling for key covariates including mMRC dyspnea
  - LGMs calculate 2 latent (or unobserved) variables for each individual: an intercept (variable for the first time point of the curve) and a slope (variable for changes in the scores over time)
  - Changes in scores are analyzed at the individual level, modeling individual variability in treatment response
  - The level of individual variability was examined to assess whether there may be groups of respondents with different slopes

Statistical Analyses: Growth-Mixture Models

- Where considerable individual variability was found, growth-mixture models (GMMs) were conducted to assess the presence of latent subgroups of individuals showing a differential response within treatment groups
  - Subjects were assigned to their most likely latent class, with different numbers of classes tested to find the best model fit
  - Evaluation of empirical criteria of goodness-of-fit statistics and visual examinations were used to determine the number of classes that best fit the data

Statistical Analyses: Post Hoc

- Post hoc comparisons were conducted to explore differences between the identified latent classes in terms of baseline characteristics
- Post hoc comparisons facilitate an investigation of the way in which, for example, treatment responders are different from nonresponders
Results: INHANCE

- LGM
  - Indacaterol 150 μg and 300 μg performed significantly better than placebo or tiotropium

- GMM
  - Two subsets of patients emerged in each treatment group

- Individual slopes: indacaterol 150 μg (200 randomly selected patients)

- Two subsets of patients emerged in each treatment group
Results: INLIGHT-2

- **LGM**
  - Indacaterol 150 μg performed significantly better than placebo and showed noninferiority with salmeterol

![Graph](image1)

**NOTE:** Patient age, sex, GOLD stage of COPD severity, smoking status, and baseline FEV1 are covariates.

- **GMM**
  - Two subsets of patients emerged in each treatment group

![Graph](image2)

**NOTE:** Patient age, sex, GOLD stage of COPD severity, smoking status, and baseline FEV1 are covariates.
Results: INVOLVE

- **LGM**
  - No significant differences at 6 months between any group
  - However, indacaterol 300 μg and 600 μg and formoterol had significant between slopes of change (improvement over time) than placebo

- **GMM**
  - Three subsets of patients emerged in each treatment group

**NOTE:** Patient age, sex, GOLD stage of COPD severity, smoking status, and baseline FEV1 are covariates
Results: Post Hoc

• In all trials, responding patients... Had better SGRQ Symptom scores at baseline Were less likely to smoke currently Had less breathlessness Were older

...than nonresponding patients

Non-Responders Responders

SGRQ Symptom Score

Treatment Time Point

NOTE: Patient age, sex, GOLD stage of COPD severity, smoking status, and baseline FEV1 are covariates

• In INVOLVE, responding patients... Had worse SGRQ Symptom scores at baseline Were more likely to smoke currently Had more breathlessness Were younger

...than partially responding patients

Responders Partial-Responders

SGRQ Symptom Score

Treatment Week

NOTE: Patient age, sex, GOLD stage of COPD severity, smoking status, and baseline FEV1 are covariates

Overview of Potential Use in Drug Development

Discovery
- Refine inclusion and exclusion criteria
- Refine responder definitions
- Help power Phase II

Innovation
- Empirical support for responder definitions
- Potential for additional label claims

Session Summary

• Clearly, heterogeneity is important when attempting to understand treatment effects
- From the patients’ point of view, they want a treatment that will work
  - Maximizing treatment effectiveness and minimizing adverse events
- From the payers’ point of view, they don’t want to pay for treatment that won’t work in individual patients
- As researchers, we can take steps to manage heterogeneity