

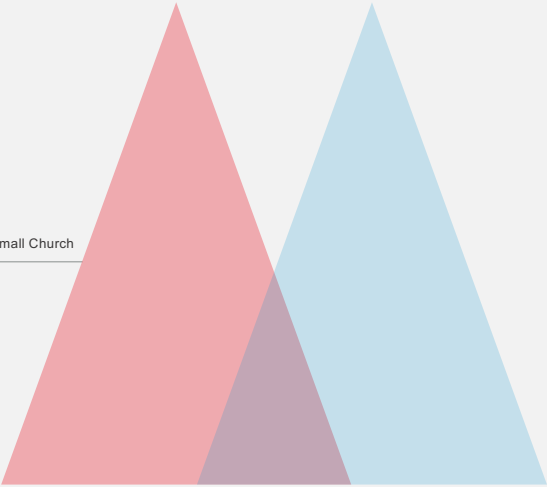
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Korean Incubating Organization for Small Church

Various Statistical Analysis Method II

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#KIOSC #TRAINING



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Recap last week

- $p\text{-value} < 0.05$
- Inferential statistics (hypothesis, population, sample)
- t-test, ANOVA, ANCOVA

2



MMRM

- Mixed model for repeated measures
- Continuous variable
- Measured longitudinally and repeatedly (i.e. blood pressure every 3 months until 2 year follow-up)
- Dynamic process
- Most flexible compare to t-test, ANOVA/ANCOVA

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Data example

- Nemolizumab for Atopic dermatitis with Pruritus (Kabashima et al. 2020 in NEJM)
- Randomized Double-blind Phase 3 study comparing Nemolizumab vs Placebo

A Change in VAS Score for Pruritus to Week 16

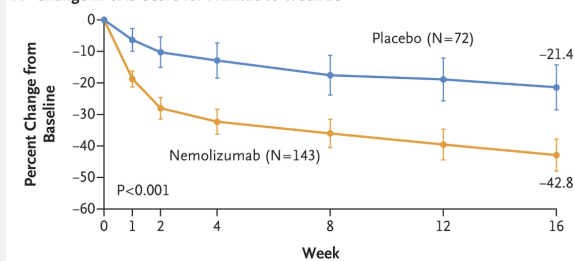


Table 2. Primary and Secondary Efficacy End Points (Modified Intention-to-Treat Population).^a

| End Point | Nemolizumab (N=143) | Placebo (N=72) | Difference (95% CI) |
|---|---------------------|----------------|-------------------------|
| Primary end point: percent change in pruritus VAS score from baseline to wk 16 | -42.8±2.6 | -21.4±3.6 | -21.5 (-30.2 to -12.7)† |
| Secondary end points‡ | | | |
| Percent change in pruritus VAS score from baseline to day 29 | -34.4±2.2 | -15.3±3.0 | -19.3 (-26.6 to -11.9) |
| Percent change in EASI score from baseline to wk 16 | -45.9±3.3 | -33.2±4.7 | -12.6 (-24.0 to -1.3) |
| Percentage of patients with a DLQI score of ≤4 at wk 16 (no./total no.)§ | 40 (51/129) | 22 (15/67) | 17 (2 to 31) |
| Percentage of patients with a decrease of ≥4 points in the DLQI score from baseline to wk 16 (no./total no.)¶ | 67 (89/133) | 50 (34/68) | 17 (3 to 31) |
| Percentage of patients with an ISI score of ≥7 at wk 16 (no./total no.) | 55 (59/108) | 21 (12/54) | 33 (17 to 48) |

^a Plus-minus values are least-squares means ±SE. Efficacy analyses were conducted in the modified intention-to-treat population, which included all randomly assigned patients who received at least one dose of nemolizumab or placebo and who had data available for evaluation. For evaluations of pruritus VAS scores, data for patients who received rescue therapy owing to exacerbations of atopic dermatitis were handled as missing values. For other evaluations (of EASI, DLQI, and ISI scores), data after receipt of rescue therapy were included in the analysis. Because the pruritus VAS score was evaluated by patients daily, the weekly mean scores were used in the analysis. CI denotes confidence interval.

† P<0.001.

‡ For the secondary end points, there were no adjustments for multiple comparisons, and therefore no clinical inferences can be drawn from these data.

§ Analysis for this end point was performed only for patients with a DLQI score of 5 or more at baseline.

¶ Analysis for this end point was performed only for patients with a DLQI score of 4 or more at baseline. A change of 4 points is considered to be the minimal clinically important difference.

|| Analysis for this end point was performed only for patients with an ISI score of 8 or more at baseline.

4



Chi-square

- Categorical data (i.e. positive/negative, yes/no, low/med/high, etc.)
- H_0 : proportion A = proportion B
- Assumptions (i.e. independence, asymptotic normal, etc.)

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Data example

- Tofacitinib for Ulcerative Colitis (Sandborn et al. 2020 in NEJM)
- Randomized Double-blind Phase 3 study comparing Tofacitinib vs Placebo

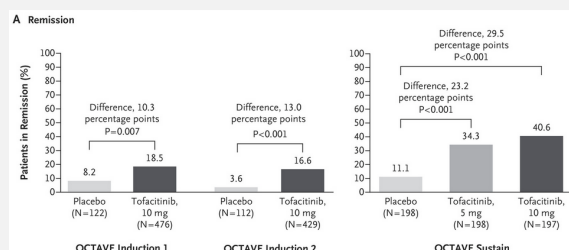


Table 3. Efficacy Outcomes in the OCTAVE Induction 1 and OCTAVE Induction 2 Trials.*

| End Point | OCTAVE Induction 1 | | | | OCTAVE Induction 2 | | | |
|--|--------------------|----------------------------|---------------------|---------|--------------------|----------------------------|---------------------|---------|
| | Placebo (N=122) | Tofacitinib, 10 mg (N=476) | Difference (95% CI) | P Value | Placebo (N=112) | Tofacitinib, 10 mg (N=429) | Difference (95% CI) | P Value |
| Based on Mayo score | | | | | | | | |
| Primary end point: remission at wk 8 — no. (%) | 19 (15.6) | 48 (10.1) | 12.9 (6.5 to 19.3) | 0.001 | 4 (3.6) | 71 (16.6) | 12.9 (6.5 to 19.3) | <0.001 |
| Mucosal healing at wk 8 — no. (%) | 19 (15.6) | 149 (31.3) | 15.7 (8.1 to 23.4) | <0.001 | 13 (11.6) | 122 (28.4) | 16.8 (9.1 to 24.5) | <0.001 |
| Clinical response at wk 8 — no. (%) | 48 (39.3) | 285 (60.0) | 27.1 (17.7 to 36.5) | <0.001 | 32 (28.6) | 236 (55.0) | 26.4 (16.8 to 36.0) | <0.001 |
| Clinical remission at wk 8 — no. (%) | 20 (16.4) | 58 (12.2) | 10.4 (4.9 to 15.9) | 0.001 | 4 (3.6) | 72 (16.8) | 13.2 (6.8 to 19.6) | <0.001 |
| Endoscopic remission at wk 8 — no. (%) | 2 (1.6) | 32 (6.7) | 5.1 (1.5 to 8.7) | 0.04 | 2 (1.8) | 30 (7.0) | 5.2 (1.8 to 8.6) | 0.04 |
| Symptomatic remission at wk 8 — no. (%) | 7 (5.7) | 36 (7.6) | 6.0 (1.0 to 11.1) | 0.06 | 1 (0.9) | 46 (10.7) | 8.0 (3.9 to 12.2) | 0.009 |
| Deep remission at wk 8 — no. (%) | 0 | 11 (2.3) | 6.0 (0.0 to 8.7) | 0.004 | 2 (1.8) | 22 (5.1) | 3.3 (0.0 to 6.6) | 0.14 |
| Change from baseline in total Mayo score at wk 8 | -1.8 (6.1) | -3.8 (6.1) | -1.9 (-2.3 to -1.4) | <0.001 | -1.8 (6.1) | -3.8 (6.1) | -1.9 (-2.3 to -1.4) | <0.001 |
| Based on IBDQ score | | | | | | | | |
| Remission at wk 8 — no. (%) | 42 (34.4) | 233 (49.2) | 14.8 (9.5 to 20.1) | 0.004 | 28 (25.0) | 178 (41.3) | 16.3 (7.2 to 25.8) | 0.002 |
| Remission at wk 8 — no. (%) | 48 (39.3) | 230 (48.3) | 14.8 (9.5 to 20.1) | 0.004 | 29 (25.9) | 212 (49.6) | 23.3 (14.1 to 32.8) | <0.001 |
| Treatment response at wk 8 — no. (%) | 82 (67.2) | 342 (71.8) | 28.2 (18.8 to 37.6) | <0.001 | 59 (52.7) | 388 (90.6) | 37.1 (28.9 to 45.3) | <0.001 |
| Treatment response at wk 8 — no. (%) | 67 (54.9) | 333 (70.0) | 33.0 (23.6 to 42.4) | 0.001 | 34 (30.3) | 303 (70.6) | 35.4 (25.3 to 45.5) | <0.001 |

* Plus-minus values are least squares means \pm SE.
 † Differences of all efficacy end points that are based on the Mayo score are provided in Table 2 in the Supplementary Appendix. The total Mayo score ranges from 0 to 12, with higher scores indicating more severe disease.
 ‡ The Inflammatory Bowel Disease Questionnaire (IBDQ) score ranges from 0 to 224, with higher scores indicating better quality of life. An IBDQ score of 170 or higher is indicative of remission, and an IBDQ score of at least 18 points higher than the baseline score in the induction trial is indicative of a treatment response.

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Logistic Regression

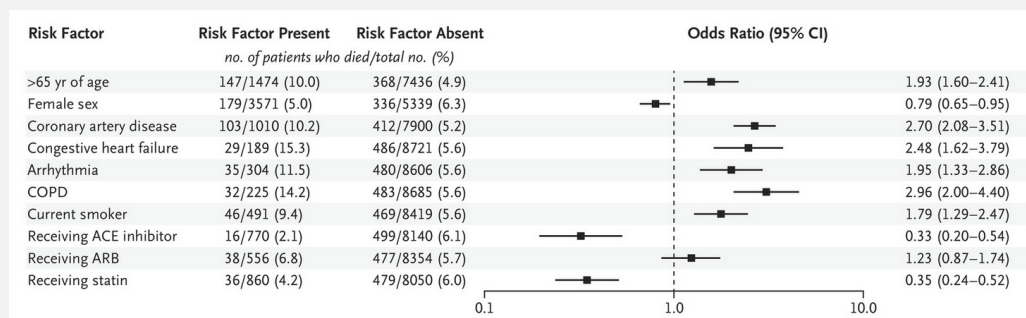
- Categorical data (i.e. positive/negative, yes/no, low/med/high, etc.)
- Examine the association between categorical outcome and covariates
- H_0 : Odds ratio = 1
- Assumptions (i.e. independence, etc.)

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Data example

- Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19 (Mehra et al. 2020 in NEJM)
- observational study



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Survival Analysis

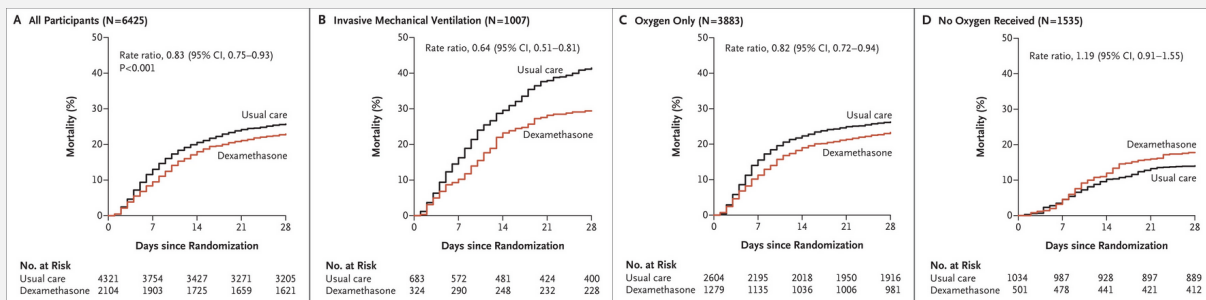
- Time to event outcome (i.e. days to death, duration of remission, etc.)
- Combination of categorical (Yes/No) and continuous (days) response
- H_0 : Hazard ratio = 1
- Log-rank test, cox-regression, etc.
- Assumptions (i.e. censoring, proportional hazard, etc.)

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Data example

- Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report (The RECOVERY Collaborative Group 2020 in NEJM)



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Summary

| Outcome | Method | Comparison |
|---------------|---------------------|------------------------------------|
| Continuous | t-test | Means of two groups |
| Continuous | ANOVA | Means of 2 or more groups |
| Continuous | ANCOVA | Adjusted Means of 2 or more groups |
| Continuous | MMRM | Adjusted Means and more |
| Categorical | Chi-square | Proportion of 2 or more groups |
| Categorical | Logistic Regression | Odds ratio and more |
| Time to Event | Survival Analysis | Hazard ratio and more |

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Thank You

Biostatistics for Non-statistician

- ☐ Basic I - Various Statistical Analysis Methods I
- ☐ Basic II - Various Statistical Analysis Methods II
- ☐ Advanced I - Study Design and Power & Sample Size
- ☐ Advanced II - Adaptive Trial Design

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