Chapter 12: Reading Biomedical Research Part I - Experiments

Reading Experimental Studies

- Start (and end) with the abstract!
  - An **abstract** is about a 150 to 300-word _____ that will typically highlight 1) the motivation and aims of the paper, 2) a short description of the methods, 3) key results, and 4) a brief statement of implications or future work needed.
  - Use the abstract to help you answer some of these key details up front.
  - If reading through the paper for more detail, come back to the abstract periodically, or once finished with the paper, to orient yourself back to the paper's key points and contributions.

Letermovir vs Valganciclovir for Prophylaxis of Cytomegalovirus in High-Risk Kidney Transplant Recipients.

Let's start by reading the abstract to identify some key pieces

1. What is the motivation for this study?

2. What is the response variable in this study? Is it a numeric or categorical outcome? Are there any other response outcomes that were used?

3. What experimental levels are being compared? How might we then phrase the "explanatory" variable in this study?

4. What kind of experiment is this, or what experimental features do you recognize?

5. Describe the population of interest and describe the sample being examined

Abstract

Importance Valganciclovir for 200 days is standard care for cytomegalovirus (CMV) prophylaxis in high-risk CMV-seronegative kidney transplant recipients who receive an organ from a CMV-seropositive donor, but its use is limited by myelosuppression.

Objective To compare the efficacy and safety of letermovir with valganciclovir for prevention of CMV disease in CMV-seronegative kidney transplant recipients who receive an organ from a CMV-seropositive donor.

Design, Setting, and Participants Randomized, double-masked, double-dummy, noninferiority, phase 3 trial in adult CMV-seronegative kidney transplant recipients who received an organ from a CMV-seropositive donor at 94 participating sites between May 2018 and April 2021 (final follow-up in April 2022).

Interventions Participants were randomized in a 1:1 ratio (stratified by receipt of lymphocyte-depleting induction immunosuppression) to receive letermovir, 480 mg, orally daily (with acyclovir) or valganciclovir, 900 mg, orally daily (adjusted for kidney function) for up to 200 days after transplant, with matching placebos.

Main Outcomes and Measures The primary outcome was CMV disease, confirmed by an independent masked adjudication committee, through posttransplant week 52 (prespecified noninferiority margin, 10%). CMV disease through week 28 and time to onset of CMV disease through week 52 were secondary outcomes. Exploratory outcomes included quantifiable CMV DNAemia and resistance. The rate of leukopenia or neutropenia through week 28 was a prespecified safety outcome.

Results Among 601 participants randomized, 589 received at least 1 dose of the study drug (mean age, 49.6 years; 422 [71.6%] men). Letermovir (n = 289) was noninferior to valganciclovir (n = 297) for prevention of CMV disease through week 52 (10.4% vs 11.8% of participants with committee-confirmed CMV disease; stratum-adjusted difference −1.4% [95% CI, −6.5% to 3.8%]). No participants who received letermovir vs 5 participants (1.7%) who received valganciclovir developed CMV disease through week 28. Time to onset of CMV disease was comparable between the groups (hazard ratio, 0.90 [95% CI, 0.56-1.47]). Quantifiable CMV DNAemia was detected in 2.1% of participants in the letermovir group vs 8.8% in the valganciclovir group by week 28. Of participants evaluated for suspected CMV disease or CMV DNAemia, none (0/52) who received letermovir and 12.1% (8/66) who received valganciclovir had resistance-associated substitutions. The rate of leukopenia or neutropenia through week 28 was lower with letermovir vs valganciclovir (26% vs 64%; difference, −37.9% [95% CI, −45.1% to −30.3%]; $P < .001$). Fewer participants in the letermovir group than the valganciclovir group discontinued prophylaxis due to adverse events (4.1% vs 13.5%) or drug-related adverse events (2.7% vs 8.8%).

Conclusion and Relevance Among adult CMV-seronegative kidney transplant recipients who received an organ from a CMV-seropositive donor, letermovir was noninferior to valganciclovir for prophylaxis of CMV disease over 52 weeks, with lower rates of leukopenia or neutropenia, supporting its use for this indication.

- Reading the Tables and Figures
    - Is there a figure or table that compares the **group demographics**? This will help support the argument that the groups are equivalent.
    - Do the researchers acknowledge any **drop-out differences** between the groups? Did they only compare those who completed the intervention, or is this an intent-to-treat comparison?
    - What kinds of measures did the researchers use to compare these groups?
        - **Relative risks** or **odds ratios** (one risk divided by the other) are generally used when comparing risks with a categorical response variable.
        - **Absolute risk reductions** (one risk minus the other) might be used with a categorical response variable as well.
        - **Hazard ratios** are used when making time-to-event comparisons. They will often accompany **Kaplan-meier plots**.
        - **Two mean** or **two median** differences are often made with a numeric response variable.
    - In addition to reporting general group differences, researchers will often share a **subgroup analysis** to denote whether there is evidence for a difference for various subgroups (e.g., women, those over age 65, etc.).
        - Keep in mind that the ***uncertainty*** in these comparisons will often be ***much higher***, especially if we have very few cases from a particular subgroup!
    - Lastly, be on the lookout for tables/figures reporting **adverse effect comparisons**. Even if a treatment is effective at treating the primary response variable, it's good to also check whether it increases other risk factors.

6. Look at Table 1. What does this table help us better understand and assess about this experiment?

7. Look at Figure 2. Based on the findings, what general answer do the researchers have toward their initial question? What statistical evidence do they use to support those claims?

8. ***If Time*****:** In the methods, the paper states: "All study drugs had a matching placebo. Participants, investigators, study staff, and sponsor personnel involved in study drug administration and clinical evaluation were masked to study drug assignments." What does that mean, and is that an advantage or limitation to this study?

Reflection Questions

12.1. What is an abstract? Why might it be helpful to read an abstract both before and after reading or skimming the rest of the paper?

12.2. Is a low p-value a good indication that a paper has made a strong causality argument? Is a low p-value a good indication that a paper has made a strong generalizability argument? Why or why not?

12.3. When looking at confidence intervals for a difference in means or medians, what value would suggest no difference? What about when looking at confidence intervals for a Relative Risk? Odds ratio? Hazard ratio?

12.4. Why might the confidence intervals for comparisons of subgroups often be much wider than the confidence intervals for the full group comparisons?