The CAPSTONE-1 Trial - Single Dose Baloxavir for Uncomplicated Influenza

Background:
Current influenza treatment consists of neuraminidase inhibitors such as oseltamivir, peramivir, and zanamivir. While viral resistance to these medications is not widespread, there have been documented strains of influenza resistant to oseltamivir. Baloxavir is a novel antiviral agent that inhibits viral mRNA replication via the viral polymerase complex. Additionally, the course of baloxavir is a one-time oral dose.

What They Did:
A phase 3 randomized, double-blind, double-dummy, placebo and active controlled trial evaluating baloxavir compared to oseltamivir and placebo for the treatment of uncomplicated influenza

- Baloxavir 40mg (for patients <80 kg) or baloxavir 80mg (for patients ≥80 kg) **versus**

- Oseltamivir 75mg twice daily for 5 days
  OR
- Placebo

Inclusion Criteria: a positive flu test was not required for study enrollment
- Age 12-64 years old
- Fever: axillary temperature ≥ 38°C
- At least one systemic symptom: chills, fatigue, myalgia, etc.
- A least one respiratory symptom: cough, sore throat, congestion etc.

Exclusion Criteria:
- Pregnancy
- Weight <40 kg
- Symptoms occurring for more than 48 hours
- Illness requiring hospitalization
- History of underlying conditions: heart disease, diabetes, etc.
- Use of agents other than acetaminophen for symptom treatment

Outcomes:
- Primary
  - Time to relief of symptoms from start of trial regimen until all seven flu related symptoms were rated as absent or mild for at least 21 hours
  - Flu-related symptoms were classified as; cough, sore throat, headache, nasal congestion, fever/chills, muscle/joint pain, fatigue
- Secondary
  - Time to fever resolution
  - Time to return to baseline health
  - Complications requiring antibiotic use

    - Change in viral load from baseline
    - Time in which virus is detectable
- Safety
    - Frequency of adverse events
    - Severity of adverse events

Results:

- 1436 patients randomized, 1366 patients completed trial, 1064 flu-positive
- Results focused on comparison between baloxavir and placebo
    - Time to resolution of symptoms: 53.7 vs 80.2 hours (intention to treat, infected)
        - Infection confirmed with PCR assay
    - Time to resolution of fever: 24.5 vs 42.0 hours
- Baloxavirvs vs placebo vs oseltamivir
    - Complications requiring antibiotic use: 3.5 vs 4.3 vs 2.4%
    - Reductions in viral load day 1: -4.8 vs -1.3 vs -2.8 $\log_{10}TCID_{50}$ per mL
    - Duration of virus detection: 24 vs 96 vs 72 hours
    - Frequency of adverse events: 20.7 vs 24.6 vs 24.8%
    - Severe adverse events were not associated with randomized flu treatment

Strengths:

- Well-blinded with double-dummy design
- Mostly well-matched baseline characteristics between flu positive and negative groups and all three treatment arms
- Meaningful primary outcome (time to symptom relief) for patients
- Serious adverse events evaluated by blinded investigators

Limitations:

- Baloxavir results compared to placebo more prominently than oseltamivir
- Significant sponsor involvement in data collection and analysis
- Only evaluated patients at low risk for flu complications
- Large proportion of total patients who were flu negative
- More American patients flu negative compared to Japanese patients
- More Japanese patients in the study than American patients
- Evaluation of flu symptoms was not a validated scale

Discussion:

- Baloxavir was superior to placebo in decreasing time to symptom resolution from the flu virus.
- Baloxavir was superior to oseltamivir in antiviral activity - decreasing viral load and duration of time being flu positive.
- Baloxavir was similar to oseltamivir in time to resolution of flu symptoms though this data was not directly reported in the paper. A Kaplan-Meir curve in the publication's supplemental appendix illustrated this point.

- Adverse effects were similar between baloxavir and oseltamivir treatment arms. No serious adverse effects were thought to be related to treatment.
- Even though there was a sizeable portion of these patients who were flu negative, results were similar in the intention-to-treat and intention-to-treat-infected groups.
- The ITT infected group included 74% of the ITT group.

Study Author Conclusion:
"Single dose oral baloxavir in these modest-size trials did not result in apparent safety concerns and was associated with clinical benefit and antiviral activity in patients with uncomplicated influenza."

Clinical Take Home Point:
Single dose oral baloxavir has similar clinical efficacy to a five day course of oseltamivir but demonstrated greater reductions in viral load compared to oseltamivir. However, the extent that reduction in influenza viral load corresponds to favorable clinical outcomes is not known. Baloxavir is an effective single dose regimen for outpatient treatment of uncomplicated influenza. However, neither the CDC not the IDSA 2018 influenza guidelines recommend treating uncomplicated influenza patients with a course of antiviral therapy. Indications of use for treatment of more severe flu in high-risk patients may be upcoming with the expected publication of the CAPSTONE-2 trial. Until this data is published, there is question on baloxavir's role in current flu treatment algorithms.

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Reference: Hayden F, Sugaya N, Hirotsu N, et al. Baloxavirmarboxil for uncomplicated influenza in adults and adolescents. NEJM 2018. PMID: 30184455