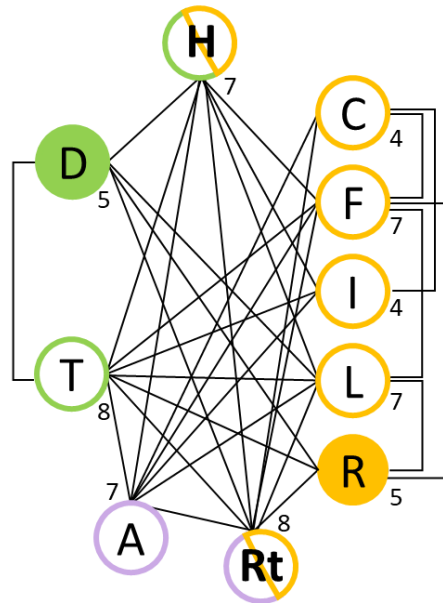# Combination Therapies for COVID-19 and Implications for Drug Safety

PharmaKB cast study to identify combination therapies in clinical trials for COVID-19

Figure 1. Status and target class of key drugs under investigation for efficacy against COVID-19 in clinical trials

Drug status

● Filled circle = Licensed by the US FDA or EMA as a treatment for COVID-19

○ Unfilled circle = investigational therapy for COVID-19

Target class

🟧 Viral target   🟪 Other non-viral/non-immune target
🟩 Immune target

——— Combination therapy under investigation excluding standard of care combinations. The number of drug combinations are indicated

A=azithromycin; C=chloroquine; COVID-19=coronavirus disease 2019; D=dexamethasone (or other corticosteroid); EMA=European Medicines Agency; F=favipiravir; FDA=Food and Drug Administration; H=hydroxychloroquine; I=ivermectin; L=lopinavir; R=remdesivir; Rt=ritonavir; T=Tocilizumab

PharmaKB[1] is a new data offering from Collaborative Drug Discovery. PharmaKB collects and collates a broad range of drug information, allowing users to fully explore the triad of company, drug, and disease. In this case study we explore how data from the COVID-19 drug set can be used to provide an overview of the drug landscape, generating insights into drug development strategies and drug safety profiles.

Using PharmaKB, we reviewed key information for drugs that have been investigated as therapies for COVID-19. The 10 drugs most frequently evaluated drugs in clinical trials against COVID-19, excluding heparin, as of April 2021 were grouped into a select set within the PharmaKB COVID-19 drug set. Of these, only 2 drugs were licensed for use in this disease. Remdesivir was licensed by both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), while dexamethasone was licensed by the EMA.[2-5]
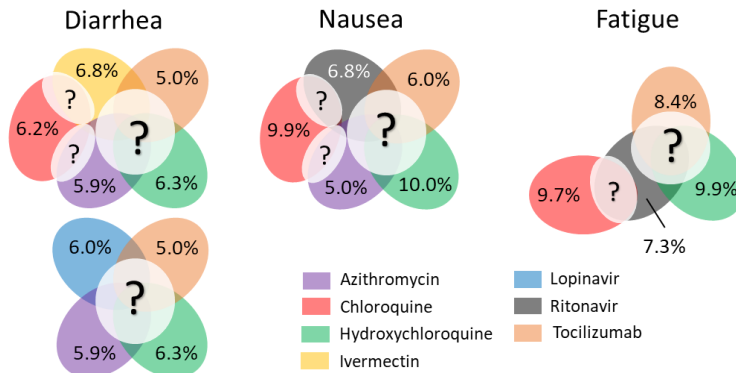
Drugs were divided by target or Anatomical Therapeutic Chemical Classification (ATCC) code into three classes: 1. drugs that act on viral proteins, 2. Drugs that act on the immune system, or 3. other targets. We also used the clinical trial information in PharmaKB to identify the drugs that had been investigated as combination therapy (excluding standard of care combinations). Of the 10 drugs in the COVID-19 drug subset, the majority (7) target viral proteins and just under a third (3) target the immune system. We found that viral- and immune-targeting drugs were evaluated in combination with other key therapies at a similar frequency (range 4-8 and 5-8 therapy combinations, Figure 1). In particular, tocilizumab and ritonavir had been studied in combination with 8 of the other frequently evaluated drugs. Combination therapies included the use of multiple viral-targeting drugs, possibly as a multi-faceted approach to reduce the viral load and resolve the infection. Viral-targeting drugs were also frequently evaluated in combination with immune-targeting drugs, possibly to reduce the harmful effects of inflammation while providing treatment for the infection.

To assess how drug combination therapy might contribute to the adverse drug reactions (ADRs) experienced by patients, we used the safety information provided in PharmaKB (based on US FDA Adverse Event Reporting System) to evaluate the potential for cumulative toxicity. We selected ADRs based on the following criteria:

- Occur at a frequency above an estimated threshold based on an average drug profile.
- Common (≥40%) among the drugs contained in the select COVID-19 drug set.
- Frequently experienced by patients (representing ≥5% of all ADRs reported for that drug)

Figure 2. Frequent (≥5%) ADRs common (≥40%) between drugs under investigation as combination therapy against COVID-19

Legend:
- Azithromycin
- Chloroquine
- Hydroxychloroquine
- Ivermectin
- Lopinavir
- Ritonavir
- Tocilizumab

Other potential interactions included headache (ivermectin 18.7% and tocilizumab 5.9%), rash (chloroquine 7.9%, hydroxychloroquine 8.1%, and tocilizumab 7.5%), and arthralgia (chloroquine 11.1%, hydroxychloroquine 11.3%, ivermectin 5.1%, and tocilizumab 12.0%). Percentages indicate the frequency of the ADR vs. all ADRs for each drug
ADR=adverse drug reaction; COVID-19=coronavirus disease 2019

Arthralgia, diarrhea, fatigue, headache, nausea, and rash met these criteria, suggesting that patients treated with combinations of these drugs may experience a higher incidence or greater severity of such adverse reactions compared with monotherapy regimens (Figure 2). Therefore, clinical trials evaluating such combination therapies should carefully monitor for these events. If present, these ADRs would impact patient compliance with treatment schedules, drug concentrations, and the long-term health of patients and their quality of life.

Overall, this case study indicates how PharmaKB can be used to investigate trends in current drug development strategies, generating new hypotheses to inform future preclinical and clinical studies.

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