Janssen Research & Development*

Study Protocol for Retrospective Observational Studies Using Secondary Data

Comparative Cohort Study of Famotidine in Hospitalized COVID-19 Patients

Protocol CCSDIH002924

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1. List of Abbreviations

Abbreviation	Description of Abbreviated Term
PPIs	Proton pump inhibitors
H1	Histamine receptor type

2. Responsible Parties

2.1. Investigator(s) and Authors

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2.2. Sponsor

This study is performed to support efforts in Consumer to understand and test the histamine hypothesis for COVID-19.

3. Abstract

The purpose of this study is to assess the effect of famotidine and the H1s (including cetirizine) on COVID-19 severity in hospitalized patients. Prior studies on the topic have had limitations due to sample size and sample design, e.g., no controls for potential confounders. A prior internal investigation used the REWARD-B project and the self-controlled cohort design to explore for a potential effect, but also found that design to exhibit significant bias. So, in this study we apply a comparative cohort design to the Premier data to further interrogate the effect.

4. Amendments and Updates

Write “None” or indicate any substantial amendment (e.g., addition of a Statistical Analysis Plan, changes to primary or secondary objectives, changes to study population, main exposure, or outcome) and/or update (e.g., adding data source, change in study timelines) to the study protocol after the start of data collection in a table as indicated below.

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	7/21/2020	8	Amended to explicitly state the sample size and power of study may increase from original feasibility analyses.	Updates to COVID-19 PHD will increase the sample size of subsequent analyses
2				

5. Rationale and Background

From a variety of sources, early clinical data indicate that famotidine treatment may reduce morbidity and mortality associated with COVID-19. A retrospective cohort study of 1,620 hospitalized COVID-19 patients reported that 84 propensity score-matched patients receiving famotidine during hospitalization (oral or IV, 20mg or 40mg daily) had a statistically significant reduced risk for death or intubation (adjusted hazard ratio (aHR) 0.42, 95% CI 0.21-0.85) and also a reduced risk for death alone (aHR 0.30, 95% CI 0.11-0.80) (Freedberg et al 2020). By contrast, proton pump inhibitor use was not associated with reduced risk for these outcomes. An anecdotal report from Wuhan, China indicated that famotidine may be partially protective for COVID-19, but that neither cimetidine nor proton pump inhibitors were protective (Borrell 2020). A sequential case series provides further support for the benefits of famotidine treatment in the outpatient setting (Janowitz et al 2020).

These data have been interpreted as indicating that this increased survival pattern is due to an off-target, non-histamine receptor-mediated effect of famotidine that is not shared with cimetidine. Famotidine is currently being tested under an IND waiver for treating COVID-19 in a double blind randomized clinical trial at high (360 mg/day) intravenous doses in combination with either hydroxychloroquine or remdesivir (ClinicalTrials.gov Identifier: NCT04370262).

Clinical studies and preclinical models with viral and bacterial pathogens other than SARS-CoV-19 have shown that histamine released from mast cells, neutrophils and/or platelets can play an important role in the pathogenesis of post-infection cytokine release, inflammation and vascular endothelial injury that lead to mortality. Studies have also shown potential anti-inflammatory activity of Histamine 1 Receptor (H1R) antagonists, immunomodulatory activity for Histamine 2 Receptor (H2R) antagonists and a potential vascular protective role for both. There have also been some epidemiologic studies and data that have been shared with J&J that suggest there could be a potential benefit for these histamine antagonists in disease interception of SARS-CoV2.

Based on these data, it is hypothesized that an H1R antagonist such as cetirizine and an H2R antagonist such as famotidine alone or in combination could ameliorate the disease severity of SARS-CoV2. Cetirizine and famotidine are attractive candidates to test this hypothesis as they are both available as Over the Counter (OTC) Products with a long history of safe use. Cetrizine is approved for the treatment of allergic diseases such as urticaria, allergic rhinitis and famotidine is approved for the control of gastric acid secretion. The PK/PD assessment of both drugs suggest that OTC doses will provide sufficient pharmacologic effect to test the hypothesis.

To further support the hypotheses and a decision to support sponsorship of a randomized well-controlled clinical trial, epidemiologic studies have been proposed. Previously the epidemiology department used REWARD-B and the self-controlled cohort design to explore for a potential effect, but found that design to exhibit significant bias. Therefore, this study will apply a comparative cohort design to the Premier data to further interrogate the effect.

6. Study Objectives and research question

The objective of the study is to assess the comparative effectiveness of famotidine and reduced severity of outcome (death or need for intensive services) in hospitalized COVID-19 patients versus use of PPIs, hydroxychloroquine or non-use of famotidine. This study will also assess the comparative effectiveness of 2nd generation H1 histamine receptor antagonists for reduced risk of death or intensive services in hospitalized COVID-19 patients versus montelukast, a leukotriene receptor antagonist, with similar indications as the H1 histamine receptor antagonist group.

6.1. Primary Objective(s)

To estimate and compare the incidence of safety outcomes (i.e., death; and death or intensive services) among hospitalized COVID-19 patients following drug exposures of:

1. Famotidine vs. proton pump inhibitors (PPIs)
2. Famotidine vs. no use of famotidine
3. Famotidine vs. hydroxychloroquine
4. H1 blockers (i.e., all 2nd generation antihistamines: cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine) vs. montelukast

7. Research Methods

7.1. Study Design and Setting

This is a retrospective comparative cohort study. The study population is comprised of hospitalized patients aged 18 or older with a diagnosis of COVID-19 available in the database (COVID-19 Premier Hospital Database).

7.2. Describe Data Source(s)

This study will use hospital billing records contained in the COVID-19 Premier Hospital Database (PHD). The PHD contains complete clinical coding, hospital cost, and patient billing data from approximately 700 hospitals throughout the United States. Premier collects data from participating hospitals in its health care alliance. The Premier health care alliance was formed for hospitals to share knowledge, improve patient safety, and reduce risks. Participation in the Premier health care alliance is voluntary. Although the database excludes federally funded hospitals (e.g., Veterans Affairs), the hospitals included are nationally representative based on bed size, geographic region, location (urban/rural) and teaching hospital status. The database contains a date-stamped log of all billed items by cost-accounting department including medications; laboratory, diagnostic, and therapeutic services; and primary and secondary diagnoses for each patient's hospitalization. Identifier-linked enrollment files provide demographic and payor information. Detailed service-level information for each hospital day is recorded; this includes details on medication and devices received. All data will be standardized to the Observational Health and Data Sciences and Informatics (OHDSI) Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) version 5.3.

7.3. Study Population(s)

7.3.1. Treatment Group

Famotidine treatment group: Patients aged 18 and older with an inpatient visit occurring after 02-01-2020; a condition, measurement or observation indicative of COVID-19 during or within 21 days prior to admission; no evidence of intensive services (i.e., mechanical ventilation, tracheostomy or extracorporeal membrane oxygenation) at or within 30 days prior to admission; and with exposure to any drug containing famotidine as an active ingredient on the day of admission (index = first admission).

H1 blocker treatment group: Patients aged 18 and older with an inpatient visit occurring after 02-01-2020; a condition, measurement or observation indicative of COVID-19 during or within 21 days prior to admission no evidence of intensive services (i.e., mechanical ventilation, tracheostomy or extracorporeal membrane oxygenation) at or within 30 days prior to admission; and with exposure to any drug containing 2nd generation antihistamine receptor antagonists (i.e., cetirizine, levocetirizine, fexofenadine, loratadine and desloratadine) as an active ingredient on the day of admission (index = first admission).

7.3.2. Comparator Groups

Comparators for famotidine:

- PPI comparator group: Patients aged 18 and older with an inpatient visit occurring after 02-01-2020; a condition, measurement or observation indicative of COVID-19 during or within 21 days prior to admission; no evidence of intensive services (i.e., mechanical ventilation, tracheostomy or extracorporeal membrane oxygenation) at or within 30 days prior to admission; and with exposure to any drug containing PPIs (i.e., rabeprazole, pantoprazole, omeprazole, esomeprazole, lansoprazole, dexlansoprazole) as an active ingredient on the day of admission (index = first admission).
- Hydroxychloroquine comparator group: Patients aged 18 and older with an inpatient visit occurring after 02-01-2020; a condition, measurement or observation indicative of COVID-19 during or within 21 days prior to admission; no evidence of intensive services (i.e., mechanical ventilation, tracheostomy or extracorporeal membrane oxygenation) at or within 30 days prior to admission; and with exposure to any drug containing hydroxychloroquine as an active ingredient on the day of admission (index = first admission).
- No famotidine comparator group: Patients aged 18 and older with an inpatient visit occurring after 02-01-2020; a condition, measurement or observation indicative of COVID-19 during or within 21 days prior to admission; no evidence of intensive services (i.e., mechanical ventilation, tracheostomy or extracorporeal membrane oxygenation) at or within 30 days prior to admission; and who have no history of exposure to any drug with famotidine as an active ingredient prior to or on the day of admission (index = first admission).

Comparators for H1 blockers:

- Montelukast comparator group: Patients aged 18 and older with an inpatient visit occurring after 02-01-2020; a condition, measurement or observation indicative of COVID-19 during or within 21 days prior to admission; no evidence of intensive services (i.e., mechanical ventilation, tracheostomy or extracorporeal membrane oxygenation) at or within 30 days prior to admission; and with exposure to any drug containing montelukast as an active ingredient on the day of admission (index = first admission).

The concept set expressions and mapped codes for all exposures, conditions, observations, and procedures used to construct study groups are available in Annex 1 and 2, respectively. Links to cohort definition full specifications in ATLAS for each study group is available in Table 7.3.2.1.

7.4. Outcome(s) of Interest

The concept set expressions and mapped codes for all exposures, conditions, observations, and procedures used to construct outcomes are available in Annex 1 and 2, respectively. The following outcomes of interest will be used for all primary research objectives:

1. Death, identified based on patient discharge status within admission records
2. Death or intensive services
    a. Intensive services will be defined as any condition, procedure or observation code indicative of mechanical ventilation, tracheostomy or extracorporeal membrane oxygenation (see Annex I for a list of codes used to query the database)

7.5. Exposure(s) of Interest

Not applicable.

7.6. Other Variables of Interest

Given the data source, there will be minimal historical data for patients in the last 30 days or last year. To the extent possible, confounding will be addressed using large scale propensity score matching in a hospital database where the only medical and other health related history may be those entered on admission. Covariates considered during large scale propensity score matching will include patient demographics (i.e., gender, age, index month) and all observed conditions within 30 days prior to or on admission. Prior drug exposure will not be considered during large scale propensity score matching.

Negative control outcomes will also be used to elucidate the extent of residual confounding. Negative controls are exposure-outcome pairs for which there is no expected causal relationship, such that unbiased analyses can be expected to generate effect estimates consistent with relative risk = 1. A list of negative controls identified empirically through characterization and evaluated for lack of causal relationship through clinical review is available in Annex III.

8. Sample Size and Study Power

The sample size of the treatment and comparator groups meeting all study inclusion criteria based on blinded feasibility analyses are available in Table 8.1. The largest sample size is achieved in the

comparison of famotidine vs. no famotidine (210 vs. 3,156 patients, respectively) while the smallest sample size is achieved in the comparison of H1 blockers vs. montelukast (145 vs. 259 patients, respectively). These patient counts are representative of the initial study population prior to statistical adjustments and provide an upper bound of sample sizes for each analysis.

Table 8.1. Sample size of all treatment and comparator groups

Comparator Groups	Treatment Group, n	Comparator Group, n
Famotidine vs. PPIs	210	266
Famotidine vs. hydroxychloroquine	210	395
Famotidine vs. no famotidine	210	3,156
H1 blockers vs. montelukast	145	259

There is no *a priori* hypothesis testing for this study; therefore, there is no prespecified requirement of sample sizes for the comparative analyses. For each study comparison group, the minimum detectable relative risk (MDRR) will be calculated after all design specifications have been implemented (Armstrong 1987). The calculation of the MDRR includes a targeted type I error rate (alpha) of 0.05 (2-sided) and a type II error rate (beta) of 0.20 (power=80%) given the treatment and comparator group patients counts, outcome event counts, and patient time-at-risk. These will all be reported as part of the study diagnostics (see §9.4).

For instance, the post-match sample size and MDRR for the first-listed study comparison group within the primary objectives (famotidine vs. PPIs) subsequent to propensity score matching and stratification (see §9) are shown in Table 8.2. As reflected by a lower MDRR, propensity score stratification provides greater power to detect differences in the relative risk in outcomes between groups. The study is powered to detect minimum relative risks of outcomes between 2.03 (analysis: propensity score stratification; outcome: death or intensive services) to 3.22 (analysis: propensity score matching; outcome: death) for the primary objective comparison.

Table 8.2. Post-match sample size and MDRR for the comparison of famotidine vs. PPI

Analysis	Treatment Group, n	Comparator Group, n	Outcome	MDRR
Propensity score matching	135	135	Death	3.22
			Death or intensive services	2.37
Propensity score stratification	169	224	Death	2.72
			Death or intensive services	2.03

These figures represent the minimum sample size and power estimates; the COVID-19 PHD database has as little as a 2-week lag from real-time, with data collected from hospitals that contribute data to the PHD on a daily, weekly, or biweekly basis. As such, subsequent analyses will capture additional patients entering the COVID-19 PHD over time.

9. Data Analysis Plan

All analyses will be conducted in a federated manner using tools previously validated and tested in numerous studies conducted by the OHDSI community. Specifically, the CohortMethod package (https://github.com/OHDSI/CohortMethod) will be used to conduct analyses. For each comparator and outcome combination, the following three analyses will be performed:

- Analysis 1: Large-scale propensity score matching, 1:1 matched using an unconditional Cox proportional hazards model
- Analysis 2: Large-scale propensity score stratification, containing 5 propensity score quintiles using a conditional Cox proportional hazards model.
- Analysis 3: Crude-unadjusted using Cox proportional hazards model

For each study comparison group, a propensity score model will be fit through large-scale regularized logistic regression fitted with Laplace prior (LASSO) with the optimal hyperparameter determined through 10-fold cross validation in which the outcome will be a binary indicator for the potential comparator (e.g., variable = 1 if patient is in the treatment group, variable = 0 if patient is in the comparator group). Matching covariates will include baseline covariates derived from the data previously described in §7.6. All covariates occurring in fewer than 0.1% of patients within the target and comparator cohorts prior to propensity score model fitting will be excluded for computational efficiency.

9.1. Calculation of Time-at-Risk

Time-at-risk is defined based on the intention-to-treat principle starting 1 day after admission to 30 days after admission. Analyses will be limited to patients with a minimum time-at-risk of 1 day.

9.2. Patient Characteristics Summary

A summary of pre-match patient characteristics, including median age in 5-year age categories and select comorbidities at or within 30 days prior to hospital admission are available in Annex IV.

9.3. Model Specification

Subjects in both study comparison groups will be removed from the study population. Furthermore, the following model specifications will be used for the analyses described in §9:

- Analysis 1: Propensity score adjustments will be made through propensity score matching. Patients will be matched at a 1:1 ratio using the nearest neighbor technique, without replacement, enforcing a caliper of 0.20. The outcome will be modeled using an unconditioned cox proportional hazards model will be fit.
- Analysis 2: Propensity score adjustments will be made through propensity score stratification dividing the propensity score into 5 strata (i.e., quintiles). The outcome will be modeled using a conditional cox proportional hazards model will be fit.
- Analysis 3: No propensity score adjustments will be made.

9.4. Evidence Evaluation

For each population-level effect estimate generated by the study (i.e., each target-comparator-outcome-analysis combination) we will report diagnostics to assess potential bias and threats to its valid interpretation.

9.4.1. Propensity score distribution

The extent of overlap in the distribution of propensity scores and preference (scaled propensity) scores between study comparison groups will be examined to provide information regarding the pre-match comparability of study groups. If the proportion of patients in clinical equipoise (i.e., patients with a preference score between 0.3 and 0.7) is less than 50%, then the estimate will be flagged for careful interpretation given potential differences between the post-match sample and the target population.

9.4.2. Covariate balance before and after propensity score matching

Covariate balance will be evaluated by plotting the standardized mean difference (SMD) of each covariate before against the SMD after propensity score matching. A balanced match will be defined as an absolute value of the standardized mean difference <0.10.

9.4.3. Empirical null distribution and systematic error model

As described in §7.6, the distribution of estimates on negative control outcomes (i.e., the empirical null distribution) describes the residual error of a study specification after confounding control has been implemented. Calibration effect plots for the negative controls will be used to visualize the empirical null distribution for assessment.

Results from study diagnostics indicate the interpretation of findings may suffer from major issues even after statistical adjustments. First, as evidenced by a poor overlap in propensity scores, there will be poor comparability between almost all study comparison groups before adjustment. Second, residual bias will be present as evidenced by the presence of covariates with absolute standardized mean differences >0.10 post-propensity score matching/stratification. Overall, these findings suggest statistical methods are unable to account for potential systematic biases. As such, study results are prone to substantial bias and any causal inferences drawn from study results are subject to a high degree of uncertainty.

10. Strengths and Limitations of the Research Methods

Strengths:

- This hospital database study will be larger than prior observational studies examining the risk of death and intensive services among hospitalized COVID-19 patients associated with famotidine exposure.
- Inpatient death will be captured; most healthcare claims databases do not reliably capture death.

Limitations:

- Selection bias might arise as the consequence of study exclusion criteria. Attrition tables will be provided to report on the impact of such exclusion criteria.
- Confounding may occur if there are differences in (observed or unmeasured) baseline characteristics between study comparison groups associated with outcome. Methods outlined in §9 offer approaches to identify and adjust for confounding but were insufficient given covariate balance was not achieved between comparison groups. Nevertheless, we note similar bias is likely to be present in prior published literature. Furthermore, based on initial diagnostics, the direction of bias in the outcomes may differ between study comparison groups as evidenced by post-match summary measures of patient clinical characteristics.
- Residual cofounding may occur due to lack of data on hospitalized patients; while the Premier database captures inpatient data including diagnoses drug administration and procedures during hospitalization, it may not capture data from periods before or after hospitalization.
- The study results will not necessarily be generalizable to all hospitals in the United States. Generalizability may be further compromised based on availability of device information and use of propensity score matching techniques and cardinality matching techniques in sensitivity analysis. The study design implicitly focuses on maximizing internal validity and thus may compromise the generalizability of the findings.
- Other unmeasurable variables, such as COVID disease severity or provider skill level, may lead to residual confounding after adjusted analyses.

11. Protection of Human Subjects

The New England Institutional Review Board (IRB) has determined that studies conducted in the Premier Healthcare Database are exempt from study-specific IRB review, as these studies do not qualify as human subjects research**.**

12. Safety Data Collection and Reporting

This study uses coded data that already exist in an electronic database. In this type of database, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available, and adverse events are not reportable as individual case safety reports [EMA GVP 2017]. The study results will be assessed for medically important results**.**

13. Plans for Disseminating/Communicating Study Results

Dissemination activities will be of a scientific nature (articles in scientific journals, presentations at conferences, etc.). Study results will be made available as soon as possible in order to support treatment decisions in the global COVID-19 pandemic.

14. List of Tables and Figures

Summary statistics will be provided in an automated process by Epi Analytics.

15. Annex (list of stand-alone documents)

Document Number	Date	Title
1		Annex I – Concept Set Expressions
2		Annex II – Mapped Concepts
3		Annex III – Negative Control Outcomes
4		Annex IV – Patient Characteristics

16. References

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