Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalised patients: a case series

Tobias Janowitz,1,2 Eva Gablenz,1,3 David Pattinson,4 Timothy C Wang,5 Joseph Conigliaro,6,7 Kevin Tracey,7 David Tuveson 1

ABSTRACT
Objective Treatment options for non-hospitalised patients with coronavirus disease 2019 (COVID-19) to reduce morbidity, mortality and spread of the disease are an urgent global need. The over-the-counter histamine-2 receptor antagonist famotidine is a putative therapy for COVID-19. We quantitatively assessed longitudinal changes in patient reported outcome measures in non-hospitalised patients with COVID-19 who self-administered high-dose famotidine orally.

Design Patients were enrolled consecutively after signing written informed consent. Data on demographics, COVID-19 diagnosis, famotidine use, drug-related side effects, temperature measurements, oxygen saturations and symptom scores were obtained using questionnaires and telephone interviews. Based on a National Institute of Health (NIH)-endorsed Protocol to research Patient Experience of COVID-19, we collected longitudinal severity scores of five symptoms (cough, shortness of breath, fatigue, headaches and anosmia) and general unwellness on a four-point ordinal scale modelled on performance status scoring. All data are reported at the patient level. Longitudinal combined normalised symptom scores were statistically compared.

Results Ten consecutive patients with COVID-19 who self-administered high-dose oral famotidine were identified. The most frequently used famotidine regimen was 80 mg three times daily (n=6) for a median of 11 days (range: 5–21 days). Famotidine was well tolerated. All patients reported marked improvements of disease related symptoms after starting famotidine. The combined symptom score improved significantly within 24 hours of starting famotidine and peripheral oxygen saturation (n=2) and device recorded activity (n=1) increased.

Conclusions The results of this case series suggest that high-dose oral famotidine is well tolerated and associated with improved patient-reported outcomes in non-hospitalised patients with COVID-19.

INTRODUCTION
Management of patients with coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses a major challenge to the biomedial community, governments and global population. Currently, most research focuses on vaccine development or pharmacological treatment strategies for hospitalised patients with COVID-19.1 However, to reduce global morbidity and mortality, effective treatment strategies for non-hospitalised patients are required.

Famotidine may be a candidate medication for this. Famotidine is a histamine-2 receptor antagonist, widely available over the counter at low cost, does not interact with other medications and has been safely used for suppression of gastric acid production over a wide range of oral doses from 20 mg once daily to 160 mg four times daily.2 In computer simulations, famotidine was identified as a potential inhibitor of the 3-chymotrypsin-like protease,3 and this and other potential mechanisms of action for famotidine in COVID-19 are an area of current research. In a propensity score matched retrospective cohort study a significantly reduced risk for death or intubation (adjusted HR 0.43, 1
95% CI 0.21 to 0.88) was identified for patients with COVID-19 who were incidentally taking famotidine before or at the point of hospital admission.

The incentive for the retrospective cohort study were the unexpected positive results from a group of 10 patients who took famotidine following onset of symptoms for COVID-19. Here, we summarise this series of 10 patients with COVID-19 who self-medicated with famotidine as outpatients. The patient-reported demographics, clinical course, drug tolerability and longitudinal symptom scores are provided.

METHODS
Consecutive patients were enrolled in this study after signing written informed consent for study participation and for deidentified data being reported in a published case series. No participant was excluded. Data were collected by two telephone interviews and two written questionnaires. Information on patient demographics, comorbidities, COVID-19 test results, famotidine use, drug-related side effects, temperature measurements, oxygen saturations and symptom scores were obtained. We collected longitudinal severity scores on five symptoms (cough, shortness of breath, fatigue, headaches and anosmia), based on an NIH endorsed Protocol to research Patient Experience of COVID-19 illness: age, sex, ethnicity and body mass index.

RESULTS
Patient characteristics
Ten individuals with the clinical diagnosis of COVID-19 who self-medicated with high dose oral famotidine were identified. Eight patients were from New York State, one from New Jersey and one from Sweden. The characteristics of all study participants are summarised in table 1. The study participants were diverse with regard to known risk factors for severity of COVID-19 illness: age, sex, ethnicity and body mass index.

Table 1 Patient characteristics

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<td>Metoprolol, ASA and rosvastatin.</td>
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<td>Nasal swab PCR</td>
<td>AB test*</td>
<td>Nasal swab PCR</td>
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<td>03/21</td>
<td>04/03</td>
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<td>Y</td>
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<td>AEs</td>
<td>Racing heartbeat and dizziness</td>
<td>Dizziness, dry skin and insomnia</td>
<td>(GI symptoms and forgetfulness)</td>
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In order to comply with journal guidelines for anonymisation ages are provided as age ranges.

†Pt 4: test by Mount Sinai Health Systems, USA, titre: 2880; pt 10: test by Mount Sinai Health Systems, USA, titre: 2880.

In addition to those symptoms scored in the questionnaire; dates displayed as monthly.

AB, antibody; AE, adverse events, in parenthesis if only possibly related to famotidine; BMI, body mass index; f, female; Fam., famotidine; HCT, hydrochlorothiazide; HTN, hypertension; M, male; N, no; Y, yes.
(BMI). Seven patients had positive PCR-based diagnoses from nasal swabs for SARS-CoV-2, two patients had positive serological tests for antibodies directed against the virus and one patient had a clinical diagnosis without molecular confirmation (table 1). All started taking famotidine while feeling unwell with COVID-19. The most commonly used dose was 80 mg oral famotidine three times daily (n=6), and the dose ranged from 20 mg three times daily to 80 mg three times daily. Median duration of famotidine self-administration was 11 days (range 5–21 days). The time period between onset of symptoms and starting treatment differed widely between patients, ranging from 2 days to 26 days (figure 1).

Patient-reported toxicity

Seven patients did not experience any adverse events. One patient reported grade 1 dizziness and very occasional perceptions of a racing heartbeat. Another patient experienced grade 1 dizziness, dry skin and insomnia. A third patient reported grade 1 gastroenterological symptoms and temporary forgetfulness (table 1). Other than forgetfulness, all of these side effects are listed in the prescription information for famotidine, and all side effects resolved on discontinuation of famotidine.

Patient-reported outcomes and symptoms

No hospitalisations were reported by any of the participants, and at the point of submission of this manuscript, patients reported feeling fully recovered apart from persistent anosmia in two cases. All patients were asymptomatic prior to developing COVID-19. They all were affected by a wide range of symptoms when they were feeling worst, and this was comparable with how they felt on the day prior to starting famotidine. On starting famotidine, all patients reported improvement of symptoms within 24–48 hours (case synopses and figure 2). When we analysed the changes of the normalised total symptom score across all patients, we found no significant difference for the day before starting famotidine compared with the day of starting famotidine, but a significant improvement in the symptom score was reported within 24 hours of starting famotidine and symptoms continued to improve and nearly normalised to preillness levels at 14 days after first famotidine use (figure 3). The improvement of symptoms was across all categories, but airway-related symptoms such as cough and shortness of breath were reported to improve more rapidly than systemic symptoms such as fatigue (figure 2).

Individual case summaries

Patient 1 is a white woman in her 40s with a medical history of epilepsy for which she takes levetiracetam 1 g daily. She took famotidine 80 mg three times daily for 11 days starting 4 days after first experiencing symptoms of COVID-19. She reported feeling very unwell at this time point. Within 1 day of the first dose of famotidine, she noticed marked improvement of her shortness of breath. This improvement was matched by an increase in her home-monitored pulse oximetry measured oxygen saturation levels from 91%–95% to 97%–98% (figure 4A). She was febrile with a temperature of 37.8°C prior to starting famotidine and afebrile on day 7 of taking famotidine.

Patient 2 is a Hispanic man in his 40s without pre-existing conditions. He took famotidine 80 mg three times daily for 11 days starting 8 days after first experiencing symptoms of COVID-19. He reported improvement of symptoms within 2 days of treatment. He was febrile with a temperature of 38.3°C prior to starting famotidine and afebrile on day 5 of taking famotidine.

Patient 3 is an Asian man in his 30s without pre-existing conditions. He took famotidine 80 mg three times daily for 7 days starting 9 days after first experiencing symptoms of COVID-19. He experienced severe shortness of breath prior to starting famotidine, and his dyspnoea and other symptoms improved by day 7. His home monitored oxygen saturation levels improved from 89% on day 2 of treatment to 96% on day 5 of treatment (figure 4A). He was febrile with a temperature of 38.9°C prior to starting famotidine and afebrile on day 5 of taking famotidine. He intermittently took paracetamol for fever during illness.

Patient 4 is a black woman in her 60s with a BMI of 38, positive smoking history and hypertension controlled by triple therapy. She took famotidine 50 mg three times daily for 12 days starting 10 days after first experiencing symptoms of COVID-19. She noticed improvement in muscle aches and chest tightness in addition to those recorded in figure 2.

Patient 5 is a white man in his 50s with hypertension and hyperlipidaemia, both treated with medications, and positive smoking history. He took famotidine 80 mg three times daily for 8 days starting 6 days after first experiencing symptoms of COVID-19. He described ongoing increase of fatigue for another 7 days after starting famotidine; the only patient to describe worsening of any symptoms during this treatment period. However, he noticed improvement in respiratory symptoms within 2 days of starting famotidine.

Patient 6 is a Hispanic woman in her 20s with no pre-existing conditions. She took famotidine 80 mg three times daily starting 9 days after first experiencing symptoms of COVID-19. She felt markedly better within 2 days of treatment but had mild dizziness and accelerated heart beats intermittently while taking famotidine.

Patient 7 is a black and Hispanic woman in her 20s with a BMI of 41 with no pre-existing conditions. She took famotidine 80 mg three times daily for 12 days starting 6 days after first experiencing symptoms of COVID-19. Within 1 week of treatment, she reported relief of most symptoms. She reported
Figure 2  Patient level symptom scores. The longitudinal data for all reported symptoms are shown for individual patients. The mean is indicated as a dashed black line. The baseline scores are indicated adjacent to the y-axis. All patients reported baseline symptoms at 1. Colour-coded lines and dots for respective symptoms are ordered alphabetically and are slightly offset to avoid overlap. Day 0 indicates the day at which patients took the first dose of famotidine. Severity score: 1=not affected, 2=little affected, 3=affected, 4=severely affected. B, baseline; Pt, patient.

grade 1 dizziness, insomnia and dry skin concurrent with taking famotidine.

Patient 8 is a white man in his 70s with history of myocardial infarction, surgery for a benign pancreatic tumour, chronic pancreatitis and chronic back pain. His diagnosis is based on clinical symptoms and signs and being from a high prevalence location, with all family members being clinically affected by COVID-19. He took Famotidine 60 mg two times daily for 5 days starting 26 days after first experiencing symptoms of COVID-19. He reported a rapid improvement and being asymptomatic within 3 days of treatment. He routinely monitors his activity using an Oura Ring device and was able to provide readings on walking equivalence, calorie usage and activity score for the weeks before and after starting famotidine, which all showed marked improvements (figure 4B–D).

Patient 9 is a South Asian ex-smoker man in his 50s with history of hyperlipidaemia controlled by rosuvastatin. He took famotidine 60 mg two times daily for 21 days starting 2 days after first experiencing symptoms of COVID-19. He described improvement in his symptoms within 2 days of starting famotidine. He reported possible famotidine associated mild forgetfulness and gastroenterological symptoms that started while he was on famotidine but resolved before he stopped the medication.
Patient 10 is a white former smoker man in his 60s with a BMI of 37.5 without known pre-existing conditions. He took famotidine 20 mg three times daily for 5 days starting 7 days after first experiencing symptoms of COVID-19. He reported a universal improvement in symptoms within the first week of taking famotidine.

**DISCUSSION**

This case series provides patient-reported outcome measures for 10 consecutively enrolled non-hospitalised patients with COVID-19. They all noticed improvements in their condition in correlation with famotidine use at doses ranging from 60 mg to 240 mg daily. Based on published pharmacokinetic data for famotidine, we estimate that these treatment regimens would have resulted in peak plasma concentrations of approximately 0.5–2 µM and average plasma concentrations of approximately 0.15–0.7 µM famotidine, assuming normal kidney function. In concordance with the clinical evidence and consensus that famotidine is safe across a wide range of doses and frequencies, famotidine was very well tolerated by all patients. Given that famotidine has only minimal inhibitory effect on the hepatic cytochrome p450 system and low risk of clinically significant alterations in oxidative drug metabolism, it may be a safe drug for testing in a trial or clinical setting where patients self-administer the medication.

A pertinent aspect of this work is the exploration and application of graded symptom scores and patient-reported outcome measures in tracking COVID-19 in the non-hospitalised setting using a four-point ordinal scale. Using these symptom scores, we were able to determine that all patients noticed a rapid improvement in symptoms within the first week of taking famotidine.
improvement in their condition within 24–48 hours of starting famotidine. Our quantitative approach to follow symptom severity may be a useful tool, in particular for outpatient studies, but requires validation. In addition, for all patients who were able to provide data, temperature readings, oxygen saturations and activity improved in correlation with taking famotidine. These findings suggest that famotidine may affect the course of COVID-19 but must be considered in the context of several limitations. Placebo effect, enrolment bias and recall bias for symptoms may affect our findings as is the case for the outcome measures of any non-blinded, non-controlled study, despite us attempting to minimise bias by asking non-leading questions. An improvement of symptoms was noticed within 48 hours by all individuals in this study, despite the symtomatic period prior to taking famotidine varying widely. There remains the possibility, however, that these changes may reflect treatment independent convalescence, as the natural course of COVID-19 in patients who do not require hospital admission is not well characterised.

Our case series suggests, but does not establish, a benefit from famotidine treatment in outpatients with COVID-19. Future work will investigate potential mechanisms of action and clinical relevance of famotidine. Mechanistically, famotidine could have a viral target, for example, one of the viral proteases, or a host target, resulting, for example, in modulation of the immunological response to the virus. Clinically, we unreservedly share the opinion that well designed and informative studies of efficacy are required to evaluate candidate medications for COVID-19 as for other diseases. A randomised phase III trial testing the efficacy of high dose intravenous famotidine three times daily in addition to hydroxychloroquine in hospitalised patients with COVID-19 has recently commenced (NCT04370262). An outpatient study of oral famotidine that investigates efficacy for COVID-19 has recently commenced (NCT04389567). There remains the possibility, however, that these changes may reflect treatment independent convalescence, as the natural course of COVID-19 in patients who do not require hospital admission is not well characterised.

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CONCLUSIONS

The results presented in this case series suggest that high-dose oral famotidine is well tolerated and associated with improved self-reported outcomes in non-hospitalised patients with COVID-19.

Author affiliations

1Cancer Center, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA
2Northwell Health Cancer Institute, New Hyde Park, New York, USA
3Medical Faculty, Ruprecht-Karls-University Heidelberg, Heidelberg, Germany
4Department of Zoology, University of Cambridge, Cambridge, United Kingdom
5Columbia University Medical Center, New York City, New York, USA
6Division of General Internal Medicine, Department of Medicine, Manhasset, New York, USA
7The Feinstein Institutes for Medical Research, Northwell Health, Manhasset, New York, USA

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Ethics approval The Cold Spring Harbor Laboratory institutional review board approved this registered study (IRB 1605914–1; NCT04389567).

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. The anonymised data from this case series are included and available on request.

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ORCID iDs Tobias Janowitz http://orcid.org/0000-0002-7820-3727 David Tuveson http://orcid.org/0000-0002-8017-2712

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