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BRIEF REPORT

Prevalence of Medical Contraindications to Nirmatrelvir/Ritonavir in a Cohort of Hospitalized and Nonhospitalized Patients With COVID-19

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This analysis describes the prevalence of contraindications to nirmatrelvir/ritonavir among 66 007 patients with coronavirus disease 2019 in a large health care system. A possible contradiction was present in 9830 patients (14.8%), with the prevalence of contraindications increasing with higher acuity of illness.

Keywords. nirmatrelvir/ritonavir; COVID-19; contraindications; Palovid.

The authorization of 2 novel oral antiviral therapies for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the US Food and Drug Administration (FDA) in December 2021, nirmaltrelvir/ritonavir and molnupiravir [1, 2], has resulted in broader availability of effective coronavirus disease 2019 (COVID-19) early treatments in high-income countries and has spurred new initiatives for improved access, such as the Test to Treat program [3]. Other therapeutics such as monoclonal antibodies and intravenous remdesivir are available but require skilled health care personnel resources to administer. Of these 2 oral antivirals, nirmaltrelvir/ritonavir reduced the risk of hospitalization by 89%, as compared with 30% with molnupiravir [4, 5], and is the preferred therapy for mild to moderate COVID-19 in nonhospitalized high-risk adults [6].

Received 19 May 2022; editorial decision 28 July 2022; accepted 01 August 2022; published online 3 August 2022

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https://doi.org/10.1093/ofid/ofac389

However, nirmaltrelvir/ritonavir is not suitable for all patients, including many who are at high risk for severe illness. Ritonavir strongly inhibits cytochrome P450 (CYP) 3A4 metabolism, which results in boosted nirmaltrelvir levels but also a multitude of drug–drug interactions. Coadministration of ritonavir with medications highly dependent on CYP3A metabolism may result in significantly elevated concentrations of those drugs, resulting in potentially serious or life-threatening reactions [7]. Conversely, coadministration with drugs that induce CYP3A can reduce nirmatrelvir concentrations and may impact treatment efficacy [6]. Many drug–drug interactions may be safely managed by discontinuing or dose-reducing the concomitant drug, but the FDA has listed others as contraindicated for coadministration due to the potential risk of serious adverse events [4]. The target population for nirmatrelvir/ritonavir includes patients with chronic medical conditions, many of whom may be taking medications that cannot be safely discontinued or dose-reduced [8]. In addition, nirmatrelvir/ritonavir is not recommended for use in patients with severe renal and hepatic impairment, another group at high risk for severe COVID-19 [4].

As nirmatrelvir/ritonavir becomes more widely available and state and local jurisdictions look to expand access for patients, it will be important to understand the prevalence of patients with contraindications who will require alternative therapies, such as monoclonal antibodies. In addition, many of the proposed strategies to ensure more reliable and equitable access to treatment, such as expansion of telehealth services, use of pharmacy-based clinics, and inclusion of treatment at community testing sites [9], may result in patients being treated by providers who do not have access to their medical record or current medications, resulting in an increased risk of drug–drug interactions.

In this analysis, we evaluated patients presenting with a diagnosis of COVID-19 to a large integrated health system in Minnesota. The primary aim was to examine the prevalence of contraindications to nirmatrelvir/ritonavir. This cohort included both hospitalized and nonhospitalized patients, including those admitted to the intensive care unit (ICU) and those who died within 28 days of hospital admission.

METHODS

We conducted a retrospective review of all patients evaluated for a diagnosis of COVID-19 in an integrated health system consisting of 11 hospitals and 55 clinics, between March 4, 2020, and March 22, 2022. This health system provides care for ~20% of the population of Minnesota. Approval was obtained from the institutional review board at the University

Table 1. Patient Characteristics and Prevalence of Possible Contraindications to Nirmatrelvir/Ritonavir

	Highest Acuity of Illness				
	Outpatient (n = 59 869), No. (%)	Inpatient (n = 3818), No. (%)	ICU (n = 1339), No. (%)	Mortality (n = 981), No. (%)	*P* Value
Use of medications dependent on CYP3A for clearance	2298 (3.8)	309 (8.1)	108 (8.1)	117 (11.9)	<.001
Use of medications that induce CYP3A	256 (0.4)	28 (0.7)	12 (0.8)	12 (1.2)	<.001
Severe renal impairment[a]	1268 (2.1)	419 (10.9)	174 (13.0)	231 (23.5)	<.001
Severe hepatic impairment[a]	284 (0.4)	93 (2.4)	61 (4.6)	42 (4.3)	<.001
Age <12 y	4671 (7.8)	49 (1.3)	21 (1.6)	0 (0.0)	<.001
Weight <40 kg and age <18 y	3702 (6.2)	41 (1.3)	17 (1.2)	0 (0.0)	<.001
Individual patients with 1+ contraindication[b]	8403 (14.0)	787 (20.6)	306 (22.9)	334 (35.1)	<.001

Abbreviations: FDA, Food and Drug Administration; ICU, intensive care unit.

[a]The FDA does not recommend use of Paxlovid in patients with severe renal and hepatic impairment due to a lack of pharmacokinetic or safety data.

[b]Patients with multiple contraindications were counted once.

of Minnesota for retrospective analysis of COVID-19 data within the health system. Patients were included if they had a positive SARS-CoV-2 polymerase chain reaction (PCR) test and at least 1 in-system encounter within a year of a positive test. The primary exposure of interest was the highest acuity of illness within 30 days of a positive test (outpatient, inpatient, ICU, or death).

We extracted the following characteristics from the electronic health record at the time of assessment (for nonhospitalized) or time of admission (hospitalized): age, sex, medical comorbidities based on International Classification of Diseases, 10th Revision, codes and patient problem lists, drug prescriptions, and laboratory data reflecting kidney function (glomerular filtration rate [GFR], as estimated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaborative (CKD-EPI) equation [10]) and hepatic function (international normalized ratio [INR], total bilirubin). We included the most recent lab value within the 6 months before a positive SARS-CoV-2 PCR. Missing labs and diagnoses were assumed to be normal. Contraindications to nirmaltrelvir/ritonavir per the US FDA and the criteria used to approximate them included drugs listed by the FDA as being contraindicated for coadministration with nirmatrelvir/ritonavir, severe renal or hepatic impairment, age <12 years or weight <40 kg in patients age <18 years (Supplementary Table 1).

We conducted the analysis in Stata 7 (StataCorp 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). The analysis was primarily descriptive, with comparisons across all levels of care performed using chi-square tests. When determining the prevalence of patients with at least 1 contraindication present, patients with multiple contraindications were counted once.

Patient Consent

Approval was obtained from the institutional review board at the University of Minnesota for retrospective analysis of COVID-19 data within the health system. Patient consent was not applicable, as this study did not contain factors necessitating patient consent.

RESULTS

Of 66 007 patients with COVID-19, 59 869 (90.7%) were managed in the outpatient setting, 3818 (5.8%) required admission, 1339 (2%) required ICU care, and 981 (1.5%) died (Table 1). A total of 2832 (4.3%) were on concomitant medications dependent on CYP3A for clearance, with the highest prevalence (11.9%) seen in those who died within 30 days. Three hundred eight (0.5%) were on medications that induce CYP3A. Severe renal impairment (eGFR <30 mL/min) was present in 2092 (3.2%), and severe hepatic impairment was present in 480 (0.7%). Moderate renal impairment (eGFR ≥30 to <60 mL/min), which would necessitate a dose reduction of nirmatrelvir/ritonavir but is not considered a contraindication to use, was present in 6347 (9.6%) patients, including 4514 (7.5%) outpatients. The prevalence of patients with at least 1 contraindication increased with higher acuity of illness, from 14% in those managed as outpatients to 20.6% in those hospitalized, 22.9% in those in the ICU, and 35.1% in those who died (Table 1). As some patients may have presented for care when already acutely ill and ineligible for nirmatrelvir/ritonavir regardless of the presence of contraindications, a second analysis was performed excluding patients who presented to an acute care setting (defined as an emergency department or higher level of care) within 3 days of a positive SARS-CoV-2 test result (Table 2). This resulted in the exclusion of 9818 patients. Of the remainder, a similarly high prevalence of contraindications was seen, from 24% of those hospitalized to 29% of those who died.

DISCUSSION

Of 66 007 patients evaluated for COVID-19, a possible contraindication to nirmatrelvir/ritonavir was present in a significant number of individuals. Our data suggest that even after the

Table 2. Patient Characteristics and Prevalence of Possible Contraindications to Nirmatrelvir/Ritonavir, Excluding Patients who Presented to an Acute Care Setting (Defined as an Emergency Department or Higher Level of Care) Within 3 Days of a Positive SARS-CoV-2 Test Result

	Highest Acuity of Illness				
	Outpatient (n = 54 200), No. (%)	Inpatient (n = 1025), No. (%)	ICU (n = 436), No. (%)	Mortality (n = 528), No. (%)	*P* Value
Use of medications dependent on CYP3A for clearance	2069 (3.8)	109 (10.6)	32 (7.3)	60 (11.4)	<.001
Use of medications that induce CYP3A	237 (0.4)	10 (1.0)	5 (1.1)	8 (1.5)	<.001
Severe renal impairment[a]	1101 (2.0)	123 (12.0)	44 (10.1)	95 (18.0)	<.001
Severe hepatic impairment[a]	151 (0.3)	25 (2.4)	18 (4.1)	13 (2.5)	<.001
Age <12 y	4251 (7.8)	13 (1.3)	6 (1.4)	0 (0.0)	<.001
Weight <40 kg and age <18 y	3326 (6.1)	10 (1.0)	6 (1.4)	0 (0.0)	<.001
Individual patients with 1+ contraindication[b]	7595 (14.0)	246 (24.0)	85 (19.5)	153 (29.0)	<.001

Abbreviations: FDA, Food and Drug Administration; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]The FDA does not recommend use of Paxlovid in patients with severe renal and hepatic impairment due to a lack of pharmacokinetic or safety data.

[b]Patients with multiple contraindications were counted once.

exclusion of patients who were likely too ill for treatment at the time of presentation, as many as 1 in 4 patients who were eventually hospitalized or who ultimately died may have had a contraindication to nirmatrelvir/ritonavir, highlighting the need for effective and accessible second-line therapies. A 3-day course of intravenous remdesivir has been shown to result in an 87% lower risk of COVID-19-related hospitalization and death and may be safely used in those with medical contraindications to nirmatrelvir/ritonavir [11]; however, the logistical barriers to its intravenous administration in the outpatient setting mean that it is not a viable alternative for the majority of patients. The only currently authorized monoclonal antibody for treatment of acute infection, bebtelovimab, lacks efficacy data from placebo-controlled clinical trials in high-risk patients but may be an acceptable alternative for those who cannot take nirmaltrelvir/ritonavir [12]. However, the emergence of new variants of SARS-CoV-2 with the ability to evade neutralization by specific monoclonal antibodies has demonstrated the need for therapies with a higher barrier to resistance [13]. Molnupiravir may be an alternative option in selected patients and has the advantage of oral administration but has lower efficacy at reducing the risk of hospitalization or death (30% compared with placebo) [5]. Finally, for pediatric patients who are at increased risk for severe illness, the only currently authorized therapy is remdesivir [14], which may not be accessible or feasible, as previously stated. Additional treatment options are urgently needed for this age group, such as expansion of the current Emergency Use Authorization for bebtelovimab and authorization of novel treatments.

A significant number of outpatients were found to have either moderate renal impairment that would require dose adjustment of nirmatrelvir/ritonavir (7.5%) or use of a medication contraindicated for coadministration with nirmatrelvir/ritonavir (4.3%). In addition, there are many other medications with potentially clinically relevant interactions for which additional management strategies may be necessary, such as temporarily withholding the concomitant medication, providing an alternative, or increasing clinical monitoring [6]. This highlights the need for collaboration with pharmacists during the prescribing process, both to ensure detection of relevant drug interactions and to optimize their management when safe to do so, allowing high-risk patients to benefit from effective COVID-19 therapy.

For patients with possible contraindications to nirmatrelvir/ritonavir, providers will need to be mindful of potential safety concerns with expanded access programs if patients are seen outside their usual health network. Many pharmacy-based clinics are participating in the federal Test to Treat program and offering on-site assessment for patients with symptoms and positive results on direct SARS-CoV-2 testing to determine eligibility for antiviral therapy. These on-site providers may not have access to medical records to assess for contraindications to use of nirmaltrelvir/ritonavir. Similar concerns exist with the use of telehealth platforms to reduce barriers to access, particularly given the lack of a comprehensive physical examination. Many of these issues can be addressed through technological innovations such as linkage to electronic health records and, to a certain extent, are no different from usual concerns regarding continuity of care and the accuracy and completeness of medical evaluation when caring for an unfamiliar patient. Those responsible for surge planning in state and local jurisdictions should take these considerations into account when developing plans for expanding access to therapeutics.

This analysis has several limitations. Patients may not have been eligible for treatment with nirmatrelvir/ritonavir regardless of other contraindications, either due to a lack of underlying risk factors, clinical presentation beyond 5 days from symptom onset, or presence of other limitations such as need for hospitalization for severe or critical COVID-19. We did not assess for the presence of other medications that, while not strictly contraindicated for coadministration with nirmatrelvir/ritonavir, still require dose modification or cessation

that may not be feasible in all cases. The strengths of this analysis include a large data set collected from a health system with multiple clinics and hospitals with broad geographic distribution spanning much of the state of Minnesota. The patient cohort also includes both hospitalized and nonhospitalized patients, allowing for generalizability to a wide population. While nirmatrelvir/ritonavir is not used in hospitalized patients, the purpose of including the full spectrum of COVID-19 illness is to be aware that those who are most likely to progress to become severely ill are more likely to have a possible contraindication.

CONCLUSIONS

Our results show that contraindications to nirmatrelvir/ritonavir are present in a significant proportion of patients presenting with acute COVID-19, with increasing prevalence in those requiring higher levels of care. These findings support the need for adequate clinical review of potential contraindications and ensuring the availability of alternative treatment options for those with contraindications, including coordinating and streamlining access to reduce obstacles to treatment for higher-risk patients.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Financial support. None.

Potential conflicts of interest. D.R.B. has conducted clinical trials of outpatient COVID-19 therapies. Otherwise, the authors declare no conflicts of interest related to this work. The authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Data availability. Data are not publicly available.

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