Nirmatrelvir-ritonavir for nonhospitalized patients with COVID-19

Case-based approach to assessment and treatment

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As of May 2023 there have been more than 50,000 deaths related to COVID-19 in Canada.[1] Fortunately, with the uptake of vaccination, morbidity and mortality have decreased, and more than 85% of Canadians aged 30 or older have completed their primary vaccination series.[2] Although the Omicron variant appears to cause less severe disease than the Delta variant,[3,4] some individuals (eg, those who are immunocompromised, are unvaccinated, are 65 years of age or older, or have multiple comorbidities)[5] continue to have an increased risk of progression to severe COVID-19 and may benefit from antiviral treatment.[6] This article provides guidance on the role of nirmatrelvir-ritonavir in treating nonhospitalized patients with COVID-19.

Case description 1

Leon is a 71-year-old White man who has been a patient in your practice for more than 20 years. Leon's past medical history includes hypertension, diabetes, and rheumatoid arthritis. He does not smoke and lives at home with his wife.

Today, Leon called your office for advice as he has been feeling unwell for the past few days and tested positive for COVID-19 this morning at home.

Evidence supporting nirmatrelvir-ritonavir use

Guidelines suggest that nonhospitalized adults at high risk of progression to severe COVID-19 should receive antiviral therapy.[7-9] Nirmatrelvir-ritonavir was approved by Health Canada in January 2022 and is preferred logistically over intravenous remdesivir and other COVID-19 therapies due to its oral administration.[10,11]

Initial evidence for nirmatrelvir-ritonavir came from the EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) randomized controlled trial (RCT), which was completed in 2022.[12,13] This trial enrolled more than 2000 COVID-19–positive patients within 5 days of symptom onset who were at high risk of progression to severe COVID-19. Patients were unvaccinated and previously COVID-19 naive. The trial showed that a combination of 300 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days reduced the composite outcome of hospitalization for COVID-19 or death from any cause. The relative risk was decreased approximately 88% compared with placebo, with a number needed to treat of 18 (95% CI 14 to 25) after 28 days of follow-up (event rate=0.77% nirmatrelvir-ritonavir vs 6.31% placebo). This trial was conducted before the emergence of the COVID-19 Omicron variant.

Observational trials have since been conducted to evaluate the effectiveness of nirmatrelvir-ritonavir in real-world settings and in patient populations excluded in the EPIC-HR trial. For example, in a retrospective population-based cohort study in Ontario, individuals treated with nirmatrelvir-ritonavir had a relative reduction of 44% in the composite outcome of hospitalization for COVID-19 or all-cause death (weighted analysis odds ratio=0.56; event rate=2.1% vs 3.7%; number needed to treat=62 after 30 days of follow-up).[6] The Omicron variant predominated during the time period of this study, and more than 93% of individuals had received 1 or more COVID-19 vaccine doses. While the relative benefit of nirmatrelvir-ritonavir in this study was smaller than that in EPIC-HR, these studies and others internationally have confirmed the real-world effectiveness of nirmatrelvir-ritonavir when given to patients at high risk.[5,14-21]

Determining risk of progression to severe COVID-19

Validated tools to calculate an individual's risk of progression to severe disease do not exist. However, a risk model[22] was created based on hospitalization rates during the Omicron wave in British Columbia, with other useful tools also listed in **Box 1**.[22-30] The risk model reflects observational data in a specific population during a specific time frame when long-term generalizability is uncertain.

When nirmatrelvir-ritonavir is initiated, assessment of baseline renal and liver function is required. Individuals with reduced function may require dose reduction or a different COVID-19 therapy.[22,23]

Back to Leon

Leon informs you his symptoms started 3 days ago and that he has a cough, headache, body aches, and a runny nose. He denies shortness of breath, fever, chest pain or pressure, or decreased food or fluid intake. This is his first time testing positive for COVID-19.

You review Leon's electronic medical record. He received his primary COVID-19 vaccine series and recommended boosters, and his most recent blood work showed no renal or hepatic dysfunction. Leon's most recent COVID-19 vaccine was administered 8 months ago.

Box 1. Nirmatrelvir-ritonavir prescribing tools

Risk calculator
- British Columbia COVID Therapeutics Committee clinical practice guide[22]

Drug interaction management resources
- British Columbia COVID Therapeutics Committee practice tool[23]
- Ontario COVID-19 Science Advisory Table and University of Waterloo School of Pharmacy science brief[24]
- University of Liverpool COVID-19 drug interactions website or mobile app[25]
- Infectious Diseases Society of America resource for clinicians[26]
- National Institutes of Health COVID-19 treatment guidelines on drug-drug interactions[27]

Patient education handouts
- medSask nirmatrelvir-ritonavir patient handout[28]
- British Columbia Centre for Disease Control COVID-19 treatment patient information about nirmatrelvir-ritonavir[29]
- Ontario Health information sheet about nirmatrelvir-ritonavir[30]

Leon's symptoms began within the 5-day window for initiating therapy and he is at increased risk of being hospitalized for COVID-19 owing to his age (ie, 71 years), medications (he is taking methotrexate, which is an immunosuppressant), and medical conditions (he has diabetes and hypertension). Using a risk model,[22] you inform Leon that his risk of COVID-19 hospitalization with his current infection could be more than 10% and that he meets the criteria for a nirmatrelvir-ritonavir prescription in your province.

Drug interaction management of nirmatrelvir-ritonavir

Nirmatrelvir is coadministered with ritonavir, a pharmacokinetic booster. Ritonavir is a strong cytochrome P450 3A4 inhibitor and a P-glycoprotein inhibitor, which inhibits the metabolism of nirmatrelvir and thus extends nirmatrelvir's duration of action.[31] Given these properties, initiating nirmatrelvir-ritonavir in a patient with multiple medications requires a thoughtful approach to drug interaction management. Observational data suggest that approximately 2 out of 3 individuals who are 70 years or older will require management of a drug interaction when prescribed nirmatrelvir-ritonavir.[6] Useful COVID-19 drug interaction tools can be found in **Box 1**.[22-30]

Patient education and setting expectations for nirmatrelvir-ritonavir

Nirmatrelvir-ritonavir is a federally acquired medication and is currently free for Canadians who meet criteria set by provinces and territories. It is accessed through community pharmacies or through COVID-19 specialty clinics in some jurisdictions.

Nirmatrelvir-ritonavir is typically well tolerated. In the EPIC-HR RCT, adverse event rates were similar between nirmatrelvir-ritonavir (22.6%) and placebo (23.9%).[12] Discontinuation due to adverse events (2.1% vs 4.2%) and rates of serious adverse events (1.6% vs 6.6%) were less common with nirmatrelvir-ritonavir than with placebo, respectively.[12] Individuals treated with nirmatrelvir-ritonavir had higher rates of dysgeusia (5.6% compared with 0.3% placebo) and diarrhea (3.1% vs 1.6%).[12] Observational data have provided similar safety results.[15]

Anecdotally, dysgeusia rates with nirmatrelvir-ritonavir have been reported more commonly in practice than in clinical trials. It is not able to be masked and typically resolves a few days after stopping nirmatrelvir-ritonavir.[32] Many patient education tools are available that discuss the mechanism of action, administration, side effects, and drug interaction management of nirmatrelvir-ritonavir (**Box 1**).[22-30]

Back to Leon

Owing to his risk factors (immunosuppression, age, and comorbidities), Leon meets the criteria for nirmatrelvir-ritonavir in your province. You discuss the benefit of lowering his risk of being hospitalized for COVID-19 as well as the chance of side effects, such as changes in taste perception, if nirmatrelvir-ritonavir is started. Leon is agreeable to starting therapy.

You compare Leon's other medications against his electronic medical record: he takes 5 mg of ramipril orally daily, 2.5 mg of amlodipine orally daily, 1000 mg of metformin orally twice per day, 10 mg of atorvastatin daily, 25 mg of methotrexate orally once weekly, 1 mg of folic acid daily on non–methotrexate days, and 200 mg to 400 mg of ibuprofen orally every 8 hours as needed. Leon does not take any other over-the-counter medications or herbal medicines.

Table 1 describes the results of your drug interaction query for Leon. You ask Leon to stop taking atorvastatin while on nirmatrelvir-ritonavir and for 2 days afterward (total 7 days). Upon further questioning, you find Leon's blood pressure is usually around 150/105 mm Hg at home. With Leon's input, you decide to continue amlodipine at the current dose with increased monitoring. Leon agrees to measure his blood pressure daily and to call your office if symptoms of low blood pressure occur. You provide supportive care suggestions and remind Leon to hold his metformin and limit ibuprofen use if his oral intake diminishes (as per SADMANS [sulfonylureas, other secretagogues; angiotensin-converting enzyme inhibitors; diuretics, direct renin inhibitors; metformin; angiotensin receptor blockers; nonsteroidal anti-inflammatory drugs; sodium-glucose cotransporter-2 inhibitors] criteria).[33]

You fax a prescription for a combination of 300 mg nirmatrelvir and 100 mg ritonavir twice daily for

Table 1. Drug interaction check for Leon

INTERACTION*	DESCRIPTION	MANAGEMENT
Nirmatrelvir-ritonavir plus atorvastatin	Increased atorvastatin levels	Hold atorvastatin and restart 2 or 3 days after finishing nirmatrelvir-ritonavir therapy
Nirmatrelvir-ritonavir plus amlodipine	Increased amlodipine levels	Monitor for symptoms of hypotension, or decrease amlodipine dose by 50%, or dose amlodipine every other day. Restart original amlodipine dose 2 to 3 days after finishing nirmatrelvir-ritonavir therapy

*There are no clinically important drug interactions between nirmatrelvir-ritonavir and ramipril, metformin, methotrexate, folic acid, or ibuprofen.

5 days to a dispensing community pharmacy. You also communicate the drug interactions management plan to the pharmacy.

Case description 2

Three days later, Leon's wife, Marion, who is also under your care, calls your office and reports symptoms similar to Leon's as well as a positive COVID-19 test. Marion is a 63-year-old White woman. She also does not smoke. Upon reviewing Marion's electronic medical record, you see she received her primary COVID-19 vaccine series and recommended boosters, with the most recent dose 8 months ago. Her medication list includes a daily multivitamin and a 2-mg estradiol vaginal ring that she uses for genitourinary symptoms of menopause.

Individuals at low risk of progression to severe COVID-19

Guidelines suggest that nonhospitalized adults at low risk of progressing to severe disease should not be provided with COVID-19 antiviral therapy.[7-9]

In the EPIC-SR (Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients) RCT of COVID-19–positive patients at standard risk, nirmatrelvir-ritonavir did not provide significant benefit over placebo (event rate=0.87% nirmatrelvir-ritonavir vs 1.76% placebo for COVID-19 hospitalization or death).[34,35] As a result, the trial was stopped early.[34,35] Similarly, observational data from a 2022 study did not find benefit of nirmatrelvir-ritonavir in COVID-19–positive adults aged 40 to 64 years at low risk of progression to severe COVID-19 (15.2 cases per 100,000 person-days among treated patients vs 15.8 cases per 100,000 person-days among untreated patients).[5]

Back to Marion

You call Marion back and confirm her past medical history, medications, and vaccination status. A risk model[22] suggests the risk of COVID-19 hospitalization from her current infection is around 1% to 2%. The best available data show that patients at low risk, such as Marion, are unlikely to benefit from nirmatrelvir-ritonavir. You advise Marion that she is at lower risk than Leon and does not meet the threshold for needing nirmatrelvir-ritonavir in your province, so you provide her with reassurance and suggest supportive care for her symptoms.

Conclusion

Nirmatrelvir-ritonavir is the preferred agent for the treatment of nonhospitalized adults at high risk of progression to severe disease with COVID-19. Prescribing includes assessing an individual's baseline risk and duration of symptoms, managing potential drug interactions, and providing patient education.

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