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COMMENTARY

Using nirmatrelvir/ritonavir in patients with epilepsy: An update from the Israeli chapter of the International League Against Epilepsy

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Abstract

Presented herein are recommendations for use of nirmatrelvir/ritonavir in patients with epilepsy, as issued by the Steering Committee of the Israeli chapter of the International League Against Epilepsy. The recommendations suggest that patients on moderate-to-strong enzyme-inducing antiseizure medications (ASMs) and everolimus should not be treated with nirmatrelvir/ritonavir; rectal diazepam may be used as an alternative to buccal midazolam; doses of ASMs that are cytochrome P450 (CYP3A4) substrates might be adjusted; and patients treated with combinations of nirmatrelvir/ritonavir and ASMs that are CYP3A4 substrates or lamotrigine should be monitored for drug efficacy and adverse drug reactions.

KEYWORDS

antiepileptic drugs, antiseizure medications, COVID-19, CYP3A4, drug–drug interactions

On December 26, 2022, 4 days after its emergency use authorization by the US Food and Drug Administration,[1] nirmatrelvir/ritonavir (Paxlovid) was approved by the Israeli Ministry of Health (MOH) for treatment

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of nonhospitalized patients with mild-to-moderate COVID-19 who are at high risk for severe disease.[2] Nirmatrelvir and ritonavir are cytochrome P450 (CYP3A4) substrates. The active component, nirmatrelvir, is an inhibitor and an inducer of CYP3A activity in vitro.[3] Ritonavir is a potent CYP3A4 inhibitor (hence added to boost nirmatrelvir effect), a weak-to-moderate inhibitor of several other CYP isoenzymes, and an inducer of uridine diphospho-glucuronosyltransferases.[1] Ritonavir inhibition of CYP3A4 is to a large extent mechanism-based (and nonreversible), implying that a major part of the enzymatic activity can be restored only through de novo protein synthesis over several days.[4] Even 100–200 mg of ritonavir can produce maximal or near-maximal CYP3A4 inhibition of both gastrointestinal and hepatic CYP3A4.[5]

Unlike protocols for human immunodeficiency virus treatment, the duration of nirmatrelvir/ritonavir's treatment in COVID-19 patients is limited to 5 days. In the absence of specific clinical outcome data for patients with epilepsy receiving antiseizure medication (ASM)–nirmatrelvir/ritonavir combinations, the Steering Committee of the Israeli chapter of the International League Against Epilepsy has been asked by an ad hoc MOH Task Force to provide recommendations for nirmatrelvir/ritonavir use in patients treated with ASMs. Here, we describe the recommendations that have been issued in Israel. Further information is available in Table S1.

- Nirmatrelvir/ritonavir has not been specifically assessed in epilepsy patient populations. In a study of 2246 COVID-19 patients who received nirmatrelvir/ritonavir, seizures were not reported among the most common adverse events (affecting at least 1% of patients).[6] Nonetheless, caution is required in patients treated with ASMs due to potential drug–drug interactions.
- In patients with epilepsy, chronic ASM treatment should not be withdrawn for the purpose of nirmatrelvir/ritonavir administration.
- Nirmatrelvir/ritonavir may not be effective in patients treated with carbamazepine, phenytoin, phenobarbital, or primidone (strong CYP3A4 inducers). Nirmatrelvir/ritonavir should not be prescribed to patients who are treated or have been treated with those ASMs in the 2 weeks prior to nirmatrelvir/ritonavir administration.[7] Alternative treatment may include anti-SARS-CoV-2 medications with lower drug–drug interaction potential (e.g., molnupiravir).[2]
- Patients treated with buccal midazolam (Buccolam; a CYP3A4 substrate) and their caretakers should be instructed to avoid the use of buccal midazolam during the nirmatrelvir/ritonavir treatment period and 72 h after its termination.[4,8] Rectal diazepam (less CYP3A4-dependent) may be used if emergency medical treatment is needed to terminate a prolonged seizure or if professional medical care service arrival is delayed. In the case of a prolonged seizure or seizure cluster, an emergency medical care service should be called and the medical team should be informed about nirmatrelvir/ritonavir treatment. Intravenous midazolam may be administered only in medical settings that allow close monitoring of vital signs and emergency respiratory support. Reduced midazolam and diazepam intravenous doses may be considered.
- Nirmatrelvir/ritonavir–everolimus combinations should be avoided due to concerns of excessive immunosuppression and other adverse everolimus effects.[9]
- Dose reduction may be considered for CYP3A4 substrates such as clobazam during the nirmatrelvir/ritonavir treatment period and 24 h after termination of nirmatrelvir/ritonavir treatment if signs of ASM toxicity are observed. Patients should be monitored for adverse effects of these drugs (Table S1).
- The changes in perampanel plasma concentrations as a result of CYP3A4 inhibition are expected to be mild to modest and develop over time.[10] Perampanel dosage adjustment is unlikely to be necessary. However, caution is required when nirmatrelvir/ritonavir is given to patients treated with perampanel, particularly toward the end of nirmatrelvir/ritonavir treatment (Table S1).
- Nirmatrelvir/ritonavir treatment might be associated with reduced lamotrigine plasma concentrations,[11] particularly toward the end of the antiviral treatment and during the week after its termination. Patients should be monitored for seizure control and lamotrigine adverse reactions during nirmatrelvir/ritonavir treatment and up to 2 weeks after its termination.
- No specific recommendations have been issued for nirmatrelvir/ritonavir comedication with weak-to-moderate CYP3A4 inducers (e.g., oxcarbazepine, eslicarbazepine, cenobamate). This is because nirmatrelvir's concentrations in plasma are 5–6 times higher than its antiviral in vitro EC_{90}, whereas weak-to-moderate CYP3A4 inducers reduce the exposure to sensitive CYP3A4 substrates by up to 80% (Table S1). However, in patients treated with these ASMs, nirmatrelvir/ritonavir may be less effective.

The treating neurologist should be informed about the administration of nirmatrelvir/ritonavir to their epilepsy patients. Finally, the current situation stresses the need for careful consideration of drug interaction potential when selecting ASMs for patients with epilepsy.

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CONFLICT OF INTEREST

S.E. has received speaker honoraria from Megapharm (Israel). None of the other authors has any conflict of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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