Treating Epilepsy Patients with Investigational Anti-COVID-19 Drugs: Recommendations by the Israeli Chapter of the ILAE

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ABSTRACT The coronavirus disease-2019 (COVID-19) and its management in patients with epilepsy can be complex. Prescribers should consider potential effects of investigational anti-COVID-19 drugs on seizures, immunomodulation by anti-seizure medications (ASMs), changes in ASM pharmacokinetics, and the potential for drug-drug interactions (DDIs). The goal of the Board of the Israeli League Against Epilepsy (the Israeli Chapter of the International League Against Epilepsy, ILAE) was to outline the main principles of the pharmacological treatment of COVID-19 in patients with epilepsy. This guide was based on current literature, drug labels, and drug interaction resources. We summarized the available data related to the potential implications of anti-COVID-19 co-medication in patients treated with ASMs. Our recommendations refer to drug selection, dosing, and patient monitoring. Given the limited availability of data, some recommendations are based on general pharmacokinetic or pharmacodynamic principles and might apply to additional future drug combinations as novel treatments emerge. They do not replace evidence-based guidelines, should those become available. Awareness to drug characteristics that increase the risk of interactions can help adjust anti-COVID-19 and ASM treatment for patients with epilepsy.

IMAJ 2020; 22: 665–672

KEY WORDS: anti-COVID-19 medications, anti-epileptic drugs, clinically-relevant drug-drug interactions, cytochrome P450, pharmacokinetics

The coronavirus disease-2019 (COVID-19) pandemic is an unprecedented situation in which many people across the globe are being treated, within a relatively short period, with medications whose efficacy against the medical condition is unknown. Currently used medications include repurposed drugs such as dexamethasone, antiretroviral protease inhibitors, and tocilizumab, as well as experimental agents (e.g., remdesivir) [1-3].

In people with epilepsy (or those who experience COVID-19-related acute symptomatic seizures), both COVID-19 infection and its management might be complex due to potential effects of anti-COVID-19 drugs on seizure control, immunomodulation by anti-seizure medications (ASMs), effects of infection and inflammation on drug pharmacokinetics, and drug-drug interactions (DDIs). DDIs with antiretroviral drugs have been described in an evidence-based guideline of the International League Against Epilepsy (ILAE) and American Academy of Neurology (AAN) [4]. The American Epilepsy Society (AES) [5] and the ILAE [6] provide resources for epilepsy clinicians who treat patients with COVID-19, and a recent review has described drug considerations in managing COVID-19 patients with epilepsy [7]. However no guidelines are yet available for the pharmacological treatment of such patients.

The board of the Israeli League Against Epilepsy (the Israeli Chapter of ILAE) prepared a guide document that summarizes key principles for investigational COVID-19 drug treatment in epilepsy patients with a focus on potential DDI and drug-disease interactions. The goal of this document is to inform physicians of potential considerations related to combinations of drugs for the treatment of epilepsy and COVID-19 based on currently available knowledge.

PATIENTS AND METHODS

We gained information on drug pharmacokinetics, adverse drug reactions, and immunomodulation from their U.S. Food and Drug Administration (FDA)-approved labels and PubMed searches for all COVID-19 drugs-ASM combinations and for combinations of the term "COVID-19" or "immune" with "epilepsy", "antiepileptic drug", or "antiseizure medication".

The ASM list included drugs whose potential DDIs were previously analyzed by us [8] (retigabine and tiagabine were not included in the current anaylsis), as well as brivaracetam, cannabidiol, cenobamate, clobazam, diazepam, everolimus, midazolam, and propofol. The anti-COVID-19 drug list was based on the U.S. National Institutes of Health (NIH) treatment recommendations [2] and included lopinavir/ritonavir, chloroquine or hydroxychloroquine, azithromycin, remdesevir, direct-acting oral anticoagulants (apixaban, bretixaban, dabigatran, rivaroxaban), corticostroids (dexamethasone, prednisone, methylprednisolone), tocilizumab, anakinra, sarilumab, siltuximab, interferons alfa and beta, baricitinib, ruxoltinib, tofacitinib, zanubrutinib, ibrutinib, and acalabrutinib.

An ad hoc committee consisting of all members of the ILAE Israeli Chapter board (three pediatric epileptologists, three adult epileptologists, and a pharmacist) reviewed the data and discussed them to create an initial version (in Hebrew) of the recommendations. The initial version was approved by all committee members on 29 March 2020 and distributed to professional organizations in Israel. The current version also refers to aspects other than DDIs and includes medications that were introcuded for the treatment of COVID-19 after the distribution of the initial document (anticoagulants and dexamethasone).

RESULTS

POTENTIAL EFFECTS OF INVESTIGATIONAL ANTI-COVID-19 DRUGS ON SEIZURES

The majority of current anti-COVID-19 treatments have not been directly implicated in seizure exacerbation. Exceptions are chloroquine and hydroxychloroquine, which might increase the risk of seizures, although reports are rare and anecdotal [5]. The liquid formulation of lopinavir/ritonavir (Kaletra) contains 42.4% ethanol and 15.3% propylene glycol, with the latter rarely inducing breakthrough seizures [5]. Corticosteroids and the adrenocorticotrophic hormone (ACTH) are used for the treatment of infantile spasms [9], but rare withdrawal seizures have been described after discontinuation of steroid therapy [10]. Anakinra and tocilizumab are emerging as potential therapies for immune-inflammatory-mediated epileptic encephalopathies [11,12].

IMMUNOMODULATION BY ASMS

Immunomodulation is involved in the therapeutic effects of cannabidiol, everolimus, and corticosteroids [13], and ASMs can exert immunomodulating activities other than induction of hypersensitivity reactions. However, the data are conflicting and mostly relate to older-generation ASMs. ASMs, including valproic acid, carbamazepine, phenytoin, and vigabatrin, modulate the serum levels of cytokines (e.g., IL-1α, IL-1β, and IL-6) [13]. Phenytoin has been shown to alter the levels of immunoglobulins. The findings related to carbamazepine's effects on immunoglobulin levels are inconsistent. ASMs can additionally affect the number of T and B lymphocytes and their function [13]. Case reports have associated treatment with sirolimus or everolimus with pneumonitis [14,15]. It is currently unknown whether these effects translate into potential modulation by ASMs of COVID-19 disease course and treatment outcomes.

ASM-INDUCED CHANGES IN PLASMA CONCENTRATIONS OF ESSENTIAL COMPOUNDS

Patients with epilepsy who are being treated with ASMs, especially EIASMs, often have low concentrations of 25-hydroxyvitamin D [25(OH)D]). Low 25(OH)D levels have been linked to susceptibility and severity of COVID-19 infection [5], although this relationship has yet to be established.

POTENTIAL COVID-19-INDUCED CHANGES IN THE PHARMACOKINETICS OF ASMS

COVID-19 can affect multiple organs, including those involved in drug absorption and elimination [16,17]. Particularly, impaired hepatic and renal function in critically ill patients may require ASM dosing adjustment [7]. Extracorporeal membrane oxygenation (ECMO) can increase drug volume of distribution and extend their elimination half-life. Alternatively, drugs may be sequestered in the ECMO circuit, resulting in reduction in their plasma concentrations (e.g., benzodiazepines, phenytoin, propofol, and phenobarbital) [18]. In addition, increased cytokine concentrations characterizing infection or inflammation can downregulate drug-metabolizing enzymes that play key roles in ASM elimination, including cytochrome P450 (CYP) isozymes 3A4, 2C9, and several uridine diphospho-glucuronosyltransferases (UGTs) [19]. Effective treatment of the disease is expected to reverse these changes. The magnitude of the drug-disease interaction may depend on the severity of the disease. Results from studies of drug pharmacokinetics in COVID-19 patients to guide drug dosing are not yet available, but potential changes in ASM levels should be considered even in milder symptomatic COVID-19 cases.

PHARMACOKINETIC DDIS BETWEEN ANTI-COVID-19 AND ASMS

Many ASMs are substrates of drug-metabolizing enzymes and their pharmacokinetics can be affected by anti-COVID-19 medications. In addition, some ASMs induce or inhibit the activity of drug-metabolizing enzymes (CYPs and UGTs) and drug transporters (including P-glycoprotein; P-gp), thus potentially affecting anti-COVID-19 treatment. Phenobarbital, primidone, phenytoin, and carbamazepine are strong enzyme-inducing ASMs (EIASMs). Oxcarbazepine, eslicarbazepine acetate, cenobamate, and rufinamide are weak-to-moderate EIASMs. Cannabidiol, cenobamate, clobazam, everolimus, eslicarbazepine acetate, felbamate, oxcarbazepine, perampanel, valproic acid, rufinamide, topiramate, and stiripentol can inhibit the activity of drug-metabolizing enzymes [Table 1].

Table 1. Routes of ASM elimination and specific recommendations for their combinations with anti-COVID-19 medications

	Percent of dose eliminated by renal excretion (percent unchanged)	Enzymes involved in metabolism (including secondary metabolism)	Induces	Inhibits	Recommendations*
Brivaracetam	95 (< 10)	Amidase, CYP2C19, CYP2C9	–	EH	–
Cannabidiol	33 (4)	CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4; 7-COOH-CBD is a substrate for P-gp	CYP1A2, CYP2B6	CYP2C8, CYP1A2, CYP2B6, CYP2C19, CYP2C9, UGT1A9, UGT2B7; 7-COOH-CBD inhibits BCRP and BSEP	–
Carbamazepine**	72 (3)	CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2E1, CYP3A4, EH	CYP1A2, CYP2C, CYP3A4, EH, UGTs, P-gp	–	Lopinavir/ritonavir should be administered twice daily (instead of once daily) [23] Combinations with DOACs should be used with great caution and surveillance, and increases in the DOAC dose may be considered [33] Alternatively, patients may be treated with low molecular weight heparin or unfractionated heparin.
Cenobamate	88 (6)	UGT2B7, UGT2B4, CYP2E1, CYP2A6, CYP2B6, CYP2C19 CYP3A4/5	CYP2B6, CYP2C8, CYP3A4	CYP2B6, CYP2C19, CYP3A	–
Clobazam	82 (2)	CYP3A4, CYP2C19	CYP3A4 (weak inducer)	CYP2D6	–
Clonazepam	50–70 (1)	CYP3A4	–	–	–
Diazepam	71 (minor)	CYP2C19, CYP3A4	–	–	–
Eslicarbazepine acetate	92 (67)	UGT1A4, UGT1A9, UGT2B4, UGT2B7, UGT2B17*	CYP3A4	CYP2C19	–
Ethosuximide	Major route (20)	CYP2B/C, CYP3A4, CYP2E1	–	–	–
Everolimus	5 (0)	CYP3A4	–	CYP3A4 (weak inhibitor)	Lopinavir/ritonavir–everolimus combinations should preferably be avoided [24] If combined, everolimus dose should be modified according to its label Everolimus concentrations should be measured 2 weeks after initiation or discontinuation of lopinavir/ritonavir [24]
Felbamate	90 (50)	CYP3A4, CYP2E1,	CYP3A4	CYP2C19	–
Gabapentin	100 (100)	–	–	–	–
Lacosamide	95 (40)	CYP3A4, CYP2C9, CYP2C19	–	–	–
Lamotrigine	94 (10)	UGT1A1, UGT1A4, UGT2B7	UGTs (weak inducer)	OCT2	When combined with lopinavir/ritonavir, therapeutic monitoring of lamotrigine is required [21,36] Patients on lopinavir/ritonavir should follow the same dosing titration/maintenance regimen used with ASMs that induce glucuronidation and increase clearance [36]
Levetiracetam	(66)	Type-B esterases	–	–	–
Midazolam	Primary route (1)	CYP3A4	–	–	–

	Percent of dose eliminated by renal excretion (percent unchanged)	Enzymes involved in metabolism (including secondary metabolism)	Induces	Inhibits	Recommendations*
Oxcarbazepine	95 (1)	Arylketone reductase, unidentified UGTs	CYP3A4	CYP2C19	–
Perampanel	22 (2)	CYP3A4, CYP1A2, CYP2B6	CYP2B6, CYP3A4, UGT1A1, UGT1A4 (weak inducer)	CYP2C8, CYP3A4, UGT1A9, UGT2B7	–
Phenobarbital/ primidone**	57 (27)***	CYP2C9, CYP2C19, CYP2E1	CYP1A2, CYP2A6, CYP2B, CYP2C, CYP3A4, UGTs, EH	–	Lopinavir/ritonavir should be administered twice daily (instead of once daily) [21] Plasma concentrations of phenobarbital should be measured frequently if used in combination with dexamethasone or prednisone. Also, the dose of corticosteroids may have to be increased [29] Combinations with DOACs should be used with great caution and surveillance, and increases in the DOAC dose may be considered [33] Alternatively, patients may be treated with low molecular weight heparin or unfractionated heparin
Phenytoin**	Major route (4)	CYP2C9, CYP2C19	CYP1A2, CYP2B, CYP2C, CYP3A4, EH, UGTs	–	Patients receiving phenytoin may require a lopinavir/ritonavir dosage increase of ~50%, while phenytoin levels should be monitored Increased phenytoin dose may be required [4] When phenytoin is used with azithromycin, careful monitoring of patients treated with phenytoin–azithromycin combinations and monitoring of free and total phenytoin levels are advised [34] Combinations with DOACs should be used with great caution and surveillance, and increases in the DOAC dose may be considered [33] Alternatively, patients may be treated with low molecular weight heparin or unfractionated heparin
Pregabalin	(90)	–	–	–	–
Propofol	88 (0.3)	UGTs, CYP2B6, CYP2C9	–	–	–
Rufinamide	85 (2)	Carboxylesterases	CYP3A4 (weak inducer)	CYP2E1 (weak inhibitor)	–
Stiripentol	16–20 (0.04)	CYP1A2, CYP2B6, and CYP3A4	CYP1A2, CYP2B6, CYP3A4	CYP2D6, CYP2C19, CYP3A4	Hydroxychloroquine should be avoided in patients treated with stiripentol [20]
Topiramate	Complete (52)	Inducible CYP isoforms	CYP3A4, beta-oxidation (weak inducer)	CYP2C19 (weak inhibitor)	–
Valproic acid	55 (2)	CYP2A6, CYP2B6, CYP2C9, CYP2C19, UGT1A3, UGT2B7 mitochondrial oxidases	–	CYP2C9, UGTs, EH	–
Vigabatrin	95 (76)	–	–	–	–
Zonisamide	62 (35)	CYP3A4	–	–	–

*Additional information on potential pharmacokinetic interactions between ASMs and anti-COVID-19 medications is provided in the text
**Strong EIAED
***The data represent phenobarbital
BCRP = breast cancer resistance protein, BSEP = bile salt export pump, CYP = cytochrome P450, EH = epoxide hydrolase, OCT = organic cation transporter, P-gp = P-glycoprotein, UGT = uridine diphospho-glucuronosyltransferase
References [36-38] and drug labels

DDIs involving lopinavir/ritonavir

Lopinavir is a CYP3A4 substrate and inhibitor. Ritonavir, a CYP3A4 and P-gp inhibitor, is added to lopinavir as a pharmacokinetic enhancer. Lopinavir and ritonavir are also inducers of several CYP isozymes and of UGTs.

Strong EIASM might reduce the plasma concentrations of lopinavir and its effectiveness [Table 1] [4,7]. Other CYP3A4-inducing ASMs may also reduce lopinavir's concentrations. Valproic acid [4] and stiripentol [20] (CYP inhibitors) may increase the plasma concentrations of lopinavir/ritonavir.

Lopinavir/ritonavir can reduce the mean steady-state plasma exposure (area under the conentration-time curve [AUC]) of phenytoin by 31% [21]. Lopinavir/ritonavir decreases lamotrigine plasma concentrations by approximately 50% [4]. Lopinavir/ritonavir can also increase the plasma concentrations of everolimus and its immunosuppressive effects [22] as well as the plasma concentrations of other ASMs [Table 1]. Ritonavir has been shown to reduce midazolam clearance by 66% [23] and therefore can substantially increase the plasma concentrations of midazolam and lead to excessive sedation [24]. Reports on the effects of lopinavir/ritonavir on valproic acid concentrations are inconsistent [4].

DDIs involving chloroquine or hydroxychloroquine

Chloroquine and hydroxychloroquine are substrates of CYP2C8, CYP3A4, and CYP2D6 [25]. Strong EIASMs, and to a lesser extent weak-to-moderate EIASMs, may reduce the plasma concentrations of chloroquine and hydroxychloroquine. Stiripentol can increase the systemic concentrations of chloroquine and enhance its side effects, particularly cardiac arrhythmias [26].

DDIs involving azithromycin

Azithromycin does not remarkably inhibit CYP enzymes and is not implicated in clinically significant pharmacokinetic interactions with ASM [27]. However, when phenytoin is used with azithromycin, careful monitoring of free and total phenytoin levels are advised [27].

DDIs involving remdesivir

Remdesivir is a substrate of CYP2C8, CYP2D6, and CYP3A4 and an inhibitor of CYP3A4 and several drug transporters. Based on the pharmacokinetic profile and the dosing regimen for treating COVID-19, the manufacturer does not anticipate DDIs. However, reduction of remdesivir's exposure by strong EIASMs, and to lesser extent weak EIASMs, cannot be ruled out [7].

DDIs involving corticosteroids

Dexamethasone is a CYP3A4 substrate and a moderate inducer of CYP 3A4, CYP2B, and CYP2E1 [29]. Phenytoin, phenobarbital, and other CYP3A4 inducers shorten the half-life of dexamethasone and prednisone. Dexamethasone has been reported to both increase and decrease phenytoin levels and alter seizure control [28,29].

DDIs involving other immunomodulators

Tocilizumab [30], interferons [31], and several other immunomodulating proteins given to treat COVID-19 can reduce the plasma concentrations of benzodiazepines (clonazepam, clobazam, diazepam, midazolam) and those of phenytoin due to normalization of their metabolism, which had been altered by the disease itself. These changes may also be induced by the very improvement in the patient's condition. Many tyrosine kinase inhibitors, currently evaluated for their anti-inflammatory potential and inhibition of the so-called cytokine storm, undergo CYP-mediated bioactivation to form chemically reactive products. Induction of their metabolism by EIASMs might therefore lead to toxicity [32].

DDIs involving direct oral anticoagulants (DOACs)

DOACs are substrates of intenstinal CYP3A4, P-gp, or both. EIAEDs are expected to reduce DOAC concentrations, thereby potentially impairing their clinical activity [33].

PHARMACODYNAMIC DDIS BETWEEN ANTI-COVID-19 AND ASMS

Drugs given to treat COVID-19 can exert adverse cardiovascular effects, which may be augmented in patients treated with certain ASMs. Chloroquine and hydroxychloroquine treatment can result in direct myocardial toxicity or exacerbate existing cardiomyopathies, prolong the QT interval, and lead to AV or bundle branch block, torsades the pointes, and ventricular fibrillation [7]. Lopinavir/ritonavir has been associated with PR and QTc prolongation, AV block, bradyarrhythmias and torsades de pointes [7]. Azithromycin can prolong the QT interval and has caused fatalities [34]. Adverse effects of interferon beta include cardiotoxicity and arrhythmias [7]. Accordingly, caution is required when these drugs are combined with ASMs that can affect cardiac conduction, induce arrythmias, or exacerbrate heart failure, including carbamazepine, cenobamate, felbamate, lacosamide, lamotrigine, phenobarbital, primidone, phenytoin, propofol, and rufinamide. Chroloquine and hydroxychloroquine risk of irreversible retinal damage, associated with long-term treatment, may be increased if combined with vigabatrin [35].

DISCUSSION

Based on the presented data, we suggest a set of recommendations be considered when treating patients with epilepsy with anti-COVID-19 medications. Although these recommendations apply to most relevant patients, high pharmacokinetic and pharmacodynamic variability across patients should also be considered, especially in patients treated with additional medications.

RECOMMENDATIONS

- The Board of the Israeli League Against Epilepsy stresses the importance of providing anti-COVID-19 treatments to patients with epilepsy, similar to all other patient populations. Based on current knowledge, epilepsy or its treatment should not be considered a contra-indication for anti-COVID-19 therapies, although they can affect drug choice or dosing.
- Several ASM-anti-COVID-19 drug combinations should be avoided. These include everolimus with ritonavir-containing combinations; stiripentol with chloroquine; and potentially strong EIASM-DOAC combinations [Table 1].
- Dosing recommendations are available for the combinations of lopinavir/ritonavir with strong EIASMs and with lamotrigine [Table 1].
- Moderate-to-severe impairment of hepatic function or renal failure with creatinine clearance lower than 60 ml/min may require adjustment of ASM dosage based on their major routes of elimination [Table 1].
- Close therapeutic monitoring of ASM concentrations in plasma (with dose adjustments if necessary) are recommended during the following phases of disease/treatment: symptomatic COVID-19 infection or recovery from infection, addition of anti-COVID-19 agents which might interact with the existing ASMs, dose changes, or termination of the anti-COVID-19 treatment, connection or disconnection to ECMO, and changing of circuit components.
- When possible, therapeutic monitoring of anti-COVID-19 drugs is recommended for patients treated with enzyme-inducing or enzyme-inhibiting ASMs [Table 1]. There is no evidence for a need for monitoring the concentrations of therapeutic antibodies in patients treated with enzyme-modulating ASMs.
- Interventions to minimize cardiovascular risk should include ECG monitoring with special attention to signs indicative of arrythmia risk (e.g., QTc interval prolongation and T-U wave distortion), correction of electrolyte imbalances (particularly hypokalemia and hypomagnesemia), and avoiding additional medications that can adversely affect the heart. Patients on lacosamide with severe disease should be monitored for bradycardia. When ECG is indicated, it should be obtained before adding a potentially interacting drug, after the drug is titrated to steady-state maintenance dose, and if there is any other indication for monitoring.
- Chloroquine or hydroxychloroquine may be combined with vigabatrin only if the benefit clearly outweigh the risks, due to concern of serious adverse ophthalmic effects such as retinopathy.
- Vitamin D concentrations should be routinely monitored in patients with epilepsy with vitamin D supplementation added if necessary.

Until more established data are available, when choosing ASMs for newly-diagnosed patients, the potential for DDI and drug-disease interactions should be considered. Phenobarbital, phenytoin, carbamazepine, and primidone should be avoided as first ASMs when possible. One should keep in mind that ACTH, oral steroids and everolimus have immunosuppressive activity, and that everolimus can interact with experimental anti-COVID-19 treatments. Currently there is no evidence for increased COVID-19-related morbidity or mortality in patients with epilepsy treated with immunosupressants, and outcomes depend on the medical condition and on the treatment.

In many patients whose seizures are controlled, ASM switches, which might increase the risk of seizures, are not indicated. In addition, enzyme induction by ASMs is not immediately reversible, hence switches would not be helpful in urgent situations. Some patients might benefit from switches, though, as in the case when treatment is replaced to alternate ASMs to minimize toxicity (e.g., cardiac arrhythmias).

Based on current information, the ketogenic diet does not complicate COVID-19 treatment.

TIMING OF PHARMACOKINETIC INTERACTIONS

The effect of enzyme-inducing anti-COVID-19 drugs added to patients already treated with ASMs is slow. It might be observed only several days or longer after onset of the investigational anti-COVID-19 treatment or after a dose change of the enzyme inducer. For patients treated with enzyme-inducing ASM for 4-6 weeks or longer, enzyme induction should be assumed from the onset of the anti-COVID-19 treatment.

Enzyme inhibition is more rapid, with maximal inhibition being expected within 4-5 half lives of the victim drug (the ASM). The same kinetics apply to treatment withdrawal. Protease inhibitors can both induce and inhibit hepatic metabolism and the effect may depend on the specific drug combination and duration of treatment.

STRENGTHS AND LIMITATIONS

Due to the paucity of available data, we did not rate literature based on the level of evidence. Accordingly, the information gathered in this document does not replace evidence-based guidelines, should they become available. Instead, we provide mostly principle-guided recommendations that can also be applied to other investigational treatments as they emerge and possibly to future epidemics which may be treated with different sets of medications. For example, some currently used investigational COVID-19 drugs might no longer be used within weeks or months whereas others, which we did not evaluate, will prove effective in future studies.

CONCLUSIONS

Epilepsy is not a contraindication for anti-COVID-19 treatment, but some combinations of ASMs and anti-COVID-19 drugs

should be avoided. Selection of the first ASM for patients with newly diagnosed epilepsy should consider the ASM potential to be involved in DDIs or otherwise negatively influence patient outcomes. The COVID-19 pandemic provides an example of a medical condition with rapidly changing treatment recommendations and protocols. Accordingly, our recommendations are based upon a relatively limited set of investigational drugs, but hopefully allow some generalizations for additional therapeutic options.

ACKNOWLEDGEMENTS

Sara Eyal is affiliated with the David R. Bloom Centre for Pharmacy and with the Dr. Adolf and Klara Brettler Centre for Research in Molecular Pharmacology and Therapeutics at Hebrew University of Jerusalem, Israel.

We acknowledge the initiative of Prof. Renana Eitan from the Jerusalem Mental Health Center and the Hebrew University–Hadassah Medical School, Jerusalem, Israel, for providing information on DDIs involving ASM for psychiatrists, which established the basis for this work.

DISCLOSURE OF CONFLICTS OF INTEREST

Sara Eyal received honoraria from Megapharm, Israel (2019, 2020).

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References

1. European Medicines Agency. Treatments and vaccines for COVID-19. [Available from https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines-covid-19]. [Accessed 16 July 2020].
2. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. [Available from https://www.covid19treatmentguidelines.nih.gov/]. Updated 25 June 2020. [Accessed 16 July 2020].
3. Segal G, Mevorach D, Elis A, Dicker D. Clinical insights and management recommendations for COVID-19 patients hospitalized in internal medicine departments: recommendations by the corona department heads in Israel. *IMAJ* 2020; 22 (5): 275-7.
4. Birbeck GL, French JA, Perucca E, et al. Antiepileptic drug selection for people with HIV/AIDS: Evidence-based guidelines from the ILAE and AAN. *Epilepsia* 2012; 53: 207-14.
5. Welty T, Gidal B. Managing Patients with Epilepsy during COVID-19 Pharmacotherapy-related Recommendations. American Epilepsy Society. Published 2020. Updated 1 June 2020. [Accessed 14 August 2020].
6. International League Against Epilepsy. COVID-19 information for clinicians. [Available from https://www.ilae.org/patient-care/covid-19-and-epilepsy/for-clinicians]. [Accessed 16 July 2020].
7. Asadi-Pooya AA, Attar A, Moghadami M, Karimzadeh I. Management of COVID-19 in people with epilepsy: drug considerations. *Neurol Sci* 2020; 41 (8): 2005-2011.
8. Ekstein D, Tirosh M, Eyal Y, Eyal S. Drug interactions involving antiepileptic drugs: assessment of the consistency among three drug compendia and FDA-approved labels. *Epilepsy Behav* 2015; 44: 218-24.
9. Mehta V, Ferrie CD, Cross JH, Vadlamani G. Corticosteroids including ACTH for childhood epilepsy other than epileptic spasms. *Cochrane Database Syst Rev* 2015; 2015 (6): CD005222.
10. Mahar S, Malhotra M. Dexamethasone-induced withdrawal seizure. *J Pharmacol Pharmacother* 2015; 6:103.
11. Bialer M, Johannessen SI, Koepp MJ, et al. Progress report on new antiepileptic drugs: A summary of the Fourteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XIV). I. Drugs in preclinical and early clinical development. *Epilepsia* 2018; 59: 1811-41.
12. Specchio N, Pietrafusa N. New-onset refractory status epilepticus and febrile infection-related epilepsy syndrome. *Dev Med Child Neurol* 2020; 62: 897-905.
13. Beghi E, Shorvon S. Antiepileptic drugs and the immune system. *Epilepsia* 2011; 52 (Suppl 3): 40-4.
14. Depuydt P, Nollet J, Benoit D, Praet M, Caes F. Fatal acute pulmonary injury associated with everolimus. *Ann Pharmacother* 2012; 46: e7.
15. Almeida F, Amorim S, Sarmento A, Santos L. Life-threatening everolimus-associated pneumonitis: a case report and a review of the literature. *Transplant Proc* 2018; 50: 933-8.
16. Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. *N Engl J Med.* 2020. Epub ahead of print. PMID: 32329974.
17. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. *N Engl J Med* 2020. Epub ahead of print. PMID: 32412710.
18. Buck ML. Pharmacokinetic changes during extracorporeal membrane oxygenation: implications for drug therapy of neonates. *Clin Pharmacokinet.* 2003; 42: 403-17.
19. Coutant DE, Hall SD. Disease-drug interactions in inflammatory states via effects on CYP-mediated drug clearance. *J Clin Pharmacol* 2018; 58: 849-63.
20. Morrison G. ZOGENIX. Interaction CBD/HydroxyChloroquine / Interactions Stiripentol/Chloroquine [Available from https://www.cing.ac.cy/images/media/redirectfile/NC/Interaction-CBD-Chloroquine-stiripentol-fenfluramine.pdf]. 27 March 2020. [Accessed 8 April 2020].
21. US Food and Drug Administration. Lopinavir and ritonavir (Kaletra). Revised December 2019. [Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021251s052_021906s046lbl.pdf]. [Accessed 25 March 2020].
22. US Food and Drug Administration. Everolimus (Afinitor). Revised February 2020. [Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022334s016lbl.pdf]. [Accessed 25 March 2020].
23. Mathias AA, West S, Hui J, Kearney BP. Dose-response of ritonavir on hepatic CYP3A activity and elvitegravir oral exposure. *Clin Pharmacol Ther* 2009; 85: 64-70.
24. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin Pharmacokinet* 2000; 38: 41-57.
25. Zeitlinger M, Koch BCP, Bruggemann R, et al. Pharmacokinetics/pharmacodynamics of antiviral agents used to treat SARS-CoV-2 and their potential interaction with drugs and other supportive measures: a comprehensive review by the PK/PD of Anti-Infectives Study Group of the European Society of Antimicrobial Agents. *Clin Pharmacokinet* 2020: 1-22.
26. US Food and Drug Administration. Stiripentol (Diacomit). Revised August 2018. [Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206709s000,207223s000lbl.pdf]. [Accessed 17 July 2020].
27. Watkins VS, Polk RE, Stotka JL. Drug interactions of macrolides: emphasis on dirithromycin. *Ann Pharmacother* 1997; 31 (3): 349-56.
28. US Food and Drug Administration. Dexamethasone (Decadron). Revised April 2018. [Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/11664slr062_decadron_lbl.pdf]. [Accessed 15 August 2020].
29. Bénit CP, Vecht CJ. Seizures and cancer: drug interactions of anticonvulsants with chemotherapeutic agents, tyrosine kinase inhibitors and glucocorticoids. *Neurooncol Pract* 2016; 3: 245-60.

30. US Food and Drug Administration. Tocilizumab (Actemra). Revised June 2019. [Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125276s114lbl.pdf]. [Accessed 25 March 2020].
31. Wills RJ. Clinical pharmacokinetics of interferons. *Clin Pharmacokinet* 1990; 19 (5): 390-9.
32. Jackson KD, Durandis R, Vergne MJ. Role of cytochrome P450 enzymes in the metabolic activation of tyrosine kinase inhibitors. *Int J Mol Sci* 2018; 19 (8): 2367.
33. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018; 39: 1330-93.
34. US Food and Drug Adminitration. Azithromycin (Zithromax). Revised April 2019. [Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050710s039,050711s036,050784s023lbl.pdf]. [Accessed 11 April 2020].
35. US Food and Drug Administration. Vigabatrin (Sabril). Revised January 2020. [Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022006s020,020427s018lbl.pdf]. [Accessed 11 April 2020].
36. US Food and Drug Administration. Lamotrigine (Lamictal). Revised July 2018. [Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022251,020764s029,020241s036lbl.pdf]. [Accessed 24 March 2020].
37. Sahinovic MM, Struys MMRF, Absalom AR. Clinical pharmacokinetics and pharmacodynamics of propofol. *Clin Pharmacokin* 2018; 57: 1539-58.
38. Han H, Mann A, Ekstein D, Eyal S. Breaking bad: the structure and function of the blood-brain barrier in epilepsy. *AAPS J* 2017; 19: 973-88.

Nobody can be exactly like me. Sometimes even I have trouble doing it.

Tallulah Bankhead (1902–1968), American actress of the stage and screen known for her husky voice, outrageous personality, and devastating wit

Capsule

Genomewide association study of severe COVID-19 with respiratory failure

There is considerable variation in disease behavior among patients infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Genomewide association analysis may allow for the identification of potential genetic factors involved in the development of COVID-19. A study group conducted a genomewide association study involving 1980 patients with COVID-19 and severe disease (defined as respiratory failure) at seven hospitals in the Italian and Spanish epicenters of the SARS-CoV-2 pandemic in Europe. After quality control and the exclusion of population outliers, 835 patients and 1255 control participants from Italy and 775 patients and 950 control participants from Spain were included in the final analysis. In total, the authors analyzed 8,582,968 single nucleotide polymorphisms and conducted a meta-analysis of the two case-control panels. The authors detected cross-replicating associations with rs11385942 at locus 3p21.31 and with rs657152 at locus 9q34.2, which were significant at the genomewide level with rs657152 at locus 9q34.2, which were significant at the genomewide level in the meta-analysis of the two case–control panels (odds ratio 1.77 and odds ratio, 1.32 respectively). At locus 3p21.31, the association signal spanned the genes SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, and XCR1. The association signal at locus 9q34.2 coincided with the ABO blood group locus. In this cohort, a blood-group-specific analysis showed a higher risk in blood group A than in other blood groups (odds ratio 1.45) and a protective effect in blood group O compared with other blood groups (odds ratio 0.65).

N Engl J Med 2020; 383: 1522

Eitan Israeli

Capsule

Covid 19 damaging the heart

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is largely considered a respiratory virus, but evidence is emerging that it can also affect the heart. In a perspective, **Topol** discussed the indirect and direct effects that the virus can have on the heart. Direct effects range from mild injury to inflammation and shock, which can lead to arrhythmia and possibly cardiac arrest. SARS-CoV-2 also has vascular effects that can indirectly affect heart function, as can systemic inflammation. Heart damage does not seem to correlate with the severity of disease, so more assessment of heart function in people infected with SARS-CoV-2 is needed to understand the frequency and what determines whether someone will develop cardiac pathology.

Science 2020; 370: 408

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