



The Potential Drug Interactions Between Multiple Sclerosis and COVID-19 Therapies

Multipl Skleroz ve COVID-19 Tedavileri Arasındaki Olası İlaç Etkileşimleri

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Dear Editor,

Since December 2019, the coronavirus disease-2019 (COVID-19) has spread rapidly all over the world and has severely affected the elderly population and patients with comorbidities. Drug interactions with agents used in the treatment of multiple sclerosis (MS) such as interferon beta, glatiramer acetate, ocrelizumab, natalizumab, and alemtuzumab are rare. Therefore, interactions between disease-modifying therapies (fingolimod, teriflunomide, dimethyl fumarate, and cladribine) and COVID-19 drugs¹ are outlined in this letter.

It is important to closely monitor all drugs used in COVID-19 treatment in terms of their adverse effects and drug-drug interactions. Favipiravir, remdesivir, lopinavir/ritonavir, colchicine, and tocilizumab are now used in the treatment of COVID-19 and are being studied continuously. Corticosteroids, which have been shown to be effective in COVID-19 depending on the time of use, are also utilized in the treatment of MS relapses, so no interaction is expected with their use.²

In patients with MS with concomitant COVID-19 infection, drug-drug interactions can partially affect the outcomes of treatment. In these patients, if disease-modifying agents and COVID-19 drugs are going to be used together, the neurologist should be aware of the potential adverse effects and drug interactions. It has been known that levels of alanin aminotransferase (ALT)

and aspartate aminotransferase (AST) may increase with the use of teriflunomide (12-14%), fingolimod (15%), and dimethyl fumarate (4%).³ Since increased levels of ALT and AST have also been reported with the use of COVID-19 therapies such as favipiravir (13%), lopinavir/ritonavir (1-11%), remdesivir (3-6%), tocilizumab (<22-36%), and colchicine, liver function tests should be monitored in patients with MS diagnosed with COVID-19 receiving these drugs.³ Cladribine has a low rate of hepatic metabolism (<10%; causes hepatic injury in <1% of patients) and low risk of interaction with other drugs. Therefore, no drug interaction is expected between cladribine and drugs used in the treatment of COVID-19.³ Moreover, colchicine may demonstrate neurotoxic effects. Hence, patients with MS who are to be given colchicine should be monitored for additional weakness and neuropathy. Considering that colchicine is a substrate of cytochrome P450 family 3 subfamily A member 4 (CYP3A4), coadministration of colchicine with lopinavir/ritonavir, which is a potent inhibitor of the CYP3A4 enzyme, is not recommended as it will increase the blood level of colchicine and its adverse effects.⁴ Teriflunomide inhibits CYP2C8 and induces the CYP1A2 enzyme.³ Thus, it should be used carefully with substrates of these enzymes such as remdesivir. Therefore, concurrent use of teriflunomide and remdesivir may increase blood concentration of remdesivir, which can potentially magnify its undesirable effects, which include rash,

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diarrhea, hypotension, nausea, abnormal liver function, and renal impairment. These were seen in 60% of patients under remdesivir treatment.⁵ Fingolimod is mainly metabolized by the CYP4F2 enzyme and is a minor substrate for the CYP2D6, 2E1, and 3A4 enzymes.³ It can be assumed that an interaction between fingolimod and lopinavir/ritonavir is possible since the latter is a potent inhibitor of CYP3A4 and CYP2D6. However, this interaction is not expected to be clinically significant because fingolimod is a minor substrate. Lastly, dimethyl fumarate is metabolized through the tricarboxylic acid cycle and is not involved in the CYP450 enzyme system.³

A majority of drug-drug interactions may be predicted and prevented. Therefore, it is important to be vigilant about potential drug interactions and to adjust clinical practice according to recent scientific evidence.

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