LETTER TO EDITOR
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The potential drug interactions between Multiple Sclerosis and COVID-19 therapies

Multipl Skleroz ve COVID-19 tedavileri arkasındaki olası ilaç etkileşimleri

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İngilizce Kısa Başlık: Interactions between MS and COVID-19 therapies

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Türkçe Kısa Başlık: MS ve COVID-19 tedavileri arasındaki etkileşimler

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Dear Editor,
Coronavirus disease (COVID-19) has spread rapidly all over the world since December 2019, and severly affected elderly population and patients with comorbidities. The treatments used in multiple sclerosis (MS), such as interferon beta, glatiramer acetate, ocrelizumab, natalizumab and alemtuzumab have low risk of drug interactions, therefore this letter outlines interactions between disease modifying treatments (fingolimod, teriflunomide, dimethyl fumarate, cladribine) and COVID-19 treatments [1]. Favipiravir, remdesivir, lopinavir / ritonavir, colchicine and tocilizumab are being studied continuously in the treatment of COVID-19. Corticosteroids, which have been shown to be effective in COVID-19 depending on the time of use, are also used in the treatment of MS relapses and no interaction is expected [2]. It is important to closely monitor all drugs used in COVID-19, in terms of their adverse effects and drug-drug interactions.
Drug-drug interactions may partially affect the treatment of MS and COVID-19. In MS patients with COVID-19 infection, if the disease-modifying agent and COVID-19 drugs are going to be used together, the neurologist should be aware of some adverse effects and drug interactions. It has been known that levels of alanin aminotranspherase (ALT) and aspartate aminotranspherase (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 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 functions tests should be monitored in MS patients diagnosed with COVID-19 [3]. Cladribine has a low rate of hepatic metabolism (<10%) (causes hepatic injury <%1) and low risk of interactions with other drugs, therefore, no drug interaction is expected with drugs used in the treatment of COVID-19 [3]. Additionally, neurotoxic effects may occur with the use of colchicine. MS patients who are planned to use colchicine should be

monitored for additional weakness and neuropathy. Due to colchicine is a substrate of cytochrome P450 family 3 subfamily A member 4 (CYP3A4), co-administration of colchicine with lopinavir/ritonavir, which is a potent inhibitor of CYP3A4 enzyme, is not recommended as it will increase the blood level of colchicine and its adverse effects [4].

Teriflunomide inhibits CYP2C8, induces CYP1A2 enzyme [3], and should be carefully used with substrate of these enzymes as remdesivir. Therefore, concurrent use of teriflunomide may increase blood concentration of remdesivir, which can result in undesirable effects of drugs used in COVID-19 treatment. Adverse effects as rash, diarrhoea, hypotension, nausea, abnormal liver function, and renal impairment were seen in 60% of the patients under remdesivir treatment [5]. Fingolimod is mainly metabolized by CYP4F2 enzyme, and a minor substrate for 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. This interaction is not expected to be clinically significant due to fingolimod is being a minor substrate. 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 on potential drug interactions and to adjust clinical practice according to the recent and scientific evidence.

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