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A case report of safe co-administration of amiodarone with short-term treatment nirmatrelvir-ritonavir, Response to Marzolini et al.

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In their recent article, Marzolini and colleagues recommend against the use of nirmatrelvir/ritonavir in amiodarone-treated patients, due to a risk of toxicity¹. They argue that its very long half-life makes it useless to stop amiodarone to mitigate the drug-drug interaction (DDI).

The report of our experience illustrates that this DDI could be managed safely provided careful monitoring.

A 72-years old patient presented with protracted COVID-19. He suffered from follicular lymphoma treated by rituximab-cyclophosphamide-doxorubicin-vincristine- prednisone, and persistent atrial fibrillation treated by amiodarone and anticoagulated by apixaban since 4 months. COVID-19 had been diagnosed 3 months earlier, and despite treatment with remdesivir, persistent high viral-load shedding and pneumonia were demonstrated, delaying next chemotherapy course.

Considering the risk-benefit balance, we started nirmatrelvir/ritonavir during hospitalization under clinical surveillance and therapeutic drug monitoring (TDM). Apixaban was transiently relayed by nadroparin.

Amiodarone was halted 48h before nirmatrelvir/ritonavir initiation and restarted 96h after completion of the 5-days antiviral course. Clinical tolerance was good and TDM of amiodarone and metabolite showed no accumulation (Table 1). The patient improved gradually and his viral-load was undetectable on day 7 and 14 after treatment initiation.

Amiodarone is known for its potent class III antiarrhythmic activity. Its lipophilic nature results in broadly accumulation in the peripheral adipous and muscular tissues, leading to a large distribution volume and a very long terminal half-life (55 days)^{2,3}. The drug is mainly eliminated by cytochrome P450 3A4 (CYP3A4) into desethylamiodarone, a metabolite with close pharmacodynamic effect to the parent drug⁴.

Knowing that DDI between amiodarone and nirmatrelvir/ritonavir is mainly mediated through irreversible CYP3A4 inhibition by ritonavir, acute toxic accumulation seems highly improbable if amiodarone is discontinued before nirmatrelvir/ritonavir initiation. Moreover, the existence of an active CYP3A4 produced metabolite, namely desethylamiodarone, makes clinical relevance of the short-term DDI further questionable. As a matter of precaution, knowing the relatively slow and variable absorption as well as the extensive enterohepatic recirculation of amiodarone,⁵ we decided to apply a two days wash-out period after the last amiodarone dose before nirmatrelvir/ritonavir start.

Our findings suggest that there might not be an irrevocable contra-indication for the use of nirmatrelvir/ritonavir in amiodarone-treated patients. Our approach deserves a formal DDI study before being accepted as standard. Meanwhile it should be restricted to selected cases, after careful weighing of risks and benefits, and provided that close supervision, notably TDM, is applied.

Table 1: Result of the TDM of amiodarone and its metabolites in a 72-years old patient co-treated with nirmatrelvir/ritonavir.

| | Amiodarone (mg/L) | Desethylamiodarone (mg/L) | Amiodarone+ metabolites (mg/L) |
|-----|-------------------|---------------------------|--------------------------------|
| D-1 | 0,65 | 0,73 | 1,4 |

| | | | |
|----|------|------|-----|
| D0 | 0,84 | 1,55 | 2,4 |
| D1 | 0,78 | 0,99 | 1,8 |
| D6 | 0,61 | 1,05 | 1,7 |

D0 refers to the start of nirmatrelvir/ritonavir

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