Zygomycetes [5]. Theoretically, some of the examined statin concentrations can be reached in the human plasma via administration of high oral doses (eg, a daily dosage of 40–80 mg).

The administration of statins together with antifungals that are predominantly metabolized by the same cytochrome P450 (CYP450) isoenzymes in the liver is contraindicated, because such drug interactions with the CYP system may cause serious adverse effects (eg, myopathy). Thus, even if combinations of lovastatin and voriconazole may well be effective against Zygomycetes in clinically available concentrations, their possible application would involve considerable risks, because both compounds are metabolized by CYP3A4. Table 1 presents examples of statins and antifungal drugs that are metabolized by different CYPs and, in principle, might be coadministered with fluvastatin, pitavastatin, or rosuvastatin: amphotericin B (3A1); posaconazole, ketoconazole, itraconazole, ravuconazole, micafungin, and griseofulvin (3A4); terbinafine (2D6); and caspofungin, anidulafungin, and fluconazole (not metabolized by the CYP system).

Table 1. Pharmacokinetic Properties of Statins

<table>
<thead>
<tr>
<th>Property</th>
<th>Atorvastatin Cmax, ng/mL</th>
<th>CYP3A4</th>
<th>Lovastatin Cmax, ng/mL</th>
<th>CYP3A4</th>
<th>Pravastatin Cmax, ng/mL</th>
<th>CYP2C19</th>
<th>Simvastatin Cmax, ng/mL</th>
<th>CYP3A4</th>
<th>Fluvastatin Cmax, ng/mL (parent)</th>
<th>CYP2C9</th>
<th>Pitavastatin Cmax, ng/mL (parent)</th>
<th>CYP3A4</th>
<th>Rosuvastatin Cmax, ng/mL (parent)</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability, %</td>
<td>10</td>
<td>60</td>
<td>5</td>
<td>18</td>
<td>5</td>
<td>19–29</td>
<td>60</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
<td>CYP2C8</td>
<td>CYP3A4</td>
<td>CYP3A4, CYP2C8</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
<td>CYP2C9</td>
<td>CYP2C9</td>
<td>CYP2C9</td>
<td>CYP3A4</td>
<td>CYP2C9</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Metabolites</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Inactive</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
</tr>
</tbody>
</table>

**NOTE.** Data are based on a 40 mg oral dose of the above-mentioned statins, with the exception of cerivastatin (0.2 mg) and pitavastatin (2 mg). The following antifungal drugs (and their CYP inhibitions) could possibly be coadministered with atorvastatin, cerivastatin, lovastatin, pravastatin, or simvastatin: amphotericin B (3A1); fluconazole and miconazole (2C9); fluconazole (2C19); terbinafine (2D6); and caspofungin, anidulafungin, and fluconazole (not metabolized by the CYP system). The following antifungal drugs (and their CYP inhibitions) could possibly be coadministered with fluvastatin, pitavastatin, or rosuvastatin: amphotericin B (3A1); posaconazole, ketoconazole, itraconazole, ravuconazole, micafungin, and griseofulvin (3A4); terbinafine (2D6); and caspofungin, anidulafungin, and fluconazole (not metabolized by the CYP system).

**Property Atorvastatin Cerivastatin a Lovastatin Pravastatin Simvastatin Fluvastatin Pitavastatin Rosuvastatin**

<table>
<thead>
<tr>
<th>Cmin, ng/mL</th>
<th>27–66</th>
<th>2</th>
<th>10–20</th>
<th>45–56</th>
<th>10–34</th>
<th>448</th>
<th>65</th>
<th>37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability, %</td>
<td>10</td>
<td>&gt;60</td>
<td>60</td>
<td>18</td>
<td>5</td>
<td>19–29</td>
<td>&gt;60</td>
<td>20</td>
</tr>
</tbody>
</table>

a Cerivastatin has been withdrawn from the market because of serious adverse effects.

References


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Reply to Galgóczi et al

To the Editor—We thank Galgóczi et al [1] for their interest in our work [2] and for sharing their unpublished and in press data regarding the use of statins for the prevention and treatment of zygomycosis. The prophylactic and even therapeutic effects of pharmacologic agents may be evident despite their subinhibitory activity, such as echinocandins against Aspergillus and Zygomycetes [3, 4]. However, we agree that, given a relatively high minimal inhibitory concentration of statins for the Zygomycetes, their efficacy may be best realized when used in conjunction with antifungal agents. We also note that statins modulate key host defenses by modification of signal transduction and cytokine transcriptional pathways, and they may exert a mediating effect on fungal infections independent of their anti-

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Potential conflicts of interest. LNy is an employee of PannonPharma. CsV has received research funding from PannonPharma. LNy, TPP, and CsV are coinventors in a patent application of PannonPharma in connection with antifungal application of statins. L.G: no conflicts.
fungal activity [5]. Finally, drugs (other than traditionally used antifungal agents) such as calcineurin inhibitors and rapamycin also have potent antifungal activity against a number of opportunistic fungi, and they have demonstrated synergy with the triazoles against some Zygomycetes species [6, 7]. Thus, further studies evaluating the interactions of statins with antifungal as well as immunosuppressive agents and their application for protection against Zygomycetes could yield potentially valuable insights into optimizing the outcomes related to zygomycosis and other opportunistic mycoses in organ transplant recipients.

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