Is Chewed Raltegravir an Option to Care for HIV-Infected Patients With Active Tuberculosis?

To the Editor—Human immunodeficiency virus (HIV) and tuberculosis are closely intertwined, and the number of coinfected patients continues to grow rapidly [1]. Treating both infections can be a challenge owing to multiple drug interactions and risk of overlapping side effects [2]. The utilization of rifampicin as part of tuberculosis treatment limits the use of antiretroviral (ARV) drugs. Rifampicin induces cytochrome P450 enzymes, which results in reduced plasma concentrations of protease inhibitors and nonnucleoside reverse transcriptase inhibitors. Rifampicin also induces phase II enzymes including Uridine 5′-diphospho-glucuronosyl transferase. The HIV integrase inhibitor raltegravir (RAL) is primarily metabolized by UGT1A1, and therefore there is the potential for a pharmacokinetic drug interaction with rifampicin. In fact, previous studies have shown a decrease in the RAL area under the concentration time curve (AUC), peak of maximum drug concentration, and trough concentrations when coadministered with daily rifampicin [3].

The recently updated recommendation for RAL now suggests a dose increase of RAL to 800 mg twice daily if coadministered with rifampicin [4]. According to 24-week results of the Agence Nationale de Recherche sur le Sida (ANRS) 12 180 REFLATE study [5], RAL 800 mg twice daily provided the highest success rate in HIV-infected patients receiving a rifampicin-based therapy for tuberculosis; in particular, 63% (95% confidence interval [CI], 46%–76%) in the efavirenz regimen group reached the primary endpoint of a viral load <50 copies per mL at 20 and 24 weeks, compared to 76% (95% CI, 65%–88%) in the 400 mg RAL group and 78% (95% CI, 67%–90%) in the 800 mg RAL group. Doubling the RAL dose to 800 mg when coadministered with rifampicin compensates for the effect of rifampicin on RAL exposure (AUC0–12) but does not overcome the effect of rifampicin on RAL trough concentrations (C12) [3]. On the other hand, doubling the RAL dose to 800 mg increased the cost of ARV regimens and, in a context of limited healthcare resources, pharmacoeconomic considerations are crucial.

Recently, it was shown that HIV-infected patients taking RAL 400 mg twice daily by chewing the tablets have higher
drug absorption than patients taking the drug at 400 mg twice daily by swallowing the whole tablet [6], suggesting that this way of administration may significantly improve the disposition of RAL. Herein we report our experience with an HIV-infected man diagnosed with disseminated tuberculosis and treated with a rifampicin-containing regimen with isoniazid, pyrazinamide, and ethambutol. Two months before the diagnosis of tuberculosis, the patient began an ARV regimen containing RAL (400 mg twice daily), tenofovir, and emtricitabine. Before starting antiretroviral therapy (ART), his CD4+ count was 40 cells/μL and 61 400 copies/mL of HIV RNA. This patient chewed all the drugs owing to swallowing difficulties.

After 3 months of treatment with a rifampicin-containing tuberculostatic regimen, a pharmacokinetic profile was recorded after intake of chewed RAL with food, and pharmacokinetic parameters were compared with reported data in HIV-infected patients on 400 mg twice daily without rifampicin [7]. As shown in Table 1, the main RAL pharmacokinetic parameters measured in our patient were comparable to those assessed in patients not concomitantly treated with rifampicin. The safety profile of tuberculosis treatment and ART was good, with no recorded adverse events due to tuberculosis treatment and/or ART. No drug shift, drug withdrawal, or dose reduction was required throughout the observational period. The patient always maintained the same ART treatment, and HIV RNA remained <37 copies/mL during the entire treatment with a rifampicin-containing tuberculostatic regimen. He also showed a good response to tuberculosis treatment as documented by disappearance of fever and significant improvement in the routine hematochemical analyses, and by the results of the chest radiographs.

To our knowledge, this is the first clinical case to report on the use of chewed RAL at 400 mg twice daily as part of antiretroviral therapy in a patient taking rifampicin. It can be reasonably speculated that our patient, by taking the drug by chewing, increased the absorption of RAL, compensating for the inductive effect of rifampicin on RAL metabolism. This hypothesis is supported by the measured RAL AUC (comparable to values measured in patients given RAL by swallowing without rifampicin) and by the clinical outcome. Indeed, ARV including chewed RAL at a conventional dose allowed a rapid and sustained virologic suppression despite concomitant rifampicin treatment.

Taken together, these findings suggest a new way to manage RAL/rifampicin drug–drug interaction in routine clinical practice and the possibility to use the conventional dose—rather than the high 800 mg twice daily dose—to treat HIV-positive patients in developing countries with high prevalence of tuberculosis, allowing enormous cost savings.

Table 1. Summary of the Main Pharmacokinetic Parameters in Our Patient Given Raltegravir and Rifampicin by Chewing Compared With HIV-Infected Patients Given Raltegravir Without Rifampicin by Swallowing

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HIV Patient Populationsa, Mean (SD)</th>
<th>Our Patient</th>
<th>Cmax, ng/mL</th>
<th>tmax, h</th>
<th>AUC0–12, ng/mL/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0, ng/mL</td>
<td>524 (534)</td>
<td>71</td>
<td>3050 (2049)</td>
<td>1 (1–2)</td>
<td>10 595 (7289)</td>
</tr>
<tr>
<td>Cmax, ng/mL</td>
<td></td>
<td></td>
<td>3702</td>
<td></td>
<td>12 505</td>
</tr>
<tr>
<td>tmax, h</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>AUC0–12, ng/mL/h</td>
<td></td>
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</table>

Abbreviations: AUC, area under the concentration time curve; Cmax, peak of maximum drug concentration; HIV, human immunodeficiency virus; PK, pharmacokinetic; SD, standard deviation; tmax, time of Cmax.

a Fifty HIV-infected patients receiving oral raltegravir 400 mg twice daily by swallowing.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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