Use of Raltegravir in Pediatric HIV-1 Infection
Marcia L. Buck, Pharm.D., FCCP, FPPAG

Treatment options for pediatric patients with HIV-1 infection continue to expand. According to the updated Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection published in August 2011, 17 antiretroviral drugs have a pediatric indication from the Food and Drug Administration (FDA). On December 21, 2011, this number grew again as the FDA extended the approval of raltegravir to include children and adolescents from 2 to 18 years of age. Raltegravir was originally approved in 2007 for use in combination with other antiretroviral agents in adults with HIV-1 infection. It is currently the only HIV-1 integrase strand transfer inhibitor (INSTI) available in the United States and offers a safe and effective option for initial therapy for HIV-1 infection or treatment of patients with multidrug-resistant viral mutations.

Mechanism of Action
Raltegravir inhibits the catalytic activity of HIV-1 integrase and blocks the strand transfer step in the integration of linear HIV-1 DNA into the host cell genome. As a result, raltegravir prevents formation of the HIV-1 provirus that is necessary for propagation of the viral infection. Raltegravir has demonstrated potent activity against HIV-1, including a wide range of isolates resistant to other antiretroviral therapies. In adults, a raltegravir dose of 400 mg twice daily as monotherapy produced a mean reduction in viral load of 1.66 log_{10} copies/mL by day 10. Additive or synergistic activity has been demonstrated when raltegravir is administered along with nucleoside analog reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI).

Pharmacokinetics
In adults, an oral dose of raltegravir reaches peak plasma concentrations within 0.5-1.5 hours. Bioavailability is approximately 30%. Administration with food does not appear to have a clinically significant effect on overall patient response. A mean area under the concentration curve (AUC_{0-12 h}) of 14.3 microM•hr and a mean concentration at 12 hours (C_{12h}) of 142 nM have been reported in adults receiving 400 mg raltegravir twice daily. Raltegravir is 83% bound to plasma proteins. It is highly metabolized, primarily to raltegravir-glucuronide via uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). In adults, the terminal half-life is approximately 9 hours (range 7-12 hours). UGT1A1 polymorphisms do not appear to affect raltegravir clearance. A study comparing mean AUC values in poor metabolizers (the *28/*28 genotype) and the wild-type genotype revealed no significant differences.

A pharmacokinetic study conducted in 44 children taking part of the IMPAACT P1066 study produced similar results to studies in adults. In the first stage of the study, children 6-18 years of age were given doses of 6 or 8 mg/kg twice daily; this was subsequently changed to dose stratification by age and weight based on the availability of new 25 and 100 mg chewable tablets. Adolescents 12 years of age and older and children between 6 and 12 years of age who weighed at least 25 kg were given the standard adult dose of 400 mg twice daily. Children from 6 to 12 years who weighed less than 25 kg and of the 112 subjects with treatment failure. More than 30 mutations in the integrase enzyme have been identified in cell culture and in treated patients. The primary mutations include Y143C/H/R, Q148H/K/R, and N155H and result in a significant increase in viral replication capacity. Secondary mutations include E92Q, associated with the N155H mutation, and G140S, found with the Q148H mutation. These secondary mutations amplify resistance of the HIV-1 virus to raltegravir and return integrase activity back to that seen without the drug.
children 2 to 6 years of age who weighed at least 10 kg received raltegravir doses according to weight: 75 mg twice daily for patients 10-13.9 kg, 100 mg twice daily for patients 14-19.9 kg, 150 mg twice daily for patients 20-27.9 kg, 200 mg twice daily for patients 28-39.9 kg, and 300 mg twice daily for patients ≥ 40 kg. Children between 6 and 12 years of age who weighed < 25 kg received the chewable tablet, and those weighing ≥ 25 kg were given the film-coated tablet. Mean AUC_{0-12 hrs} values (Table 1) were similar among the groups, while C_{12hr} increased with increasing age or weight.³

<table>
<thead>
<tr>
<th>Group</th>
<th>AUC_{0-12 hrs} (microM•hr)</th>
<th>C_{12hr} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-6 yrs</td>
<td>18.0 (59%)</td>
<td>71 (55%)</td>
</tr>
<tr>
<td>6-12 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25 kg</td>
<td>22.6 (34%)</td>
<td>130 (88%)</td>
</tr>
<tr>
<td>≥ 25 kg</td>
<td>15.8 (120%)</td>
<td>246 (221%)</td>
</tr>
<tr>
<td>12-18 yrs</td>
<td>15.7 (98%)</td>
<td>333 (78%)</td>
</tr>
</tbody>
</table>

*C*mean with coefficient of variation

Clinical Studies
The approval of raltegravir in pediatric patients was based on the results of a Phase I/II multicenter open-label dose-finding trial in 126 children with HIV-1 infection.³ The IMPAACT P1066 study was designed to evaluate the safety and efficacy of raltegravir in children between 2 and 18 years of age. As described earlier, dosing was based on patient age and weight. Nine-six of the study participants were included in the clinical assessment. The median age of these patients was 13 years. At baseline, they had a mean plasma HIV-1 RNA of 4.3 log_{10} copies/mL, a median CD4 count of 481 cells/mm³ (range 0-2361 cells/mm³), and a median CD4% of 23.3% (range 0-44%). Most patients had previously received treatment, with 78% having taken at least one NNRTI and 83% having taken at least one PI. Ninety-three children completed the 24-week treatment period. Three patients were excluded because of non-adherence. At the completion of the study, 54% of the children had an HIV-1 RNA < 50 copies/mL and 72% had achieved an HIV-1 RNA decrease of at least 1 log_{10} copies/mL from baseline. The mean increase in CD4 count from baseline was 199 cells/mm³, or 3.8%. These results were similar to those reported in the two Phase III studies conducted by the manufacturer in adults (BENCHMRK 1 and BENCHMRK 2).³

Other evidence of the efficacy of raltegravir comes from the French Expanded Access Program.⁷ Eight in 2009, Thuret and colleagues from the Service d’Hématologie Pédiatrique described the use of combination therapy with raltegravir, darunavir, and etravirine in 12 adolescents from 12 to 17 years of age with multidrug-resistant HIV-1 infection.⁷ At follow-up (median 12 months), all patients had an HIV-1 RNA < 400 copies/mL and six had an HIV-1 RNA < 50 copies/mL. No serious adverse effects were reported.

In a subsequent abstract, the authors updated their results with the Expanded Access program.⁸ Twenty-three adolescents had been treated by December 2007. At follow-up (median 9 months), 86% had an HIV-1 RNA < 400 copies/mL and 68% had an HIV-1 RNA < 50 copies/mL. Median CD4 cell count increased from 194 cells/mm³ to 402 cells/mm³ at 6 months. Only one patient had discontinued raltegravir, due to persistent headaches.

Additional information comes from a case report published in the *Journal of Antimicrobial Chemotherapy* in 2009.⁹ The authors describe the successful use of raltegravir in the treatment of a 9-year-old boy who experienced efavirenz-associated liver failure. He was started on raltegravir, lamivudine, and zidovudine 6 months after transplantation, resulting in an undetectable viral load within 2 weeks and a CD4 cell count of 500 cells/mm³.

A case report published last year provides preliminary information on the potential role of raltegravir in infants.¹⁰ Brolund and colleagues describe a 3-month-old infant initially treated with zidovudine, lamivudine, and nevirapine who developed multidrug-resistance. The authors initiated treatment with raltegravir using a dose of 6 mg/kg twice daily, lopinavir/ritonavir, and lamivudine. At 16 weeks, the infant’s HIV-1 RNA decreased from 2.5 log_{10} copies/mL to 164 copies/mL, and his CD4% increased from 37 to 39%. No adverse effects were noted and the patient demonstrated catch-up growth, moving from <3rd percentile to >25th percentile.

Warnings and Precautions
As with other antiretrovirals, patients beginning therapy with raltegravir should be monitored for immune reconstitution syndrome, an inflammatory response to residual opportunistic infections. These infections may include *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jiroveci*, *Mycobacterium tuberculosis*, or reactivation of varicella zoster.² ⁵
Severe dermatologic reactions have been reported in patients receiving raltegravir. These cases have included hypersensitivity reactions, Stevens Johnson syndrome, and toxic epidermal necrolysis. Use of raltegravir should be discontinued immediately in any patient with a severe rash or any rash associated with elevated serum aminotransferases or eosinophilia, or a rash accompanied by fever, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, or angioedema. Families of patients with phenylketonuria should be made aware that the chewable tablet formulations of raltegravir contain phenylalanine.2-5

**Adverse Effects**

In clinical trials conducted in adults, the most commonly reported adverse effects with raltegravir have included insomnia in 4% of patients, and headache, neutropenia, anemia, or thrombocytopenia in 1-2%. Other adverse effects included dizziness, fatigue, pruritus, abdominal pain, and vomiting (all occurring in < 2% of patients). Elevated serum aminotransferases, bilirubin, glucose, and lipid values occurred in 1-6% of patients. Rates of discontinuation in clinical trials have been no different in the raltegravir and placebo groups. Post-marketing reports include rare cases of elevated creatine kinase, myopathy, and rhabdomyolysis, as well as nephrolithiasis, renal and liver failure, and hypersensitivity or severe dermatologic reactions.2-5

The manufacturer reports that the adverse effects documented in children participating in the IMPAACT P1066 trial were similar to those seen in adults.3 One child experienced hyperactivity and insomnia and another experienced a serious allergic rash. One patient experienced elevated serum aminotransferases.

**Drug Interactions**

Rifampin, a strong inducer of UGT1A1, increases the rate of metabolism of raltegravir and reduces plasma concentrations. In adults taking raltegravir who require treatment with rifampin, the raltegravir dose should be increased to 800 mg twice daily. There have been no studies to determine the appropriate dosage adjustment in children requiring this combination.2,3,11

The effect of concomitant administration of other medications used for the treatment of HIV-1 infection has also been studied. Administration with antiretrovirals that induce UGT1A1 such as efavirenz, etravirine, or tipranavir/ritonavir reduce raltegravir concentrations, but the clinical significance of these interactions has not been assessed and no dosage adjustment is recommended. Although atazanavir is a strong inhibitor of UGT1A1 and has been shown to produce a 30-70% increase in plasma raltegravir concentrations, the interaction has not been found to result in increased toxicity.2,3,12

Medications that increase gastric pH, such as H2 blockers or proton pump inhibitors, may increase raltegravir absorption and result in higher plasma concentrations. Studies have demonstrated no significant difference in clinical response, so no dosage adjustment is recommended.2,3

**Availability and Cost**

Raltegravir (Isentress®) is available as 25 mg and 100 mg scored, orange-banana flavored chewable tablets and 400 mg film-coated tablets.3 The cost of sixty 400 mg tablets (a one-month supply) ranges from $1,000 to $1,300. Merck provides a patient assistance program with reimbursement for eligible patients and coupons to assist insured patients with their copay. Information can be obtained by calling 1-888-204-3713 or through their website at  http://www.isentress.com/raltegravir/isentress/consumer/coupon_for_isentress/index.jsp. Cost information on the chewable tablets is not yet available.

**Dosing Recommendations**

The recommended dose of raltegravir in adults and adolescents 12 years of age and older is 400 mg given twice daily. In children 6 to 12 years of age weighing at least 25 kg, either the adult dose or weight-based dosing may be used as described in the table below. If the child weighs less than 25 kg, or in children 2 to 6 years of age, weight-based dosing should be used, to a maximum of 300 mg twice daily.3 No dosage adjustment is needed for patients with renal impairment or mild to moderate hepatic impairment.13 The administration of raltegravir to patients with severe hepatic impairment has not been studied.

<table>
<thead>
<tr>
<th>Table 2. Raltegravir Weight-Based Dosing*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
</tr>
<tr>
<td>10-13.9 kg</td>
</tr>
<tr>
<td>14-19.9 kg</td>
</tr>
<tr>
<td>20-27.9 kg</td>
</tr>
<tr>
<td>28-39.9 kg</td>
</tr>
<tr>
<td>≥ 40 kg</td>
</tr>
</tbody>
</table>

*all doses given twice daily
Raltegravir can be given with or without food. The film-coated tablets must be swallowed whole, while the chewable tablets may be chewed, crushed, or swallowed whole. The two tablet formulations are not bioequivalent, and therefore are not interchangeable.  

Summary
Since its introduction in 2007, raltegravir has been a valuable addition to the options available for treatment of HIV-1 infection. The availability of new study data confirming its safety and efficacy in children, as well as the introduction of a chewable dosage formulation, extend the benefits of raltegravir to the pediatric population.

References

Formulary Update
The following actions were taken by the Pharmacy and Therapeutics Committee at their December meeting:

1. Rivaroxaban (Xarelto®) was added to the Formulary for prophylaxis of deep vein thrombosis in adults undergoing knee or hip replacement or in those with nonvalvular atrial fibrillation.
2. Clobazam (OnfiTM) was added as adjunctive therapy for children and adults with Lennox-Gastaut syndrome.
3. Belatacept (Nulojix®) was added to the Formulary with restriction to kidney transplant, EBV-seropositive patients who are unable to tolerate standard immunosuppression regimens.
4. Romidepsin (Istodax®) was added for outpatient use in patients with cutaneous T cell lymphoma or peripheral T cell lymphoma.
5. Asparaginase Erwinia chrysanthemi (ErwinazaTM) was added for use in patients who have developed hypersensitivity to E. coli-derived asparaginase.
6. Boceprevir (VictrelisTM) and telaprevir (IncivekTM) were added to the Formulary for adults with chronic hepatitis C infection. Prescribing is restricted to prior authorization by Gastroenterology, Infectious Disease, and Drug Information.
7. Ribavirin inhalation (Virazole®) was returned to the Formulary for use in patients following stem cell transplant. It is restricted to Antimicrobial Category A.
8. The restriction on ferumoxytol was amended to include use by Hematology/Oncology for the treatment of patients with iron deficiency anemia.
9. Promethazine injection was removed from the Formulary. A supply will be reserved for oncology patients who have failed other antiemetic therapies.

Contributing Editor: Marcia Buck, Pharm.D.
Editorial Board: Kristi N. Hofer, Pharm.D. Michelle W. McCarthy, Pharm.D., FASHP Susan B. Cogut, Pharm.D.
If you have comments or suggestions for future issues, please contact us at Box 800674, UVA Health System, Charlottesville, VA 22908 or by e-mail to mlb3u@virginia.edu. This newsletter is also available at http://www.medicine.virginia.edu/clinical/departments/pediatrics/education/pharmnews