New Drug

Raltegravir: The First HIV Integrase Inhibitor

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ABSTRACT

Background: The availability of new classes of antiretroviral drugs has made it possible for HIV-infected individuals who are highly treatment experienced to achieve the goals of immunologic recovery and virologic suppression. Raltegravir is the first integrase inhibitor to be approved by the US Food and Drug Administration for use in antiretroviral treatment–experienced adult patients with viral resistance.

Objective: This article reviews the pharmacology, pharmacokinetics, pharmacodynamics, efficacy, tolerability, resistance profile, drug interactions, and dosing and administration of raltegravir.

Methods: Searches of MEDLINE and International Pharmaceutical Abstracts from 1964 to July 2008 were conducted using the terms *integrase*, *raltegravir*, and *MK-0518*. Relevant information was extracted from the identified clinical trials and review articles. Abstracts from the Conference on Retroviruses and Opportunistic Infections (1998–2008); Interscience Conference on Antimicrobial Agents and Chemotherapy (1999–2007); International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (2001–2007); and European AIDS Conference (2001–2007) were also searched.

Results: Raltegravir blocks HIV replication by inhibiting essential strand-transfer activities of integrase. Raltegravir is rapidly absorbed, with a median T_{max} of ~4 hours in the fasting state. No dose adjustment is recommended in patients with moderate renal or hepatic insufficiency, and raltegravir may be taken without regard to meals. In Phase II studies in treatment-naive patients, raltegravir had efficacy similar to that of standard initial therapies. In 2 interrelated Phase III clinical studies in treatment-experienced patients with drug-resistant disease, the addition of raltegravir to an optimized background regimen significantly lowered HIV RNA compared with optimized background treatment alone (62.1% vs 32.9%, respectively; $P < 0.001$). Raltegravir was generally well tolerated. The most common adverse effects reported in Phase II/III trials in treatment-experienced patients were diarrhea (16.6%), nausea (9.9%), and headache (9.7%). Cytochrome P450–related drug interactions are not expected, as raltegravir is not a CYP substrate, inducer, or inhibitor. However, to prevent failure of raltegravir, the drug should not be coadministered with rifampin.

Conclusion: Raltegravir is a potent and generally well tolerated antiretroviral agent that may play an important role in the treatment of patients harboring resistance to other antiretrovirals. (*Clin Ther*. 2008; 30:1747–1765) © 2008 Excerpta Medica Inc.

Key words: raltegravir, antiretroviral, integrase inhibitor, HIV.

INTRODUCTION

After 25 years, HIV infection remains a significant cause of morbidity and mortality. Major advances in HIV treatment have revolutionized patient care and prolonged survival, with the result that HIV infection can now be effectively managed as a chronic disease. It is estimated that 1.3 million persons in the United States are currently living with HIV infection.[1] Treatment challenges—including increasing drug resistance, adverse effects, drug interactions, and nonadherence—continue to limit use of highly active antiretroviral therapy. During the past 2 decades, >23 antiretroviral agents have been approved by the US Food and Drug Administration (FDA). In addition to existing FDA-approved antiretroviral classes—the nucleoside and nucleotide reverse-transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs),

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and protease inhibitors (PIs)—3 distinctly different classes of antiretroviral agents were approved in the past year, expanding the therapeutic options for highly treatment-experienced individuals. With the availability of entry inhibitors, chemokine (C-C motif) receptor 5 coreceptor antagonists, and integrase inhibitors, highly treatment experienced individuals who harbor drug-resistant virus and experience drug intolerance/toxicity may be able to achieve immunologic recovery and complete virologic suppression, goals that were once attainable only in treatment-naive individuals.

Raltegravir (RAL),* the first HIV integrase inhibitor, was approved by the FDA on October 12, 2007, for use in antiretroviral treatment–experienced adult patients with viral resistance.[2] The present review focuses on the clinical pharmacology, pharmacodynamics and pharmacokinetics, clinical efficacy, tolerability, drug interactions, and dosing and administration of RAL.

METHODS

MEDLINE and International Pharmaceutical Abstracts were searched for papers published in English from 1964 to July 2008 using the terms *integrase*, *raltegravir*, and *MK-0518*. Relevant information was extracted from the identified clinical trials and review articles. The reference lists of the retrieved articles were reviewed for additional pertinent papers. The same terms were used to search abstracts of the Conference on Retroviruses and Opportunistic Infections (1998–2008); Interscience Conference on Antimicrobial Agents and Chemotherapy (1999–2007); International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (2001–2007); and European AIDS Conference (2001–2007).

*Trademark: Isentress® (Merck & Co., Inc., Whitehouse Station, New Jersey).

PHARMACOLOGY

RAL is the first commercially available antiretroviral agent to target HIV integrase, 1 of 3 enzymes that play a crucial role in viral replication. Integration of proviral DNA into human DNA is a multistep process that involves binding of the enzyme to the viral DNA, formation of a stable preintegration complex, movement of the preintegration complex from the cell cytoplasm to the nucleus, and subsequent transfer of viral DNA strands to the host DNA.[3] For its enzymatic activity, integrase depends on 3 key amino acids at positions 64, 116, and 152 (aspartate, aspartate, and glutamate, respectively) to bind divalent cations.[4] RAL inhibits the strand-transfer step of integration by blocking the enzyme's active site. With RAL present, the preintegration complex is unable to bind to host DNA.[4,5] The nonintegrated proviral HIV DNA is repaired via normal cellular DNA repair mechanisms and is rendered inactive.

The ability of earlier integrase inhibitors to inhibit strand transfer was attributed to a specific β-diketo acid chemical moiety. Using structure-based drug design, the diketo acid moiety of previous integrase inhibitors was substituted with diketones, naphthyrine ketones, and naphthyrine carboxamides, resulting in improved chemical stability.[4] RAL is a pyrimidine carboxamide integrase inhibitor whose structure was based on these previous compounds.[6,7] Its chemical name is *N*-[(4-fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt (**Figure**).[8]

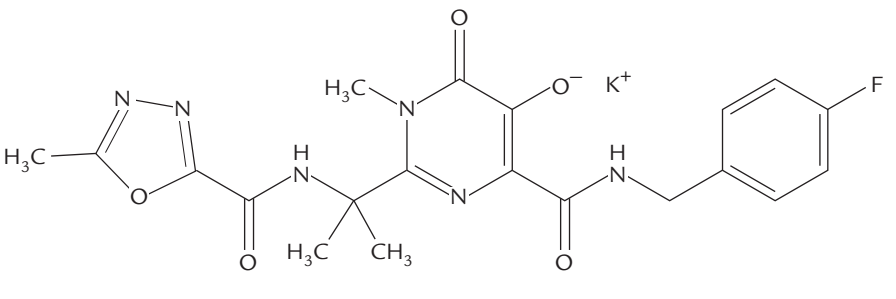

Figure. Chemical structure of raltegravir.[8]