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Raltegravir

Jamie D. Croxtall, Katherine A. Lyseng-Williamson and *Caroline M. Perry*

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Conshohocken, Pennsylvania, USA

Contents

Abstract

▲ Raltegravir, the first in a new class of orally administered HIV type-1 (HIV-1) integrase inhibitors, selectively inhibits the strand transfer activity of HIV-1 and its integration into human DNA, a key stage in retroviral propagation, thereby limiting viral replication and the infection of new cells.

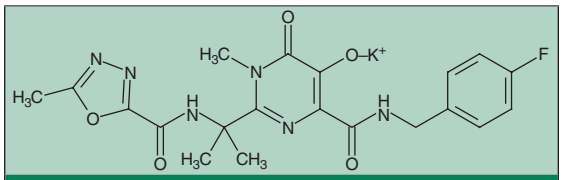
▲ In two randomized, double-blind (with in-house blinding), placebo-controlled, multicentre, ongoing phase III trials, the proportion of patients achieving HIV-1 RNA loads of <400 copies/mL (primary endpoint) was significantly greater in raltegravir plus optimized background therapy (OBT) recipients than in placebo plus OBT recipients (preliminary 24-week results).

▲ The proportion of patients achieving viral loads of <50 copies/mL was significantly greater with raltegravir plus OBT than with placebo plus OBT in the two studies.

▲ In addition, mean CD4+ cell counts (secondary endpoint) were significantly increased from baseline in patients receiving raltegravir plus OBT relative to those receiving placebo plus OBT.

▲ Raltegravir therapy was well tolerated overall. The incidence of mild to moderate adverse events was similar in the raltegravir and placebo arms of the two randomized trials.

Features and properties of raltegravir; MK-0518 (Isentress™)	
Indication	
Antiretroviral-resistant HIV type-1 (HIV-1) infection	
Mechanism of action	
Inhibits the integration of viral complimentary DNA into the host genome	
Dosage and administration	
Dose	400 mg
Route of administration	Oral
Frequency of administration	Twice daily
Pharmacokinetic profile (at steady state, 400 mg twice daily as monotherapy) in healthy volunteers (n = 6)	
Mean area under the plasma concentration-time curve (0–12 h)	14.2 μmol • h/L
Mean peak plasma concentration	4.5 μmol/L
Plasma concentration at the end of interval (12 h)	142 nmol/L
Adverse events	
Most frequent drug-related moderate to severe adverse events (incidence ≥2%) in treatment-experienced adult patients	Nausea, headache and diarrhoea



Raltegravir; MK-0518 (Isentress™)

HIV type-1 (HIV-1) infection continues to be a major global problem, with nearly 40 million individuals infected worldwide and an estimated 2.1 million in North America and Europe.[1,2] Currently, treatment regimens consist of three or more drugs from four classes of antiretroviral therapy (ART) drugs: (i) nucleoside reverse transcriptase inhibitors (NRTIs); (ii) non-nucleoside reverse transcriptase inhibitors (NNRTIs); (iii) protease inhibitors; and (iv) fusion inhibitors.[3,4] Although treatment regimens with a combination of various drugs from these classes have greatly reduced the incidence of HIV-1-related morbidity and mortality, it is estimated that 78% of treatment-experienced patients harbour viruses that are resistant to one or more of these classes of inhibitors.[5] Therefore, there remains a critical need for new treatment approaches for patients with HIV-1 infection.

Integrase is an HIV-1-specific enzyme that catalyzes the integration of viral complementary DNA (cDNA) into the host genome.[6] Integration is not only required for stable maintenance of the viral genome and viral gene expression, but also represents a key stage in the cycle of viral replication.[6] The absence of a host-cell integrase homologue means that inhibitors that target this enzyme provide a new modality of therapeutic intervention that does not interfere with normal cellular processes.[6]

Raltegravir (MK-0518; Isentress™)[1], the first drug in the new class of HIV-1 integrase strand-transfer inhibitors, recently received accelerated approval by the US FDA.[7] This review focuses on the pharmacological properties of oral raltegravir and its clinical and tolerability profile, primarily in patients with HIV-1 infection resistant to conventional ART.[8,9]

1. Pharmacodynamic Properties

The pharmacodynamic properties of raltegravir have been examined using both strand transfer reaction *in vitro* and integration of HIV-1 DNA into cellular DNA in cell culture.[10] Viral resistance to raltegravir has been evaluated in clinical isolates of HIV-1 from patients with multidrug-resistant HIV-1 in human T-lymphoid cells.[11] Additional data are available from the manufacturer's prescribing information.[7]

Mechanism of action

- Raltegravir is a hydroxypyrimidinone carboxamide that, although structurally distinct from diketo acids and naphthyridines, is mechanistically similar to these compounds in the inhibition of integrase activity.[12]
- Selective inhibition of integrase activity at nanomolar concentrations is the hallmark of this class of inhibitors.[12] These compounds are specific inhibitors of viral cDNA integration and exert their antiviral effect on HIV-1 solely as a consequence of their ability to inhibit the strand transfer activity of integrase.[6]
- HIV-1 integrase inhibitors, such as raltegravir, are ineffective against HIV-1 reverse transcriptase and HIV-1 protease.[10] However, when used in combination with other ART agents, such as NNRTIs (e.g. efavirenz), NRTIs (e.g. lamivudine, tenofovir), protease inhibitors (e.g. atazanavir, ritonavir) or the entry inhibitor enfuvirtide, raltegravir showed additive or synergistic antiretroviral activity in human T cells infected with HIV-1 isolates.[7,10]

Antiretroviral Activity

- The strand transfer activity of purified HIV-1 integrase was inhibited by raltegravir *in vitro* with a 50% inhibitory concentration of 2–7 nmol/L and >1000-fold greater selectivity for integrase over oth-

1 The use of trade names is for identification purposes only and does not imply endorsement.

er phosphoryltransferases tested, including the polymerase and ribonuclease H activities of HIV-1 reverse transcriptase and the human polymerases α, β and γ.[10]

- Cell culture studies showed potent activity against HIV-1 in the presence of both 10% fetal bovine serum and 50% human serum with 95% inhibitory concentrations of 19 nmol/L and 33 nmol/L.[10]
- Quantitative polymerase chain reaction assays showed raltegravir prevented integration into cellular DNA and enhanced the formation of 2-long terminal repeats circular forms. The synthesis of HIV-1 cDNA was unaffected.[10]

Viral resistance

Viral resistance to raltegravir has been observed in clinical isolates of HIV-1 from patients with HIV-1 infection and appears to be associated with mutations of the integrase gene.[11] In a randomized, phase II, dose-ranging study (protocol 005), virological resistance was investigated in isolates from 133 evaluable treatment-experienced patients resistant to ART[11] from a larger ongoing trial in patients receiving raltegravir 200, 400 or 600 mg twice daily[13] (see section 3 for trial design details). Integrase mutations were identified in 35 (26.3% of patients) of 38 patients with virological failure (defined as not achieving <400 copies/mL HIV RNA). Two genetic pathways defined by mutations N155H or Q148H/K/R that reduce susceptibility by 10- or 25-fold appear to be associated with resistance.[11] Secondary mutations (e.g. L74M/R, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, H138P, Y226D/F/H, S230R and D232N) resulted in enhanced resistance.[7] Amino acid substitution at Y143 (to C, H or R) has been identified as another mechanism of resistance to raltegravir.[7,11]

Other effects

- There are no reports of hyperlipidaemia in the manufacturer's prescribing information for raltegravir, and preliminary data from clinical trials in patients with HIV-1 infection suggest that the drug is not associated with the development of clinically relevant hyperlipidaemia.[7] Fasting serum cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol and triglyceride levels in treatment-naive HIV-1-infected patients had not changed from baseline levels to a significant extent after 24 weeks of treatment with raltegravir 100–600 mg twice daily in combination with tenofovir and lamivudine.[14]

2. Pharmacokinetic Properties

The recommended dosage of oral raltegravir for treatment of HIV-1 infection in ART-resistant patients is 400 mg twice daily.[7] The pharmacokinetic properties of single-dose raltegravir have been evaluated in several studies in healthy male and female volunteers.[15-19] Additional data are derived from the manufacturer's prescribing information.[7]

In two randomized, crossover studies, healthy male volunteers received either single doses of 100–1600 mg raltegravir or a single 400 mg dose in combination with a high-fat meal (n = 20 in both trials).[15] Similarly, in two further studies, healthy volunteers received either a single 10–1600 mg dose of raltegravir (n = 24 males in nine treatment groups)[19] or a single 400 mg dose of raltegravir (n = 15 males, 8 females).[19]

The absorption, metabolism and excretion of the drug were studied in healthy male volunteers receiving a single oral 200 mg (200 μCi) dose of [^{14}C]raltegravir.[16] Age, gender, race, hepatic and renal impairment evaluated by composite analysis had no appreciable effects on the pharmacokinetic profile of raltegravir.[7,19] Similarly, moderate- and high-fat meals had no clinically meaningful effect on the pharmacokinetics of raltegravir,[15] which may therefore be administered with or without food.[7]

Absorption and Distribution

- Mean maximal plasma concentrations (C_{max}) and the area under the plasma concentration time curve (AUC) from time zero to infinity of raltegravir increased proportionally with doses of 100–800 mg and slightly less than proportionally with doses of up to 1600 mg (n = 20).[15,19]

• Absorption was rapid, usually with a time to C_{max} in the fasted state of 3 hours.[7] Typically, after administration of raltegravir 400 mg twice daily, a steady-state mean C_{max} of 4.5 μmol/L was achieved with an AUC from time 0 to 12 hours of 14.2 μmol • h/L.[20] The plasma concentration of raltegravir at the end of the dosing interval (12 hours) was 142 nmol/L.[20] Approximately 83% of raltegravir remained bound to human plasma protein over the concentration range 2–10 μmol/L.[7]

Metabolism and Elimination

• Metabolism of raltegravir in humans is predominantly through uridine diphosphate-glucuronosyltransferase (UGT)-mediated glucuronidation.[16] The major plasma entity was raltegravir (70%), with the remainder accounted for by the glucuronide of raltegravir.[16] No oxidative metabolism of raltegravir was observed in liver microsomes.[21]

• Following a single oral dose of raltegravir 200 mg, plasma concentrations declined rapidly and were below the limit of quantitation after 24 hours.[16] The terminal half-life of raltegravir was between 7 and 12 hours.[15,19]

• After oral administration of ^{14}C-labelled raltegravir, the drug was eliminated in substantial amounts in both the urine (32%) and faeces (51%).[16] In the urine, 23% of raltegravir was accounted for by the glucuronide metabolite, whereas in the faeces, no metabolite was found.[16]

Drug Interactions

• Systemic exposure to raltegravir is increased when it is coadministered with atazanavir,[17] but is not affected by coadministration of ritonavir or efavirenz.[18]

• Atazanavir is an inhibitor of glucuronidation, which is the primary route of metabolic clearance of raltegravir.[16] After single-dose coadministration of raltegravir 100 mg with oral atazanavir 400 mg (n = 12), maximum plasma raltegravir concentrations increased by 53% and trough plasma (12 hours after administration) concentrations by 95%.[17] No increased toxicity following coadministration with atazanavir was observed and therefore no dose adjustment of raltegravir is advised.[7]

• The pharmacokinetic profile of a single 400 mg dose of raltegravir was not affected by coadministration with either ritonavir 100 mg or efavirenz 600 mg (n = 12).[18]

• Raltegravir is not expected to interact with drugs that are metabolized by cytochrome P450 (CYP) isoenzymes (e.g. protease inhibitors, NNRTIs, methadone, opioid analgesics, statins, azole antifungals, proton pump inhibitors, oral contraceptives and anti-erectile dysfunction agents), because it was not associated with inhibition of CYP activity or induction of CYP3A4.[7,21]

• As raltegravir is predominantly metabolized by UGT-mediated glucuronidation, coadministration with strong inducers of UGT enzymes, such as rifampicin (rifampin), should be used with caution.[7]

3. Therapeutic Efficacy

This section focuses primarily on data in patients with ART-resistant HIV-1 receiving oral raltegravir 400 mg twice daily, the recommended dosage (see section 5) in the two BENCHMRK (Blocking integrase in treatment Experienced patients with a Novel Compound against HIV: MeRcK) trials. Additional data are also derived from the manufacturer's prescribing information.[7] BENCHMRK-1[8] and BENCHMRK-2[9] (protocols 018 and 019) are identically designed, ongoing, randomized, double-blind (with in-house blinding), placebo-controlled, multicentre, phase III trials in patients with HIV-1 infection resistant to at least one drug from three classes of ART drugs. BENCHMRK-1 was conducted in Europe, Asia, the Pacific and Peru,[8] whereas BENCHMRK-2 was conducted in North, Central and South America.[9]

In both trials, patients presented with similar baseline characteristics, with median plasma HIV-1 RNA levels of 4.5–4.7 $\log_{10}$ copies/mL and median CD4+ cell counts of 146–163 cells/mm^3.[7-9] Interim data after 16 weeks of treatment are currently available in abstracts.[8,9] Patients aged ≥16 years, were randomized 2 : 1 to receive either raltegravir

400 mg twice daily plus optimized background therapy (OBT) [n = 232[8] or 230[9]] or placebo twice daily plus OBT (n = 118[8] or 119[9]). Randomization was stratified on the basis of the extent of resistance to previous protease inhibitor therapy and the inclusion of enfuvirtide in the OBT.[7] Genotypic/phenotypic resistance testing and prior ART history determined OBT selection prior to randomization.[7] A small number (16.2%) of patients with chronic (but not acute) active hepatitis B and/or hepatitis C were enrolled.[7] Pooled data from both BENCHMRK studies after 24 weeks of treatment are also available in the manufacturer's prescribing information.[7] Both studies are scheduled to continue through to 96 weeks.

In both studies, the primary endpoint was defined as the proportion of patients achieving suppression of HIV-1 RNA levels to <400 copies/mL at week 24; secondary endpoints were defined as a change from baseline in HIV-1 RNA (log_{10} copies/mL) and CD4+ cell counts after 24 and 48 weeks of treatment.[8,9,22]

Raltegravir, as short-term monotherapy (10 days)[20] or as a component of long-term (24- and 48-week) combination therapy[23] has also shown efficacy in ART-naive patients in a two-part, dose-ranging, phase II trial (protocol 004). Results of these trials are not discussed further as they are beyond the scope of this review.

Phase III Trials

- In the ongoing BENCHMRK-1[8] and BENCHMRK-2[9] trials in patients with ART-resistant HIV-1, raltegravir 400 mg twice daily plus OBT demonstrated significantly ($p < 0.001$) greater antiretroviral efficacy than placebo plus OBT after 16 weeks of treatment (figure 1).
- HIV-1 RNA levels were reduced to <400 copies/mL in a significantly ($p < 0.001$) greater proportion of raltegravir than placebo recipients in BENCHMRK-1 (figure 1a) [between-group difference 37%; 95% CI 26, 47][8] and BENCHMRK-2 (difference 34%; 95% CI 24, 45).[9]
- The difference between raltegravir plus OBT and placebo plus OBT in the proportion of patients achieving viral loads of <50 copies/mL was also significant ($p < 0.001$) in both BENCHMRK-1 (28%; 95% CI 17, 38)[8] and BENCHMRK-2 (26%; 95% CI 15, 36) [figure 1a].[9]
- Following raltegravir treatment, CD4+ cell counts rose by a mean of 83 cells/mm^3 (95% CI 71, 95) versus a mean increase of 31 cells/mm^3 (95% CI 18, 45) in the placebo group in BENCHMRK-1[8] and by a mean of 86 cells/mm^3 (95% CI 72, 99) versus a mean of 40 cells/mm^3 (95% CI 26, 53) in BENCHMRK-2[9] (figure 1b).

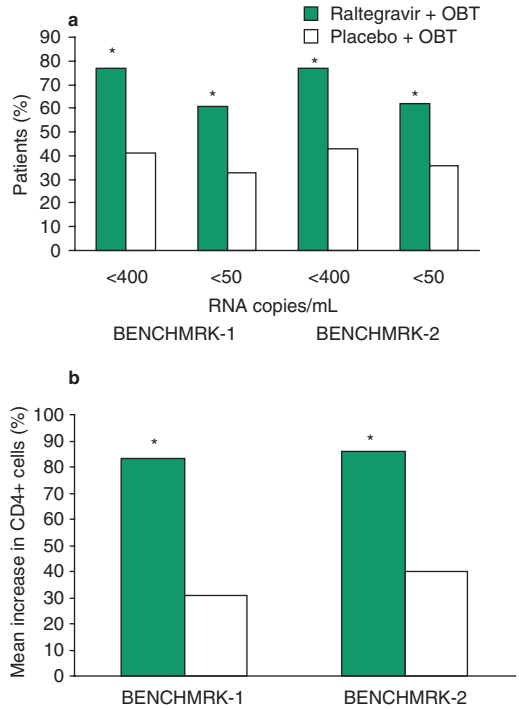


Fig. 1. Efficacy of oral raltegravir 400 mg twice daily in patients with HIV type-1 (HIV-1) resistant to antiretroviral therapy (ART). (**a**) Proportion of patients achieving plasma HIV-1 RNA levels of <400 or <50 copies/mL and (**b**) mean change from baseline in CD4+ cell counts in the evaluable population at the pre-planned 16-week interim analysis of the BENCHMRK trials. BENCHMRK-1 and BENCHMRK-2 are identically designed, ongoing, randomized, double-blind (with in-house blinding), placebo-controlled, multicentre, phase III trials in patients with ART-resistant HIV-1 receiving raltegravir 400 mg twice daily plus optimized background therapy (OBT) [n = 232[8] or 230[9]] or placebo twice daily plus OBT (n = 118[8] or 119[9]). * $p < 0.001$.

• Preliminary data indicate that the antiretroviral efficacy of raltegravir was maintained at 24 weeks in the ongoing BENCHMRK trials.[24]

• Pooled data from both BENCHMRK studies showed that, after 24 weeks, HIV-1 RNA levels were reduced to <400 copies/mL in 75.5% of patients treated with raltegravir 400 mg twice daily plus OBT compared with 39.3% of patients in the placebo plus OBT group (n = 237).[7] Similarly, HIV-1 RNA levels were reduced to <50 copies/mL in 62.6% of the raltegravir treatment arm versus 33.3% in the placebo arm.[7] CD4+ cell counts increased by a mean of 89 cells/mm^3 in patients receiving raltegravir plus OBT and by a mean of 35 cells/mm^3 in those receiving placebo plus OBT.[7]

Dose-Ranging Trial

The BENCHMRK trial data are supported by results from a phase II, randomized, double-blind, dose-ranging trial in ART-experienced patients with HIV-1 infection (protocol 005).[13,25] Primary endpoints were defined as a change from baseline in HIV-1 RNA (log_{10} copies/mL) at week 24; secondary endpoints were defined as the proportion of patients achieving viral loads of <400 copies/mL, <50 copies/mL and a change from baseline in CD4+ cell counts at week 24.[25]

• In ART-resistant patients, the addition of raltegravir to OBT resulted in significantly greater virological efficacy compared with OBT alone. In a 24-week trial in 178 patients, all dosages of raltegravir (200, 400 and 600 mg twice daily) provided better viral suppression than placebo ($p < 0.0001$) when added to an OBT regimen.[13]

• At week 24, the proportion of patients with HIV-1 RNA <400 copies/mL was 70% in the 200 mg group, 64.5% in the 400 mg group and 62.5% in the 600 mg group compared with 12.1% in the placebo group ($p < 0.0001$ all groups). The proportion of patients with HIV-1 RNA <50 copies/mL was 65% (200 mg group), 56% (400 mg group), and 67% (600 mg group) versus 13% in the placebo group ($p < 0.0001$ all groups). The CD4+ cell count increase from baseline, following 24 weeks of raltegravir treatment, was 60.5 cells/mm^3 (200 mg group), 102.3 cells/mm^3 (400 mg group) and 93.8 cells/mm^3 (600 mg group) versus 8.4 cells/mm^3 with placebo ($p < 0.0001$ all groups).[13]

• After 48 weeks of therapy, the corresponding proportions of patients with HIV-1 RNA copies <400 copies/mL were 69% (200 mg group), 64% (400 mg group) and 71% (600 mg group) versus 13% in the placebo group. The proportion of patients with HIV-1 RNA copies <50 copies/mL were 64% (200 mg group), 46% (400 mg group) and 53% (600 mg group) versus 9% in the placebo group.[25] The mean increase from baseline in CD4+ cell counts at week 48 ranged from 64 to 110 cells/mm^3 across the raltegravir groups with an increase of 93.7 cells/mm^3 at 400 mg twice daily.[25]

4. Tolerability

The tolerability profile of raltegravir as a component of combination therapy in ART-experienced patients (aged ≥16 years) has been evaluated in both BENCHMRK trials,[7-9] and in one fully published, dose-ranging, phase II trial.[13] Similarly, tolerability of both short-term monotherapy (10 days)[20] and long-term combination therapy (24 and 48 weeks)[23] has also been evaluated in a fully published, two-part, dose-ranging trial in ART-naive patients (protocol 004).

• Raltegravir therapy was generally well tolerated across all studies, with the most frequent drug-related adverse events (incidence ≥2%) reported being nausea, headache and diarrhoea.[7-9,13,20,23]

• In patients with ART-resistant HIV-1 infection receiving raltegravir 200–600 mg twice daily for 24 weeks, the tolerability profile of raltegravir was broadly similar to that of placebo,[13] with 2% of patients in each treatment group discontinuing therapy because of adverse experiences. Raltegravir 400 mg twice daily (n = 45) resulted in 2.2% of patients experiencing diarrhoea and 4.4% experiencing nausea.[13]

• Adverse events, mostly mild to moderate, were seen with similar frequency in the raltegravir and placebo arms in the two randomized BENCHMRK studies.[8,9] Approximately 83% of patients, regard-

less of which treatment they received, experienced at least one mild adverse event.

- In pooled data from the BENCHMRK studies, drug-related moderate to severe adverse events occurring in ≥2% of patients were diarrhoea (3.7% of raltegravir vs 4.6% of placebo recipients), nausea (2.2% vs 3.2%) and headache (2.4% vs 1.4%); statistical analysis was not reported.[7]
- The tolerability profile of raltegravir was broadly similar in patients with hepatitis B and hepatitis C co-infection.[7]
- Patients responding to ART during the initial phase of treatment may develop an inflammatory response to opportunistic infections (such as cytomegalovirus, pneumonia, tuberculosis or varicella zoster virus), which may require further treatment.[7]
- An imbalance of malignancies was observed in the raltegravir arms of both BENCHMRK studies,[8,9] which was anticipated in a severely immunodeficient HIV-1 population. However, further follow-up of the same study cohorts has shown that this imbalance of malignancies was not maintained after an additional 7 months of follow-up.[26]

5. Dosage and Administration

In adult patients with ART-resistant HIV-1 infection, the recommended dosage of raltegravir is 400 mg twice daily with or without food.[7] Coadministration with strong inducers of UGT 1A1 (e.g. rifampicin) should be exercised with caution due to reduced plasma concentrations of raltegravir. Treatment with raltegravir in pregnancy should only be considered if maternal benefit outweighs fetal risk.[7] Local prescribing information should be consulted for other contraindications, warnings or recommended dosage adjustments in special patient groups.

6. Raltegravir: Current Status

Raltegravir received accelerated approval in the US for treatment of HIV-1 infection in treatment-experienced adult patients exhibiting resistance to one or more classes of antiretroviral agents.[7] In two large, well designed, phase III, ongoing trials (BENCHMRK-1 and BENCHMRK-2),[8,9,24] raltegravir has been shown to produce beneficial effects in terms of viral load and CD4+ cell counts in ART-experienced patients with HIV-1 infection after 24 weeks of therapy. Treatment with raltegravir was generally well tolerated.

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Correspondence: *Jamie D. Croxtall*, Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand. E-mail: demail@adis.co.nz