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Raltegravir

Updated: January 30, 2018.

OVERVIEW

Introduction

Raltegravir is an integrase inhibitor, the first of the class of antiviral agents active against the human immunodeficiency virus (HIV) that targets the viral integrase. Raltegravir is used in combination with other antiretroviral agents in the treatment of HIV infection. Raltegravir has not been linked convincingly to serum aminotransferase elevations during therapy or to episodes of acute, clinically apparent liver injury.

Background

Raltegravir (ral teg' ra vir) is relatively new antiretroviral drug that targets the HIV integrase, one of the three enzymes involved in viral replication. Raltegravir blocks the binding site of the HIV integrase and prevents the strand transfer activity and integration of the provirus into the host genome. Raltegravir has both in vitro and in vivo activity against HIV, and several randomized controlled trials have shown that it leads to significant decline in HIV RNA levels and rises in peripheral CD4 T cell counts. Raltegravir was given accelerated approval for use in HIV infection in the United States in 2007 and is currently used in an increasing proportion of antiretroviral regimens. Raltegravir is available as 400 mg tablets generically and under the brand name Isentress. The recommended dose regimen is 400 mg twice daily in combination with other classes of antiretroviral agents. Common side effects include diarrhea, headache, nausea and fever.

Hepatotoxicity

In large clinical trials, therapy with raltegravir was associated with alanine aminotransferase (ALT) elevations in up to 10% and elevations of greater than 5 times the upper limit of normal (ULN) in 3% to 4% of patients, but these rates were similar to those in comparator groups receiving matched background optimized antiretroviral therapy without raltegravir. These elevations were not associated with clinical symptoms and generally did not require dose modification. There have been no published reports of clinically apparent cases of liver injury attributed to raltegravir. Nevertheless, the product label for raltegravir mentions hepatitis and hepatic failure as a potential adverse reactions, but without specific details. Raltegravir has also been linked to instances of Stevens Johnson syndrome and drug hypersensitivity reactions, which can be accompanied by hepatic involvement. Finally, initiation of antiretroviral therapy with raltegravir can result in the immune reconstitution syndrome which may cause a worsening or flare of an accompanying chronic hepatitis B or C in coinfected individuals.

Likelihood score: E* (unproven but suspected cause of clinically apparent liver injury).

Mechanism of Injury

Raltegravir is metabolized by the liver and undergoes glucuronidation as a part of its metabolic clearance. It does not have an effect on the CYP 450 system.

Outcome and Management

Serum enzyme elevations during raltegravir therapy are not uncommon but are generally mild to moderate in severity and often are attributable to other agents taken in combination with raltegravir. Nevertheless, aminotransaferase elevations above 5 times the ULN, if confirmed, warrant dose interruption and evaluation for other causes of acute liver injury. There is no information about the cross sensitivity to liver injury among the various HIV integrase inhibitors, but some degree of cross reactivity should be expected.

Drug Class: Antiviral Agents

Other Drugs in the Subclass, Integrase Strand Transfer Inhibitors: Bictegravir, Cabotegravir, Dolutegravir, Elvitegravir

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Raltegravir – Isentress®

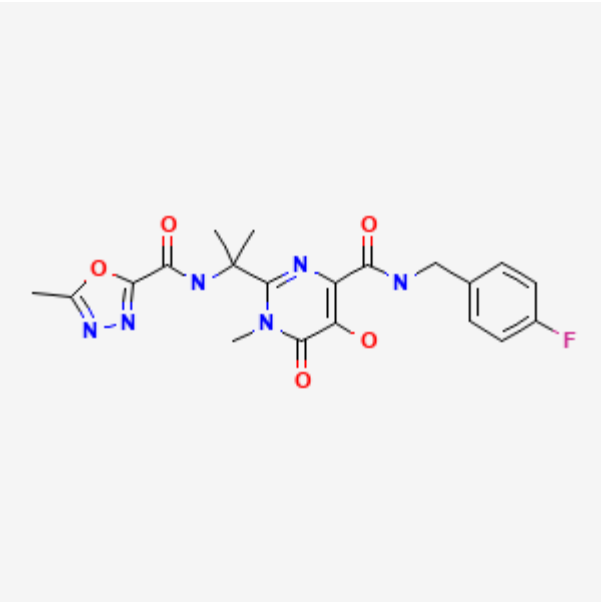
DRUG CLASS

Antiviral Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Raltegravir	518048-05-0	C20-H21-F-N6-O5	

ANNOTATED BIBLIOGRAPHY

References updated: 30 January 2018

Núñez M. Hepatic toxicity of antiviral agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 505-18.

(Review of hepatotoxicity of antiviral agents including raltegravir).

Flexner C. Antiretroviral agents and treatment of HIV infection. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1623-64.

(Textbook of pharmacology and therapeutics).

Available at: https://hivinfo.nih.gov/hiv-source/medical-practice-guidelines/hiv-treatment-guidelines

(Clinical guidelines on the use of antiretroviral agents in HIV-1 infected adults, adolescents and children).

Markowitz M, Nguyen BY, Gotuzzo E, Mendo F, Ratanasuwan W, Kovacs C, Prada G, et al. Protocol 004 Part II Study Team. Rapid and durable antiretroviral effect of the HIV-1 Integrase inhibitor raltegravir as part of combination therapy in treatment-naive patients with HIV-1 infection: results of a 48-week controlled study. J Acquir Immune Defic Syndr. 2007;46:125–33. PubMed PMID: 17721395.

(Results of a phase II trial of 4 doses of raltegravir vs efavirenz in 198 patients on background optimized regimen for 48 weeks; ALT and AST elevations were rare and similar in rate in both groups).

Grinsztejn B, Nguyen BY, Katlama C, Gatell JM, Lazzarin A, Vittecoq D, Gonzalez CJ, et al; Protocol 005 Team. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial. Lancet. 2007;369:1261–9. PubMed PMID: 17434401.

(Results of phase II trial of in 133 patients with HIV given raltegravir and 45 placebo in combination with background antiretrovirals for at least 24 weeks; tolerability with raltegavir therpay was no different than placebo, although pruritus [4.5% vs 0%] and hyperbilirubinemia [6.8% vs 4.4%] were more common; ALT levels not reported).

Two new drugs for HIV infection. Med Lett Drugs Ther. 2008;50:2–4.

(Concise summary of role of ralegravir and maraviroc in treatment-refractory or treatment-experienced patients with HIV infection; hepatotoxicity was reported with maraviroc [with rash and eosinophilia], but not with raltegravir).

Croxtall JD, Lyseng-Williamson KA, Perry CM. Raltegravir. Drugs. 2008;68:131–8. PubMed PMID: 18081377.

(Brief review of structure, activity, pharmacokinetics and pharmacodynamics, clinical efficacy and tolerability of raltegravir; no mention of hepatotoxicity).

Evering TH, Markowitz M. Raltegravir: an integrase inhibitor for HIV-1. Expert Opin Investig Drugs. 2008;17:413–22.

(Review of raltegravir, first integrase inhibitor of HIV approved for use in US, no mention of hepatotoxicity).

Cocohoba J, Dong BJ. Raltegravir: the first HIV integrase inhibitor. Clin Ther. 2008;30:1747–65. PubMed PMID: 19014832.

(Review of the mechanism of action, pharmacokinetics, and phase I-III studies of raltegravir; in combined phase III studies, ALT elevations above 5 times ULN occurred in 4.3% of 462 raltegravir treated vs 3.4% of 237 placebo treated patients who were receiving optimized background therapy; no hepatic serious adverse events were reported).

Siegel MO, Kan VL, Benator DA. Raltegravir for postexposure prophylaxis following occupational exposure to HIV. AIDS. 2008;22:2552–3. PubMed PMID: 19005284.

(Two health care workers with multidrug resistant HIV exposures were given raltegravir with 3-4 other agents, no apparent side effects from raltegravir and neither became HIV positive).

Fleischbein E, O'Brien J, Martelino R, Fenstersheib M. Elevated alkaline phosphatase with raltegravir in a treatment experienced HIV patient. AIDS. 2008;22:2404–5. PubMed PMID: 18981785.

(45 year old man with AIDS developed elevated Alk P [85 rising to 1053 U/L], which resolved upon stopping and recurred on rechallenge with raltegravir; serum bilirubin, ALT and GGT levels were normal, but authors suspected liver as the source anyways).

Steigbigel RT, Cooper DA, Kumar PN, Eron JE, Schechter M, Markowitz M, Loutfy MR, et al; BENCHMRK Study Teams. Raltegravir with optimized background therapy for resistant HIV-1 infection. N Engl J Med. 2008;359:339–54. PubMed PMID: 18650512.

(Combined results of 2 large trials of raltegravir [n=462] vs placebo [n=237] with optimized background antiretrovirals for HIV infection reported similar rates of adverse events in two groups; ALT >5 times ULN in 4.3% vs 3.4%, Alk P >5 times ULN in 1.1% vs 1.7%, bilirubin >2.5 times ULN in 3.7% vs 2.5%; all not significantly different; no reports of hepatitis, one case of liver cancer).

Hammer SM, Eron JJ Jr, Reiss P, Schooley RT, Thompson MA, Walmsley S, Cahn P, et al; International AIDS Society-USA. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. JAMA. 2008;300:555–70. PubMed PMID: 18677028.

(Recommendations on use of antiviral therapy in adults with HIV infection including use of recently approved agents: raltegravir, maraviroc and etravirine).

Evering TH, Markowitz M. Raltegravir: an integrase inhibitor for HIV-1. Expert Opin Investig Drugs. 2008;17:413–22.

(Review of chemical structure, mechanism of action, pharmacology, clinical efficacy and safety of raltegravir; no mention of ALT elevations, jaundice or clinically apparent hepatotoxicity; rates of side effects were similar in raltegravir to those in comparator arms).

Hughes CA, Robinson L, Tseng A, MacArthur RD. New antiretroviral drugs: a review of the efficacy, safety, pharmacokinetics, and resistance profile of tipranavir, darunavir, etravirine, rilpivirine, maraviroc, and raltegravir. Expert Opin Pharmacother. 2009;10:2445–66. PubMed PMID: 19678794.

(Review of tipranavir, darunavir, etravirine, rilpivirine, maraviroc and raltegravir; "Raltegravir was well tolerated.." with similar rates of adverse events for raltegavir and comparator arms).

Lennox JL, DeJesus E, Lazzarin A, Pollard RB, Madruga JV, Berger DS, Zhao J, et al; STARTMRK investigators. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naï patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. Lancet. 2009;374:796–806. Erratum in: Lancet 2009; 374: 786. Lancet 2009; 374: 2054. PubMed PMID: 19647866.

(Trial comparing raltegravir to efavirenz and optimized background antiretroviral therapy for 48 weeks in 566 patients with HIV infection; ALT and AST elevations >5 times ULN occurred in 2% of both groups).

Moreno A, Quereda C, Fortún J, Bárcena R, Pérez-Elías MJ, Casado JL, Rodríguez-Sagrado MA, et al. Safe co-administration of raltegravir, pegylated-interferon and, ribavirin in HIV individuals with hepatitis C virus-related liver damage. AIDS. 2010;24:1231–3. PubMed PMID: 20421744.

(Among 5 patients with HIV infection and severe hepatitis C treated with peginterferon and ribavirin while on an antiretroviral regimen including raltegravir, 2 had a sustained response [both genotype 3], 2 did not respond and 1 died of a bacterial infection).

Vispo E, Mena A, Maida I, Blanco F, Cordoba M, Labarga P, Rodriguez-Novoa S, et al. Hepatic safety profile of raltegravir in HIV-infected patients with chronic hepatitis C. J Antimicrob Chemother. 2010;65:543–7. PubMed PMID: 20032006.

(Among 218 patients with HIV starting on raltegravir, ALT elevations occurred in 8% without and 25% with HCV coinfection over a 2 year period, and elevations >5 times ULN occurred only in coinfected patients [n=3; 4%], and each could be attributed to other factors and resolved without stopping raltegravir).

Ortu F, Weimer LE, Floridia M, Manconi PE. Raltegravir, tenofovir, and emtricitabine in an HIV-infected patient with HCV chronic hepatitis, NNRTI intolerance and protease inhibitors-induced severe liver toxicity. Eur J Med Res. 2010;15:81–3. PubMed PMID: 20452889.

(43 year old woman with HIV/HCV coinfection who developed symptomatic elevations of serum enzymes on saquinavir, fosamprenavir and again on darunavir, was adequately maintained on tenofovir/emtricitabine and raltegravir).

Rockstroh J, Teppler H, Zhao J, Sklar P, Harvey C, Strohmaier K, Leavitt R, et al. Safety and efficacy of raltegravir in patients with HIV-1 and hepatitis B and/or C virus coinfection. HIV Med. 2012;13(2):127–31. PubMed PMID: 21599819.

(Review of 3 trials of raltegravir for rate of adverse events in patients with HIV infection with and without hepatitis B or C; ALT elevations >5 times ULN occurred in higher proportion of patients with hepatitis coinfection, but rates were similar with raltegravir as with comparator arms).

Macías J, Neukam K, Portilla J, Iribarren JA, de Los Santos I, Rivero A, Márquez M, et al. HEPRAL study team. Liver tolerance of raltegravir-containing antiretroviral therapy in HIV-infected patients with chronic hepatitis C. J Antimicrob Chemother. 2011;66:1346–50. PubMed PMID: 21398295.

(Among 108 patients with HIV-HCV coinfection started on antiretroviral therapy including raltegravir, 10 patients [9.3%] developed ALT elevations >5 times ULN, but all resolved and no patient discontinued raltegravir permanently for liver test abnormalities).

Mangiafico L, Perja M, Fusco F, Riva S, Mago D, Gringeri A. Safety and effectiveness of raltegravir in patients with haemophilia and anti-HIV multidrug resistance. Haemophilia. 2012;18:108–11. PubMed PMID: 21762404.

(Among 7 patients with hemophilia and HIV-HCV coinfection on antiretroviral regimens including raltegravir, only 1 had an increase in liver enzyme levels and "cholestasis", which resolved promptly when maraviroc was discontinued while raltegravir was continued).

Rockstroh J, Sklar P, Wan H, Teppler H, Harvey C, Strohmaier K, Leavitt R, et al. Safety and efficacy of raltegravir in patients co-infected with HIV and hepatitis B and/or C virus: complete data from Phase III double-blind studies. .J Int AIDS Soc. 2012;15(S4):1–2.

(Abstract: among 743 raltegravir and 519 comparator treated subjects, ALT elevations >5 times ULN occurred in similar proportions of patients, but were more common in those with HCV or HBV coinfection [6-15%] than in those with HIV infection alone [3-4%]).

Annandale D, Richardson C, Fisher M, Richardson D. Raltegravir-based post-exposure prophylaxis (PEP): a safe, well-tolerated alternative regimen. .J Int AIDS Soc. 2012;15(S4):1–1.

(Abstract: among 33 persons given a 28 day course of three antiretroviral drugs including raltegravir after a high risk HIV exposure, none developed significant liver or renal toxicity).

Mateo-Carrasco H, Gálvez-Contreras MC, Fernández-Ginés FD, Nguyen TV. Elevated liver enzymes resulting from an interaction between raltegravir and Panax ginseng: a case report and brief review. Drug Metabol Drug Interact. 2012;27:171–5. PubMed PMID: 23092794.

(Abstract: patient with chronic hepatitis C and HIV infection on long term therapy with raltegravir, lopinavir/r, aspirin and esomeprazole developed jaunidce 39 days after starting ginseng, which improved on stopping ginseng; the authors suggest that drug-drug interactions accounted for the hepatotoxicity).

Weimer LE, Fragola V, Floridia M, Guaraldi G, Ladisa N, Francisci D, Bellagamba R, et al; ISS-NIA Study Group. Response to raltegravir-based salvage therapy in HIV-infected patients with hepatitis C virus or hepatitis B virus coinfection. J Antimicrob Chemother. 2013;68:193–199. PubMed PMID: 22984206.

(Among 275 patients with HIV infection who were switched to a raltegravir containing antiretroviral regimen, 23 developed ALT or AST elevations above 5 times ULN [16% in coinfected; 3.6% non-coinfected], but no details given).

Surgers L, Lacombe K. Hepatoxicity of new antiretrovirals: a systematic review. Clin Res Hepatol Gastroenterol. 2013;37:126–33. PubMed PMID: 23522569.

(Review of evidence of liver injury in large clinical trials of newer antiretroviral agents including raltegravir concluded that "the overall hepatic tolerance is far better with the novel drugs in this review than with former ARV regimens"; ALT elevations occurred with equal frequency in raltegravir and comparator arms, and one patient on raltegravir developed DRESS syndrome).

Cahn P, Pozniak AL, Mingrone H, Shuldyakov A, Brites C, Andrade-Villanueva JF, Richmond G, et al. extended SAILING Study Team. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet. 2013;382:700–8. PubMed PMID: 23830355.

(Among 715 patients with HIV infection treated with either dolutegravir or raltegravir combined with background antiretroviral therapy, adverse events were similar between the two groups and 3% vs 2% developed ALT elevations above 5 times ULN; no mention of clinically apparent liver injury).

Eron JJ, Cooper DA, Steigbigel RT, Clotet B, Gatell JM, Kumar PN, Rockstroh JK, et al; BENCHMRK Study Teams. Efficacy and safety of raltegravir for treatment of HIV for 5 years in the BENCHMRK studies: final results of two randomised, placebo-controlled trials. Lancet Infect Dis. 2013;13:587–96. PubMed PMID: 23664333.

(Combined analysis of two large trials of raltegravir vs placebo in 699 patients with HIV infection for up to 5 years found a low rate of ALT elevations above 5 times ULN [6-7%] that was similar to the rate in controls [4.2%]; no mention of clinically apparent liver injury).

Vispo E, Fernández-Montero JV, Labarga P, Barreiro P, Soriano V. Low risk of liver toxicity using the most recently approved antiretroviral agents but still increased in HIV-hepatitis C virus coinfected patients. AIDS. 2013;27:1187–8. PubMed PMID: 23739226.

(Among 1982 HIV infected persons with 2717 initation episodes of antiretroviral therapy, 9% developed enzyme elevations, 6% in HCV negative and 17% in HCV positive subjects, but enzyme levels were above 5 times ULN in only 0.4% of cases).

Hurt CB, Napravnik S, Moore RD, Eron JJ Jr. Hepatic safety and tolerability of raltegravir among HIV patients coinfected with hepatitis B and/or C. Antivir Ther. 2014;19:415–22. PubMed PMID: 24458137.

(Among 456 adults with HIV infection treated with raltegravir, those coinfected with HCV [n=138] or HBV [n=17] or both [n=11] were more likely to have serum enzyme elevations at baseline and had a 2.7-fold increased rate of severe elevations [above 5 times ULN] during therapy).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology. 2015;148:1340–52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 12 were due to antiretroviral agents, but none were attributed to raltegravir or other HIV integrase inhibitors).

de Castro N, Braun J, Charreau I, Lafeuillade A, Viard JP, Allavena C, Aboulker JP, et al; EASIER ANRS 138 study group. Incidence and risk factors for liver enzymes elevations in highly treatment-experienced patients switching from enfuvirtide to raltegravir: a sub-study of the ANRS-138 EASIER trial. AIDS Res Ther. 2016;13:17. PubMed PMID: 27042193.

(Extensive analysis of ALT elevations that occurred in 169 HIV positive patients who were maintained on enfuvirtide or switched to raltegravir suggested that the elevations were most likely due to concurrent tipranavir use).

Neukam K, Mira JA, Collado A, Rivero-Juárez A, Monje-Agudo P, Ruiz-Morales J, Ríos MJ, et al; HEPAVIR SEG-HEP-2007 Study Group of the Sociedad Andaluza de Enfermedades Infecciosas (SAEI). Liver toxicity of current antiretroviral regimens in HIV-infected patients with chronic viral hepatitis in a real-life setting: The HEPAVIR SEG-HEP Cohort. PLoS One. 2016;11:e0148104. PubMed PMID: 26848975.

(Among 192 adults with HIV and either HBV or HCV coinfection who were started on antiretroviral therapy and monitored under "real life" conditions, ALT and AST elevations above 5 times ULN occurred in 10 patients [5%], but all were self limited and none required discontinuation of therapy for this reason).

Cahn P, Kaplan R, Sax PE, Squires K, Molina JM, Avihingsanon A, Ratanasuwan W, et al; ONCEMRK Study Group. Raltegravir 1200 mg once daily versus raltegravir 400 mg twice daily, with tenofovir disoproxil fumarate and emtricitabine, for previously untreated HIV-1 infection: a randomised, double-blind, parallel-group, phase 3, non-inferiority trial. Lancet HIV. 2017;4(11):e486–e494. PubMed PMID: 28918877.

(Among 802 adults with HIV infection treated with once or twice daily raltegravir for 48 weeks, efficacy and tolerability were similar in the two groups, while ALT elevations above 2.5 times ULN occurred in 2.5% of patiients on once vs 0.8% on twice daily raltegravir).