New therapeutic strategies for raltegravir

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Raltegravir (Isentress®) is the first approved HIV integrase inhibitor. Agents in this class target a different viral enzyme compared with agents inhibiting reverse transcriptase and protease. A wide number of patients are currently susceptible to integrase inhibitors, including heavily antiretroviral-experienced patients harbouring drug-resistant viruses. The good tolerability and convenience of raltegravir have recently begun to be appreciated, leading to the consideration of other indications for the drug. Data recently released using the drug as first-line therapy or in switch strategies are very promising and the role of raltegravir in intensification therapy is currently under investigation. Altogether, the current information supports a broad use of raltegravir beyond its initial approval for antiretroviral-experienced HIV-infected patients.

Keywords: HIV, integrase inhibitors, antiretroviral therapy

Introduction

Integration is one of the essential steps in the HIV-1 replication cycle. It comprises five different steps, all of which could be considered as potential inhibition targets, although only strand transfer inhibitors have so far successfully been developed for therapeutic purposes. Raltegravir (Isentress®) is the first-in-class marketed HIV-1 integrase inhibitor. It was approved by the US FDA in October 2007 for use as part of antiretroviral therapy in heavily drug-experienced patients.

Nonetheless, due to its excellent safety profile and proven potency, raltegravir has increasingly been considered for alternative therapeutic situations, including naive individuals. In July 2009, the drug received its approval for use as part of first-line HIV-1 therapy. Results from the main trials evaluating raltegravir are summarized in Table 1. In addition, several ongoing trials are being conducted in order to evaluate raltegravir performance in the setting of: (i) simplification strategies in patients experiencing adverse events or complaining of inconvenience while having undetectable viraemia under another therapy; (ii) intensification purposes in patients with poor CD4 gains despite undetectable viraemia with their current therapy; and (iii) anecdotal and/or investigational situations, as part of attempts for eradication or in cases of post-exposure prophylaxis. Although raltegravir is only another antiretroviral in the already large HIV armamentarium, its innovative features may position it first past the winning post. In this review we will discuss some of the most attractive indications for raltegravir use.

Mechanism of action and resistance to raltegravir

Raltegravir harbours a structural motif with metal-chelating functions and therefore it has been shown that it may interact with divalent metals within the active site of the HIV-1 integrase, preventing the strand transfer step during the integration process. Since raltegravir targets a different enzyme from the classical antiretroviral agents, reverse transcriptase and protease inhibitors, a lack of cross-resistance between raltegravir and other currently available antiretroviral drugs is expected. This is why raltegravir was initially conceived for the treatment of heavily antiretroviral-experienced patients with limited treatment options.

However, failure on raltegravir is associated with the development of mutations in the integrase region. There are three major resistance mutations: N155H; Q148H/K/R; and Y143R. They generally do not overlap and do not appear together in the same viral genome. These mutations have proven to cause high-level resistance to elvitegravir, another HIV integrase inhibitor in the late stages of clinical development. The high degree of cross-resistance between raltegravir and elvitegravir precludes these two drugs being used in sequence. In contrast, S/GSK1349572 and S/GSK1265744 are two new second-generation integrase inhibitors under development that have proven to be active against viral isolates harbouring resistance mutations to raltegravir and elvitegravir. Clinical trials are being conducted, evaluating their use as salvage therapy in patients failing first-generation integrase inhibitors.

Long-term data with clinical experience using raltegravir are not yet available and knowledge about resistance is still scarce. Data from clinical trials as well as clinical experience show that a high proportion of patients (30%–60%) failing raltegravir do not develop resistance mutations in the integrase, suggesting that other factors, such as drug compliance, drug interactions or pharmacokinetic parameters, might influence virological failure under raltegravir therapy.
Salvage therapy

Raltegravir was originally approved for the treatment of antiretroviral-experienced patients failing other therapy, mainly based on its lack of cross-resistance to other antiretroviral agents. The pivotal BENCHMRK-1 and -2 trials\(^9,10\) tested the safety and efficacy of 400 mg of raltegravir twice daily compared with placebo, always along with an optimized background therapy (OBT), in HIV-1 patients with triple-class drug resistance. Results at week 96 revealed that 58% of patients on raltegravir had viral suppression compared with 26% of patients in the placebo arm. CD4 gains were also superior in the raltegravir group compared with the control arm, with a mean increase of 123 versus 49 cells/mm\(^3\), respectively.

The best virological responses in the BENCHMRK studies were obtained when raltegravir was administered along with two fully active drugs, and especially if darunavir or enfuvirtide were included in the OBT and used for the first time. These results were further confirmed in the ANRS 139 TRIO trial, which evaluated the combination of raltegravir, darunavir and etravirine in patients with multidrug-resistant strains, showing that up to 86% of patients achieved undetectable viraemia.\(^9,13\) Conversely, patients on functional monotherapy with raltegravir were more likely to fail therapy and develop resistance.\(^9,13\) In this regard, efficacy results stratified by genotypic sensitivity score (GSS) showed that when raltegravir was the only fully active drug (GSS = 0), 45% of patients achieved undetectable viraemia, while when the GSS was 1, the rate increased to 67%; lastly, with a GSS/C21 the percentage of aviraemic patients rose to 75%.\(^10\)

Overall, raltegravir was generally well tolerated in the BENCHMRK studies, with very few serious drug-related adverse events (2.8% compared with 3.8% in the placebo arm) and a low proportion of patients experiencing grade 3–4 laboratory abnormalities (always <10%). A prior dose-ranging study also conducted in antiretroviral-experienced patients (study P005)\(^14\) showed similar results, with 56%–67% of patients achieving

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QD, once daily dosing; BID, twice daily dosing; RAL, raltegravir; EFV, efavirenz; ENF, enfuvirtide; LPV/r, lopinavir/ritonavir.

Values in parentheses after dosing regimens express the number of patients included in the study.
undetectable viraemia and mean CD4 gains of 63–113 CD4+ T cells/mm³ at week 24. Besides the information derived from registrational trials, all available data from Phase IV studies and clinical experience using raltegravir in patients with multidrug-resistant viruses have been equally satisfactory.\(^{15}\)

**First-line therapy**

Given the good results obtained in antiretroviral-experienced patients, raltegravir use has been tested in other situations, one of the most attractive being first-line therapy. Two clinical studies (P004\(^{16–18}\) and STARTMRK\(^{19}\)) have evaluated the outcomes of raltegravir in drug-naive individuals. Both studies proved that raltegravir was non-inferior to efavirenz in its ability to suppress plasma HIV-RNA to <50 copies/mL. Study P004 recruited 198 drug-naive patients, who received raltegravir at different doses or efavirenz, along with tenofovir plus lamivudine.\(^{18}\) At week 48, 83%–88% (depending on doses) of patients receiving raltegravir achieved undetectable viraemia compared with 87% of patients in the efavirenz group. The mean change in CD4 counts at that time was 170 cells/mm\(^3\) in the efavirenz arm and ranged from 144 to 221 cells/mm\(^3\) in the raltegravir groups. After week 48, a raltegravir dose of 400 mg twice daily was chosen for all patients and the study continued until week 96.\(^{17}\) Then, 83% of patients on efavirenz and 84% of those on raltegravir remained with plasma HIV-RNA at <50 copies/mL, CD4 gains being similar in both arms (220 versus 232 cells/mm\(^3\), respectively). Clinical adverse events were less frequent in the raltegravir group than in the efavirenz arm (51% versus 74%, respectively), while laboratory abnormalities were very infrequent in both treatment arms. At week 144, 78% of patients on raltegravir remained aviraemic compared with 76% in the efavirenz arm, and CD4 gains were of 252 versus 233 cells/mm\(^3\), respectively.\(^{18}\)

The STARTMRK trials 1 and 2 randomized 563 previously untreated HIV-1 individuals to 400 mg of raltegravir twice daily or 600 mg of efavirenz once daily, each in combination with fixed-dose tenofovir/emtricitabine (Truvada\(^{9,19}\)). At week 48, fewer virological failures occurred in patients allocated to raltegravir rather than efavirenz (10% versus 14%, respectively). Moreover, time to virological response was significantly shorter in the raltegravir arm than in patients on efavirenz. Although the clinical relevance of this finding remains unclear, this observation might be important in special situations, such as: (i) in primary HIV-1 infection, in order to rapidly reduce viral replication and, consequently, the size of the infected reservoir; or (ii) in pregnant women, to reduce the possibility of fetal transmission. Patients receiving raltegravir experienced significantly fewer moderate to severe drug-related clinical adverse events than those treated with efavirenz (16% versus 32%; \(P<0.001\)), including fewer grade 3–4 lipid abnormalities. These results led to the FDA approval of raltegravir for the treatment of drug-naive patients in July 2009.\(^{5}\)

**Simplification**

Since raltegravir has not only proven high virological and immunological benefit but also an excellent safety profile, it has been proposed as a good candidate as part of simplification strategies in patients with already undetectable viraemia but complaining of side effects. In the EASIER–ANRS 138 study\(^{20}\) and the CHEER study,\(^{21}\) a switch to raltegravir replacing enfuvirtide was tested. In the EASIER trial, 170 patients clinically stable with an enfuvirtide-containing regimen were randomized to either remain on the same treatment or to switch to raltegravir. After 48 weeks, 90% of patients kept undetectable viraemia and CD4 counts remained stable in both arms. In the CHEER study, 52 patients switched from enfuvirtide to raltegravir, resulting in the maintenance of undetectable viraemia in 49 (94.2%) of them after 24 weeks. On the basis of these results, changing from enfuvirtide to raltegravir in patients with undetectable viraemia appears to be safe.

Besides the two prior studies conducted by external investigators, Merck, the company marketing raltegravir, tested the drug as a switch strategy in the SWITCHMRK trial.\(^{22}\) A total of 699 patients with undetectable viraemia under a lopinavir-based regimen were randomized to switch to raltegravir or continue on lopinavir/ritonavir. After 24 weeks, 90.3% of patients on lopinavir remained with undetectable viraemia, compared with only 84.4% of those who switched to raltegravir. The study did not prove the non-inferiority of a raltegravir switch and, accordingly, the trial was halted prematurely. It should be noted, however, that the study design of the SWITCHMRK trial might have been biased against raltegravir. In the PI arm, the study only recruited patients who tolerated lopinavir well and were experiencing virological success and any negative behaviour of lopinavir had already been filtered and excluded. However, this was not the case for the new tested drug. In addition, almost all failures in the raltegravir arm occurred in patients harbouring viruses resistant to nucleoside analogues received in the past. A critical review of the SWITCHMRK results has concluded that a switch to raltegravir in patients having undetectable viraemia under a lopinavir-based regimen is safe, as long as no prior failures on nucleoside analogues have occurred. Otherwise, functional monotherapy is risky using a drug such as raltegravir, with a relatively low genetic barrier to resistance.

Other studies [e.g. SPIRAL and the ODIS (‘Once Daily Isentress’)] are being conducted to test raltegravir as part of switch strategies, mainly in patients treated with protease inhibitors, because of the metabolic side effects and the general inconvenience of these drugs. Moreover, the ODIS trial, in which raltegravir is given once a day, has been designed based on pharmacodynamic evidence, which supports a long intracellular half-life of the raltegravir inhibitory activity,\(^{23,24}\) and the preliminary results of a pilot clinical study.\(^{25}\) The ODIS study assesses the efficacy and safety of raltegravir once a day as part of a simplification strategy. The results will be released in early 2010.

**Intensification**

Although most recommended triple antiretroviral regimens are able to suppress plasma viraemia to undetectable levels in the majority of patients who are compliant with their medication, it is clear that ongoing residual replication persists in most cases. Using ultrasensitive viral load assays, low-level plasma viraemia (from 1 to 49 HIV-RNA copies/mL) is recognized in the majority of patients. The source of this virus escape seems to
be long-lived infected cells that persistently release virions or, alternatively, anatomical compartments where drugs do not reach adequate inhibitory concentrations. A different situation exists in patients in whom the achievement of undetectable viraemia is not accompanied by a satisfactory CD4 gain. Patients on antiretroviral therapy remaining with <200 cells/mm$^3$ despite persistent undetectable plasma viraemia might continue to be at risk of developing opportunistic infections and/or neoplasms (although less so than patients with high viraemia). In the past, this subset of immunological non-responders has been subjected to several experimental interventions (e.g. treatment with interleukin 2). In all these situations, addition of another potent antiretroviral agent could further reduce the viral burden and, hopefully, permit an extra CD4 gain. A few studies are currently testing whether adding raltegravir to a virologically suppressive regimen could be beneficial in terms of maximizing viral load reductions and/or raising CD4$^+$ T cells. Preliminary results at week 12 in one of these trials, unfortunately, did not show a significant reduction in plasma HIV-RNA in patients treated with raltegravir versus placebo using ultrasensitive methods (−0.3 versus −0.1 log copies/mL, respectively), although there was a trend for greater CD4 gains (+42 versus −44 cells/mm$^3$, $P=0.08$).

**Other potential therapeutic indications**

The results obtained in adults with raltegravir have made it attractive to explore whether the drug could be used in other particular situations. This is the case for acute HIV-1 infection, HIV-infected children, pregnant women, post-exposure prophylaxis, co-infection with viral hepatitis and, finally, in individuals infected with non-B HIV variants, including HIV-2.

**Acute HIV infection**

Preliminary data indicate that antiretroviral treatment of primary HIV infection is associated with benefits in terms of laboratory markers of disease progression and may be accompanied by significant reductions in the risk of transmission. In addition, during the first weeks of HIV infection the establishment of the HIV cellular reservoir occurs. Given its mechanism of action, preventing viral integration, raltegravir therapy has been envisioned as a way to minimize the size of the body HIV reservoir. Ongoing studies will prove if this is the case.

**Paediatric use**

The approval of raltegravir for the treatment of HIV-infected children requires the collection of information regarding pharmacokinetic behaviour, in order to determine the most adequate dosing. Moreover, safety issues have to be checked carefully in this population. In this regard, the IMPAACT P1066 study has proven that raltegravir can safely be used in children as long as dosing is conveniently adjusted.

**Pregnant women**

HIV-infected women who become pregnant require effective treatment in order to minimize the risk of HIV transmission to the fetus. Since maximal suppression of plasma HIV-RNA in the mother is the best way to ensure both of these goals, the results using raltegravir in both antiretroviral-experienced and drug-naïve individuals are very encouraging. Moreover, the observation of a particularly rapid decay in viraemia in the STARTMRK$^{19}$ trials might be especially convenient for pregnant women who are unaware of their infection and are diagnosed around the time of delivery, in order to maximally reduce the chance of transmission to the newborn. Up to now, raltegravir is classified as FDA pregnancy category C, since no studies have been conducted in pregnant women or neonates. Animal studies, however, have not show any evidence for serious mutagenic teratogenicity or other toxicities in fetuses, although an increase in the incidence of supernumerary ribs has been noted in rats exposed to 3-fold higher doses than the equivalent recommended dose in humans.

**Post-exposure prophylaxis**

The lack of cross-resistance between raltegravir and other antiretroviral agents, along with its good safety profile and high potency, have attracted much attention for using the drug to prevent HIV infection following accidental exposure. The particular mechanism of action of raltegravir, blocking viral integration into the infected cell, is a further argument to defend its use in this setting. Since the design of studies to prove the benefit of any single antiretroviral agent in this situation is very difficult, it is likely that reports of anecdotal cases in which the drug has been associated with lack of HIV transmission will push its use in this situation.

**Patients co-infected with viral hepatitis**

Chronic hepatitis B affects 5%–10% of HIV-infected patients in Western countries, while chronic hepatitis C may be recognized in up to 25%–40% of this population, largely dependent on the proportion of intravenous drug users and/or haemophiliacs. Raltegravir is largely metabolized in the liver by glucuronidation, evading the cytochrome P450 pathway. Although no evidence for liver toxicity was found in the registrational trials, outside minimal increases in bilirubin, it should be noted that co-infected patients were minimally represented in these studies. More recent data testing a large number of co-infected individuals have confirmed the good hepatic safety profile of raltegravir, even in cirrhotic patients.

**HIV-1 non-B subtypes, group O and HIV-2**

The large genetic variability of the HIV genome explains that naturally occurring changes may account for a reduced or absent susceptibility to some compounds that already have proven efficacy against the subtype B variant of HIV-1, which is predominant in Western countries. This is the case for non-nucleoside reverse transcriptase inhibitors when confronting HIV-2 or HIV-1 group O. Fortunately, this does not seem to be the case for raltegravir, which has shown in vitro and in vivo high-inhibitory activity against all HIV variants, including HIV-1 non-B subtypes, group O$^{19,37}$ and HIV-2. This observation is particularly important for HIV-2 and group O carriers, since therapeutic options beyond first-line therapy are often very limited for them.
**Raltegravir limitations**

In light of the good results regarding the efficacy, safety and convenience of raltegravir in the different trials conducted so far, a broader and wider use of the drug must be expected in the near future. However, some caveats merit consideration. First, the current label recommends twice daily dosing for raltegravir, which is obviously less convenient for the patient than once daily dosing, especially when the most prescribed nucleoside analogue backbones (e.g. Truvada® and Kivexa®) are given once daily. The results of clinical studies that are testing the performance of once daily raltegravir (e.g. the currently ongoing ODIS trial mentioned earlier) will clarify if once daily dosing is possible or not. Secondly, the barrier for resistance to raltegravir is low, which may undermine the benefit of the drug when its prescription is not accompanied by at least another potent antiretroviral agent.13 Furthermore, complete cross-resistance to elvitegravir,6 another integrase inhibitor expected to be marketed soon, is of concern. Lastly, but not less important, the cost of raltegravir is high and makes it prohibitive for many patients, mainly in developing countries. Hopefully, the new second-generation integrase inhibitors under development will keep the advantages of raltegravir but overcome some of its limitations, as they will be administered once daily and display a higher genetic barrier to resistance.7,8

**Summary and conclusions**

The arrival of raltegravir has represented a great therapeutic option for HIV-infected patients with multidrug-resistant viruses and limited treatment options. The appreciation of the good safety profile of the drug has rapidly encouraged its consideration in situations other than salvage therapy. Raltegravir has recently been approved for the treatment of drug-naive patients and, awaiting properly designed studies, there is no doubt that the drug will be broadly used as part of simplification regimens. Treatment with raltegravir in particular situations, such as primary HIV infection, co-infection with hepatitis viruses, pregnancy or post-exposure prophylaxis, warrants further consideration, as preliminary evidence supports its use in these situations. Unsolved aspects include the efficacy of once daily administration and efforts to reduce the price. A sustained benefit of this drug will always require a wise selection of accompanying agents, given its low genetic barrier to resistance.

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**References**


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None to declare.


