Integrase inhibitors in the treatment of HIV-1 infection

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Agents active against HIV type 1 (HIV-1) that target the viral integrase by inhibiting the strand transfer step of integration have now entered the clinical arena. Raltegravir is the first in this new class. Clinical trials in treatment-experienced and in treatment-naive patients have shown that raltegravir-containing regimens have potent antiretroviral activity and are well tolerated. Drug resistance emerges relatively frequently in patients who fail therapy and is associated with mutations in the gene encoding the integrase enzyme. Although such mutations often confer cross-resistance to other integrase inhibitors, newer agents in development, such as S/GSK1349572, show promise as potential second-generation integrase inhibitors. Given their potency, safety and novel mechanism of action, integrase inhibitors represent an important advance in HIV-1 therapy.

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Introduction

The identification of three HIV-specific, virally encoded enzymatic processes in the late 1980s offered clear targets for antiviral therapy. Although inhibitors for reverse transcriptase and protease were available for clinical use fairly rapidly, inhibition of the viral integration process was more elusive and the first approved integrase strand transfer inhibitor (INSTI), raltegravir, has only recently entered clinical usage. Nonetheless, this class seems likely to prove a durable and effective part of the anti-HIV armamentarium for the foreseeable future.

Integration is an essential element of the HIV type 1 (HIV-1) replication cycle, allowing the transfer of virally encoded DNA into the host chromosome.1 The process occurs in three steps: formation of a preintegration viral DNA complex; 3′ processing; and strand transfer. Raltegravir (and similar drugs in clinical trials) inhibit the strand transfer step, probably by interacting with divalent cations of the catalytic core of the integrase. This inhibition provides potent in vitro activity against a wide variety of HIV-1 strains (including non-B subtypes) as well as HIV-2 isolates.2 Furthermore, because of their unique mode of action, integrase inhibitors retain activity against isolates that have acquired resistance to other classes of antiretroviral agents.

Activity in treatment-experienced patients

Lack of cross-resistance made study in patients failing antiretroviral therapy a logical first step for the use of a new class of agents such as integrase inhibitors. The pivotal BENCHMRK trials demonstrated that the use of raltegravir was highly effective in achieving viral suppression when combined with an optimized background regimen.3 After 96 weeks of therapy, 57% of raltegravir recipients achieved viral suppression (plasma HIV-1 RNA <50 copies/mL) compared with 26% of placebo recipients (who received only optimized therapy). Subgroup analysis showed, unsurprisingly, that the best results were seen when raltegravir was given with two new agents that were also active against the patient’s virus (in most cases, these two agents were darunavir and enfuvirtide). In these cases, 79% of patients achieved viral suppression, compared with 63% of placebo patients. Nonetheless, even in patients without alternative options (as measured genotypically or phenotypically), a surprisingly large number (41%–48%) had sustained viral suppression with the use of raltegravir compared with placebo (5% response rates). Further subgroup analyses showed that raltegravir was consistently effective in every patient group, even those with traditionally poor prognostic factors, such as high HIV RNA viral load or low CD4 count at initiation of therapy. Significant immunological improvement was seen also, with the CD4 count rising by a mean of 123 cells/mm3 in the raltegravir group (compared with a mean increase of 49 cells/mm3 in the placebo group). Use of raltegravir in these studies was safe, with similar rates of serious clinical or laboratory adverse events in both patient groups. An initial concern about increased cancer rates was alleviated by analysis of all randomized raltegravir trials, which showed that the rates of cancers (either narrowly or broadly defined) were lower in raltegravir-treated patients.6

These studies demonstrated the potency and safety of raltegravir (leading to initial approval in both the USA and Europe) and were also pivotal in informing the clinical community that it was possible to achieve durable, long-term viral suppression in patients with multidrug-resistant HIV, provided one could construct a potent regimen with drugs in classes the patient had not previously seen.
Use in treatment-naive patients

Although there has been a clinical imperative to develop drugs for patients with resistant HIV-1, there is also recognition that although there are many potent regimens that are effective in treatment-naive patients, issues relating to long-term toxicity have limited the actual number of options that are widely available or preferable. Given the potency of the INSTIs and the relative safety of raltegravir in initial trials, there has been considerable interest in exploring its role in treatment-naive patients. An initial dose-finding study in previously untreated patients showed that rates of viral suppression at 24 weeks with raltegravir were similar to those with efavirenz (both on a backbone of tenofovir and emtricitabine), although patients receiving raltegravir achieved a more rapid reduction in viral load over the initial 8 weeks of therapy. The efficacy of raltegravir was more definitively established in the STARTMRK trial, which randomly assigned 563 previously untreated HIV-infected individuals to receive 400 mg of raltegravir twice daily or 600 mg of efavirenz once daily, each in combination with fixed-dose tenofovir/emtricitabine. This study concluded that raltegravir was non-inferior to efavirenz, with 86% of patients receiving raltegravir and 82% of patients receiving efavirenz achieving viral suppression (HIV-1 RNA <50 copies/mL) at 48 weeks. As was noted in early studies, treatment with raltegravir was associated with faster virological responses. In addition, raltegravir was associated with a modest but significantly greater CD4+ cell count increase compared with efavirenz—although the difference is unlikely to be clinically relevant. Subgroup analyses confirmed the non-inferiority of raltegravir compared with efavirenz in all patient subgroups, including those with high HIV-1 RNA and CD4+ cell counts <200 cells/mm³. Although both treatment regimens were well tolerated, fewer CNS adverse events were observed in patients receiving raltegravir compared with those receiving efavirenz. Perhaps importantly in considering the long-term role of raltegravir, the changes in lipids in the raltegravir-containing arm were more favourable than those seen with efavirenz. By 48 weeks of treatment, total cholesterol increased from baseline by a mean of 0.55 mmol/L for the raltegravir-treated patients compared with 1.82 mmol/L for the efavirenz arm. There were also significant differences in changes in triglycerides, although interestingly there was no difference in the changes in total cholesterol/high-density lipoprotein (HDL) cholesterol ratios at 48 weeks.

Most of the initial experience involved evaluation of raltegravir combined with a nucleoside (or nucleotide) reverse transcriptase inhibitor (NRTI). Several recent studies examined combinations of raltegravir with a protease inhibitor as an NRTI-sparing option in treatment-naive patients. The combination of raltegravir plus ritonavir-boosted lopinavir had virological outcomes at 48 weeks similar to those of a raltegravir/tenofovir/emtricitabine combination, although the lipid levels were lower in the combination with an NRTI backbone, probably reflecting the lipid-lowering effect of tenofovir. In contrast, a smaller study evaluating raltegravir and atazanavir (unboosted) was terminated by its data safety monitoring committee because of a greater number of virological failures and higher bilirubin levels compared with the control group, who received ritonavir-boosted atazanavir plus tenofovir/emtricitabine. The two studies cannot be compared directly but should provide a note of caution and indicate that more studies of novel combinations are needed (especially in patients with high viral loads) before NRTI-sparing regimens that include raltegravir can be widely recommended.

Where do the results of these trials put raltegravir in current therapeutic approaches to patients initiating therapy for HIV? The combination of efavirenz, tenofovir and emtricitabine has become recognized as the gold standard in antiviral therapy for treatment-naive patients. The fact that the combination of raltegravir, tenofovir and emtricitabine is non-inferior from a virological perspective and is at least as well tolerated makes it a viable option as an alternative—a fact that has been recognized by some of the more recent guideline panels. One limitation in many treatment-naive patients may be the need for twice-daily dosing. Once-daily regimes (whether based on a backbone of efavirenz or of ritonavir-boosted protease inhibitors) are generally preferred for most treatment-naive patients. An ongoing Phase III trial comparing once-daily with twice-daily raltegravir in treatment-naive patients will provide important insights into this issue.

Choice of initial therapy is also heavily influenced by long-term toxicity (as experience with lipoatrophy and increased cardiovascular risk have shown us). Antiretrovirals such as efavirenz and ritonavir-boosted protease inhibitors have been used extensively as first-line agents and have been shown to be effective, durable and generally safe. Since raltegravir is a new drug from a new class, long-term experience in initial therapy is limited, as is its use in combination with drugs other than tenofovir and emtricitabine. To date, however, no major toxicity issues have emerged and its relatively benign metabolic profile will likely make it an attractive candidate for long-term use, especially in older patients with other risk factors for cardiovascular disease (such as hyperlipidaemia and hypertension).

Use in other clinical situations

An increasingly attractive approach to antiretroviral therapy is the simplification of currently successful regimens. The underlying rationale is to attempt to preserve the durability of a successful regimen by either reducing the complexity of a regimen (e.g. the number of pills a patient needs to take), replacing a drug believed to be causing a side effect (such as diarrhoea or dyslipidaemia) or substituting to prevent a major, potentially life-altering toxicity (e.g. lipoatrophy). Raltegravir has been evaluated in a number of such settings and the results are generally encouraging. A number of studies have examined the substitution of raltegravir for enfuvirtide in patients with resistant virus who were virally suppressed—a switch that eliminated the need for injection therapy. In these small open-label studies the substitution was successful, with over 90% of patients maintaining undetectable viraemia after 48 weeks.

Two large studies have examined the strategy of switching from a ritonavir-boosted protease inhibitor to raltegravir with slightly different results. The SWITCHMRK trials compared virological efficacy and metabolic parameters in 702 patients with undetectable HIV-1 RNA for ≥3 months on a regimen of lopinavir/ritonavir plus at least two NRTIs. Patients were randomly assigned to switch lopinavir/ritonavir to raltegravir or continue lopinavir/ritonavir (while the NRTIs were continued unchanged). At 24 weeks, the proportion of patients who maintained HIV-1 RNA <50 copies/mL was 78% in the raltegravir arm compared with 65% in the control arm. In a different study, the SWITCH trial, patients maintained for at least 48 weeks on a ritonavir-boosted protease inhibitor regimen who had undetectable HIV-1 RNA and CD4 cell counts ≥350 cells/μL were randomly assigned to switch lopinavir/ritonavir to raltegravir or continue lopinavir/ritonavir (while the NRTIs were continued unchanged). At 48 weeks, the proportion of patients who maintained HIV-1 RNA <50 copies/mL was 86% in the raltegravir arm compared with 76% in the control arm.
RNA <50 copies/mL was 6% greater among patients in the lopinavir/ritonavir arms compared with those who switched to raltegravir; this difference was such that the switch strategy failed to meet the criteria for virological non-inferiority. Overall, confirmed virological failure (HIV-1 RNA >50 copies/mL) occurred in 32 patients receiving raltegravir and in 17 patients continuing lopinavir/ritonavir. In contrast, the SPIRAL study included 273 patients who were virally suppressed for at least 6 months. Patients were assigned to switch to raltegravir or to continue a ritonavir-boosted protease inhibitor regimen. At 48 weeks, there was no difference in the rates of viral failure (3.1% in the raltegravir arm and 4.9% in those who remained on protease inhibitor therapy) and the study concluded that the switch strategy was indeed non-inferior.

In both studies, the lipid profile was more favourable in the raltegravir arm, which would encourage the use of this strategy if the difference in viral failures can be better understood. One important difference in the trials may have been the degree and duration of viral suppression prior to switching. The patients in the SPIRAL study appear to have had a longer period of viral suppression. In the SWITCHMRK studies, most of the patients who failed after a switch to raltegravir (84%) were not on their first antiretroviral regimen at entry. Indeed, 66% of these had previously documented virological failure. The high rates of virological failure in patients with a history of prior treatment failure on other regimens, suggest that there may have been background resistance to NRTIs that was not clinically discernible because of the potent effect of lopinavir/ritonavir. In this respect, the SWITCHMRK trials seem to be similar to early studies that evaluated patients switching from protease inhibitor-containing regimens to triple-NRTI regimens containing abacavir. In those studies, the switch strategy was more likely to fail if the treatment history or available resistance testing (from prior failures) suggested the presence of archived resistance mutations to NRTIs. With this in mind, I would be cautious in switching from a currently successful regimen to raltegravir plus NRTIs in patients with extensive NRTI experience (especially those with documented prior treatment failure on NRTIs). In contrast, switching to raltegravir plus NRTIs may still be reasonable to consider in selected virologically suppressed patients who have no history of virological failure of NRTI-containing regimens, especially patients with significant treatment-induced dyslipidaemia.

Three major resistance mutations have been described; N155H, Q148H/K/R and Y143R (the latter being the least frequent). Interestingly, they appear to be mutually exclusive and rarely appear on the same viral genome. The Q148 pathway may outcompete the N155H pathway over time. Additional mutations often accumulate as failing patients continue to receive drug. This is often associated with increased resistance of the virus. This suggests that the accumulation of additional mutations may act in a manner similar to the accumulation of protease inhibitor mutations, where the second and subsequent mutations may function to compensate for the reduced viral activity induced by the first primary mutation. Raltegravir-induced mutations appear to cause high-level resistance to the investigational INSTI, elvitegravir. However, the situation is less predictable with other investigational INSTIs (such as S/GSK1349572) and depends on the pattern of resistance to raltegravir. Recent data suggest that viruses with primary mutations at codon 155 or codon 143 remain susceptible in vitro to S/GSK1349572. In contrast, viruses that have the 148 mutation plus additional mutations (usually 140S with or without others) have decreased susceptibility to S/GSK1349572.

Investigational integrase inhibitors

The investigational compounds in more advanced clinical development (elvitegravir and S/GSK1349572) are also strand transfer inhibitors, similar in mode of action to raltegravir. Elvitegravir has been shown to be potent in early clinical trials but requires pharmacological boosting with ritonavir (or alternative pharmacokinetic enhancers) and more data will be needed to determine its utility in clinical practice. S/GSK1349572 is earlier in clinical development but showed very potent virological activity in a 10 day monotherapy study that led to rapid and more extensive clinical development. Early data from Phase Ib studies of S/GSK1349572 in treatment-naive patients have recently been reported. The study examined three doses (10, 25 and 50 mg) with a comparator arm of efavirenz, each combined with two NRTIs. By 16 weeks, 90% of patients in the S/GSK1349572 arms had achieved viral load suppression to <50 copies/mL, without any serious adverse events. This rapid suppression of viral replication (significantly faster than with the efavirenz comparator) is very consistent with results from similar studies of raltegravir and elvitegravir. S/GSK1349572 has a long half-life that allows once-daily dosing (without pharmacological boosting), and importantly appears to be active in vitro against some raltegravir- and elvitegravir-resistant strains. This in vitro activity is supported by recently reported initial in vivo experience, which examined the short-term activity of S/GSK1349572 in patients with documented raltegravir resistance. Such patients received 10 days of functional monotherapy with S/GSK1349572 and the results of this study suggested that the efficacy of S/GSK1349572 depended on the pattern of raltegravir resistance. All patients whose virus had integrase resistance mutations on screening at codon 155 or codon 143 responded to treatment within 10 days. In contrast, there was less clinical activity in situations where the primary resistance mutation was at codon 148 and the virus had additional secondary mutations. In summary, S/GSK1349572 is a promising agent whose clinical development bears watching.
Conclusions

With the development of over 20 different agents active against HIV-1, it could be easy to be blasé about another new drug. However, the development of raltegravir as the first of a new class of agents, INSTIs, was a true milestone in antiretroviral therapeutics. Clinical trials in patients with prior treatment failure offered a paradigm shift in the management of salvage therapy, as they demonstrated that potent new therapeutic combinations could achieve durable complete suppression even in patients with multidrug-resistant virus. Further large, well-conducted clinical trials have suggested a place for the drug in earlier treatment strategies, particularly in patients with co-morbidities that might increase the impact of long-term side effects of other agents. Additional data are needed about both the long-term safety of the drug and its use in other clinical situations, such as paediatrics and pregnancy, and as post-exposure prophylaxis. However, there is no doubt that INSTIs have emerged as very useful and potent agents in the current management of HIV infections.

Transparency declarations

W. G. P. has served on data and safety monitoring boards for Tibotec.

References