Dual therapy with etravirine plus raltegravir for virologically suppressed HIV-infected patients: a pilot study

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Background: Clinical use of protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) may be hampered by toxicity, interactions or resistance issues. Simple and effective antiretroviral regimens avoiding both drug classes may be needed for selected patients.

Methods: This was a prospective cohort study. Virologically suppressed patients on PI or NRTI regimens, with problems of tolerability, safety concerns due to comorbidities or risk of drug interactions for both PIs and NRTIs, were given the opportunity to switch their regimen to etravirine plus raltegravir. Patients were required not to have prior virological failure to raltegravir and if there was prior non-nucleoside reverse transcriptase inhibitor (NNRTI) virological failure, only patients in whom efficacy of etravirine could be anticipated through the Stanford Drug Resistance Database were included. Follow-up was scheduled for at least 48 weeks, unless the patient was lost to follow-up or discontinued therapy.

Results: Twenty-five patients were included. Their median age was 54 years; they had a median of 16 years on antiretroviral therapy and a median of nine previous regimens; 21 (84%) patients had previous virological failure; and 15 (60%) patients had a genotypic test that showed three or more NRTI mutations in 9 (36%), four or more PI mutations in 11 (44%) and at least one NNRTI mutation in 8 (32%) patients. At 48 weeks efficacy was 84% (95% CI 65.3%–93.6%) by intent-to-treat analysis and 91.3% (95% CI 73.2%–97.6%) by per-protocol analysis. One (4%) patient died, two (8%) discontinued due to intolerance and one (4%) experienced virological failure. The CD4/CD8 ratio and plasma lipids improved.

Conclusions: Dual therapy with etravirine plus raltegravir was well tolerated and maintained durable viral suppression in selected virologically suppressed patients for whom both PI and NRTI therapy was challenging.

Keywords: dual antiretroviral therapy, antiretroviral therapy efficacy, PI/NRTI sparing regimen

Introduction

Antiretroviral therapy has changed the natural history of HIV infection. However, antiretroviral therapy must be maintained for life. Its potential long-term adverse effects may interact synergistically with the ageing process, resulting in a higher incidence of comorbidities. The increasing number of non-antiretroviral drugs used to treat comorbidities may also place the patient at a higher risk of clinically meaningful interactions.1,2 At a time when antiretroviral therapy was suboptimal, virological failure with cumulative resistance mutations was common. Surviving patients from the initial antiretroviral era may harbour resistance mutations despite having now achieved sustained virological suppression with currently available antiretroviral therapy. Nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) have been substantially involved in the toxicity and resistance issues mentioned above, as they appeared earlier and have been more widely used than other classes of antiretrovirals, and older drugs within their classes were particularly toxic.3,4

New antiretrovirals, such as the integrase inhibitor raltegravir and the non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine, have not shown major limiting toxicities, are effective in patients with prior resistance to NRTIs and PIs and pose a low risk of clinically significant drug interactions.5–10

Nowadays, efficacy is less of a problem compared with previous times. A substantial number of HIV-infected patients from areas where antiretroviral therapy is widely available have achieved sustained suppression of plasma HIV replication.7 In contrast, the contributions of antiretroviral therapy to the development and progression of comorbidities and to the risk of potentially severe
interactions have gained increasing importance as HIV-infected patients are getting older. More than half of HIV-infected patients aged ≥50 years have been reported to suffer from two or more concomitant comorbidities. In some of these patients, maintenance of antiretroviral therapy with combinations including NRTIs or PIs may be challenging.

We report here the preliminary 48-week efficacy and safety results of a longitudinal pilot study with a dual regimen containing etravirine plus raltegravir in antiretroviral-experienced HIV-infected patients unable to maintain NRTI and PI regimens.

Methods

Study population

We conducted a longitudinal study at Hospital Clinic Barcelona (Spain) in which patients receiving an NRTI-containing or a PI-containing regimen or both had their regimen switched to a regimen consisting of 200 mg of etravirine/12 h plus 400 mg of raltegravir/12 h due to any intolerance, toxicity or risk of drug interactions for both NRTIs and PIs.

Plasma HIV RNA was required to have been < 50 copies/mL in the previous 6 months. Patients with acute antiretroviral discontinuations were allowed to enter the study as long as their clinical condition stabilized shortly after drug discontinuation. Patients already taking raltegravir or etravirine in combination with other antiretrovirals were not excluded.

Patients with prior documented virological failure to etravirine- or raltegravir-containing regimens were excluded. Patients with prior virological failures to nevirapine- or efavirenz-containing regimens were excluded if they had no genotypic resistance testing performed or if their genotypic resistance tests showed NNRTI mutations conferring any degree of resistance to etravirine according to the Stanford Drug Resistance Database. Patients unable to satisfactorily comply with the study regimen for any reason were also excluded.

Participants were visited at baseline, at 1 month and every 3–6 months thereafter. At baseline, HIV-related data were collected, including years since HIV infection diagnosis, potential HIV transmission route, prior AIDS-defining events, and history and duration of exposure to antiretroviral therapy and previous virological failure; results of prior genotypic resistance testing were collected when available. The reason for switching antiretroviral therapy was also recorded at baseline. The clinical evaluation at each follow-up visit included the reason for the antiretroviral therapy switch and the tolerability of the new regimen. CD4 and CD8 cell counts and measurements of plasma HIV-1 RNA, triglycerides and total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were performed. LDL cholesterol was measured indirectly whenever triglycerides were <400 mg/dL; otherwise it was measured directly. The total cholesterol/HDL cholesterol ratio was calculated and Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations were used to estimate renal function. Raltegravir plasma concentrations were determined by HPLC with a fluorescence detector (Multifluorescence Detector 2475; Waters, MA, USA) at month 1 or later. In cases of virological failure, serum samples were tested for resistance, including reverse transcriptase, protease and integrase genotyping of virus using the ViroSeq HIV-1 genotyping system according to the manufacturer’s instructions (Applied Biosystems, Foster City, CA, USA).

Secondary endpoints were changes in CD4 and CD8 cell counts, CD4/CD8 ratio and fasting plasma lipids, incidence of possible adverse events related to treatment and improvement of condition or symptom underlying antiretroviral therapy switch.

Statistical analysis

Intent-to-treat and per-protocol analyses were done. Virological failure, discontinuation of antiretroviral therapy or loss to follow-up were considered therapeutic failures in the intent-to-treat analysis. In the per-protocol analysis, discontinuation of antiretroviral therapy or loss to follow-up were censored. The sign rank test was used to test the hypothesis that changes in laboratory and immunological parameters were different from 0. All analyses were carried out using SPSS software for Windows Version 15.0 (SPSS, Chicago, IL, USA).

Results

Population characteristics

Twenty-five patients were included between February 2009 and February 2012 and completed at least 48 weeks of follow-up, with a median (IQR) follow-up of 102 (52–150) weeks. The study profile is shown in Figure 1. Patients had received a median (IQR) of 9 (6–11) different antiretroviral regimens for a median (IQR) of 16 (15–20) years. The median (IQR) CD4 + T cell count at baseline was 391 (235–728) cells/mm³. Raltegravir plasma concentrations at 6 months were adequate in all patients (median 0.2, IQR 0.1–0.3 μg/mL).

Antiretroviral regimens discontinued at baseline included an NRTI in 6 (24%), a PI in 10 (40%) and a combination of both in 9 (36%) patients. One patient had an etravirine-containing regimen, six patients had a raltegravir-containing regimen and three patients had an etravirine + raltegravir-containing regimen prior to changing to dual therapy. Although 16 (64%) patients were nevirapine experienced and 15 (60%) efavirenz experienced, most were etravirine naive (21, 84%). Eleven (44%) patients had previously experienced treatment with raltegravir. The characteristics of the participants are shown in Table 1.

Lipid alterations and lipodystrophy were the most prevalent reasons for switching (seven patients, 28%). Gastrointestinal disorders, such as diarrhea, nausea and abdominal pain, were also reported in isolation or in association with lipodystrophy or risk of drug interactions. Other reasons were renal toxicity and neuropsychiatric symptoms. An association of two or more reasons was observed in eight (32%) patients. Causes of switching to dual therapy are shown in Table 2. Causes varied widely according to the previous regimen. For instance, all but one of those who changed due to gastrointestinal intolerance were receiving PI-based therapies. In addition, drug interaction and lipid abnormalities were all reported for all patients on PI-based therapy. Renal toxicity was a cause for switching in patients receiving tenofovir. Neuropsychiatric symptoms were mostly reported in efavirenz-treated patients. Lipodystrophy was a frequent reason for changing therapy in patients on NRTIs.

Virological failure to a prior regimen had been diagnosed in 21 (84%) patients and 15 (60%) had at least one resistance genotype
test performed because of virological failure. By standard genotype testing, three or more NRTI mutations were observed in 9 (60%) patients and 11 (73%) presented more than four PI resistance mutations. Eight patients (32%) had a plasma sample containing NNRTI mutations; six individuals had an isolated 103N, one had 103N plus 98G and one patient had 190A isolated.

Virological and immunological response
At 48 weeks the therapeutic efficacy of dual therapy was 84% (21/25) (95% CI 65.3%–93.6%) by intent-to-treat analysis and 91.3% (21/23) (95% CI 73.2%–97.6%) by per-protocol analysis. Regarding the immunological response, at week 48 of follow-up there was a median increase of 114 cells/mm³ in CD4+ T cell counts (IQR 217, 24; 21 patients, P = 0.075) associated with a decrease of 223 cells/mm³ in CD8+ T cell counts (IQR 26, 323; 23 patients; P = 0.020) and an increase of 0.14 in the T4/T8 ratio (IQR 0.37, 0.06; 19 patients, P = 0.001).

Virological failure was observed in one patient (4.0%, 95% CI 0.7%–19.5%) at week 28, with good compliance and an adequate raltegravir level (0.3 mg/mL). Resistance genotype testing revealed a high level of resistance to etravirine (103N, 179F, 179I, 181C and 225H) and no integrase mutations. The patient had been previously exposed to nevirapine and efavirenz with no documented virological failure and was receiving lamivudine, fosamprenavir/ritonavir and raltegravir before switching to etravirine/raltegravir dual therapy due to diarrhoea, dyslipidaemia, diabetes, lipodystrophy and osteoporosis. Diarrhoea as well as lipids improved with treatment. After confirmation of virological failure, therapy was changed to darunavir/ritonavir and maraviroc, achieving virological suppression. All 21 patients who reached week 48 continued on etravirine/raltegravir dual therapy, follow-up ranged from 51 to 61 weeks.
194 weeks and no further treatment interruption or death was observed.

**Safety and tolerability**

Overall, two (8%) patients discontinued treatment due to gastrointestinal intolerance after 8 weeks, attributed to etravirine. There were no cases of rash. One patient died due to biliary sepsis at week 40; this was considered unrelated to antiretroviral therapy. Improvement of at least one of the conditions underlying therapy switch was found in 22 (88%) subjects. All three patients who changed due to abnormalities in renal function showed improvement in estimated glomerular filtration rate. All patients with gastrointestinal intolerance improved except for one case of diarrhoea in a patient with cirrhosis. Neuropsychiatric symptoms improved in all patients who discontinued efavirenz-based therapy.

Median percentage changes in chemistry tests from baseline to week 72 are shown in Figure 2. There was a decrease in median plasma triglyceride level of $-27.78\%$ (IQR $-49.64\%, 9.14\%$; $P=0.02$), glucose level of $-7.06\%$ (IQR $-13.47\%, 4.01\%$; $P=0.05$) and total cholesterol/HDL cholesterol ratio of $-15.61$ (IQR $-24.87, 1.36; P=0.001$) and an increase in HDL cholesterol of $6.96\%$ ($-7.17\%, 34.31\%$, $P=0.02$) after 48 weeks of treatment. Some patients with a follow-up longer than 48 weeks (16 subjects) showed a further decrease in plasma triglycerides of $-33.54\%$ (IQR $-58.63\%, -6.65\%$; $P=0.05$) and total cholesterol/HDL cholesterol ratio of $-26.32$ (IQR $-33.36, -5.31; P=0.006$) 72 weeks after the

*Figure 2.* Median percentage changes in chemistry tests from baseline to week 72. TC, total cholesterol.
switch. There were no overall changes in estimated glomerular filtration rate, except in three patients who switched to dual therapy due to renal toxicity. No patient discontinued lipid-lowering drugs and two had the dosage reduced after changing to dual therapy. No patient interrupted treatment due to any laboratory-related adverse event.

Discussion

In the Hospital Clinic HIV Unit, where >4000 patients have been actively cared for in the previous 5 years, there were 25 patients over a 3-year period who had their regimen switched to etravirine plus raltegravir because of therapeutic concerns with both PIs and NRTIs. All patients were older than average in the HIV Unit and had a long history of HIV infection and extensive treatment experience, and changed to dual therapy mostly for toleration and toxicity problems. The most frequent reasons for switching were metabolic issues and/or lipodystrophy, although many of them had two or more different reasons to enter the study. In this regard etravirine plus raltegravir may represent an interesting simple option considering that these drugs, so far, have not been associated with metabolic, CNS, renal or bone toxicities. Indeed, we observed a mild but significant reduction in triglycerides, total cholesterol/HDL cholesterol ratio and glucose levels.

Improvement in at least one of the conditions underlying regimen switch was reported in >80% of patients; these conditions were mostly gastrointestinal symptoms and lipid abnormalities but also included renal laboratory parameters. The improvement of the condition or symptom that motivated switching to dual therapy depended fundamentally on the frequency of the symptom/condition and its association with the antiretroviral regimen discontinued. In a recent study of the lipid-lowering effect of an etravirine-based regimen in 121 patients, lipids improved in >70% of patients, although a greater effect was observed, as expected, in those who switched due to lipid alterations, especially in fosamprenavir- and lopinavir-treatment patients.13 In our study seven patients were using PI-based regimens when they changed to etravirine + raltegravir dual therapy (two darunavir, one lopinavir, one tipranavir, one fosamprenavir/ritonavir, one boosted atazanavir and one unboosted atazanavir). Despite hyperlipidaemia not being a common reason for a change in patients receiving darunavir and unboosted atazanavir, all patients presented lipid improvement and two had their dosage of lipid-lowering drugs reduced or discontinued. Consistent with this, in previous studies in which a PI was changed to raltegravir, fasting lipids improved irrespective of the PI that was discontinued.9,10

With respect to safety and tolerability, regardless of the report of two treatment discontinuations due to gastrointestinal intolerance, probably related to etravirine, clinical tolerability was good; there were no cases of rash or any laboratory-related adverse events.

Although caution is needed with cross-study comparisons, the efficacy results seen in this study are similar to reported data obtained in similar settings. In a recent published database review reporting 18 patients who were switched from different antiretroviral regimens to 200 mg of etravirine twice daily plus 400 mg of raltegravir twice daily, 94.4% achieved virological suppression to <50 copies/mL at 6 months and 83.3% at 12 months (intent-to-treat analysis).14

It is important to note that in the present study virological failure was restricted to one patient (4%), whose resistance genotype testing confirmed a high level of resistance to etravirine with no integrase mutations. The patient had several comorbidities and long-term NRTI and PI adverse effects. Initially, he maintained virological control and showed improvement in metabolic parameters, but at week 28 experienced virus rebound (viral load 103400 copies/mm3) in spite of having raltegravir plasma concentrations in the therapeutic range.

A single mutation is often enough to cause resistance to the first-generation NNRTIs nevirapine and efavirenz, but the development of resistance to etravirine is a complex phenomenon that requires the coexistence of multiple mutations, and varies with the number and type of mutations present.15 In the present study, standard genotypic resistance testing after virological failure revealed the presence of the five NNRTI resistance mutations K103N, V179F, V179I, Y181C and P225H. The presence of K103N is often associated with efavirenz failure and confers cross-resistance to nevirapine, but in isolation has no effect on susceptibility to etravirine.6,16 It was present in seven patients at baseline. V179F and V181C are 2 of the 13 etravirine DUET study mutations.17,18 By itself, V179F has no effect on etravirine susceptibility, but in combination with Y181C it causes high-level etravirine resistance. V179F almost always occurs in combination with Y181C and they are often selected by etravirine.15,19 The K103N and Y181C mutations frequently emerge in patients failing on first-generation NNRTIs, with K103N tending to emerge more in patients failing efavirenz and Y181C in patients failing nevirapine.20 In the case with virological failure, the patient had been treated with efavirenz and nevirapine, for 6 years in total, with no documented virological failure.

The risk of interactions between antiretrovirals is an important issue in the management of HIV-infected patients. The potential of etravirine for reducing raltegravir concentrations and the need to adjust the dosage of raltegravir in HIV-infected patients who are also receiving etravirine is an issue of concern. However, several studies, besides ours, have confirmed the therapeutic viability of this combination.11–24 We found therapeutic drug levels to be adequate in all patients including the case of viral failure, who developed high-level of etravirine resistance but no raltegravir mutations.

Beyond virological suppression, patients experienced a decrease in CD8 count and an increase in CD4/CD8 ratio, which suggests that virological suppression with this study regimen was as effective as expected, given the prior regimens. Recently, the CD4/CD8 ratio has been independently associated with T cell activation,25,26 and immune activation has been associated with premature ageing and adverse outcomes, and is therefore an important issue to be considered in long-term HIV treatment.1

The present study has some potential limitations. First, we should be cautious in interpreting data from studies on a limited number of patients, aside from the inherent limitations of the observational design. Second, genotype resistance tests were not available for all patients. Third, standard direct PCR sequencing detects the most common circulating HIV-1 variants within a clinical sample but may overlook less-prevalent drug-resistant variants.27

Despite these limitations, this study provides novel and clinically relevant data on the simplification of antiretroviral therapy in selected patients in whom there are concerns about both PI and NRTI therapy. These data reinforce the conception of an individual-
based approach taking into account cumulative resistance mutations and historical treatment as a strategy to optimize treatment outcome in pre-treated patients when switching to a better tolerated antiretroviral regimen. Based upon these considerations, our results suggest that a regimen with etravirine and raltegravir might ensure convenience and tolerance and provide enough potency to achieve viral suppression in selected pre-treated patients. The relatively low genetic barrier to resistance of raltegravir, together with the cross-resistance within the NNRTI class and the possibility of accumulating mutations, does not encourage its use in individuals who experienced viral replication during raltegravir treatment and/or who have accumulated NNRTI resistance mutations. Taking all these considerations together, we believe that this strategy deserves further attention in an adequately powered, randomized clinical trial.

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Author contributions
P. M. participated in study design, data acquisition and data analysis, and drafted the manuscript. E. M. and J. M. G. conceived the study and participated in study design and data analysis, and drafted the manuscript. M. L., M. M.-R., A. G.-C., M. L., J. M. and J. L. B. participated in recruiting patients, data acquisition, supervising data integrity and analysis, and critically revised the manuscript. I. P. performed the statistical analysis. All authors were involved in data interpretation and read and approved the final manuscript.

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