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Background: Reducing drug burden is a key challenge for achieving long-life suppressive therapy. Dolutegravir with a high potency, long half-life and high genetic barrier offers potential for monotherapy.

Methods: This observational single center study enrolled all patients with HIV-RNA (VL) < 50 copies/ml for at least 12 months, CD4> 350 cells/mm^3, with no failure under integrase inhibitor who had switched suppressive antiretroviral therapy (ART) for dolutegravir monotherapy 50 mg/day. Primary outcome was proportion of patients with VL < 50 copies/mL at W24.

Results: Twenty eight patients treated for a median ART duration of 17 years (IQR:11-20), virally suppressed for 79 months (IQR:42-95) with a median 624 CD4 count (IQR:524-761) were enrolled. Baseline ART consisted in a 3-drug (n=10), a 2-drug (n=10) or single drug regimen (n=8) with integrase inhibitor exposure in 13 patients. The proportion of patients maintaining VL< 50 copies/mL was: 96% (95% CI: 79-100) at W4, 100% (85-100) at W8, 93% (76-99) at W12 and 92 % (75-99) at W24. Three patients (3.70%; 95% CI: 3.4-10.8) with prior integrase inhibitor experience had HIV-RNA rebound with presence of resistance mutations. Genotypic resistance in HIV-DNA using Sanger method or ultradeep sequencing showed no integrase inhibitor-RAM except for the mutation 74I in one on a suppressive elvitegravir-regimen. The median within- and between-subject variability of dolutegravir C24h was 25% and 34%, respectively. Nine patients with a year follow up remained virally suppressed.

Conclusion: Dolutegravir has the potency to be further investigated as single ART in randomized studies particularly in patients with no prior exposure to integrase inhibitor.

Introduction

The need for long-term ART in an aging HIV infected population is a challenging issue with a double objective: maintaining maximal viral suppression with a minimal treatment-associated toxicity. Because long-term virological success has become more and more frequent, and considering the high potency of the newest antiretroviral drugs, concepts in antiretroviral strategy are moving: towards the use of lighter antiretroviral strategies to maintain viral suppression, similarly to standard triple drug approach [1–3].

Dolutegravir is the most recently licensed integrase inhibitor indicated in both naïve and pre-treated HIV infected patients [4,5]. As with first generation integrase inhibitor, dolutegravir has a high antiviral potency with an average 2 to 2.5 $\log_{10}$ reduction in viral load leading to viral suppression within few weeks [6–11]. It exhibits a predictable pharmacokinetic profile, a well-defined exposure–response relationship and has shown a good safety profile with limited metabolic, renal or bone toxicity. In addition, dolutegravir has a minimal intra- and inter-pharmacokinetic variability and a low potential for drug-drug interactions by avoiding CYP 450 or UGT enzymes induction or inhibition [12]. In addition, unlike the other integrase inhibitor dolutegravir appears to have a more robust resistance profile. It remains efficient on HIV-1 strains harbouring raltegravir or elvitegravir resistance associated mutation and very few dolutegravir resistance associated mutation has been selected in patients failing a dolutegravir-based regimen [7–10].

Here, we wanted to report our experience of dolutegravir as monotherapy in heavily pre-treated HIV-1 infected individuals.

Patients and Methods

This observational study evaluated all patients followed at the HIV clinical unit of Infectious Diseases department at Pitie-Salpetriere hospital (Paris, France) who were switched from any ART to dolutegravir 50 mg once daily from May 2014 to January 2015, with a plasma (p) HIV-1 RNA below 50 copies/mL for at least 12 months on ART, without history of virological failure on integrase inhibitor, and nor hepatitis B or C co-infection, nor pregnancy. This observational study used the clinical and biological data of all patients who gave their consent to have their clinical and biological data recorded in an electronic medical record (NADIS). As part of routine clinical work under the responsibility of an HIV specialist, all patients were informed and consented to ART modification.

The primary outcome was the proportion of individuals with pHIV-1 RNA < 50 copies/mL at week 24. Secondary outcomes included resistance profile in case of viral rebound, dolutegravir plasma concentrations. Virological failure was defined as 2 consecutive values of pHIV-1 RNA ≥ 50 copies/mL two weeks apart or one value > 200 copies/mL As part of routine procedure in any antiretroviral regimen modification, pHIV-1 RNA and CD4 cells count are routinely assessed at day 0, week 4-8, week 12, week 24 and every six months thereafter. Plasma HIV-1 RNA was quantified using the Cobas AmpliPrep/CobasTaqMan HIV-1 assay version 2.0 (Roche Diagnostics; lower detection limit of 20 copies/mL). Below this cut-off, the assay indicates the qualitative detection of pHIV-1 RNA in the range of 1 to 20 copies/mL. Quantification of whole blood HIV DNA level and resistance testing were performed retrospectively on frozen samples at day 0 and week 24 using a real-time PCR method as previously described [13].Genotypic resistance testing was performed in HIV DNA and in HIV RNA in case of virological rebound using Sanger methods and was interpreted using ANRS genotypic algorithm (http://www.hivfrenchresistance.org).

To search for resistant minority variants, Ultradeep sequencing was performed retrospectively on HIV integrase gene using Illumina technology. Briefly, a 573 bp fragment was PCR-amplified [14] and the Nextera XT DNA Library Preparation Kit (Illumina®, San Diego, USA) allowed the preparation of sequencing-ready libraries rapidly sequenced with MiSeq Illumina system. Presence of minority resistant variants (>5%) were analyzed with Smartgene®.

Dolutegravir plasma concentrations were determined on frozen sample (C24h) at week 4-8, week 12 and week 24 using liquid chromatography-tandem mass spectrometry (Waters Acquity UPLC-TQD; lower limits of quantification 5 ng/mL). Any value above 1,000 ng/mL was considered as adequate as it has been reported associated with a 80% probability of reaching HIV-RNA < 50 copies/mL at week 48 [15].

Continuous variables were expressed as median and interquartile range. Nominal variables were expressed as percentages. Statistics analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

Study population

Twenty-eight individuals were evaluated. All were followed up to week 24 and all except one remained on dolutegravir monotherapy during this period. Baseline characteristics are shown in table 1. They were middle-aged patients with a long ART history of 17 years [11-20], virologically suppressed for a median of 6.6 years [3.5 -7.9]. Two thirds of patients (n=19) had a pHIV-1 RNA < 1 copy/mL. Baseline antiretroviral therapy consisted in triple drug strategy (36%), dual therapy (32%) and monotherapy (32%). Thirteen had been previously exposed to integrase inhibitor (raltegravir n=12, elvitegravir n=1) and six of them were on an integrase inhibitor containing regimen before switching to dolutegravir monotherapy.

Efficacy

At week 24, the proportion of patients with a pHIV-1 RNA < 50 copies/mL was 89% (25/28; 95% CI 72-98). It was 100% (85-100) at week 4 (23/23), 100% (85-100) at week 8 (22/22) and 96% (82-99) at week 12 (27/28). All the 19 patients with a baseline pHIV-1 RNA < 1 copy/mL remained so over the study period. Three patients had virological failure (Figure 1).

- Patient 1 is a 35 year-old female with a CD4 nadir of 262 cells/mm^3, on ART for 7 years, with a plasma HIV-1 viremia suppressed for 6.7 years, a baseline CD4 count of 525 cells/mm^3 and HIV DNA of 310 copies/10^6 cells. She had been suppressed on raltegravir and etravirine during seven months then switched to tenofovir/ emtricitabine/ ritonavir-boosted darunavir because of pregnancy. After delivery, she was switched to dolutegravir monotherapy. Dynamics of viral load is shown on Figure 1. Virological failure occurred at week 24 (2220 copies/mL) with emergence of resistance mutations to all integrase inhibitors (Figure 1). No mutation was detected in the HIV-1 DNA at baseline nor at week 13. Dolutegravir plasma concentrations were above adequate values at week 4, 12 and 24.

- Patient 2 is a 56 year-old man, with a CD4 nadir of 60 cells/mm^3, on ART for 18 years with a pHIV-1 viremia suppressed for 17 months, a baseline CD4 count of 1108 cells/mm^3 and a total HIV-1 DNA of 1459 /10^6 cells. Prior to dolutegravir monotherapy, he received tenofovir/ emtricitabine/ cobicistat-boosted elvitegravir for seven months with three assessments of pHIV-1 RNA < 20 copies/mL. At week 12, virological failure was detected (pHIV-1 RNA=138 then 469 copies/mL) with presence of the E92Q mutation on the integrase gene that confers resistance to raltegravir and elvitegravir (Figure 1) and L74I. Baseline genotyping resistance test on HIV-1 DNA revealed retrospectively the presence of the L74I mutation.

- Patient 3 is a 57 year-old man, with a CD4 nadir of 233 cells/mm^3, on ART for 6 years with a pHIV viremia suppressed for 5.8 years, a baseline CD4 count of 940 cells/mm^3 and a total HIV-1 DNA of 174 copies/10^6 cells. He received tenofovir/emtricitabine/ raltegravir for 72 months with a pHIV-1 RNA < 20 copies on 23 measurements except for one value of 37 copies. Virological failure occurred at week 24, (pHIV-1 RNA=291 copies/mL) associated with emergence of the N155H mutation, conferring resistance to raltegravir, elvitegravir and dolutegravir 50 mg (Figure 1).

Ultra-deep sequencing

Twenty-five patients were evaluated at baseline for presence of integrase inhibitor minority resistant variants (MRV) in HIV DNA. None of the three patients with virological rebound had MRV in integrase gene. Two patients had MRV in integrase gene: E138K (6.6%); G140S (5.4%); N155H (8.1%) leading to resistant for all integrase inhibitor in one patient and S147G (8.2%) leading to elvitegravir resistance in the second patient. Both had been exposed to integrase inhibitor in the past with no virological failure. Importantly none of them experienced virological failure on dolutegavir monotherapy had MRV with a follow up of 15 months.

Plasma drug concentrations

Median (IQR25-75%) values for dolutegravir plasma C24h were 1,411 ng/mL (1,014-1,745), 1,699 ng/mL (1,441-1,912) and 1,571 ng/mL (1,252-1,913) in the 28 patients, at Week 4-8, Week 12 and Week 24, respectively. All C24h were above the *in vitro*, protein-adjusted 90 % inhibitory concentration (IC_{90}) of dolutegravir for wild-type virus (64 ng/mL). Five patients had 6 measurements below threshold (1,000 ng/mL). The median within- and between-subject variability of dolutegravir C24h determined in the 28 patients with approximately 3 values per patient over the follow up were 25% and 34%, respectively.

Discussion

This study reports our experience of using dolutegravir as monotherapy in highly treatment-experienced HIV infected patients with long-term suppressed viremia. Indeed, there is currently a need, in real life, for lighter antiretroviral regimen leading to less cumulative drug exposure. There are two main findings in our study: first, a potential for using dolutegravir as a monotherapy with a large proportion of patients maintaining viral suppression with a suppression rate of 89% at week 24. Secondly, as resistance mutations were evidenced in three patients, the suggestion that the genetic barrier to resistance for dolutegravir, high in naïve patients [7], can be challenged when used as a single agent in this population of patients with an ART history of over 15 years and integrase inhibitor experience for nearly half of them.

None of the three patients with virological rebound, had compliance issues. There was no co-medications that could induce drug-drug interactions as attested by dolutegravir plasma concentrations. Finally no mutation conferring resistance to dolutegravir was found in HIV DNA neither by standard Sanger assay nor by Ultradeep sequencing assay. However, the mutation L74I, evidenced in one patient prior to switch, associated to a possible low resistance level according to Stanford interpretation (http://hivdb.stanford.edu/) contrarily to the ANRS one, may have favored virological rebound. One possible explanation for virologic rebound could be the acquisition at low level of integrase resistance mutations during the previous raltegravir or elvitegravir containing regimen. However, our results using ultradeep sequencing for those patients do not favor this hypothesis. Indeed, we know that raltegravir can select resistance mutations even at low level of replication [16,17] and dolutegravir can also select integrase resistance mutations, such as N155H and R263K, in experienced patients, but integrase inhibitors naïve [18]. In this study, the R263K mutation was not evidenced at failure as previously described[18,19]. The patients reported in the SAILING study [18] were integrase inhibitor-naïve and on a triple dolutegravir-containing regimen once daily while the three patients here were integrase inhibitor-experienced (raltegravir or elvitegravir-experienced but dolutegravir-naïve), which could explain the difference in integrase resistance mutation selection.

With regards to dolutegravir pharmacologic monitoring, we confirm here the pharmacologic robustness of dolutegravir with a low coefficient of variation of 25% compared to raltegravir and elvitegravir with values of 212 % and 33–72 % respectively [20,21] .

This study has several limitations. It is an observational, single center study, on a limited number of patients with a short follow-up. However, our routine management of patients with blood storage and standardized monitoring is close to clinical trials assessments allowing assessments of dolutegravir concentrations and genotypic testing in HIV DNA both using Sanger method and Ultradeep sequencing.

Gubavu et al [22] reported the successful switch to dolutegravir monotherapy over a median follow-up of 32 weeks in 21 patients very similar to our study population except for much less frequent exposure to integrase inhibitor. Similarly, Rojas et al reported [23] their experience of 31 patients, heavily pretreated mostly under a protease inhibitor-containing regimen of successful switch to dolutegravir 50 mg once daily monotherapy.

In summary, these pilot experiences from real life suggesting potential for using dolutegravir monotherapy have to be evaluated in randomized clinical trials. According to our results, pre-exposure to integrase inhibitors should be viewed with great caution in this context as episodes of viral replication could have enhanced the emergence of integrase resistance mutations.

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Transparency declarations

CK had served on advisory board for Merck-Sharpe-Dohme MSD, Janssen and clinical investigator for MSD, Janssen, ViiV Health Care.

All other authors: none to declare.

Author contributions

CK, CS, FC, AD, AGM, VC participated in the conception and design of the study.

CK, FC, LS, MAV, RT, MK included the patients in the study.

CB, LS collected the clinical data. C.K C.S, AG.M analysed and interpreted the data.

CS, AG. M, VC performed the virology analysis.

GP performed the pharmacology analysis.

CK, CS, FC, AG. M wrote the manuscript.

All the authors reviewed, revised for content and approved the final version of this paper.

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