



## Resistance associated mutations to dolutegravir (S/GSK1349572) in HIV-infected patients – Impact of HIV subtypes and prior raltegravir experience

Carolina Garrido<sup>a,\*</sup>, Vincent Soriano<sup>a</sup>, Anna Maria Geretti<sup>b</sup>, Natalia Zahonero<sup>a</sup>, Silvia Garcia<sup>c</sup>, Clare Booth<sup>b</sup>, Felix Gutierrez<sup>d</sup>, Isabel Viciano<sup>e</sup>, Carmen de Mendoza<sup>a</sup>

<sup>a</sup> Infectious Diseases Department, Hospital Carlos III, Calle Sinesio Delgado 10, 28029 Madrid, Spain

<sup>b</sup> Department of Virology, Royal Free Hampstead NHS Trust and University College London Medical School, London, United Kingdom

<sup>c</sup> Microbiology Department, Hospital La Paz, Madrid, Spain

<sup>d</sup> Infectious Diseases Department, Hospital Universitario, Elche, Spain

<sup>e</sup> Microbiology Department, Hospital Virgen de la Victoria, Málaga, Spain

### ARTICLE INFO

#### Article history:

Received 14 January 2011

Revised 28 February 2011

Accepted 7 March 2011

Available online 23 March 2011

#### Keywords:

Dolutegravir  
S/GSK1349572  
Raltegravir  
Integrase  
Drug resistance  
HIV subtypes

### ABSTRACT

Dolutegravir (S/GSK1349572) is a second-generation HIV-1 integrase inhibitor (INI) in advanced clinical development. It has shown good antiviral activity in most patients with prior raltegravir failure, although changes at the integrase codon 148, particularly when combined with other mutations, confer reduced susceptibility and may impair dolutegravir activity.

Mutations believed to be associated with dolutegravir resistance at positions 92, 101, 124, 148, 153, and 193 were assessed in patients either INI-naïve or experiencing failure to raltegravir-based regimens. The integrase coding region was sequenced using an in-house nested-PCR protocol. HIV-1 subtyping was carried out using the Stanford algorithm.

A total of 638 plasma samples were analyzed from 535 INI-naïve and 103 raltegravir-experienced patients. Non-B subtypes were recognized in 20.8% patients. Mutations L101I and T124A were significantly more prevalent in patients with non-B subtypes (66.9% vs. 45.7% for L101I; 61.7% vs. 25.9% for T124A; and 39.1% vs. 12.7% for L101I + T124A;  $p < 0.001$  in all cases). E92Q and Q148H/R were only seen in raltegravir-experienced patients and exclusively infected with subtype B (1.9% vs. 0%,  $p = 0.026$ , for E92Q and 12.6% vs. 0%,  $p < 0.001$ , for Q148H/R). On the contrary, T124A was more frequent in INI-naïve than raltegravir-experienced patients (35.1% vs. 24.3%,  $p = 0.040$ ). S153Y/F was absent in this dataset.

Polymorphic changes L101I and T124A were more frequent in HIV-1 non-B than B subtypes. T124A was more frequent in INI-naïve patients but E92Q and Q148H/R were only seen in raltegravir-experienced individuals. Thus, both HIV-1 subtype and raltegravir exposure may influence the antiviral activity of dolutegravir.

© 2011 Elsevier B.V. All rights reserved.

### 1. Introduction

Dolutegravir, formerly S/GSK1349572 (Shionogi/GlaxoSmithKline) is a second-generation HIV integrase inhibitor (INI), which preferentially blocks the strand transfer step during the viral integration process. The drug has demonstrated potent antiviral activity both in vitro (Johns et al., 2010) and in vivo (Rockstroh et al., 2010; Eron et al., 2010a). Dolutegravir displays some important advantages relative to first-generation INIs raltegravir and elvitegravir, as it is administered once daily, does not require boosting, and displays activity against most isolates resistant to raltegravir or elvitegravir (Eron et al., 2010a; Kobayashi et al., 2010; Seki et al., 2010; Sato et al., 2009).

Limited information exists about the resistance profile of dolutegravir. Two in vitro studies have identified changes at the integrase gene following serial virus passages, including E92Q, L101I, T124A, S153Y/F and G193E (Kobayashi et al., 2010; Seki et al., 2010; Sato et al., 2009). In the first study, after 56 days of virus culture in the presence of dolutegravir, mutation T124A either alone or accompanied by S153F, emerged. At days 84 and 112, four different mutants appeared: T124A, S153Y, T124A + S153Y and L101I + T124A + S153F. Interestingly, these mutants displayed only limited phenotypic resistance to dolutegravir with a maximum fold change of 4.1 (Sato et al., 2009). In another in vitro experiment, after 56 days of serial virus passages with dolutegravir, mutants harboring E92Q or G193E were selected, once again with minor impact on phenotypic susceptibility (average fold change 3.2) (Kobayashi et al., 2010). Mutations E92Q and S153Y have been associated with raltegravir and/or

\* Corresponding author.

E-mail address: [garridocarolina@yahoo.es](mailto:garridocarolina@yahoo.es) (C. Garrido).

elvitegravir resistance, while changes at residue 124 have occasionally been observed in some *in vitro* experiments using different integrase inhibitors with no significant impact on drug susceptibility (Kobayashi et al., 2008). Mutation L101I had never been described so far.

Recently, Marcelin et al. (2010) examined the rate of dolutegravir-associated resistance mutations in a group of INI-naïve and raltegravir-experienced patients infected with HIV-1 subtype B in France. They found a significantly higher rate of T124A and L101I+T124A in patients with prior raltegravir failure than in INI-naïve subjects. Another study (Underwood et al., 2009) found that mutations at codon 148 along with some secondary changes such as G140S or E138K, which are often selected in patients failing raltegravir, were associated with a reduced phenotypic susceptibility to dolutegravir, with a median of 19-fold loss of susceptibility. The aim of our study was to assess the rate of dolutegravir resistance associated mutations in a large group of INI-naïve and raltegravir-experienced patients infected with different HIV-1 subtypes.

## 2. Patients and methods

Consecutive plasma specimens collected from HIV-1-infected individuals on regular follow-up at several Spanish HIV outclinics and one referral hospital in London during year 2008 were analyzed. Bulk sequencing of the HIV-1 integrase coding region was carried out following an in-house nested-PCR protocol described elsewhere (Garrido et al., 2010). All sequences were analyzed using Seqscape v2.5. We considered as resistance mutations potentially associated with dolutegravir those that had been reported in prior *in vitro* studies (Kobayashi et al., 2010; Seki et al., 2010; Sato et al., 2009), besides changes at residue 148, given its well demonstrated clinical relevance. Changes L101I, E92Q, T124A, S153Y/F and G193E, as well as Q148H/R, were recorded for each specimen. HIV-1 subtyping based on the integrase region was performed using the Stanford algorithm, available at <http://hivdb.stanford.edu> through the Sierra software.

### 2.1. Statistical analysis

All specimens were split out according to prior raltegravir exposure and HIV-1 subtype. All results are expressed as absolute numbers and percentages. The chi-square test was used to compare the prevalence of dolutegravir resistance associated mutations in distinct study groups. All reported *p* values were two-sided and significant differences were considered only for *p* values below 0.05. All analyses were performed using the SPSS v15.0 software (SPSS Inc., Chicago, IL).

## 3. Results

A total of 638 HIV-1 integrase sequences were analyzed. They belonged to 535 (83.9%) INI-naïve and 103 (16.1%) raltegravir-experienced patients, all of them naïve for dolutegravir. Overall, 505 (79.2%) belonged to subjects infected with clade B variants and 133 (20.8%) to individuals infected with non-B subtypes. The distribution of non-B subtypes was as follows: 15 (11.3%) A, 19 (14.3%) C, 10 (7.5%) D, 20 (15%) F, 18 (13.5%) G, 18 (13.5%) CRF01\_AE, and 33 (24.8%) CRF02\_AG.

Some mutations associated with dolutegravir resistance *in vitro* were common in the study population, such as L101I (50.2%), T124A (33.4%) and L101I+T124A (18.2%). In contrast, E92Q (0.3%) and G193E (5.5%) were rare. Mutation S153F/Y was absent in the study population (Table 1).

Significant differences in the rate of dolutegravir resistance associated mutations were found comparing INI-naïve and raltegravir-experienced patients. This was the case for E92Q (0% vs. 1.9%, respectively; *p* = 0.026) and Q148H/R (0% vs. 12.6%, *p* < 0.001), which only appeared in sequences from raltegravir-experienced patients. In contrast, T124A was more frequent in INI-naïve than raltegravir-experienced patients (35.1% vs. 24.3%, *p* = 0.040). Regarding viral subtypes, mutations L101I and T124A, either alone or in combination, were significantly more prevalent in non-B than B subtypes (66.9% vs. 45.7% for L101I; 61.7% vs. 25.9% for T124A; and 39.1% vs. 12.7% for L101I+T124A; *p* < 0.001 in all cases).

Table 2 records the rate of dolutegravir resistance associated mutations according to HIV-1 subtype. Change L101I appeared more frequently in clades C, F and CRF02\_AG (100%, 95% and 84.8%, respectively) than in clades D and CRF01\_AE (10% and 16.7%, respectively). Change T124A was more prevalent in clades D, CRF01\_AE and CRF02\_AG (80%, 77.8% and 75.8%, respectively) than in subtypes F and B (25% and 26.4%, respectively). The mutational pattern L101I+T124A was quite prevalent in CRF02\_AG and C variants (63.6% and 63.2%, respectively) while it was rare in subtypes D and B (10% and 12.6%, respectively). Finally, change G193E was only present in subtypes B and F (6.5% and 15%, respectively).

As previously mentioned, changes at codon 148 were only recognized in patients with prior raltegravir failure. Q148H/R was present in 13 (12.6%) out of 103 raltegravir failures. All but one of them also harbored mutation G140S/A. In more detail, seven patients harbored Q148H+G140S, one patient added Q95P and another added A128V. One subject harbored Q148R+G140A, and another added E157Q. One patient had Q148R+G140S and another showed Q148R+E138K+S147G. Of note, all these patients were infected with HIV-1 subtype B.

## 4. Discussion

The advent of INIs has expanded the therapeutic options for HIV-infected individuals. Raltegravir, the first drug approved in this class, has shown potent antiviral activity as well as a satisfactory safety profile (Lennox et al., 2009; Steigbigel et al., 2008). Accordingly, the drug has been approved for the treatment of both

**Table 1**  
Prevalence of dolutegravir resistance associated mutations in the study population, according to prior raltegravir exposure and HIV-1 subtype.

Study population	S/GSK1349572 resistance mutations	Clade B (%)	Non-B clades (%)	<i>p</i>
INI-naïve ( <i>n</i> = 535)		408	127	
	Y143R/H/C	0	0	–
	Q148H/R/K	0	0	–
	N155H	0	0	–
	L101I	44.1	65.4	<b>&lt;0.001</b>
	T124A	26.7	62.2	<b>&lt;0.001</b>
	L101I+T124A	12.3	38.6	<b>&lt;0.001</b>
	S153F/Y	0	0	–
	E92Q	0	0	–
	G193E	6.9	0.8	<b>0.006</b>
Raltegravir-experienced ( <i>n</i> = 103)	No.	97	6	
	Y143R/H/C	5.2	16.7	0.309
	Q148H/R/K	13.4	0	1
	N155H	16.5	16.7	1
	L101I	52.6	100	<b>0.032</b>
	T124A	22.7	50	0.152
	L101I+T124A	14.4	50	0.055
	S153F/Y	0	0	–
	E92Q	2.1	0	1
	G193E	4.1	33.3	<b>0.038</b>

Significant *p* values in bold.

Download English Version:

<https://daneshyari.com/en/article/2510252>

Download Persian Version:

<https://daneshyari.com/article/2510252>

[Daneshyari.com](https://daneshyari.com)