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Dolutegravir montherapy in HIV-infected naïve patients with <100,000 copies/ML HIV RNA load, an update of a little cohort in Verona

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ABSTRACT:

Dolutegravir is an integrase inhibitor that has a high antiviral activity and unique profile of resistance. In this report we described our experience with fourteen naïve HIV-infected patients who started dolutegravir monotherapy, rapidly achieving viral suppression. We analyzed CD4 lymphocytes and lipid profile finding a rapid immune restore and favorable metabolic impact. Despite this is an observational study of a little cohort of patients, it suggests the safety and efficacy of dolutegravir monotherapy.

Keywords: Dolutegravir, Monotherapy, HIV naïve patients.

INTRODUCTION

Dolutegravir (DTG) is an HIV integrase inhibitor with a potent antiviral activity, distinct resistance profile and favorable pharmacokinetic profile[1] recently approved for use in naive and highly active retroviral therapy-experienced patients. Its efficacy and safety have been demonstrated in various clinical trials conducted both in naive and experienced patients[2]. In a dose-ranging study, DTG monotherapy has shown a potent antiviral activity, with a significant reduction in plasma HIV-RNA levels from baseline to day 11 for various doses[1]. DTG is approved for use in association with an abacavir/lamivudine or emtricitabine/tenofovir backbone in antiretroviral-naïve patients at a 50-mg once-daily dose. In 3 phase III randomized controlled clinical studies in antiretroviral-naïve patients, DTG plus 2 nucleoside reverse transcriptase inhibitors was superior to both tenofovir/emtricitabine/efavirenz and darunavir/ritonavir regimens, and not inferior to raltegravir[3-5]. If compared with the other two drugs of its class approved for clinical use, raltegravir and elvitegravir, DTG has shown a higher genetic barrier. Previous we reported our experience about nine antiretroviral naive HIV-1 infected patients followed at the Infectious Diseases Outpatient Department of G.B. Rossi Hospital in Verona, Italy, who started dolutegravir monotherapy after refusing nucleoside reverse transcriptase inhibitors[6].

PATIENTS AND METHODS

In this small observational study, we consider fourteen patients with updated data. They all gave written informed consent to the use of dolutegravir as the only antiretroviral drug. The 12 men and 2 women were all HIV monoinfected, with a mean age of 43.5 years (range 28-76). We assessed changes in CD4 lymphocytes and blood lipid profile between pre-treatment values and last controls. Statistical analysis of differences was performed using *t*-test for paired samples.

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Table 1. Baseline characteristics of the patients, HIV RNA level and number of CD4 cells at baseline, HIV RNA level* and number of CD4 lymphocytes at last control, and months on dolutegravir monotherapy.

Patient number	Age/Gender/ sexual orientation	CDC stage	CD4/µL at baseline	HIV RNA copies/mL at baseline	HIV-RNA copies/mL at last visit	CD4/µL at last visit	Months on Dolutegravir
1	40/F/hetero	A2	248	20,400	<20	683	17
2	36/M/omo	A2	335	18,400	not detectable	458	13
3	38/F/hetero	A2	356	90,500	not detectable	827	14
4	40/M/omo	A2	350	39,000	<20	819	11
5	39/M/omo	A2	329	43,300	<20	532	10
6	44/M/omo	A2	229	17,500	<20	440	12
7	47/M/omo	A2	785	18,200	not detectable	965	9
8	45/M/bisexual	A2	214	16,900	not detectable	334	12
9	76/M/omo	A2	345	52,000	<20	496	10
10	56/M/bisexual	A1	619	13,900	<20	747	6
11	46/M/bisexual	A2	438	52,900	not detectable	545	7
12	47/M/omo	A1	519	28343	<20	612	6
13	28/M/omo	A2	200	39,700	<20	206	6
14	28/M/omo	A2	395	32,300	<20	415	4

*The blood samples were collected from HIV-1 seropositive patients by venipuncture. All plasma were extracted and quantified by the COBAS AmpliPrep/COBAS TaqMan HIV-1 test, version 2.0 (Roche, Mannheim, Germany), following the manufacturers' instructions. The amount of HIV-1 RNA is shown as the number of copies per milliliter of plasma. The lower quantitative detection limit is determined at 20 copies/ml.(HIV RNA< 20 copies/ml or not detectable.

RESULTS

Pre-treatment characteristics of the patients, HIV RNA level and number of CD4 cells at baseline, HIV RNA level and a number of CD4 lymphocytes at the last control, and duration of dolutegravir monotherapy are indicated in Table 1. The second table shows total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides levels before starting dolutegravir and at the last control. No patients had baseline HIV resistance mutations for NRTI, NNRTI, PI or INSTI. The mean duration of effective DGT monotherapy was 9.8 months (range 4-17) and all fourteen patients achieved a viral load less than 20 copies/ml at last control. For CD4 cell count the mean increase was 198 cells/µL, with statistical significance (p <0.01). Serum lipids mildly increased only in 2 patients (n. 1 and n. 5, Table 2), who had also an increase in their body weights. But analyzing mean values of total cholesterol we found no statistical difference between pre-treatment values and last control values (172.2 mg/dl and 180.9 mg/dl with p = 0.21). LDL cholesterol and triglycerides mean values didn't show significant increasing

Table 2. Serum levels of total colestherol, LDL and HDL colestherol and triglycerides before starting dolutegravir and at last control. LDL: Low-density lipoprotein, HDL: high-density lipoprotein, n.v.: normal value.

Patient number	Pretreatment total cholesterol (Total C. n.v.: <200 mg/dL)	Pretreatment LDL and HDL cholesterol (LDL n.v. <130 mg/dL) (HDL d.v. >40 mg/dL)	Total cholesterol at last visit (Total C. n.v.: <200 mg/dL)	LDL and HDL cholesterol at last visit (LDL n.v. <130 mg/dL) (HDL d.v. >40 mg/dL)	Pretreatment Triglycerides (n.v. <150 mg/dL)	Triglycerides at last visit (n.v. <150 mg/ dL)
1	194	111 / 52	252	163 / 76	153	62
2	107	72 / 42	118	52 / 59	43	36
3	173	107 / 51	211	122 / 67	75	106
4	138	112 / 26	168	106 / 33	157	145
5	132	95 / 36	180	116 / 41	76	112
6	170	118 / 34	206	148 / 41	92	79
7	160	104 / 42	193	126 / 49	68	90
8	221	144 / 59	192	117 / 51	90	119
9	160	99 / 48	157	89 / 55	59	61
10	175	109/ 49	170	98 / 52	82	94
11	208	142 / 42	209	139 / 39	115	145
12	225	129 / 76	210	114 / 80	92	78
13	123	71 / 40	128	74 / 41	59	63
14	150	81 / 43	139	81 / 47	126	54

(from 106.8 mg/dl to 110.4 mg/dl with $p = 0.54$ and from 91.9 mg/dl to 88.9 mg/dl with $p = 0.76$ respectively). HDL cholesterol mean values increased significantly (from 45.7 mg/dl to 52.2 mg/dl, with $p = 0.01$).

DISCUSSION

The treatment of HIV infection continues to be based on the combination of three antiretroviral drugs. Monotherapy with protease inhibitors in antiretroviral-naïve patients is inferior to standard antiretroviral regimens in clinical studies[7]. Dolutegravir in association with two nucleosides is superior to efavirenz and darunavir in naive patients. Dolutegravir 50 mg daily showed a high antiviral potency with a reduction of viral load of 2.5 log10 after ten days of monotherapy. Recently a combination of dolutegravir and lamivudine was virologically effective in 20 treatment-naive patients in a pilot study[8]. The results of our small and time-limited study suggest the feasibility of a dolutegravir monotherapy in patients with a viral load lower than 100,000 copies/mL.

CONCLUSIONS

With all its limitations our experience shows a safe lipid profile of DTG monotherapy, with maybe an increase in HDL cholesterol. More extended clinical trials with long follow-up should be performed to confirm our results. Then dolutegravir monotherapy strategy could be used to preserve future antiretroviral drug options, reducing side-effects and healthcare costs.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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